Rapid Eye Movement Sleep Disturbances in Huntington Disease

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Background: Sleep disorders including insomnia, movements during sleep, and daytime sleepiness are common but poorly studied in Huntington disease (HD).

Objective: To evaluate the HD sleep-wake phenotype (including abnormal motor activity during sleep) in patients with various HD stages and the length of CAG repeats. Because a mild hypocretin deficiency has been found in the brains of some patients with HD (hereinafter referred to as HD patients), we also tested the HD patients for narcolepsy.

Design and Patients: Twenty-five HD patients (including 2 premanifest carriers) underwent clinical interview, nighttime video and sleep monitoring, and daytime multiple sleep latency tests. Their results were compared with those of patients with narcolepsy and control patients.

Results: The HD patients had frequent insomnia, earlier sleep onset, lower sleep efficiency, increased stage 1 sleep, delayed and shortened rapid eye movement (REM) sleep, and increased periodic leg movements. Three HD patients (12%) had REM sleep behavior disorders. No sleep abnormality correlated with CAG repeat length. Reduced REM sleep duration (but not REM sleep behavior disorders) was present in premanifest carriers and patients with very mild HD and worsened with disease severity. In contrast to narcoleptic patients, HD patients had no cataplexy, hypnagogic hallucinations, or sleep paralysis. Four HD patients had abnormally low (<8 minutes) daytime sleep latencies, but none had multiple sleep-onset REM periods.

Conclusions: The sleep phenotype of HD includes insomnia, advanced sleep phase, periodic leg movements, REM sleep behavior disorders, and reduced REM sleep but not narcolepsy. Reduced REM sleep may precede chorea. Mutant huntingtin may exert an effect on REM sleep and motor control during sleep.

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Huntington disease (HD) is an inherited neurodegenerative disorder characterized by behavioral and cognitive disturbances and chorea. In addition, up to 87.8% of patients report sleep problems, rated as important by 61.7%. Spouses complain of increased movements during sleep, sleep-onset insomnia, nocturnal waking, and daytime sleepiness. Overnight sleep studies have been performed in small series lacking genetic confirmation and/or detailed sleep monitoring. These studies showed difficulties initiating and maintaining sleep and reduced duration of slow wave and rapid eye movement (REM) sleep. There was, however, no indication whether the sleep abnormalities could be premanifest in HD and whether they correlated with disease severity or CAG repeats. In addition, these studies did not look for abnormal motor activity during sleep that could be indicative of REM sleep behavior disorders and periodic leg movements, which are highly prevalent in other polyglutamine diseases and neurodegenerative movement disorders.

Insomnia may be caused by anxiety, depressive mood, disturbed circadian sleep-wake rhythms (as observed in the mouse R6/2 model of HD), and possibly nocturnal choreic movements. The association of nighttime insomnia and daytime sleepiness is also suggestive of narcolepsy, a REM sleep disorder characterized by hypocretin-1/orexin-A deficiency. Loss of hypocretin-1 has been demonstrated in the R6/2 mouse model (~71%), but the decrease was only mild (~10%) in the YAC128 mouse model. In a study of 5 human brains of patients with HD (hereinafter referred to as HD patients), there was some mild loss.
of hypocretin-1 cells (–27%). In contrast, cerebrospinal fluid hypocretin-1 levels were within reference ranges in 2 studies involving 10 and 37 HD patients. Because a 73% decrease in hypocretin-1 neurons is necessary to observe a 50% decrease in cerebrospinal fluid hypocretin-1 levels, it is possible that cerebrospinal fluid hypocretin-1 levels are not sensitive enough to detect an early deficiency of hypocretin-1 transmission in HD patients. In contrast, nighttime and daytime sleep monitoring (multiple sleep latency tests) is highly sensitive for identifying polygraphic signs of narcolepsy, that is, short sleep-onset latency and multiple REM sleep-onset periods. These tests have not been performed in HD patients.

We therefore set out to better characterize the sleep-wake phenotype (including monitoring of overnight motor activity) in HD patients in a large group, including patients with premanifest HD. In view of the evidence of hypocretin cell loss in HD, we specifically tested the hypothesis that HD patients have polygraphic signs of narcolepsy.

