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Fatigue and daytime sleepiness in patients with myotonic dystrophy type 1: To lump or split?

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ABSTRACT

We assessed the relationship and clinical correlates of fatigue and Excessive Daytime Sleepiness (EDS) in 200 myotonic dystrophy type 1 (DM1) patients by means of questionnaire and neuropsychological evaluation. Fatigue levels were higher in patients with EDS and daytime sleepiness levels higher in patients with excessive fatigue. However, EDS without fatigue was rarely observed. Also, DM1 patients with fatigue (with or without EDS) showed greater muscular impairment, CTG repeats, abnormalities regarding personality, depressive symptoms and lower health-related quality of life (HRQoL) than patients without these symptoms. These findings do not readily support the contention that fatigue and EDS constitute distinct clinical manifestations in DM1. Clinicians should systematically evaluate both symptoms since fatigue and EDS have a greater impact on HRQoL than fatigue alone. However, specific rating scales for fatigue in DM1 have yet to be devised.

1. Introduction

Myotonic dystrophy type 1 (DM1), an autosomal dominant disorder, is the most common adult form of muscular dystrophy [1]. DM1 results from an unstable CTG repeat expansion in the 3′ untranslated region of the myotonic dystrophy protein kinase (*DMPK*) gene at 19q13.3 [2]. It is not only a muscle disease but a multisystemic disorder, including impairment of the central nervous system [1]. Excessive Daytime Sleepiness (EDS) has long been associated with DM1 and has been referred as the patients' most frequent non-muscular symptom [3]. It may be apparent as one of the earliest symptoms of the disorder, with many patients complaining of EDS for years before DM1 is diagnosed [4–6]. With virtually all systems of the body affected in some way, the causes of EDS in DM1 are potentially multifactorial. However, available evidence is in favor of EDS being due to a specific central mechanism unrelated to respiratory drive [7–9]. In addition, fatigue is more common in DM1 than in other neuromuscular disorders and can, alike EDS, reportedly be salient in some patients with only mild muscular impairment [1,10]. While DM1 is recognized as a neurological disorder causing central fatigue [11], not much is known about its clinical characteristics, mechanisms, and therapeutics.

Although the terms fatigue and sleepiness are often used interchangeably, they should be differentiated [12] since they may constitute two distinct, albeit interrelated symptoms [13]. In DM1, the first of two studies that assessed the relationship of fatigue to daytime sleepiness detected no significant association but mentioned that the sample of 36 patients was insufficient to confidently exclude the absence of an effect [5]. More recently, a study of 32 consecutive ambulant patients revealed that fatigue scores were increased irrespectively of the presence of daytime sleepiness and that both these symptoms were unrelated to disease severity, suggesting different pathophysiological mechanisms [14]. A frequent lesson in medical education relates daytime sleepiness complaints to a potential sleep disorder, and complaints of fatigue, tiredness, or lack of energy to psychiatric or medical diagnoses [15]. As regards DM1, one may contend that fatigue has an indirect cause that is not specifically related to the disease process but secondary to other possible consequences of DM1, such as sleep disturbances or depression. In view of the specific pathways for evaluating and treating EDS [16,17] and central fatigue [11], on the one hand, and of the heavy toll that both these symptoms exact upon physical and social functioning of DM1 patients [1,5,10,18],

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on the other, it was deemed important to investigate further their clinical characteristics in this condition.

This study aims to document whether age, gender, body mass index (BMI), degree of muscular impairment, and CTG repeats are related to daytime sleepiness and fatigue, as assessed by standardized rating scales, and to assess the relationship between these latter symptoms. In an effort to augment our understanding of potential correlates and outcomes of fatigue and daytime sleepiness in DM1, we also explored the association of fatigue and daytime sleepiness to sleep-related complaints, habitual sleep duration, personality patterns, intensity of depressive symptoms, Intellectual Quotient (IQ), and Health-Related Quality of Life (HRQoL).

2. Methods

The study cohort included two-hundred patients with adult DM1 (79 men, 121 women; 47.0 ± 11.8 years, range 20–81) followed at the Neuromuscular Clinic of the Centre de Santé et de Services Sociaux (CSSS) de Jonquière (Québec, Canada). Patients with congenital and infantile forms of DM1 were excluded. All patients were examined by a neurologist and had their muscular impairment categorized according to the Muscular Impairment Rating Scale (MIRS) [19]: grade 1 (no sign of muscular impairment, $n = 10$), grade 2 (minimal signs of muscular impairment, $n = 31$), grade 3 (distal weakness, $n = 36$), grade 4 (mild proximal weakness, $n = 98$), and grade 5 (severe proximal weakness, $n = 25$). Molecular confirmation of the diagnosis was obtained for each patient. The mean CTG repeat of the 200 participants was 809.2 ± 529.4. Twenty-four subjects were taking methylphenidate. Finally, to make sure of the accuracy of the information, age at onset of symptoms was noted only if it was precisely and unequivocally given by the patient ($n = 142$); the median age at onset of symptoms was 19.0 years (range 10–62 years). Procedures for the DM1 patients selection are described elsewhere [20]. This study was approved by the CSSS de Chicoutimi Institutional Review Board and informed consent was obtained from all participants.

