Toward Understanding Cognitive Impairment in Patients with Myotonic Dystrophy Type 1

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Abstract

Cognitive dysfunction and sleep disruption are two frequent but underestimated features of adult onset myotonic dystrophy type 1 (MD1). In order to investigate the MD1 cognitive profile and its relationship with sleep disruption, 23 patients with genetically proved MD1 (mild–moderate in severity) underwent neuropsychological (nps) and polysomnography assessment. Patients scored lower than controls on almost all nps tests but cognitive impairments were mostly observed in executive functions (z-score = −2.14), with complex attention (z-score = −1.04), memory (z-score = −0.65), constructions (z-score = −1.29), and reasoning (z-score = −0.75) being slightly affected. Moderate–severe sleep apnea (apnea–hypopnea index [AHI] ≥15) was very frequent with most of the apneas being of the obstructive type. However, we found hardly any evidence of association between subjective, objective sleep parameters, and nps performance (p > .001).

Thus, in our cohort of 23 adult MD1 patients, mild cognitive dysfunction, which is mostly related to the dysfunction of frontal association cortex and its underlying neural networks, does not seem to be significantly influenced by sleep disruption, which is mainly caused by obstructive apnea events.

Keywords: Myotonic dystrophy; Cognition; Neuropsychological dysfunctions; Sleep breathing disorders

Introduction

Myotonic dystrophy type 1 (MD1) is the commonest genetically transmitted muscular dystrophy of adulthood, with an incidence of around 1 in 8,000 births (Harley et al., 1992). The causal mutation is an expanded sequence of a trinucleotide cytosine–thymine–guanine (CTG) on chromosome 19q 13.3 (Brook et al., 1992). Despite its categorization among muscular dystrophies, it is a progressive disorder which affects many tissues, including the brain.

Myotonia, muscle weakness, and cataract are the most frequent signs that are present in almost all the patients with adult onset MD1. Other abnormalities including cognitive dysfunction and sleep breathing disorders may be poorly recognized, as they may not be reported by patients and thus not evaluated by most physicians. A mild cognitive dysfunction, which has been considered as an expression of central nervous system (CNS) involvement, has been reported in adult onset MD1 patients. Neuropsychological (nps) findings include lower intellectual level, impaired executive functions, impaired visuospatial and constructional abilities, slowed information processing, dysfunction of memory, attention, and some linguistic aspects, as well as personality changes (Gaul et al., 2006; Meola et al., 2003; Modoni et al., 2004; Perini et al., 1999; Rubinsztein, Rubinsztein, McKenna, Goodburn, & Holland, 1997; Winblad, Lindberg, & Hansen, 2006). A matter of debate remains whether this cognitive dysfunction is a stable (i.e., Tuikka, Laaksonen, & Somer, 1993) or a progressive condition (i.e.,...
Wilson, Balleny, Patterson, & Hodges, 1999). The role of demographic data and major disease’s characteristics, such as disease’s duration and severity, have been examined in the emergence of cognitive impairment in MD1 patients (Bird, Follett, & Griep, 1983; Censori, Danni, Del Pesce, & Provinciali, 1990; Modoni et al., 2004), whereas the effect of CTG expansion is still unclear (Kuo, Hsieh, Wang, Chuang & Huang 2008; Modoni et al., 2004; Perini et al., 1999; Winblad et al., 2006).

A high incidence of excessive daytime sleepiness (EDS) and prolonged sleep periods has been observed in patients with MD1 (Laberge, Bégin, Montplaisir, & Mathieu, 2004). Most researchers have considered them as a dysfunction of the sleep regulatory system (Gibbs, Ciafaloni, & Radvke, 2002) leading to a narcoleptic (Martinez-Rodriguez et al., 2003) or an idiopathic hypersomnia with extended sleep periods (Laberge et al., 2004), as well as a dysfunction of the central breathing control mechanism during sleep, leading to central apnea events (Gilmartin et al., 1991). It is well known that chronic sleep fragmentation may interfere with cognition and especially with executive functions (Jones & Harrison, 2001).

