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Research Report

Cognitive Deficits Associated with Sleep Apnea in Myotonic Dystrophy Type 1

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Abstract. Although sleep-disordered breathing and cognitive impairment are common features of patients with myotonic dystrophy type 1 (DM1), little is known about their relationship. Forty-three adult DM1 patients underwent 2 sequential polysomnographic sessions and a neuropsychological test battery (intellectual functioning, attention, language, memory, and executive functions). Lower scores in attention, vigilance, and executive functioning tests were associated with higher number of apneic/hypopneic episodes per hour of sleep and longer total sleep time at an oxyhemoglobin saturation of less than 90%. Results suggest a potential role for nighttime breathing problems in the cognitive impairment often observed in DM1 patients.

Keywords: Myotonic dystrophy type 1, neuromuscular disorders, sleep-disordered breathing, BMI, neuropsychological tests, cognitive function

INTRODUCTION

Cognitive alterations have been largely described in patients with myotonic dystrophy type 1 (DM1). In the adult phenotype, the neuropsychological profile is characterized by deficits in the domain of higher cognitive functions. More particularly, concentration and attention problems, impairments in visuo-spatial and visuo-constructive skills, and perseveration and rigidity in cognitive tasks were reported [1–3]. While some studies noted a link between CNS alterations and neuropsychological data [4], others did not [5].

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Sleep-disordered breathing (SDB), hypercapnia and nocturnal oxygen desaturation have also been consistently reported in DM1. During sleep, patients with DM1 may namely develop apneas and hypopneas of the central, obstructive, or mixed types [6]. The associated sleep disruption may yield diminished neurocognitive performance. For example, a relationship between an elevated sleep apnea index and such cognitive impairments as decrements in attention/vigilance, executive functions, language, memory, and psychomotor speed has been reported [7–9]. Yet, only two studies have evaluated the relationship between cognitive function and sleep-related breathing disturbances in DM1 [10, 11]. Results indicated no significant relationship between the degree of cognitive deficit and sleep fragmentation or respiratory problems

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at night but these studies may have been limited by their relatively small sample sizes (respectively $n = 8$ and $n = 23$).

The main objective of the present study is to reappraise the relationship between the severity of SDB and the nature and extent of cognitive deficits in a larger sample of patients with classical and late onset phenotypes of DM1. A secondary objective is to explore the effect of SDB on the extent of cognitive deficits.

METHODS

Participants

Forty-three adult patients (29 females; *M* (age) ± SD = 49 ± 10 years) with a molecular diagnosis of DM1 were selected without regards to daytime/nocturnal sleep complaints. All patients were registered at a university affiliated neuromuscular clinic (Saguenay, Québec). Patients with congenital or childhood forms of DM1 were excluded. Information was gathered regarding age, sex, disease duration, and body mass index (BMI). CTG repeat was determined using Southern blot analysis. Muscular impairment was assessed using the Muscular Impairment Rating Scale (MIRS). Ethical approval and informed consent were obtained. More details of the study design and protocol have been published elsewhere [12].

Neuropsychological assessment

All participants underwent neuropsychological testing at home, including intellectual functioning (WAIS-R 7 subtests form), perceptual functions (Hooper Visual Organisation Test [HVOT]), attention (Ruff 2&7), language abilities (60-item Boston Naming Test [BNT]), memory (California Verbal Learning Test [CVLT], WAIS-R Digit Span, Rey Complex Figure Test – Recall subtests), perception construction (Rey Complex Figure Test [RCFT] – Copy, WAIS-R Block design) and executive functions (Stroop Color and Word Test, Letter and Category Fluencies). All neuropsychological test scores were age-normalized.

Sleep assessment

Participants underwent two sequential polysomnographic sessions in the sleep unit of an academic hospital. Only data from the second night are presented herein. Apnea-hypopnea index (AHI) was defined as the average number of apneic/hypopneic episodes per hour of sleep, and SaO_2 90%, as the percentage of sleep time with oxyhemoglobin saturation below 90%.

Daytime sleepiness and fatigue

Participants were asked to rate their level of sleepiness and fatigue with the Daytime Sleepiness Scale (DSS), the Epworth Sleepiness Scale (ESS) and the Krupp Fatigue Severity Scale (FSS).

