Sleep complaints in patients with myotonic dystrophy

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SUMMARY The aim of this study was to document the clinical picture of excessive daytime sleepiness (EDS) and of other sleep disturbances, and to study the relationship of daytime sleepiness to anthropometric data, muscular impairment, and CTG trinucleotide repeat expansion in myotonic dystrophy type 1 (DM1). A total of 157 DM1 patients were surveyed using a modified version of the Sleep Questionnaire and Assessment of Wakefulness. Other measurements included muscular impairment rating and the size of the trinucleotide repeat. Factor analysis and reliability estimates were used to produce a daytime sleepiness scale with five items of the questionnaire. Thirty-eight healthy family members were studied as control subjects. It was found that EDS was present in 33.1% of DM1 patients. Severity of daytime sleepiness correlated with the degree of muscular impairment but not with age, gender, body mass index, age at onset of symptoms, duration of illness, and CTG repeat. DM1 patients reported a longer sleep period, a less restorative sleep, and more difficulty falling asleep, being alert in the morning and staying awake after meals than controls, but a similar incidence of narcolepsy auxiliary symptoms. Compared with DM1 patients without EDS, those with EDS reported greater hypnagogic hallucinations, and greater pain associated with nocturnal awakenings and in their legs upon morning awakenings. In sum, both DM1 patients with and without EDS exhibit characteristics of sleep duration and sleepiness comparable with those found in idiopathic hypersomnia. The severity of daytime sleepiness is weakly related to the extent of muscular impairment but not to CTG repeat.

KEYWORDS ctg repeat, excessive daytime sleepiness, idiopathic hypersomnia, myotonic dystrophy type 1, narcolepsy, restless leg syndrome

INTRODUCTION

Myotonic dystrophy type I (DM1) is a progressive and pleiotropic disorder caused by an unstable CTG repeat expansion in the 3’ untranslated region of the DM1 protein kinase gene (DMPK), located on chromosome 19q13.3 (Harley et al. 1992). This disorder segregates as an autosomal dominant trait with incomplete penetrance and greatly variable expressivity. DM1 is not only a muscle disease but a multiorgan disorder, and one of the organs affected is the central nervous system (Harper 2001).

Excessive daytime sleepiness (EDS) has been termed as the most common complaint of DM1 (Ashizawa 1998), reportedly present in up to 77–80% of patients (Hilton-Jones 1997; van der Meche et al. 1994), and has repeatedly been reported as one of the earliest symptoms of the disorder (Kilburn et al. 1959; Park and Radtke 1995; Phemister and Small 1961; Rubinszteine et al. 1998; van der Meche et al. 1994). Extended sleep periods in DM1 patients with EDS (Phemister and Small 1961) and regular napping behavior have been documented (Jozefowicz and Griggs 1988; Manni et al. 1991; Park and Radtke 1995; Phillips et al. 1999; van der Meche et al. 1994). Central and obstructive sleep apneas (Broughton et al. 1990; Gilmartin et al. 1991; Guilleminault et al. 1978; Leygonie-Goldenberg et al. 1977; Manni et al. 1991; Park and Radtke 1995) are yet other commonly reported sleep abnormalities in
DM1. In addition, DM1 patients may exhibit sleep-onset rapid-eye movement periods in the multiple sleep latency test such as that classically found in narcolepsy (Gibbs et al. 2002; Park and Radtke 1995). Decreased hypocretin-1 (Hcrt-1) levels in the cerebrospinal fluid of DM1 patients with EDS were recently observed, suggesting a dysfunction of the hypothalamic hypocretin system in this population (Martinez-Rodriguez et al. 2003).

The present study was undertaken to provide added definition to the clinical spectrum of EDS and of other sleep disturbances in DM1. The major aims of the present study were thus: (1) to document the clinical picture of EDS and of other sleep disturbances, including symptoms of narcolepsy and restless legs syndrome (RLS), and (2) to assess the relationship of daytime sleepiness severity to age, gender, body mass index (BMI), age at onset of symptoms, duration of illness, degree of muscular impairment, and CTG repeat. In this regard, a daytime sleepiness scale (DSS) was built with items from the Stanford Sleep Questionnaire and Assessment of Wakefulness (SQAW) (Miles 1982).