**METHODS**

**PATIENTS**

Twenty-five HD patients (from 25 HD families) were included from 4 European centers in Paris, France (n=11), Copenhagen, Denmark (n=7), Aachen, Germany (n=4), and London, England (n=3). The HD patients carried an abnormal CAG repeat expansion in the HD1 gene (OMIM 143100, symbol HTT [formerly HD1, IT15]) with sizes ranging from 39 to 49 and a mean (SD) of 43.0 (3.0) repeats. Two subjects with genetic CAG abnormal repeats but no neurological symptoms of HD (premanifest carriers, who asked for presymptomatic testing) participated in this study. The genetic, clinical, and sleep analyses were performed in the 4 European HD reference centers. All patients gave written informed consent, approved by the local ethics committee.

Narcoleptic control patients were 25 patients with narcolepsy/cataplexy and HLA-DQB1*0602, a group in which the probability of a hypocretin-1 deficiency is 99%. They were collected from our sleep clinics and matched for age and sex with the HD patients.

In addition, we selected 25 age- and sex-matched controls from a series of 104 subjects treated in the Department of Internal Medicine, Pitie-Salpetriere Hospital, for suspected venous thromboembolism, subsequently disproved, who completed, after signed agreement, a sleep interview and polysomnography within 1 month. They were free of neurological disease.

**CLINICAL INTERVIEW**

Patients were all interviewed and examined by a neurologist from the HD referring centers (E.L. and A.D. [France], J.N. [Denmark], J.S. [Germany], and S.T. [England]). The standardized evaluations included a total functional capacity score ranging from 0 (no functional capacity) to 13 (normal capacity) and a Unified Huntington Disease Rating Scale (UHDRS), including a psychiatric score (0-88) and a motor score (0-124). The motor score includes chorea (score range, 0-20) and dystonia (0-28) subscores. A sleep specialist (I.A. and E.K. [France], P.J. [Denmark], and E.W. and M.W. [England]) interviewed the patient using criteria for sleep disorders from the International Classification of Sleep Disorders–Revised, including criteria for insomnia (difficulty to initiate or maintain sleep with daytime consequences, ≥ 4 nights a week for > 3 months), narcolepsy, restless legs syndrome, and REM sleep behavior disorders (a history of enacted dreams during sleep, associated with loss of normal chin atonia or visible complex behaviors during REM sleep on video polysomnography). The specialist then asked the patient to complete the Epworth Sleepiness Scale (for which 0 indicates no sleepiness and 24, maximal sleepiness). Care was taken to perform the sleep monitoring without any drugs affecting sleep. This was the case for all but 2 HD patients and 1 control who used neuroleptics (olanzapine and sulpiride), 3 HD patients and 2 controls who used selective serotonin uptake inhibitors (paroxetine hydrochloride, venlafaxine hydrochloride, and fluvoxamine maleate), and 1 patient and 4 controls who used zopiclone or bromazepam in the evening. Because the patients were mildly affected, we chose to group our patients according to their UHDRS motor score as (1) premanifest (n=2; 34 and 35 years of age) and very mild (n=5) (defined as a UHDRS score of ≤ 8, with a total functional capacity maximum score of 13 for all) (n=7); (2) mild (defined as a UHDRS score between 9 and 25 and a total functional capacity score of ≥ 10) (n=8); and (3) moderate (defined as a UHDRS score of ≥ 26) (n=10).

**SLEEP MONITORING**

Nighttime sleep was monitored from lights off (ad libitum) to 6:30 AM (all patients woke up spontaneously before that time). All patients, but no controls, underwent 5 clinical multiple sleep latency tests the following day. Briefly, patients were asked to lie down and try to fall asleep every 2 hours for a 20-minute period. If they fell asleep, they were allowed to sleep for 15 minutes. The mean daytime sleep latency was measured as the mean of all 5 sleep latencies, or 20 minutes per attempt if no sleep occurred. Sleep monitoring included electroencephalography, eye movements measured by means of electro-oculography, chin and bilateral tibialis anterior surface electromyography, measurement of nasal pressure, recording of tracheal sounds through a microphone, use of thoracic and abdominal belts to measure respiratory movements, measurement of pulse rate, oximetry, electrocardiography, synchronized infrared videography, and monitoring of patient sounds. The sleep stages, arousals, periodic leg movements, and respiratory events were scored visually according to standard criteria, as previously described. Muscle activity was quantified continuously during REM sleep using chin electromyography; tonic muscle activity during REM sleep was defined as prolonged muscle activity with an amplitude at least equal to that observed during quiet wakefulness. From this finding we calculated the percentage of REM sleep without atonia. Muscle activity was also measured continuously using leg electromyography, and phasic muscle activity was detected as a transient and frank elevation of muscle tone. The duration of leg muscle activity was divided by REM sleep duration to obtain the percentage of leg muscle activity during REM sleep.