There is only one study with eight MD1 patients that evaluates the relation between nps deficits and sleep abnormalities (Broughton, Stuss, Kates, Roberts, & Dunham, 1990). In this study, the patients underwent nps assessment and overnight polysomnography that showed substantial nps deficits, fragmented nocturnal sleep, and, in half of patients, sleep apnea and/or hypopnea, mainly of central type in both cases. There was no significant correlation between the degree of daytime cognitive deficit and the degree of sleep fragmentation or respiratory problems at night. It was concluded that nps deficit in MD1 cannot be attributed to a secondary effect of nocturnal sleep apnea or sleep disruption but probably represents a direct effect of CNS lesions. In a later study that did not include polysomnography, Phillips, Steer, Soldan, Wiles, and Harper (1999) studied 35 patients with adult onset MD1 and found that cognitive dysfunction was related to somnolence, a common symptom among MD1 patients. Recently, Laberge and colleagues (2009) reported that 86% of 43 patients with adult onset MD1 were found to have an apnea–hypopnea index (AHI) ≥5, predominantly of obstructive type. Obstructive sleep apnea syndrome is a well-studied cause of sleep fragmentation that relates to executive dysfunction (Beebe, Groesz, Wells, Nichols, & McGee, 2003; Decary, Rouleau, & Montplaisir, 2000; Kim et al., 1997; Naegle et al., 1995; Redline et al., 1997), whereas eliminations of the apnea–hypopnea events with noninvasive ventilation result in a consistent improvement in cognition (Naegle et al., 1995).

The aim of the present study was to examine cognitive dysfunction in patients with adult form of MD1 in relation to sleep fragmentation and sleep-disordered breathing.

Materials and Methods

Participants

Twenty-three patients were recruited from the department of “muscle diseases” of the Eginition Hospital over a 36-month period. All individuals were given a clinical examination by the same neurologist. The initial sign–symptom of the disease and the age at onset were recorded and used as markers of the type and duration of the disease. The severity of the disease (mild–moderate–severe) was assessed by the muscular impairment rating scale (MIRS) in myotonic dystrophy (Mathieu, Boivin, Meunier, Gaudreault, & Begin, 2001). All patients underwent arterial blood gas measurement. Patients with hypercapnic respiratory failure were excluded from the study. Moreover, we did not include patients with severe depression according to their Beck Depression Inventory (BDI) score (Tzemos, 1987). A control group of 23 healthy participants matched individually to patients according to demographic characteristics was included in order to evaluate patients’ cognitive profile. The control group consists of healthy participants who have been recruited and included in two previous research protocols concerning the standardization study of the Trail Making Test (TMT) and the Stroop Neuropsychological Screening Test (SNST) in Greek healthy population. None of our patients and healthy controls presented significant motor, verbal, or visual disturbances that could affect their nps performance. All participants first provided a written informed consent to participate in the study, whose protocol was approved by the local area ethics committee.

Neuropsychological Assessment

A comprehensive nps battery was administered to assess multiple cognitive domains, including “complex attention” (TMT part A and B [TMTA and TMTB; Zalonis, Kararizou et al., 2008], Digit Symbol WAIS subtest [Wechsler, 1955; Kokkevi et al., 1979]); “memory function” (Digit Span WAIS subtest [Wechsler, 1955; Kokkevi et al., 1979], Rey Auditory Verbal Learning Test [RAVLT; Rey, 1964], Babcock Story Recall Test [BSRTIm.Recall and BSRTDel.Recall; Zalonis, Christidi et al., 2008], Rey’s Complex Figure Test recall form [RCFTRecall; Meyers & Meyers, 1995]); “perceptual and constructive dexterities” (Rey’s Complex Figure Test copy form [RCFTCopy; Meyers & Meyers, 1995], and Block Design and Object Assembly WAIS subtests [Wechsler, 1955; Kokkevi et al., 1979]); “verbal and visual concept formation and reasoning”
A prescheduled, standard sleep history assessed the presence of subjective sleep measures (excessive daytime sleepiness [EDS], the tendency to fall asleep during the day [sleep episodes during the day], insomnia, total night sleep time, snoring, apneas, parasomnias, difficulty in morning awakening, restless leg syndrome, and signs of narcolepsy [cataplexy, sleep paralysis, hypnagogic hallucinations]). All patients completed the Epworth Sleepiness Scale (ESS), which represents the only questionnaire intended to measure daytime sleepiness and been evaluated in the Greek population (Tsara, Serasli, Amfilochiou, Constantinidis, & Christaki, 2004). A score of >11 in the ESS was accepted as indicative of EDS.

