Sleep Disorders and Myotonic Dystrophies, More than Sleep Apnea!

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Myotonic dystrophies are autosomal, dominantly inherited, progressive, multisystemic disorders characterized by neuromuscular weakness, myotonia, early-onset cataracts, endocrine abnormalities and involvement of other organs including CNS, heart, and gastrointestinal system [1]. There are two heterogeneous, but clinically and genetically distinct forms of myotonic dystrophy: type1 (DM1) and type2 (DM2) [2]. The presence of sleep dysfunction probably represents a key issue for morbidity and mortality in patients with neuromuscular disorders [2]. Persistent nocturnal hypoxemia, sleep disordered breathing (SDB) may trigger cardiovascular and pulmonary failure; in addition, sleep fragmentation and excessive daytime sleepiness lead to disability and may affect both mood and cognition. DM1 represents the neuromuscular disorder with the most prominent propensity to sleep disorders and excessive daytime sleepiness [3]. SDB, resulting in nocturnal hypoxia and hypercapnia, PLMS, REM sleep dysregulation and daytime somnolence seem to be the most common sleep disorders in DM1 [3,4]. In addition DM1 may modulate sleep regulatory circuits in the CNS as demonstrated by the loss of serotoninergic neurons of dorsal raphe nucleus and low cerebrospinal fluid (CSF) orexin A levels [5,6]. These patients may also exhibit sleepiness of “central” origin out of proportion to SDB, fatigue and abnormalities of REM sleep [2-4]. Excessive Daytime Sleepiness (EDS) is the most common non-muscular symptom in DM1, which occurs in up to 70-80% of adult-onset DM1 and in ~50% of childhood-onset DM1 patients [4,7]. Several studies demonstrated that EDS may be an early DM1 symptom, sometimes even years before the disease is recognized [8,9]. EDS in DM1 is characterized by persistent sleepiness unaffected by unrefreshing and without dream content naps. Although DM1-related EDS is strongly associated with SDB (obstructive and central apnea) and/or hypventilation [4,8], some authors reported the lack of correlation between EDS and sleep apnea in DM1 [4,6]. On the other hand, a neuropathological study showed a selective loss of serotoninergic neurons of dorsal raphe nucleus, a key region involved in sleep-wake modulation, in DM1 patients complaining of EDS [5]. Furthermore, low CSF levels of orexin A were described in hypersomnolent DM1 patients similarly to narcolepsy [6], albeit this finding was not successively confirmed [10]. Therefore a “central” origin of hypersomnolence in DM1 was conjectured. On the other hand scarce data are available regarding sleep disorders in DM2, due to the more recent genetic definition and to the rarity of the disease in some geographic areas [1]. DM2, similarly to DM1, may be characterized by SDB, sleepiness [11-13] and REM sleep dysregulation [13], albeit few polysomnographic data are available. In striking contrast with DM1, in which EDS is a critical issue, a controlled study based on subjective scales [11] found that EDS was less prominent in DM2. Only 6.9% of DM2 patients had EDS compared with 44.8% of DM1 patients and 6.2% of controls. Poor sleep quality as evaluated by means of Pittsburgh Sleep Quality Index (PSQI) in both DM2 and DM1 was evident, and significantly poorer than healthy controls. Nocturnal sleep impairment was not explained by psychiatric disorders such as depression or other co morbidities, but it was mainly due to nocturnal pain, albeit this finding is not confirmed by a recent controlled polysomnographic study [13]. Very recently, a small DM2 sample has reported EDS in 6 patients and MSLT performed in 4 patients showed pathological mean sleep latency (MSL) without SOREMPs [13]. Thus, daytime drowsiness due to a primary CNS hypersomnia can be seen also in DM2, but it is unclear if this represents a central pathophysiologic mechanism due to multiple brain and/or brainstem damages [14]. The clinical spectrum of DM2 also includes PLMS and RLS, insomnia and REM without atonia with dream enacting behavior [12]. The latter finding may be emblematic. RSWA and/or REM behavior disorders (RBD) may represent a further mechanism of REM sleep dysregulation, suggesting that despite distinct genetic mechanisms, sleep dysfunction may be similar in both DM2 and DM1 [2,13,15].

However, the pathogenesis of sleep disturbance in DM2 patients remains conjectural due to few polysomnographic studies. Obstructive sleep apnea may be due to upper airway muscle weakness and myotonia. As in DM1, an abnormality of central control of breathing and sleep-wakefulness related to cerebral involvement may be responsible for sleep-wake and respiratory dysfunction [14]. RSWA and/or RBD may represent a further mechanism of REM sleep dysregulation, suggesting that despite distinct genetic mechanisms, sleep dysfunction may be similar in DM2 and DM1 [2,13,15]. Very recently Lam et al. [16] published a case-control study of 43 genetically confirmed DM2 subjects by means of subjective scales. These authors found significant sleep disturbances in DM2 (probable RLS, EDS, sleep quality and fatigue). Authors stated that RLS, EDS, and fatigue are frequent sleep disturbances in patients with DM2, while OSA and RBD symptoms seemed to be not. In our controlled polysomnographic study comparing DM2 patients with DM1 and controls we found quite different results [2]. PSG data showed increased arousability and low sleep efficiency (<90%) in all DM2 patients. Seven DM2 patients (58%) were affected by obstructive sleep apnoea, whereas 25% presented PLMS (PLMI >90%) in all DM2 patients. Seven DM2 patients (58%) were affected by obstructive sleep apnoea, whereas 25% presented PLMS (PLMI >90%) in all DM2 patients. Seven DM2 patients (58%) were affected by obstructive sleep apnoea, whereas 25% presented PLMS (PLMI >90%).

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DM1 patients with milder hypoxia, and lower daytime sleep shown in previous studies [4]. On the other hand, RSWA could be also related to the brainstem and diencephalon involvement in DM2 [15], particularly at the level of the pedunculopontine and laterodorsal tegmental nuclei that are the critical modulators of activated behavioral states such as wakefulness and REM sleep [18].

Therefore sleep disturbances and excessive daytime somnolence are common and disabling features in DM1, on the other hand insufficient clinical and polysomnographic data are available regarding the real prevalence of sleep disorders in DM2. Prospective evaluation and trials in larger samples are strongly requested in order to clarify the actual magnitude of sleep dysfunction and for optimally treating patients affected by these progressive neurodegenerative conditions.

References