METHODS

Subjects

The study cohort included 157 consecutive DM1 patients (74 men, 83 women) with onset of symptoms after 10 years of age who were seen at the Saguenay Neuromuscular Clinic (Quebec, Canada) over an 18-month period, and 38 healthy controls accompanying DM1 patients who were either healthy spouses or unaffected siblings (14 men, 24 women). Control subjects were similar to DM1 patients in terms of age, gender, and BMI. Each patient met the diagnostic criteria for definite DM1 or obligate carrier (Griggs and Wood 1989). Molecular confirmation of the diagnosis was available for 114 patients (72.6%), but a founder effect was already demonstrated in this population (Heyer et al. 1997; Mathieu et al. 1990). All individuals were examined by a neurologist (J. Mathieu) and had their muscular impairment categorized as mild (grades 1 and 2: no or minimal signs of muscular impairment), moderate (grade 3: distal weakness) or severe (grades 4 and 5: mild to severe proximal weakness), based on our previously published muscular impairment rating scale (Mathieu et al. 2001). To make sure of the accuracy of information, age at onset was recorded only if it was precisely and unequivocally given by the subject (n = 121). However, the DM1 phenotype, a categorical variable based on the age at onset (Koch et al. 1991) – early adult form (11–20 years), adult form (21–40 years) and mild form (over 40 years) – was available in 144 subjects.

Sleep questionnaire

The sleep questionnaire used in the present study consisted of 24 items derived from the SQAW of Stanford University (Miles 1982) and originally adapted by J. Montplaisir (Poirier et al. 1987). This instrument examines a number of daytime and nocturnal sleep behavior variables, including the sleep/wake cycle, quantity and quality of sleep, signs of EDS, signs of sleep disorders, narcolepsy symptoms and RLS-related symptoms. The subjects had to indicate whether each question always, often, seldom or never applied. All answers were dichotomized by the pairing of choices ‘never/seldom’ (scored 0) and ‘often/always’ (scored 1). The subjects were also asked two additional open-ended questions pertaining to their habitual sleep/wake schedule. Total nighttime in bed was subsequently computed from habitual bedtime and rising time.

Daytime sleepiness scale

A factor analysis was first performed in order to screen items related to daytime sleepiness. Eight factors with eigenvalues greater than 1.00 were identified in the principal factors solution, accounting for 59.2% of the variance. On the basis of the content of the items retained in each factor, factor 1 subscale was labeled ‘daytime sleepiness’ and five items with loadings > 0.40 were used to produce the DSS. Items pertaining to daytime sleepiness were further analyzed using principal component and reliability analyses. The principal component analysis was used to explore whether the five items (see Table 1) clustered into a single set of components. It revealed that the five items of the DSS measured a single factor, supporting the construct validity of the measure, and had high normalized factor loadings (0.60–0.80). Cronbach’s z reliability coefficients for the five items was 0.72, reflecting an acceptable level of internal consistency. Finally, the z-value did not increase after deleting any one of the five items, further delineating a reasonably high level of internal consistency between the components. The DSS score can vary from 0 to 15: the choices never, seldom, often, and always were scored 0, 1, 2, and 3 for all items except ‘great shape during the day’ for which the latter choices were scored in reverse order. Given that EDS constitutes a significant problem in about 5% of the general population (Bixler et al. 1979), the 95th percentile value of control subjects on the DSS was thus considered as indicative of EDS, corresponding to a score of ≥7 on the DSS.

Data analysis

Between group comparisons were carried out using Student’s t-test for independent samples for continuous variables (sleep/wake schedule exclusively), and Pearson chi-square test for all other nominal/categorical variables. Partitioning procedure for r x k contingency tables was used for post hoc comparisons. Spearman’s rank order correlation coefficient was used to

Table 1 The five items of the Daytime Sleepiness Scale

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Take one or more naps during the day</td>
</tr>
<tr>
<td>2.</td>
<td>At times, sudden need to sleep during the day</td>
</tr>
<tr>
<td>3.</td>
<td>Fall asleep while watching TV/at the movies</td>
</tr>
<tr>
<td>4.</td>
<td>Difficulty being inactive for prolonged periods</td>
</tr>
<tr>
<td>5.</td>
<td>Generally in great shape during the day</td>
</tr>
</tbody>
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characterize the strength of the association between the severity of daytime sleepiness and potential explanatory variables. Bonferroni correction was applied to take into account the number of comparisons. Analyses were carried out using the SPSS package (release 10.0; SPSS, Chicago, IL, USA).