A full-night diagnostic polysomnography was performed on all 23 patients. Electroencephalogram, electro-oculogram, and electromyogram of the submentalis muscle were obtained in order to determine the stages of sleep. Arterial blood oxyhemoglobin was recorded with the use of a finger pulse oximeter. Respiratory effort was measured by inductive plethysmography with respiratory effort sensors placed over the rib cage and abdomen. Airflow was monitored using an oral thermistor and a nasal cannula/pressure transducer. All variables were recorded with a digital acquisition system (Somnologica 3.3, Medcare Flaga, Iceland). Sleep scoring was made manually by an experienced neurologist according to the new AASM scoring criteria (Iber, Ancoli-Israel, Chesson, & Quan, 2007). From the full-night polysomnography study, the following objective sleep measures were calculated in the present study: Total sleep time in minutes recorded from time the lights were turned off (“sleep period”); onset of sleep from time the lights were turned off (“sleep latency”); the number of minutes of sleep divided by the number of minutes in bed (“sleep efficiency”); percentage of sleep stage 1 (“S1%”); percentage of sleep stage 2 (“S2%”); percentage of slow wave sleep (“SWS%”); percentage of REM sleep (“REM%”); percentage of time the patient spend in wake state after sleep onset (“Wake%”); number of arousals/hour (“Arousal Index [AI]”); number of arousals related to apneas and hypopneas/hour (“Resp Ar”); number of arousals related to leg movements/hour (“LM Ar”); number of arousals without identifiable cause/hour (“Arousals”); arousals related to increased upper airway resistance/hour (“RERA”); events of apnea–hypopnea/hour (“AHI”); events of obstructive type apnea/hour (“Obs”); events of central type apnea/hour (“Cent”); events of mixed type apnea/hour (“Mix”); and events of hypopnea/hour (“Hyp”). We have to mention that variables such as the new sleeping environment can influence some sleep indices resulting from the full-night polysomnography study, and this may be the case for the following variables: Sleep period, sleep latency, sleep efficiency, S1%, S2%, SWS%, REM%, and Wake%.

The time interval between the neurological evaluation, the nps assessment, and the evaluation of objective and subjective indices was not more than 2 weeks. Moreover, sleep evaluation was performed after the neurological and nps examination.

**Statistical Analysis**

Differences between patients and controls on demographic characteristics were analyzed by means of independent samples t-test (age and years of education) and $\chi^2$ (gender distribution). Given that the relative assumptions were not markedly violated, parametric analyses were used. Comparisons of nps performance between 23 patients and 23 healthy participants were examined with independent samples t-test. In order to specify the level of nps performance for our patients, z-scores were also calculated, using the controls’ scores and standard deviations as the reference point. Within 23 MD1 patients with the polysomnography study, nps scores and subjective sleep indices were analyzed using Pearson’s correlation analysis (ESS) and independent samples t-test (EDS, naps per day sleep). On the other hand, given that some of the objective sleep measures could be influenced by external factors, as mentioned previously, and in order to minimize the number of analyses, we used only the following objective sleep variables: Sleep efficiency, AI, and AHI. Analyses were performed using Pearson’s correlation analysis. Patients were further categorized according to their AI score, resulting in two groups (AI $< 15$ and AI $\geq 15$), as well as according to their AHI, also resulting in two groups (AHI $< 10$ and AHI $\geq 10$). Independent samples t-test was used. Because of the multiple comparisons, Bonferroni’s correction was applied and the p level was adjusted at .001. The Statistical software package (version 8.0) was used for all analyses.
Results

Demographics Characteristics and Clinical Data

For healthy controls (18 men and 5 women), mean age and education was 42.22 years (SD = 13.18; range: 20–69 years) and 11.22 years (SD = 2.86; range: 6–16 years), respectively. MD1 patients (18 men and 5 women) had a mean age of 42.43 years (SD = 13.05; range: 20–67 years) and a mean education of 11.35 years (SD = 2.95; range: 6–16 years). Both groups did not differ in age or level of education (p = n.s.). Within patients’ group, the mean duration of the disease was 14.43 years (SD = 9.77; range: 0–33 years). All patients were ambulatory (mild–moderate in severity; mean grade in MIRS = 2.00; SD = 1.04; range: 0–3) and had a mean number of CTG repeats of 487.5 (SD = 231.54; range: 120–840). Patients’ mean BDI score was 10.35 (SD = 5.40; range: 0–19).