**STATISTICS**

We performed statistical analysis using analysis of variance for comparison of continuous variables between groups, with a significance level of P < .05. Frequencies were compared using χ² tests, corrected as required. Simple regression analysis was also performed. Because this was a descriptive study in a rare disease, there was no primary outcome, we performed no power calculations, and we made no correction for multiple comparisons. Results are reported as mean (SD).
Table 1. Clinical and Genetic Characteristics of 25 HD Patients According to Their Severity Score

<table>
<thead>
<tr>
<th>HD Severity</th>
<th>Premanifest and Very Mild (n=7)</th>
<th>Mild (n=8)</th>
<th>Moderate (n=10)</th>
<th>All HD Patients (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at examination, y</td>
<td>38.0 (8.3 [28-54])</td>
<td>48.0 (9.9 [36-65])</td>
<td>55.8 (11.3 [38-68])</td>
<td>48.3 (12.2 [28-68])</td>
</tr>
<tr>
<td>Age at HD onset, y</td>
<td>35.4 (9.8 [25-49])</td>
<td>42.9 (11.7 [29-63])</td>
<td>47.4 (11.5 [33-65])</td>
<td>42.9 (11.6 [25-65])</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>4 (57)</td>
<td>5 (62)</td>
<td>3 (30)</td>
<td>12 (48)</td>
</tr>
<tr>
<td>CAG repeat expansion</td>
<td>42.3 (2.8 [40-48])</td>
<td>43.9 (3.6 [39-49])</td>
<td>42.9 (2.8 [39-48])</td>
<td>43.0 (3.0 [39-49])</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>21.5 (3.2)</td>
<td>24.5 (5.0)</td>
<td>23.1 (1.4)</td>
<td>23.1 (3.5)</td>
</tr>
<tr>
<td>Total functional capacity score</td>
<td>13.0 (0 [13])</td>
<td>9.8 (1.9 [9-12])</td>
<td>6.3 (3.1 [3-13])</td>
<td>9.3 (3.5 [3-13])</td>
</tr>
<tr>
<td>UHDRS scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>4.0 (3.5 [0-8])</td>
<td>18.5 (5.7 [9-25])</td>
<td>45.9 (15.6 [28-66])</td>
<td>25.4 (20.7 [0-66])</td>
</tr>
<tr>
<td>Chorea</td>
<td>2.0 (2.2 [0-5])</td>
<td>6.1 (3.1 [2-10])</td>
<td>11.8 (4.0 [6-17])</td>
<td>7.2 (5.2 [0-17])</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0.1 (0.4 [0-1])</td>
<td>1.4 (1.5 [0-4])</td>
<td>4.9 (4.2 [0-11])</td>
<td>2.4 (3.4 [0-11])</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>8.3 (11.1 [5-23])</td>
<td>17.6 (10.1 [6-37])</td>
<td>15.0 (21.2 [9-30])</td>
<td>12.9 (12.0 [9-33])</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HD, Huntington disease; UHDRS, Unified Huntington Disease Rating Scale.

RESULTS

CHARACTERISTICS OF HD PATIENTS

The clinical and genetic characteristics of the HD patients are given in Table 1. Their mean age at HD onset was similar, but those with the most severe disease were the oldest at the time of the examination (P = .007). As expected, the total functional capacity decreased with severity of the disease (P = .001), whereas the motor (P = .001), chorea (P = .001), and dystonia (P = .006) UHDRS scores increased. In contrast, the psychiatric scores did not differ between groups (P = .46). The HD group was matched with patients with narcolepsy and with controls for age and sex, but mean body mass indexes (calculated as weight in kilograms divided by height in meters squared) were lower in the HD patients (23.1 [3.5]) than in the patients with narcolepsy (26.7 [6.2]) and the controls (27.6 [7.2]; P = .02). This lower body mass index was not related to HD severity or to CAG repeat length.

SLEEP SYMPTOMS

Almost two-thirds of the HD patients complained of insomnia, a frequency that was higher than in the controls (P = .001) (Table 2). Although nighttime insomnia and daytime sleepiness increased with HD severity, the differences between groups were not significant (P = .30). Lengths of CAG repeats were similar in patients with (+42.9 [2.3]) and without (+43.2 [4.0]) insomnia (P = .82). Insomnia also was not associated with restless legs syndrome. The HD patients fell asleep earlier than did the controls, whatever their disease severity (P = .84) or their CAG repeat length (P = .10), but the advanced sleep phase was similarly frequent in patients with (6 of 15 patients [40%]) or without (3 of 10 [30%]) insomnia. In contrast, HD patients did not have more frequent daytime sleepiness (according to patient reports of excessive daytime sleepiness or Epworth Sleepiness Scale scores) or narcolepsy-like symptoms (eg, cataplexy, sleep paralysis, and hypnagogic hallucinations) compared with controls, whereas these symptoms were highly prevalent in patients with narcolepsy. Two HD patients and their bed partners reported symptoms of REM sleep behavior disorders (mainly shouting and speaking during sleep, sometimes associated with hand and arm movements), that were later confirmed during video polysomnography. An additional patient had no self-report or spouse report of violent nocturnal behaviors but exhibited them during video monitoring.

