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Original Article

Excessive fragmentary myoclonus in Machado–Joseph disease

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ABSTRACT

Objective: Machado–Joseph disease (MJD) is a neurodegenerative disease which usually presents several clinical findings including cerebellar ataxia and other extracerebellar features, such as Parkinsonism, dystonia, peripheral neuropathy, and lower motor neuron disease. Some data have demonstrated a high frequency of sleep disorders in these patients, including excessive daytime sleepiness (EDS), insomnia, obstructive sleep apnea (OSA), rapid eye movement (REM) sleep behavior disorder (RBD), and restless legs syndrome (RLS). Herein, we aimed to describe the high frequency of excessive fragmentary myoclonus (EFM) in MJD.
Materials and methods: We recruited 44 patients with MJD and 44 healthy controls. All participants underwent an all-night polysomnography (PSG). EFM was evaluated and defined in accordance to the criteria of the American Academy of Sleep Medicine.
Results: Half of the MJD patients ($n = 22$) had EFM diagnosed through PSG, though no healthy control participant presented this finding ($P < .0001$). In the MJD group, older participants and men had a higher frequency of EFM. There was no correlation between EFM and the following data: body mass index (BMI), apnea–hypopnea index (AHI), EDS, loss of atonia during REM sleep, periodic limb movements during sleep (PLMS), RLS, RBD, ataxia severity, the number of cytosine–adenine–guanine trinucleotide (CAG) repeats, disease duration, sleep efficiency, sleep fragmentation, and sleep stage percentages between patients with or without EFM.
Conclusion: EFM is highly prevalent in patients with MJD. Our study demonstrates that EFM must be included in the clinical spectrum of sleep disorders in MJD patients.

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1. Introduction

Spinocerebellar ataxia type 3 or Machado–Joseph disease (MJD) is a neurodegenerative disorder which usually leads to marked and irreversible functional impairment. This entity is the most common autosomal-dominant spinocerebellar ataxia worldwide and is caused by a cytosine–adenine–guanine trinucleotide (CAG) repeat expansion at exon 10 of the ataxin 3 gene, *ATXN3*, located on chromosome 14q32 [1,2]. MJD may present with wide clinical manifestations, including cerebellar ataxia, Parkinsonism, dystonia, peripheral neuropathy, and ophthalmoplegia [2,3]. For the last few decades, several data have been established a more diffuse neurodegenerative involvement in MJD with high frequency of nonmotor manifestations, such as sleep disorders, cognitive impairment, olfactory dysfunction, and psychiatric symptoms [4–7].

Sleep disorders are frequent in MJD patients and the most common are rapid eye movement (REM) sleep behavior disorder (RBD), restless legs syndrome (RLS), excessive daytime sleepiness (EDS), and insomnia [8–13]. The frequency of RLS ranges from 30% to 55% in this group of patients [14,15]. Interestingly, sleep disorders may precede the cerebellar symptoms by years [16]. Moreover, a higher frequency of obstructive sleep apnea (OSA) and RBD, especially in patients who are older with longer disease duration, has been observed in MJD patients compared to healthy controls [8,16]. For excessive fragmentary myoclonus (EFM), the first description was in 1984 by Broughton and Tolentino [17] in a patient with EDS. In 1985, these authors described EFM associated with several sleep disorders, such as OSA, narcolepsy, periodic limb movements during sleep (PLMS), hypersomnia, fragmented sleep, and insomnia [18]. Although EFM was apparently a physiologic finding and was described as a sleep-related disorder of simple movements and short duration, this sleep disorder may impair sleep quality, particularly when presenting with high frequency [19–21].

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EFM is defined as a sleep disorder characterized by subtle movements presenting as fine movements at the fingertips, feet, or lips that persist throughout all stages of sleep. These movements resemble fasciculations and may be clinically unnoticed; they are only observed through polysomnography (PSG). Usually EFM is not initially reported by the patient. Moreover, EFM is more common in older individuals and is present in up to 5–10% of patients with EDS, no matter the etiology. Pathophysiology involving EFM is still not well-established [22,23]. Herein we aimed to demonstrate the higher frequency of EFM in patients with MJD compared to healthy control participants. We also performed a correlation between EFM and clinical and molecular features of the disease and provided a discussion on the possible pathophysiologic mechanisms involved (See Fig. 1).

2. Methods

2.1. Participants and clinical protocol

Forty-four patients with clinically and molecular-proven MJD and 44 healthy participants (control group) matched for age and gender were recruited. The control group was comprised by hospital workers and volunteers with no family relationship with MJD patients. Controls shared the same social background and had no notable medical history. All participants signed an informed consent to be enrolled in our study and the study was approved by our local ethics institutional review board.