Statistical analysis

Pearson's or Spearman's correlations were performed according to data normality using SPSS (version 18.0). A series of hierarchical multiple regression analyses were conducted to determine whether SDB parameters (AHI and SaO_2 90%) can increase the proportion of variance accounted for cognitive test scores, after that other potential explanatory or independent variables are entered: age, *n*CTG, MIRS, disease duration, BMI, fatigue, and daytime sleepiness. Preliminary analyses were conducted to ensure that there was no violation of the assumptions of normality, linearity, multicollinearity, and homoscedasticity. Collinearity was examined with a matrix of correlations, using the Spearman rank correlation coefficient between independent variables, with an $r > 0.7$ in at least 1 correlation as the criterion for multicollinearity. For each regression model, only independent variables that correlated at $p > 0.25$ with the dependent variable (neuropsychological test score) were entered in Block 1 (Table 1). Since AHI and SaO_2 90% were strongly correlated ($p = 0.603$), they were entered separately in each regression model (Block 2).

RESULTS

Regarding scores on the MIRS, participants' muscular impairment was categorized as mild ($n = 7$), moderate ($n = 6$), or severe ($n = 30$). Mean (±SD) BMI, AHI, SaO_2, and CTGn were respectively 28.7 (±6.6) kg/m^2, 21.8 (±14.4) per hour of sleep, 18.2 (±29.9) % and 839.8 (±580.4). Apneas and hypopneas were of the obstructive type in 87% of events. AHI was categorized as normal (AHI <5; $n = 6$, 14%), mild (AHI = 5–15; $n = 10$, 23.3%), moderate (AHI = 15–30; $n = 15$, 34.9%) and severe (AHI >30; $n = 12$, 27.9%). SaO_2 was categorized as normal (SaO_2 ≥95% per hour of sleep; $n = 9$, 20.9%), mild decrease (90%<SaO_2 <95%; $n = 16$, 37.2%) and severe decrease (SaO_2 ≤90%; $n = 18$, 41.9%). Weight was categorized as normal (BMI ≤25; $n = 12$, 27.9%), overweight (25

Table 1
Summary of hierarchical multiple regression analyses for variables predicting sleep-disordered breathing

Models	R	R^2	Adjusted R^2	R^2 change	F	Sig
Stroop color word						
Block 1: *n*CTG; MIRS; DD	0.55	0.30	0.23	0.30	4.68	0.008
Block 2: *n*CTG; MIRS; DD - AHI	0.64	0.41	0.34	0.11	6.15	0.019*
Block 2: *n*CTG; MIRS; DD - SaO_2	0.56	0.31	0.23	0.01	0.67	0.419
Ruff 2 & 7 - Total speed						
Block 1: *n*CTG; DD	0.65	0.43	0.40	0.43	12.77	0.000
Block 2: *n*CTG; DD - AHI	0.70	0.49	0.44	0.06	3.87	0.058
Block 2: *n*CTG; DD - SaO_2	0.70	0.50	0.45	0.07	4.42	0.043*
Ruff 2 & 7 - Total accuracy						
Block 1: DD; BMI	0.41	0.16	0.12	0.16	3.35	0.047
Block 2: DD; BMI - AHI	0.41	0.17	0.09	0.00	0.03	0.874
Block 2: DD; BMI - SaO_2	0.41	0.16	0.09	0.00	0.00	0.991
RCFT recognition						
Block 1: ESS; DD; BMI	0.59	0.35	0.29	0.35	5.94	0.002
Block 2: ESS; DD; BMI - SaO_2	0.60	0.36	0.28	0.01	0.58	0.452
WAIS-R block design						
Block 1: *n*CTG; DD; BMI	0.54	0.29	0.22	0.29	4.42	0.010
Block 2: *n*CTG; DD; BMI - SaO_2	0.54	0.29	0.20	0.00	0.02	0.888

*$P < 0.05$. MIRS = Muscular Impairment Rating Scale; DD = disease duration; AHI = Apnea hypopnea Index; BMI = body mass index; ESS = Epworth severity scale.

