Decreased Hypocretin-1 (Orexin-A) Levels in the Cerebrospinal Fluid of Patients with Myotonic Dystrophy and Excessive Daytime Sleepiness

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Study Objectives: Myotonic dystrophy type 1 is a multisystem disorder with myotonia, muscle weakness, cataracts, endocrine dysfunction, and intellectual impairment. This disorder is caused by a CTG triplet expansion in the 3' untranslated region of the DMPK gene on 19q13. Myotonic dystrophy type 1 is frequently associated with excessive daytime sleepiness, sharing with narcolepsy a short sleep latency and the presence of sleep-onset rapid eye movement periods during the Multiple Sleep Latency Test. Since narcolepsy is characterized by a dysfunction of the hypothalamic hypocretin system, we investigated whether patients with myotonic dystrophy type 1 with excessive daytime sleepiness have abnormalities in the hypocretin system.

Design/Participants: Six patients with myotonic dystrophy type 1 complaining of excessive daytime sleepiness and 13 healthy controls without a sleep disorder were included. The patients with myotonic dystrophy type 1 were evaluated using clinical interviews, nocturnal polysomnograms, and Multiple Sleep Latency Tests. All patients had a confirmed genetic diagnosis for DM1 and were HLA typed. Cerebrospinal fluid hypocretin-1 levels were measured using a direct radioimmunoassay in patients and controls.

Setting: University hospital sleep laboratory.

Interventions: N/A.

Measurement and Results: The mean sleep latency on Multiple Sleep Latency Tests was abnormal in all patients (<5 minutes in 2, ≤8 in 4) and 2 sleep-onset rapid eye movement periods were observed in 2 subjects. All patients were HLA-DQB1*0602 negative. Hypocretin-1 levels were significantly lower in patients versus controls (p<0.001); 1 case with 2 sleep-onset rapid eye movement periods had hypocretin-1 levels in the range generally observed in narcolepsy (<110 pg/mL). Three cases had intermediate levels (110-200 pg/mL). Hypocretin-1 levels did not correlate clinically with disease severity or duration or with subjective or objective sleepiness reports.

Conclusions: A dysfunction of the hypothalamic hypocretin system may mediate sleepiness and abnormal Multiple Sleep Latency Test results in patients with myotonic dystrophy type 1.

Key words: Myotonic dystrophy; excessive daytime sleepiness; MSLT; SOREMP; hypocretin; orexin

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INTRODUCTION

MYOTONIC DYSTROPHY TYPE 1 (DM1, MIM160900), AN AUTOSOMAL DOMINANT DISORDER, is a progressive multisystem disease caused by the abnormal expansion of a CTG repeat (typically more than 50 repeats) in the 3' untranslated region of the DMPK gene on 19q13.1 DM1 is one of the most common inherited neuromuscular diseases. Clinical characteristics include myotonia, muscle weakness, cataracts, frontal baldness, intellectual impairment, cardiac abnormalities, and endocrine disturbances such as testicular atrophy and insulin resistance. The constellation of variable symptoms is believed to be due to long-range molecular effects of the expansion on DMPK gene or a number of neighboring genes, such as the homeobox SIX5, and probably other mechanisms as well.2 The size of the CTG repeat increases generation after generation and is correlated with severity and age of onset, providing a basis for genetic anticipation. The brain is affected, as documented by imaging and neuropathologic studies that have shown neuronal loss and neurofibrillary degeneration.3,4 The disease is also commonly associated with variable hypothalamic-pituitary abnormalities.10-12 Excessive daytime somnolence (EDS) is a common complaint in DM1.13-18 In some patients, daytime sleepiness has been associated with sleep fragmentation secondary to sleep apnea or chronic alveolar hypoventilation.19-21 However, adequate treatment of sleep-disordered breathing does not always eliminate the EDS.22,23 Some authors have hypothesized that a central dysfunction is also probably involved.14,18,24 Furthermore, DM1 shares some features with narcolepsy, such as severe EDS and the presence of sleep-onset rapid eye movement (REM) periods (SOREMP) in the multiple sleep latency test (MSLT).25 Furthermore, amphetamine-like stimulants and modafinil can be used successfully to treat this symptom.22,26 Narcolepsy has recently been associated with a dysfunction of the hypothalamic hypocretin (orexin) system.27 Cerebrospinal fluid (CSF) levels of hypocretin-1 (Hcrt-1) are undetectable or low (<110 pg/mL) in almost 90% of narcoleptic patients with cataplexy, almost all with HLA-DQB1*0602.28-30 Neuropathologic studies in narcoleptic brains have shown severe and selective loss of the hypocretin neurons in the posterior hypothalamus.31,32 In this study, we hypothesized that the EDS in DM1 results from hypothalamic damage to the hypocretin system. To test this hypothesis, CSF Hcrt-1 levels were measured in DM1 patients complaining of EDS and compared with normal control subjects' CSF Hcrt-1 levels. DM1 subjects were also evaluated polygraphically and using the MSLT.