Neuropsychological Assessment

Nps performance and between-group comparisons for our 23 MD1 patients and healthy participants are presented in Table 1. Despite the fact that MD1 patients scored worse than the control group on almost all nps tests, their intelligence level remains within the normal performance range, with a z-score of $-0.90$.

Differences between patients’ and controls’ scores reached significance at $p < .001$ on tests of “perceptual organization” (RCFTCopy, $t(44) = 3.53$, $p = .001$), “visual memory” (RCFTRecall, $t(44) = 4.27$, $p < .001$), “social judgment” (Comprehension WAIS, $t(44) = 4.59$, $p < .001$), as well as the following measures of “executive functions” (SNST, $t(44) = 3.85$, $p < .001$; WCSTc, $t(44) = 6.42$, $p < .001$; WCSTe(%), $t(44) = -5.12$, $p < .001$; WCSTpr(%), $t(44) = -3.78$, $p < .001$; WCSTclr(%), $t(44) = -5.33$, $p < .001$).

The cognitive profile of our patients was assessed using z-scores. Cognitive domain z-scores were computed by averaging the z-scores for nps tests within each respective cognitive domain. When the level of performance was calculated using the z-scores for each cognitive domains, the resulting z-scores were: “complex attention,” $z$-score = $-1.04$; “memory,” $z$-score = $-0.65$; “perception-constructions,” $z$-score = $-1.29$; “concept formation and reasoning,” $z$-score = $-0.75$; “executive functions,” $z$-score = $-2.14$. Thus, the only clearly impaired cognitive domain was that of executive functions, whereas perception/constructions and complex attention were only mildly affected and memory and concept formation/reasoning remained within the normal range.

Looking more directly on each nps test, $z$-scores for MD1 patients varied from $-0.12$ to $-3.35$, as can be seen in Fig. 1. With the exception of the RCFTCopy ($z$-score = $-2.65$) as well as WCST measures (WCSTc, $z$-score = $-3.35$; WCSTe(%), $z$-score = $-2.15$; WCSTpr(%), $z$-score = $-2.44$; WCSTclr(%), $z$-score = $-2.27$), patients’ performance levels were lower but never below 2 SD from those of healthy controls.

Sleep History and Polysomnography

Sleep history: The main complain of the patients was that of difficulty to arouse in the morning (56.5%) followed by the feeling of inadequacy of night sleep (52%), EDS (13%), and prolonged sleep periods >10 hr if they are not aroused (13%) and sleep episodes during the day (13%). Three patients (13%) scored above 11 in the ESS. None of the patients complained about parasomnia, insomnia, restless leg syndrome, or signs of narcolepsy.

Polysomnography: In total, 7,295.50 min of sleep were analyzed. Table 2 presents sleep parameters for the 23 patients as mean, SD, along with the normal range (reference data from Carskadon & Dement, 2000) of sleep indices. Twelve patients (52%) had an AHI > 10. The mean AHI was 17.47 (SD = 22.31), with three patients (13%) having an AHI > 30 (severe apnea syndrome), and seven (30.4%) between 15 and 30 (moderate apnea syndrome). In six patients (26%), obstruction was the main mechanism of apneas. Eleven patients (47.8%) had increased AI (AI ≥ 15) mainly due to respiratory events. Seven patients (30.4%) had low-sleep efficiency (SE < 80), spending more than 20% of their sleep period in “wake” state. In total, wake state was increased ($M = 16.32; SD = 12.46$) and REM stage was decreased ($M = 13.64; SD = 6.38$).