Table 2
Correlation coefficients between neuropsychological test scores and potential explanatory variables of the hierarchical regression models

	AHI	SaO_2	nctg	MIRS	Disease duration	BMI	AGE	ESS	DSS	FSS
Stroop color-word (T)	−0.474**	−0.577**	−0.402**	−0.448**	−0.572**	−0.296	0.042	0.121	−0.116	0.035
Ruff 2&7 total speed (T)	−0.376*	−0.432**	−0.631**	−0.277	−0.515**	−0.177	0.178	0.052	−0.070	−0.039
Ruff 2&7 total accuracy (T)	−0.341*	−0.376*	−0.124	−0.003	−0.326*	−0.370*	−0.154	0.031	0.031	0.111
RCFT recognition (T)	−0.167	−0.473**	−0.182	−0.179	−0.376*	−0.359*	0.003	−0.323*	−0.150	−0.069
WAIS-R block design (z)	−0.067	−0.371*	−0.494**	−0.060	−0.390*	−0.376*	−0.188	0.073	0.162	0.025

*$P < 0.05$; **$P < 0.01$.

<BMI<30; $n = 15$, 34.9%) and obese (BMI ≥30; $n = 16$, 37.2%). Neuropsychological results are presented in Supplementary Table 1. Mean levels of sleepiness were 9.9 (±5.7) on the ESS and 5.4 (±3.3) on the DSS. Mean level of fatigue was 4.9 (±1.4) on the FSS.

AHI and SaO_2 were positively related to BMI ($r = 0.54$, $p < 0.001$ and $r = 0.67$, $p < 0.001$) and *n*CTG repeats ($r = 0.33$, $p < 0.05$ and $r = 0.35$, $p < 0.05$).

Among all the neuropsychological tests, scores of executive functions (Stroop color-word subtest: $r = -0.47$, $p < 0.01$ and $r = -0.58$, $p < 0.01$; Stroop interference: $r = -0.39$, $p < 0.05$ and $r = -0.46$, $p < 0.01$) and visual attention (Ruff 2 & 7 measures: $r = -0.33$ to $r = -0.43$, $p < 0.05$) were negatively correlated with both AHI and SaO_2 90%. In addition, scores of visual memory (RCFT-Recognition: $r = -0.47$, $p < 0.01$) and visuo-constructive abilities (WAIS-R block design subtest score: $r = -0.37$, $p < 0.05$) were negatively correlated with SaO_2 90% (Table 2). Hierarchical multiple regression analyses were then conducted to assess the ability of AHI and SaO_2 90% to separately predict levels of Stroop color word, Ruff 2 & 7 total speed and total accuracy, RCFT-Recognition, and WAIS-R block design scores, after controlling for the influence of additional potential explanatory variables. Results showed that after controlling for *n*CTG, MIRS and disease duration, AHI explained an additional 11% of the variance of the Stroop color word task scores ($R^2 = 0.41$; Adjusted $R^2 = 0.34$; $p < 0.05$); and that after controlling for *n*CTG and disease duration, SaO_2 90% explained an additional 7% ($R^2 = 0.50$; Adjusted $R^2 = 0.45$; $p < 0.05$) and AHI explained an additional 6% ($R^2 = 0.49$; Adjusted $R^2 = 0.44$; $p = 0.058$) of the variance of the Ruff 2 & 7 total speed scores (Table 1).

DISCUSSION

These findings suggest a role for respiratory problems at night in the cognitive impairment often reported in DM1. More particularly, after controlling for disease severity variables, sleep apnea severity explained partially the variance in executive functioning and tended to explain the variance in attention speed abilities in

patients with DM1, which is consistent with previous findings in other conditions [13]. In addition, oxygen desaturation partially explained the variance in attention speed abilities. A wide range of potential mechanisms have been advanced to explain how sleep apnea may negatively impact upon cognitive function, namely after brain injury [14]. Considering these results, SDB may be involved in the fronto-subcortical modifications (anatomical or functional) explaining decreased psychomotor speed and executive dysfunction in DM1. Future studies using functional neuroimaging techniques in combination with neuropsychological testing comparing DM1 patients with and without SDB, may be useful to further document this association.

Moreover, the strong relationship between BMI and AHI observed herein is in agreement with data obtained from general population studies [15]. Given the prevalence of obesity in DM1 [16] and its link to both AHI and SaO_2 in the general population, weight reduction program could be an important treatment strategy to help reduce AHI in DM1 patients [17], and ultimately, have an indirect positive impact on cognitive functioning. In addition, CPAP treatment in patients with severe obstructive sleep apnea was recently shown to result in mild, transient improvement in measures of executive functioning [18]. These latter findings should be replicated in DM1 patients.