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Patients and Controls

Patients were 5 men and 1 woman (patient 4), mean age 42.5 ± 7.3 years (range, 19-68 years), with a complaint of EDS and clinical symptoms of DM1. All patients had a molecular diagnosis of DM1, as confirmed by the presence of CTG repeats longer or equal to 100 (Table 1). Control samples were 8 males and 5 females without a sleep disorder and a mean age of 39 ± 4.5 years (range, 22-69 years). The study was approved by the local Institutional Review Board.

Evaluation of Daytime Sleepiness and Sleep-Disordered Breathing

Sleepiness was evaluated subjectively using the Epworth Sleepiness Scale (ESS) and objectively using the MSLT. The MSLTs were performed following nocturnal polysomnography (PSG), and consisted of 5 naps at 9:30, 11:30, 13:30, 15:30, and 17:30. In cases where significant sleep-disordered breathing was observed (apnea-hypopnea index greater than 10 and oxyhemoglobin desaturations), treatment with bilevel positive airway pressure (BiPAP) and oxygen therapy (if needed) was initiated. The PSG and MSLT studies were performed several months prior to lumbar puncture. The ESS scores were gathered the day of the lumbar puncture.

RESULTS

Clinical Evaluation of DM1 Patients

Clinical, PSG, MSLT, and laboratory findings are summarized in Table 1. All patients were fully ambulatory, with a mean disease duration of 17.3 ± 2.8 years. Two patients were obese (body mass index [BMI] >30), and 1 patient was overweight (BMI=26.2). Severity, age, symptomatology, and disease duration represented a wide spectrum.

Sleepiness in DM1 Patients

The mean ESS was 13.3 ± 6.6. In 4 patients, EDS started several years after the onset of muscle weakness and myotonia (range, 2-14 years), while in patients 1 and 4, sleepiness started 12 years and 20 years before, respectively. None of the patients had cataplexy, sleep paralysis, or hypnagogic hallucinations. Four patients (1, 2, 4, and 6) had significant sleep-disordered breathing. In patients 1, 2, and 4, a second PSG was performed to titrate BiPAP pressures and treat this symptom. These patients continued using BiPAP treatment. Patients 1 and 2 also required oxygen therapy. Patient 6 did not tolerate BiPAP and remained untreated for sleep-disordered breathing. After several months of ambulatory treatment, these patients reported that BiPAP did not resolve their sleepiness.

The nocturnal PSGs showed decreased REM sleep latency in 2 patients (3 and 55 minutes). The MSLTs demonstrated decreased sleep latency in all the patients, with a mean of 5.5 ± 3.9 minutes (range, 1 minute 50 seconds-8 minutes) and the presence of 2 SOREMPs in 2 subjects.

CSF Hcrt-1 and HLA Typing

None of the subjects were HLA-DQB1*0602 positive. The mean CSF Hcrt-1 levels were significantly decreased when compared to normal control values (181 ± 49 pg/mL versus 340 ± 15 pg/mL, mean ± SEM, p<0.001) (Figure 1). The CSF Hcrt-1 levels were in the narcolepsy range (<110 pg/mL) in 1 subject (patient 1), in the intermediate range (110-200 pg/mL) in 3 subjects (patient 2, 3, and 6), and in the normal range (>200 pg/mL) in 2 subjects.

Relationship Between CSF Hcrt-1 Levels and Clinical Symptomatology

Low CSF Hcrt-1 levels did not correlate clinically with disease symptomatology, severity, or duration or with the number of CTG repeat expansion. The 3 patients with the longest disease duration had low (patient 1), intermediate (patient 2), and normal (patient 4) Hcrt-1 levels. The Hcrt-1 levels also did not correlate clinically with disease severity, as evaluated using the MDSR. No obvious relationship with sleepiness, as reported subjectively using the ESS or objectively using the MSLT, was noted. Of the 2 patients with the most abnormal MSLT results, patients 1 and 4, I had Hcrt-1 levels in the narcolepsy range while the other was in the normal range.
DISCUSSION

Our results indicate that CSF Hcrt-1 levels are decreased in patients with DM1 who complain of EDS. Although the number of patients studied is small, this finding suggests that the pathophysiology of EDS in some DM1 patients might be explained by a dysfunction of the hypothalamic hypocretin system. The decreased CSF Hcrt-1 levels did not correlate clinically with disease severity, suggesting it is unlikely to be related to nonspecific effects such as decreased locomotor activity, a parameter that has recently been linked with hypocretin activity in animals. Importantly, however, decreased Hcrt-1 levels also did not correlate well with sleepiness severity.