Neuropsychological Scores and Subjective Sleep Measures

Within 23 patients, correlation analysis revealed that ESS was positively correlated with most nps scores, with the exception of negative correlations with RCFTCopy ($r = -0.12$), WCSTc ($r = -0.01$), and WAIS Similarities ($r = -0.16$), Digit Span ($r = -0.07$), Block Design ($r = -0.14$), Picture Arrangement ($r = -0.07$), Object Assembly ($r = -0.46$), as well as Performance IQ ($r = -0.11$). However, none of the correlations reached significance, even without the Bonferroni correction.
It was only the case of WAIS Object Assembly in which a trend toward significant association with ESS at $p < .05$ was observed ($p = .054$). EDS did not affect nps performance at $p < .001$ and patients who indeed reported EDS ($n = 4$) scored higher on most of the nps tests than patients without EDS ($n = 19$). A worse performance (but at $p > .05$, thus n.s.) for EDS patients was observed only on the perceptual/spatial organization (RCFTCopy; $t(21) = .32$, $p = .75$), construction dexterities (Object Assembly WAIS; $t(21) = .69$, $p = .50$), common judgment (Comprehension WAIS; $t(21) = .30$, $p = .77$), and abstract reasoning (Similarities WAIS; $t(21) = .46$, $p = .65$), as well as executive processes (WCSTc; $t(21) = 1.05$, $p = .30$; WCSTe($\%$); $t(21) = -.44$, $p = .66$; WCSTcrl($\%$); $t(21) = .06$, $p = .96$). The effect of sleep episodes during the day on nps performance was not significant. Patients with sleep episodes during the day ($n = 3$) revealed better performance on all nps tests, except for the perceptual/spatial organization (RCFTCopy; $t(21) = .71$, $p = .49$), visual memory (RCFTRecall; $t(21) = .11$, $p = .92$), construction dexterities (Object Assembly WAIS; $t(21) = .82$, $p = .42$), common judgment (Comprehension WAIS; $t(21) = .38$, $p = .70$), and abstract reasoning (Similarities WAIS; $t(21) = .55$, $p = .59$), as well as the number of categories completed in WCST (WCSTc; $t(21) = .54$, $p = .60$). However, either favoring patients who reported sleep episodes during the day or those who did not report them, none of the nps differences were significant ($p > .05$, n.s.).

| Notes: | MD1 = myotonic dystrophy type 1; WAIS = Wechsler Adult Intelligence Scale; TMTA and TMTB = Trail Making Test part A and part B; RAVLT = Rey Auditory Verbal Learning Test; RAVLT1st = RAVLT first recall; RAVLT1st–5th = RAVLT trials first–fifth sum of words; RAVLTrRecall = RAVLT delayed recall; BSRTIm.Recall = Babcock Story Recall Test Immediate Recall; BSRTDl.Recall = Babcock Story Recall Test Delayed Recall; RCFTRecall = Rey’s Complex Figure Test copy form; COWAT = Controlled Oral Word Association Test; SNST = Stroop Neuropsychological Screening Test; WCSTc. = WCST categories completed; WCSTe($\%$) = WCST percent of errors made; WCSTcrl($\%$) = WCST percent of perseverative responses made; WCSTcrl($\%$) = WCST percent of conceptual level achieved; VIQ = WAIS Verbal IQ; PIQ = WAIS Performance IQ; FIQ = WAIS Full IQ. | Significant differences at $p = .001$ after the Bonferroni correction for multiple comparisons. |