RESULTS

Subjects

The age at onset of symptoms was 21.4 ± 8.8 years. The DM1 phenotype was distributed as follows: 53.5% of early adult form, 35.4% of adult form, and 11.1% of mild or late form. The degree of muscular impairment was determined as mild in 36.4%, moderate in 29.9%, and severe in 33.7%. Finally, CTG repeat classes were: <200 CTG (*n* = 7), 200–400 CTG (**n** = 11), 401–850 CTG (**n** = 25), 851–1100 CTG (**n** = 28), 1101–1500 CTG (**n** = 23), and >1500 CTG (**n** = 20).

Prevalence of EDS and correlates of daytime sleepiness severity in DM1

The DM1 patients presented a significantly higher DSS score than control subjects (5.5 ± 3.2 versus 2.5 ± 2.2, *P* < 0.001). The proportion of DM1 patients and control subjects with EDS was 33.1 and 7.9% (*P* = 0.002). Daytime sleepiness severity was significantly related to the degree of muscular impairment (*r* = 0.22, *P* < 0.05). DM1 patients with mild muscular impairment presented significantly lower DSS scores than those with moderate or severe muscular impairment (4.6 ± 3.3 versus 5.7 ± 3.1 and 6.1 ± 3.1, *P* < 0.05). However, daytime sleepiness severity was not significantly associated with age, gender, BMI, age at onset of symptoms, duration of illness, and with the CTG repeat class.

Sleep disturbances in DM1 patients and controls

Sleep/wake schedule

On average, DM1 patients retired at 23:45 hours and rose at 9:30 hours, for a total nighttime in bed of 585 min while control subjects retired at 23:04 hours (*P* < 0.01) and rose at 7:42 hours (*P* < 0.01), for a total nighttime in bed of 518 min (*P* < 0.001). DM1 patients with and without EDS did not differ relative to their habitual bedtime (23:47 and 23:44 hours), habitual rising time (9:46 and 9:22 hours), and total nighttime in bed (598 and 578 min). More DM1 patients than controls reported a total nighttime in bed ≥10 h (51.0% versus 13.5%, *P* < 0.001). Finally, significantly more DM1 patients with EDS than without EDS spent ≥10 h in bed (63.3 and 44.4%, *P* < 0.05).

Daytime/nocturnal sleep behaviors

Table 2 presents the daytime and nocturnal sleep behaviors of DM1 patients with and without EDS and of control subjects.

| Table 2 Percentage of DM1 patients with (*n* = 52) and without excessive daytime sleepiness (EDS) (*n* = 105), and of control subjects (*n* = 38) with specific daytime and nocturnal sleep behaviors |
|---------------------------------|----------|--------|--------|--------|
| DM1                            | With EDS | Without EDS | Total | Controls |
| Early morning awakenings       | 32.7     | 16.2    | 21.7   | 23.7    |
| Alert and receptive following morning awakening | 21.2*** | 52.4    | 42.0*** | 86.8    |
| Use of caffeine/stimulants to remain alert | 13.5     | 6.7    | 8.9    | 2.6    |
| Facility to stay awake after meals | 25.0**   | 49.5   | 41.4*** | 89.5    |
| Medication/alcohol to facilitate sleep | 5.8      | 7.6   | 7.0    | 0      |
| Fall asleep within 30 min      | 48.1     | 46.7   | 47.1*  | 76.3    |
| Capacity to go to bed very late on occasions | 44.2*** | 71.4   | 62.4   | 68.4    |
| One or more nocturnal awakenings | 28.8     | 16.2   | 20.4   | 10.5    |
| Agitation during sleep         | 48.1     | 43.8   | 45.2   | 23.7    |
| Feeling of pain following nocturnal awakenings | 32.7**   | 12.4   | 19.1   | 10.5    |
| Choking or breathing cessation | 7.7      | 4.8    | 5.7    | 5.3     |
| Snoring                        | 32.7     | 21.0   | 24.8   | 7.9     |
| Urinating                      | 42.3     | 21.9   | 28.7   | 15.8    |
| Very restorative sleep         | 50.0     | 61.0   | 57.3***| 94.7    |

*P* < 0.05; **P** < 0.01; ***P*** < 0.001.