Sleepiness is a common complaint in patients with DM1, with 39% to 77% of patients reporting this symptom.23,37 Two main causes have been proposed to explain EDS in DM1: 1) respiratory disturbances and 2) an intrinsic dysfunction of sleep–wake mechanisms due to central nervous system impairment. Several respiratory disturbances during sleep have been described in myotonic dystrophy. Moderate to severe obstructive sleep apnea can be found in 10% to 75% of DM1 patients.16,18,19,22 although its presence is not clearly associated with EDS.18,22 In addition, EDS is often present in patients without sleep-disordered breathing or when this symptom is adequately controlled using noninvasive ventilation and supplemental oxygen therapy, as found in the present study and others.22,23 Chronic alveolar hypoventilation related to respiratory muscle weakness has also been proposed as a potential cause of EDS in DM1.20,21,23 However, the EDS is not always related to the degree of muscular weakness,21,37 and EDS may precipitate manifest muscular disease by many years,37 as we found in 2 of our patients (patient 1 and 4). Another cause of chronic alveolar hypoventilation may be a dysfunction of the central respiratory control circuitry causing central apneas.7,19,22,24

The presence of complex sleep abnormalities in patients with DM1 also suggests a central mediation of EDS. Patients with DM1 have disrupted sleep-wake rhythm, with abnormally stable non–REM/REMcycle duration across the night and no time-of-day effect on MSLT sleep latencies.14 A hypothalamic alteration has been hypothesized to cause somnolence in DM1,18,24 but this hypothesis has never been demonstrated, although there are reports showing endocrinologic dysfunctions of the hypothalamic-pituitary axis in DM1 patients.10-12

Our observation suggests a primary dysfunction of sleep-wake regulation in the central nervous system of DM1 patients independent of sleep-disturbed breathing. The degenerative process of DM1 is known to affect the central nervous system. Neuropathologic abnormalities, including neuronal loss, intracytoplasmic inclusion bodies, and neurofibrillary degeneration, have been reported in several brain areas such as the thalamus, cortex, and medullary autonomic respiratory center.3,4,6-7,9 However, except for a single case report of neurofibrillary changes in the hypothalamus of a DM1 patient,6 there are no detailed neuropathologic studies of this brain area in DM1.

In both DM1 and narcolepsy, sleepiness is associated with the presence of SOREMPs in the MSLT.18,25 Two or more SOREMPs may be present in the MSLT in up to 47% of patients with sleep apnea, and this finding correlates with oxyhemoglobin desaturations.38 Since patients 1 and 4 had sleep-disordered breathing with oxyhemoglobin desaturations, we can not exclude this as the cause of the observed SOREMPs in at least these 2 cases. Other studies in DM1, however, have also shown SOREMPs without sleep-disordered breathing.18,25

In narcolepsy, a dysfunction of the hypocretin system probably underlies EDS and the REM sleep abnormalities such as cataplexy.27,30,39 Hypocretin-1 levels in CSF are undetectable in more than 90% of HLA-DQB1*0602 positive narcoleptic patients with cataplexy,26,30 and neuropathologic studies in narcoleptic brains show the absence or important reduction in the number of hypocretin neurons in the posterior hypothalamus.31,32 Besides narcolepsy, low (<110 pg/mL) to intermediate CSF Hcrt-1 levels have also been detected in some hyporsomnia patients without cataplexy, some patients with Guillain-Barré syndrome, and in patients with secondary narcolepsy, for example in association with hypotalamic lesions or in Prader-Willi syndrome.30,40 In addition, intermediate levels are also detected in some subjects with head trauma, encephalitis, and intracranial tumors.30 Intermediate levels (110-200 pg/mL) are currently interpreted as a partial hypocretin deficiency.30 We did not find any patient with undetectable hypocretin levels, as is usually reported in narcolepsy-catalepsy. In fact, 3 patients had intermediate levels, and 1 patient had low levels that were near the intermediate range. The finding that, unlike in narcolepsy, our DM1 patients were HLA-DQB1*0602 negative, suggests that the decrease of Hcrt-1 in these diseases might have different etiopathogenic mechanisms. In addition, it is also interesting to note that although our DM1 patients have decreased Hcrt-1 levels, they did not have cataplexy. It could thus be speculated that the development of cataplexy needs lower Hcrt-1 levels than those found in our DM1 patients. Neuropathologic studies of the hypocretin system in subjects with DM1 are needed to extend this observation. In addition, future studies including DM1 patients without EDS will be needed to support the hypothesis that hypocretin deficiency is not a non-specific aspect of DM1.

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