2.2. Primary outcome measures

To clinically evaluate sleep disorders in MJD patients, we performed RBD Screening Questionnaire (RBDSQ) and a validated translation of the Epworth Sleepiness Scale [24,25]. The diagnosis and severity of RBD was based on the RBDSQ using a 5-point scale. Bed partners described RBD symptoms and those who met the criteria for the five questions were considered to have clinically defined RBD [24]. RLS was diagnosed in accordance with standard protocols [26,27]. Ataxia severity in MJD was measured through the Brazilian-translated and validated Scale for the Assessment and Rating of Ataxia (SARA) and the International Cooperative Ataxia Rating Scale (ICARS) [28,29]. The CAG repetition length also was evaluated in all patients.

2.3. PSG

All patients underwent an all-night PSG. The following tests also were performed using a computerized PSG system (Alice 5, Healthyne): electroencephalogram, electrooculogram, submental electromyogram (EMG), tibial EMG, electrocardiogram, chest and abdomen movement (plethysmography), nasal-oral airflow (three-way thermistor and nasal cannula pressure transducer), and oxyhemoglobin saturation. Patients were monitored by video camera and were continuously observed by experienced technicians. The EFM was defined according to the criteria of the American Academy of Sleep Medicine, which is EMG activity of a maximum duration of 150 ms and 5 EMG potentials per minute for at least 20 min of non-REM sleep. Analysis of sleep, arousals, cardiorespiratory parameters, PLMS, and loss of atonia during REM sleep also was performed according to the American Academy of Sleep Medicine criteria [30]. Following this testing, the loss of atonia during REM was characterized by sustained muscle activity in REM sleep in the chin EMG or excessive transient muscle activity during REM in the chin or limb EMG. Sleep stages and the estimated PSG indices (such as PLMS index) also were scored according to these criteria. Medications that could potentially interfere with sleep, such as benzodiazepines, cholinergic drugs, and

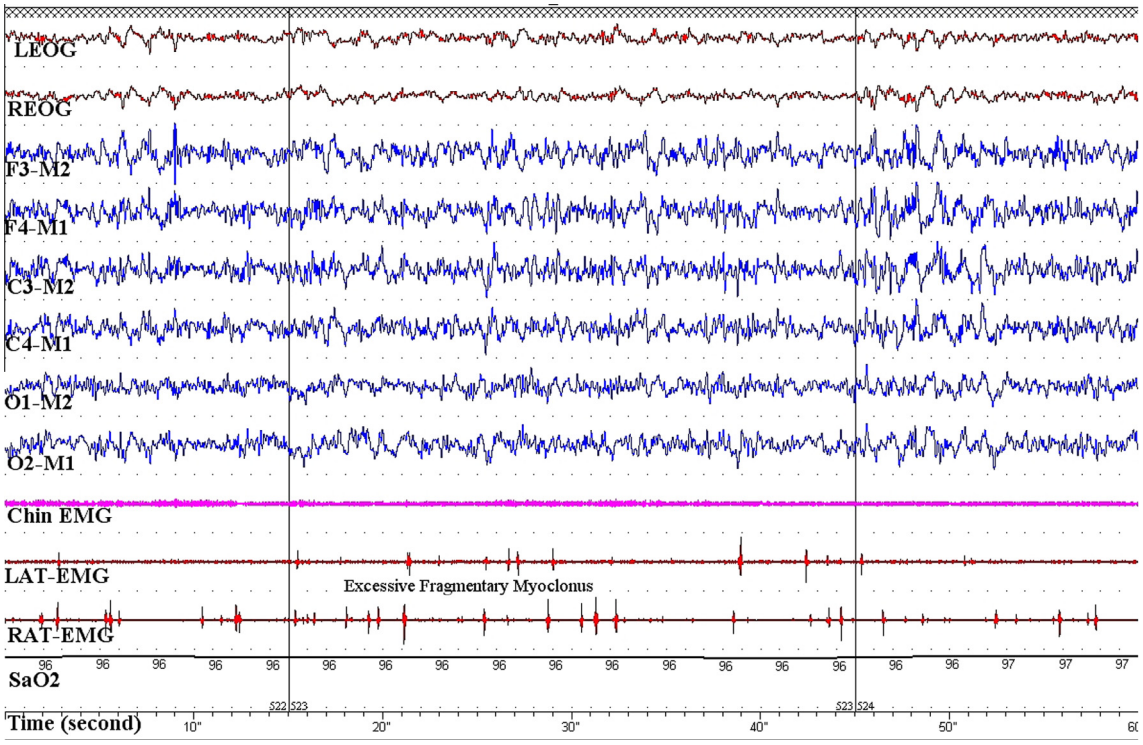

Fig. 1. Example of an epoch of polysomnography during nonrapid eye movement sleep (stage 2), showing electromyographic activity with maximum duration of 150 ms in a frequency of more than five electromyographic potentials per minute characterizing excessive fragmentary myoclonus. *Abbreviations:* LEOG, left electrooculogram; REOG, right electrooculogram; LAT-EMG, left anterior tibialis electromyogram; RAT-EMG, right anterior tibialis electromyogram; SaO_2, peripheral saturation of oxygen. Signals from the cannula, thermistor, electrocardiogram, and thoracic and abdominal belts revealed no abnormalities.

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