**Table 1. Comparisons of neuropsychological performance between MD1 patients and healthy participants**

<table>
<thead>
<tr>
<th></th>
<th>Controls ($n = 23$)</th>
<th>Patients ($n = 23$)</th>
<th>Statistics</th>
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<tbody>
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<td></td>
<td>Mean</td>
<td>$SD$</td>
<td>Mean</td>
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<td>Complex attention</td>
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<tr>
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<td>8.61</td>
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<td>VIQ</td>
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<td>FIQ</td>
<td>104.96</td>
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We did not note significant correlations (at \( p < .001 \)) between objective sleep measures and nps scores. In general, patients with more efficient sleep tended to show better nps performance. Trend toward correlations (.001 < \( p < .05 \)) were observed between sleep efficiency and TMTB (\( r = .56, p = .02 \)), Digit Symbol WAIS (\( r = .46, p = .03 \)), Arithmetic WAIS (\( r = .43, p = .04 \)), Picture Completion (\( r = .47, p = .02 \)), SNST (\( r = .54, p = .007 \)), and PIQ (\( r = .42, p = .05 \)). A significant effect of the number of AHI was not detected, and patients with increased arousals (AHI \( \geq 15 \), \( n = 10 \)) had better performance (but at \( p > .05 \), n.s.) than patients with less than 15 arousals per hour of sleep (\( n = 13 \)) on most of the nps tests. The AHI \( \geq 15 \) group performed worse (but at \( p > .05 \), n.s.) on some tests of memory (RAVLT1st; \( t(21) = 1.36, p = .19 \); BSRTIm.Recall; \( t(21) = .68, p = .50 \); BSRTDel.Recall; \( t(21) = .68, p = .50 \); RCFTRecall; \( t(21) = .03, p = .98 \)), constructions (Object Assembly WAIS; \( t(21) = .20, p = .84 \)), reasoning (Comprehension WAIS; \( t(21) = .76, p = .45 \); Picture Arrangement WAIS; \( t(21) = .25, p = .81 \)), and executive functions (WCSTc; \( t(21) = .61, p = .54 \); WCSTclr(\%); \( t(21) = 14, p = .89 \)). The effect of increased apneas–hypopneas per hour of sleep was not significant. AHI \( \geq 10 \) patients’ performance was generally better (but at \( p > .05 \), n.s.) than AHI \( < 10 \) patients’ one, except for two tests of memory (RAVLT1st; \( t(21) = .78, p = .44 \); BSRTDel.Recall; \( t(21) = .08, p = .93 \)) and two tests of reasoning (Comprehension WAIS; \( t(21) = 1.45, p = .16 \); Arithmetic WAIS; \( t(21) = .01, p = .99 \)).

Discussion

Our study sought to evaluate cognitive functions in patients with adult onset MD1 and investigate the role of underlying sleep disruption on patients’ nps performance. Despite the fact that the intellectual level of our patients was within the normal range of performance, their IQ scores were significantly lower when compared with those of control group, consistently with previous results (Chang et al., 1993; Colombo, Perini, Miotti, Armani, & Angelini, 1992; Palmer, Boone, Chang, Lee, & Black, 1994; Portwood, Wicks, Lieberman, & Duveneck, 1986; Turnpenny, Clark, & Kelly, 1994; Winblad et al., 2006; Woodward, Heaton, Simon, & Ringel, 1982). The role of motor impairment in cognitive dysfunction has been ruled out since the group consisted of ambulatory patients with mild to moderate in severity disease, whose both verbal and nonverbal WAIS subtests and IQ scores differed from those of neurologically healthy participants (Perini et al., 1999).

Performing a comprehensive series of nps tests, we found that our patients performed significantly worse than healthy participants but still within normal ranges in the majority of the nps tests and we mostly detected mild cognitive impairments, related to executive dysfunction. According to \( z \)-score analyses, our patients performed lower than healthy controls but never below \(-1.5 SD\) on most of the nps tests; only five measures exceeded \(-2 SD\) and for the rest of the nps measures...
Table 2. Sleep parameters of our 23 myotonic dystrophy patients