All 200 DM1 patients completed the Epworth Sleepiness Scale (ESS) [21], the Daytime Sleepiness Scale (DSS) [22], the Krupp's Fatigue Severity Scale (FSS) [23], a Visual Analog Scale (VAS) for fatigue, and the Short-Form Survey (SF-36) [24]. Also, a modified version of the Sleep Questionnaire and Assessment of Wakefulness (SQAW) [25] and the Symptom Check-List-90-Revised (SCL-90-R) [26] were completed by 197 and 172 patients, respectively. Finally, the WAIS Full scale IQ [27] and NEO-FFI [28] were, respectively, completed by 188 and 110 patients.

The ESS was developed to measure the general level of sleepiness, conceptually defined as sleep propensity. It consists of eight questions asking patients to rate their chance to fall asleep in situations commonly encountered in daily life. The unidimensional aspect of this metric has been confirmed by factor analysis [29]. This measure was also shown to be stable over time in DM1 patients [30]. ESS scores $\geqslant 11$ correspond to pathological sleepiness or EDS. The DSS was specifically devised to assess the level of daytime sleepiness in patients with DM1 [22]. The DSS was found to correlate with the degree of muscular impairment, and its five items are consistent with the clinical features most commonly noted in association with DM1-related daytime sleepiness. Principal component analysis in 157 DM1 patients revealed that the DSS measured a single factor. Its internal consistency and test–retest reliability was also demonstrated [22,30]. A DSS score $\geqslant 7$ is considered as indicative of EDS [22].

The 9-item FSS evaluates the effect of fatigue on daily activities [23]. This scale has demonstrated high internal consistency, adequate concurrent validity, and criterion-related validity [23]. More particularly, an evaluation in DM1 patients suggested that the measure is stable over time [30]. Scores of 4 or higher are considered as indicative of pathological or excessive fatigue. The VAS for fatigue asks patients to indicate on a 10-cm line the point that best depicts their fatigue, ranging from "no fatigue" to "severe fatigue".

The sleep questionnaire used in the present study consisted of 19 items derived from the SQAW of Stanford University [25]. This instrument examines a number of daytime and nocturnal sleep behavior variables, including quantity and quality of nocturnal sleep and signs of sleep disorders. DM1 patients had to indicate whether each item always, often, sometimes or never applied. Answers were dichotomized as always/often and sometimes/never. In addition, the patients were asked two open-ended questions pertaining to their habitual bedtime and waketime, from which habitual total nighttime in bed was computed.

The NEO Five-Factor Inventory (FFI) is an abridged version of the NEO-PI-R (the NEO Personality Inventory), a commonly used measure devised to provide a general description of normal personality [28]. This is a 5-point Likert-type scale that ranges from "Strongly disagree" (0) to "Strongly agree" (4). This 60-item scale includes five major domains (factors) of personality: Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness. The NEO-FFI shows correlations of 0.75 to 0.89 with the NEO-PI validimax factor. Internal consistency values range from 0.74 to 0.89.

The SCL-90-R [26] measures 9 primary symptom dimensions that provide an overview of a patient's psychological symptoms and their intensity at a specific point in time. It consists of 90 items, each rated on a 5-point scale of distress ranging from 0, reflecting absence of distress, to 4, representing the upper scale of distress. The SCL-90-R has been used with a broad range of individuals, including alcoholics, cancer patients, and medical patients with numerous other dysfunctions and complaints [26]. It has shown high level of internal consistency and test–retest reliability as well as construct validity. The SCL-90-R Depression scale reflects a broad range of concomitant clinical depressive symptoms and often is employed as a screening instrument for depression.

The SF-36 is the most frequently used generic HRQoL questionnaire. Data from the 36 questions are transformed into eight subscales: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Higher scores are associated with a better HRQoL [24].

Spearman non-parametric rank order correlation coefficients were used to characterize the strength of the association between fatigue and daytime sleepiness scores. Student's *t*-tests for independent samples were carried out to compare daytime sleepiness levels of DM1 patients with excessive fatigue, and conversely, to compare fatigue levels of DM1 patients with EDS. In addition, chi-square tests and one-way analysis of variance were used to assess whether age, gender, BMI, muscular impairment, CTG repeats, habitual total nighttime in bed, sleep-related complaints, personality domains, intensity of depressive symptoms, IQ, and HRQoL differed among DM1 patients with and without excessive fatigue and/or EDS. Post hoc comparisons were performed using chi-square and Tukey tests. As regards sleep-related complaints, the *p*-value for individual tests was divided by the number of comparisons made to correct for multiple testing (Bonferroni method). Significant testing was two-sided, with α set at 0.05.

3. Results

3.1. Fatigue and daytime sleepiness levels

The mean (SD) scores were 8.1 (5.0) for ESS, 4.9 (3.0) for DSS, 4.6 (1.7) for FSS, and 5.1 (2.6) for VAS. The proportion of DM1 patients