First, significantly less DM1 patients than controls reported being alert and receptive upon morning awakening, having facility to stay awake after meals, falling asleep within 30 min, and having a very restorative sleep. Secondly, it was found that DM1 patients with EDS were less alert and receptive in the morning, and had more difficulty to stay awake after meals and to delay their bedtime very late on occasions compared with DM1 patients without EDS. Also, DM1 patients with EDS reported more feelings of pain following nocturnal awakenings than DM1 patients without EDS.

Narcolepsy and RLS-related symptoms

Table 3 presents narcolepsy and RLS-related symptoms for DM1 patients and controls. No significant difference was found between these two groups. Nevertheless, hypnagogic hallucinations and feelings of weariness or pain in the legs upon morning awakening were more frequently reported by DM1 patients with EDS than by those without EDS.

DISCUSSION

About one-third (33.1%) of the 157 DM1 patients were found to present severe levels of daytime sleepiness on the DSS. This is in keeping with Rubinsztein et al. (1998) who determined that 38.9% of DM1 patients satisfied minimal diagnostic criteria of idiopathic hypersomnia (IH). Rinaldi et al. (2001)
recently emphasized the importance of tailoring sleepiness questionnaires to the specific population studied. In this respect, the items of our DSS are consistent with the clinical features we most commonly observed in association with DM1-related EDS, namely daytime napping and sleepiness when attention is not being held (Hansotia and Frens 1981; Harper 2001; Phemister and Small 1961). By contrast, the commonly used Epworth Sleepiness Scale (Johns 1991) asks for activities that are not habitually carried out by DM1 patients. In the present study, we found no relationship between the severity of daytime sleepiness and current age, age at onset of symptoms and duration of illness, suggesting that daytime sleepiness may appear anytime during the course of the disease. We found that the severity of daytime sleepiness relates weakly to the extent of muscular impairment, a measure of the progression of the involvement. This weak correlation is another illustration of the variability of EDS in the course of the disease. Hilton-Jones (1997) also noted a broad correlation between EDS and the overall severity of the condition but underlined the many exceptions to this rule. Of the three studies that have investigated the relationship between daytime sleepiness and CTG repeat (Giubilei et al. 1999; Phillips et al. 1999; Rubinsztein et al. 1998), none reported a significant association. Rubinsztein et al. (1998) considered their sample of 36 DM1 patients not large enough to confidently exclude that association. Given our large number of DM1 patients, the potential of a false negative result now appears unlikely, as is the inheritance of a gene closely linked to the DMPK gene.

Not only DM1 patients with EDS but also those without EDS present characteristics of sleep duration and sleepiness that resemble those of classical IH: long sleep period, non-restorative sleep and difficulty being alert and receptive following morning awakening (Roth 1976). Indeed, DM1 patients with EDS reportedly live on a background of continuous sleepiness, as suggested by their difficulty being alert and receptive in the morning, staying awake after meals, and postponing bedtime very late on occasions. In a related line of evidence, Phemister and Small (1961) earlier debated whether DM1-related EDS expressed true narcolepsy, and decided that it did not because the tendency to sleep did not occur in an episodic fashion or during activity. In our clinical experience, such sudden and uncontrollable attacks of deep sleep during normal awake times are not seen in DM1.