<table>
<thead>
<tr>
<th>Sleep period</th>
<th>Sleep latency</th>
<th>Sleep efficiency%</th>
<th>S1%</th>
<th>S2%</th>
<th>SWS%</th>
<th>REM%</th>
<th>Wake%</th>
<th>Al</th>
<th>Resp Ar</th>
<th>LM Ar</th>
<th>Spontaneous Arousals</th>
<th>RERA</th>
<th>AHI</th>
<th>Obs</th>
<th>Cent</th>
<th>Mix</th>
<th>Hyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal values</td>
<td>—</td>
<td>&lt;20</td>
<td>&gt;85</td>
<td>50–60</td>
<td>15–20</td>
<td>20–25</td>
<td>&lt;5</td>
<td>&lt;15</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>&lt;10</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mean</td>
<td>317.2</td>
<td>17.5</td>
<td>82.7</td>
<td>9.1</td>
<td>42.8</td>
<td>18.3</td>
<td>13.6</td>
<td>16.3</td>
<td>10.6</td>
<td>0.2</td>
<td>5.6</td>
<td>15</td>
<td>4.9</td>
<td>3.5</td>
<td>1.6</td>
<td>7.5</td>
<td>10.0</td>
</tr>
<tr>
<td>SD</td>
<td>54.8</td>
<td>13.9</td>
<td>10.4</td>
<td>6.5</td>
<td>17.4</td>
<td>11.7</td>
<td>6.4</td>
<td>12.5</td>
<td>18.7</td>
<td>18.9</td>
<td>0.5</td>
<td>4.1</td>
<td>3.0</td>
<td>22.3</td>
<td>9.7</td>
<td>7.3</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Notes: Normal values are presented according to Carskadon and Dement (2000); Sleep period = total sleep time (in minutes) recorded from time the lights were turned off; Sleep latency = onset of sleep from time (in minutes) the lights were turned off; Sleep efficiency% = the number of minutes of sleep divided by the number of minutes in bed; S1% = percentage of sleep stage 1; S2% = percentage of sleep stage 2; SWS% = percentage of slow-wave sleep; REM% = percentage of REM sleep; Wake% = percentage of time the patient spend in wake state after sleep onset; AI = arousal index (number of arousals/hour); Resp Ar = number of arousals related to apneas and hypopneas/hour; LM Ar = number of arousals related to leg movements/hour; Spontaneous Arousals = number of arousals without identifiable cause/hour; RERA = arousals related to increased upper airway resistance/hour; AHI = events of apnea–hypopnea/hour; Obs = events of obstructive type apnea–hypopnea/hour; Cent = events of central type apnea–hypopnea/hour; Mix = events of mixed type apnea–hypopnea/hour; Hyp = events of hypopnea/hour.
cables and belts adjusted on his body. Indices such as AHI and AI are more representative of chronic sleep fragmentation. Thus, it is not a representative index of sleep fragmentation especially when the patient sleeps in a new environment with state that the patient spends after sleep onset and can be influenced from variables such as the new sleeping environment. Representative sleep indices for sleep disruption. As it was mentioned previously, sleep efficiency depends on the wake state that the patient spends after sleep onset and can be influenced from variables such as the new sleeping environment. Experimental sleep fragmentation is reported to result in objective sleepiness and cognitive dysfunction. Moreover, some preliminary analyses, which are beyond the primary goal of the present study, had not revealed any significant correlation between BDI score and nps measures. Few patients are reported to meet the criteria for a depressive disorder (Bungener, Jouvent, & Delaporte, 1998; Colombo et al., 1992; Cuthill, Gattereau, & Viguie, 1988) and most of them are likely to present an emotional deficit, rather than significant depressive or anxiety symptoms (Bungener et al., 1998). It is known that apneas lead to hypoxemia and arousals that disrupt the continuity of sleep with consequences such as daytime sleepiness, poor concentration, and depressive symptoms. In our cohort, moderate to severe sleep apnea (AHI ≥ 15) was found to be very frequent with most of the apneas being of the obstructive type. This is in agreement with the recently published work of Laberge and colleagues (2009). Thus, sleep fragmentation due to obstructive sleep apnea, which is a potentially treated condition, appears frequently in mild–moderate affected MD1 patients. It is interesting that this was the case even in patients without EDS and with a low body mass index, a finding that is possibly related to early involvement of the frontal lobes (Lezak et al., 2004). Thus, our patients’ significant RCFTCopy score could be interpreted in the light of the previous mentioned points, indicating a frontal/executive-like rather than a fine-distal-control effect on RCFTCopy performance. Our findings, similar to previous studies, suggest that executive processes are impaired in patients with adult onset of myotonic dystrophy and mild muscular impairment, since patients’ performance on tests sensitive or related to frontal dysfunction (such as TMTB, RCFTCopy, SNST, and WCST) was significantly lower than the performance of well-matched healthy participants. Impaired executive functions, along with the dysfunction of visual perception, construction ability, and visual memory, can be detected even in patients with IQ scores similar to those of normal participants (Grazia D' Angelo & Bresolin, 2006). The profile of nps deficits is in agreement with imaging studies demonstrating that patients with adult-onset myotonic dystrophy had significantly reduced cerebral perfusion which is more severe in the frontal and temporoparietal association cortex (i.e., Abe et al., 1994; Damian et al., 1994; Ogata, Terae, Fujita, & Tashiro, 1998) and is consistent with a diffuse brain injury (Censori et al., 1994; Chang et al., 1993; Perini et al., 1999). The underlying cause of our patients’ mild cognitive impairments, mostly related to executive dysfunction, could be attributed to similar CNS abnormalities.