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CONFLICTS OF INTEREST STATEMENT

The Authors declare that they have no conflict of interest related to the publication of this manuscript.

REFERENCES

[1] D'Angelo, M. G., and Bresolin, N. Cognitive impairment in neuromuscular disorders. Muscle & Nerve. 2006; 34(1): 16-33.

[2] Sistiaga, A., Urreta, I., Jodar, M., et al. Cognitive/personality pattern and triplet expansion size in adult myotonic dystrophy type 1 (DM1): CTG repeats, cognition and personality in DM1. Psychol Med. 2009; 40(3): 487-495.

[3] Meola, G., and Sansone, V. Cerebral involvement in myotonic dystrophies. Muscle Nerve. 2007; 36(3): 294-306.

[4] Kuo, H. C., Hsieh, Y. C., Wang, H. M., et al. Correlation among subcortical white matter lesions, intelligence and CTG repeat expansion in classic myotonic dystrophy type 1. Acta Neurol Scand. 2008; 117(2): 101-107.

[5] Minnerop, M., Weber, B., Schoene-Bake, J. C., et al. The brain in myotonic dystrophy 1 and 2: Evidence for a predominant white matter disease. Brain. 2011; 134(Pt 12): 3530-3546.

[6] Laberge, L., and Dauvilliers, Y. Myotonic dystrophy and sleepiness. In: Thorpy M, Billiard M, editors. Medical, Psychiatric and Neurological Causes of Sleepiness Cambridge, UK: Cambridge University Press; 2011.

[7] Bucks, R. S., Olaithe, M., and Eastwood, P. Neurocognitive function in obstructive sleep apnoea: A meta-review. Respirology. 2013; 18(1): 61-70.

[8] Wilde, M. C., Castriotta, R. J., Lai, J. M., et al. Cognitive impairment in patients with traumatic brain injury and obstructive sleep apnea. Arch Phys Med Rehabil. 2007; 88(10): 1284-1288.

[9] Naismith, S., Winter, V., Gotsopoulos, H., et al. Neurobehavioral functioning in obstructive sleep apnea: Differential effects of sleep quality, hypoxemia and subjective sleepiness. J Clin Exp Neuropsychol. 2004; 26(1): 43-54.

[10] Broughton, R., Stuss, D., Kates, M., et al. Neuropsychological deficits and sleep in myotonic dystrophy. Can J Neurol Sci. 1990; 17(4): 410-415.

[11] Zalonis, I., Bonakis, A., Christidi, F., et al. Toward understanding cognitive impairment in patients with myotonic dystrophy type 1. Arch Clin Neuropsychol. 2010; 25(4): 303-13.

[12] Laberge, L., Begin, P., Dauvilliers, Y., et al. A polysomnographic study of daytime sleepiness in myotonic dystrophy type 1. J Neurol Neurosurg Psychiatry. 2009; 80(6): 642-646.

[13] Gelir, E., Basaran, C., Bayrak, S., et al. Electrophysiological assessment of the effects of obstructive sleep apnea on cognition. PLoS ONE. 2014; 9(2): e90647.

[14] Mollayeva, T., Kendzerska, T., Mollayeva, S., et al. Sleep apnea in traumatic brain injury: Understanding its impact on executive function. J Sleep Disorders Ther. 2013.

[15] Young, T. B., and Peppard, P. Epidemiology of obstructive sleep apnea. In: McNicholas WT, Phillipson EA, editors. Breathing disorders in sleep. London, UK: WB Saunders; 2002, 222-35.

[16] Gagnon, C., Chouinard, M. C., Laberge, L., et al. Prevalence of lifestyle risk factors in myotonic dystrophy type 1. Can J Neurol Sci. 2013; 40(1): 42-7.

[17] Tuomilehto, H., Seppa, J., Uusitupa, M., et al. The impact of weight reduction in the prevention of the progression of obstructive sleep apnea: An explanatory analysis of a 5-year observational follow-up trial. Sleep Med. 2014; 15(3): 329-335.

[18] Kushida, C. A., Nichols, D. A., Holmes, T. H., et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: The Apnea Positive Pressure Long-term Efficacy Study (APPLES). Sleep. 2012; 35(12): 1593-1602.