Discrepancies in the quality of nocturnal sleep in DM1 patients are longstanding, with self-reports of long sleep latencies, repeated awakenings and restless sleep on one hand (Gilmartin et al. 1991; Leygonie-Goldenberg et al. 1977; Phemister and Small 1961), and self-reports of deep and undisturbed nighttime sleep on the other (Manni et al. 1991; Phillips et al. 1999). Polysomnographic (PSG) studies also yielded contradictory results, either showing sleep disruption (Broughton et al. 1990; Leygonie-Goldenberg et al. 1977) or essentially normal PSG findings (Gibbs et al. 2002; Gilmartin et al. 1991; Giubilei et al. 1999; Manni et al. 1991). Studies assessing the relationship of sleep disruption to self-reported sleepiness provided conflicting results (Gilmartin et al. 1991; Phillips et al. 1999). In the present study, we observed no difference between DM1 patients with and without EDS in the frequency of self-reported nocturnal awakenings, early morning awakenings, snoring, breathing cessation during the night, urinating during the night, and agitation during sleep. Thus, it appears unlikely that sleep disruption is an important cause of EDS in this condition.

The relationship of EDS and respiratory disturbances was not assessed in the present study. Our group previously reported that EDS was an independent risk factor for chronic hypercapnia in DM1 (Bégé et al. 1997). However, hypercapnia was not of sufficient magnitude to account for EDS and no relation was found between the occurrence of EDS and lung volume restriction or respiratory muscle weakness. Symptoms of sleep-related respiratory disturbances are likely to be underreported in the present survey, but one must note that apneas are generally considered of insufficient severity to account for EDS, and that their treatment does not systematically relieve EDS in DM1 patients (Gibbs et al. 2002; Gilmartin et al. 1991; Harper 2001; Manni et al. 1991; Park and Radtke 1995).

In accordance with previous reports (Gibbs et al. 2002; Manni et al. 1991; Martinez-Rodriguez et al. 2003; Park and Radtke 1995), we found no difference in the reporting of cataplexy, sleep paralysis and hypnagogic hallucinations between DM1 patients and controls. Still, we observed a greater frequency of hypnagogic hallucinations in DM1 patients with EDS than in those without EDS. In this respect, Ohayon et al. (1996) reported that 37% of a large UK community sample experienced hypnagogic hallucinations, and significantly more so in subjects with symptoms of EDS. However, the authors questioned the validity of hypnagogic hallucinations as a true indicator of narcolepsy.

As regards the presence of RLS-related symptoms in DM1 patients, we found that leg restlessness at bedtime was similar in prevalence to that found in the general population (Lavigne and Montplaisir 1994). However, feelings of weariness or pain in the legs upon morning awakening were more frequent in DM1 patients with EDS than in those without

| Table 3 Narcolepsy and restless legs syndrome-related symptoms (%) of DM1 patients with excessive daytime sleepiness (EDS) (n = 52), without EDS (n = 105), and of control subjects (n = 38) |
|-----------------|-----------------|-----------------|-----------------|
| DM1             | EDS             | EDS             | Controls        |
| Cataplexy       | 23.1            | 16.2            | 18.5            | 5.3             |
| Sleep paralysis | 11.5            | 1.9             | 5.1             | 2.6             |
| Hypnagogic hallucinations | 15.4* | 2.9            | 7.0             | 5.3             |
| Legs restlessness at bedtime | 17.3 | 7.6            | 10.8            | 5.3             |
| Feeling of weariness or pain in the legs upon morning awakening | 21.2* | 6.7            | 11.5            | 2.6             |

*P < 0.01.

Total DM1 patients are compared with controls, and DM1 patients with EDS are compared with those without EDS.
EDS. It should be stressed that peripheral vascular symptoms such as coldness and episodic pallor of hands and feet are commonly found in DM1 patients (Harper 2001). Although our question pertaining to feelings of pain during the night was not specific (pain, headache, arthritis, cramps), it could relate somehow to the pain experienced in the legs in the morning and may suggest some unique etiology of EDS among patients with DM1.

In all, daytime sleepiness was more prominent in DM1 patients than in control subjects, particularly in those with higher degree of muscular impairment. In addition, DM1 patients sleep longer at night and those with EDS more frequently reported hypnagogic hallucinations and feelings of weariness and pain in the legs upon morning awakening. Given the multiple potential etiologies of daytime sleepiness in DM1, an individual patient with EDS deserves sleep studies and respiratory function testing. Also, systematic sleep studies with both diurnal and nocturnal recordings of EEG activity in a significant number of patients are required in order to elucidate the role of sleep disruption with respect to daytime sleepiness, establish the criteria for initiating treatment for EDS, and clarify the hypothesis of a central disturbance of sleep regulation in this population.

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