In addition to the previously mentioned nps finding, our 23 MD1 patients showed significantly lower performance on social thinking and common judgment (Comprehension WAIS subtest). Impaired social cognition in myotonic dystrophy has been linked to patients’ personality characteristics, such as suspicious attitude, egocentricity, indifference, less cooperation, empathy, and avoidant traits (Grazia D’ Angelo & Bresolin, 2006; Meola et al., 2003), as well as to patients’ difficulty in facial expression depicting emotional excitement (Takeda, Kobayakawa, Suzuki, Tsuruya, & Kawamura, 2009). Dysfunction of the front portion of the temporal lobe, the insular cortex, and the orbital surface of the frontal lobe could be related to difficulty in processing affect and resulting impaired social cognition (Takeda et al., 2009).

A direct effect of depression on cognitive performance is unlikely, since our MD1 patients did not show severe depression (according to their BDI score) and denied pronounced depressive symptoms, as previous studies have mentioned (Meola et al., 2003). Moreover, some preliminary analyses, which are beyond the primary goal of the present study, had not revealed any significant correlation between BDI score and nps measures. Few patients are reported to meet the criteria for a depressive disorder (Bungener, Jouvent, & Delaporte, 1998; Colombo et al., 1992; Cuthill, Gattereau, & Viguie, 1988) and most of them are likely to present an emotional deficit, rather than significant depressive or anxiety symptoms (Bungener et al., 1998).

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that can lead to cognitive dysfunction. However, we observed better nps performance in our affected AI and AHI groups (with AI ≥ 10 and AHI ≥ 15, respectively). This finding is in concordance with the view that cognitive impairment is unrelated to a secondary effect of nocturnal sleep apnea in MD1 and could be linked to a direct effect of CNS lesions (Broughton et al., 1990).

We acknowledge that our study has some limitations. One of the main limitations is the relatively small sample size, which does not permit definite conclusions, despite the fact that all of the 23 patients completed both the nps and the polysomnography assessment. However, the sample-to-population ratio was adequate when compared with other samples collected in the USA (i.e., \( n = 43 \); Portwood et al., 1986), United Kingdom (i.e., \( n = 55 \); Turpenny et al., 1994), Italy (i.e., \( n = 60 \); Modoni et al., 2004), Sweden (i.e., \( n = 47 \); Winblad et al., 2006), or even Greece (\( n = 14 \); Kazis, Kimiskidis, Georgiadis, & Kapinas, 1996). Another caveat was that we did not have the opportunity to follow-up these patients who had been treated with noninvasive ventilation. The MD1 patients could hardly tolerate CPAP or BiPAP, probably due to mask interface in relation to facial and bulbar weakness and also to irregular respiratory patterns. Our clinical experience is that a behavioral component contributes to that intolerance. Nevertheless, the purpose of our next study is to re-evaluate those patients who managed to tolerate CPAP and to compare pre- and post-therapy results. These drawbacks, notwithstanding, our study proceeded to evaluate cognitive functions in patients with adult-onset myotonic dystrophy, thus comparing them with an adequate sample of age- and education-matched healthy participants. In order to avoid recruitment bias, we included consecutive patients who underwent a comprehensive nps battery, and their cognitive abilities were not only evaluated by means of a brief screening tool (i.e., Mini-Mental State Examination). In addition, it is of note that our cohort consisted of ambulatory patients without severe involvement of the respiratory muscles. This excludes patients with hypoventilation during sleep and probably greater nps deficits due to severe sleep fragmentation and CO\(_2\) retention. This question will be the subject of a future study.

In conclusion, our present findings demonstrate that adult patients with mild-to-moderate MD1 show subtle cognitive dysfunctions, mostly related to executive dysfunction. Sleep disruption caused mainly by obstructive apnea events is very common among MD1 patients even in those without daytime sleepiness and in those with low-normal body mass index. However, in our cohort of mild to moderate in severity 23 MD1 patients, cognitive dysfunction does not seem to be influenced significantly by the sleep disruption that characterizes their sleep.

**Conflict of Interest**

None declared.

**References**