NIGHTTIME SLEEP MEASURES

Compared with controls, HD patients had lower sleep efficiencies and longer duration of wakefulness after sleep onset but unchanged sleep-onset latency, indicating problems primarily in maintaining sleep (Table 3). They also spent more time in light sleep stages, as indicated by increased percentages of stage 1 sleep, but their sleep was not more fragmented by arousals or respiratory events. However, the HD patients had more frequent periodic leg movements (range, 0-39 movements per hour) than did controls (range, 0-23 movements per hour), causing more arousals than in controls; 6 HD patients (24%) had more than 15 movements per hour (an index considered abnormal) vs 1 control (4%) (corrected P = .12). In 5 HD patients (20%), nonperiodic leg movements were reported during sleep but these movements were not associated with arousals. The HD patients had normal non-REM sleep percentages, including slow wave sleep.
We compared the sleep measures between HD patients with (n = 16) and without (n = 9) a complaint of insomnia. Only sleep efficiency (but not total sleep time, sleep-onset latency, REM sleep latency, percentages and duration of sleep stages, or arousal index) was different between HD patients with and without insomnia. The 2 oldest patients in the HD group (66 and 67 years) had apnea-hypopnea indexes severe enough to require

Table 2. Sleep Symptoms in 25 HD Patients Compared With 25 Matched Patients With Narcolepsy or Cataplexy and 25 Control Patients a

<table>
<thead>
<tr>
<th>Patients</th>
<th>HD Severity</th>
<th>Controls</th>
<th>Patients With Narcolepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premanifest or Very Mild (n = 7)</td>
<td>Mild (n = 8)</td>
<td>Moderate (n = 10)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>38.0 (8.3)</td>
<td>48.0 (9.9)</td>
<td>55.8 (11.3)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (57)</td>
<td>5 (62)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (43)</td>
<td>5 (62)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Sleep onset before 9 PM</td>
<td>2 (29)</td>
<td>4 (50)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>REM sleep behavior disorders</td>
<td>0</td>
<td>1 (12)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>1 (14)</td>
<td>2 (25)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>ESS score, mean (SD)</td>
<td>7.7 (4.7)</td>
<td>5.1 (3.5)</td>
<td>7.5 (5.3)</td>
</tr>
<tr>
<td>ESS score &gt; 10</td>
<td>2 (29)</td>
<td>1 (12)</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

Abbreviations: ESS, Epworth Sleepiness Scale; HD, Huntington disease; REM, rapid eye movement.

a Unless otherwise indicated, data are expressed as number (percentage) of patients.

b Patients with HD were significantly different from controls (P < .05).

c Only 12 patients with narcolepsy or cataplexy responded to this question.

d Patients with HD were significantly different from narcoleptic patients (P < .05).

e Includes sleep paralysis, cataplexy, and hypnagogic hallucinations.

Table 3. Sleep Measures in 25 HD Patients Compared With 25 Age- and Sex-Matched Patients With Narcolepsy or Cataplexy and 25 Control Patients a

<table>
<thead>
<tr>
<th>Sleep Measures</th>
<th>HD Patients (n = 25)</th>
<th>Controls (n = 25)</th>
<th>P Value b</th>
<th>Patients With Narcolepsy/Cataplexy (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nighttime sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sleep period, min</td>
<td>474 (92)</td>
<td>467 (86)</td>
<td>.79</td>
<td>501 (62)</td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>366 (122)</td>
<td>405 (88)</td>
<td>.21</td>
<td>423 (69)</td>
</tr>
<tr>
<td>Wakefulness after sleep onset, min</td>
<td>104 (89)</td>
<td>63 (41)</td>
<td>.04</td>
<td>78 (71)</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>77 (20)</td>
<td>86 (8)</td>
<td>.03</td>
<td>85 (13)</td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep onset</td>
<td>23 (30)</td>
<td>31 (42)</td>
<td>.43</td>
<td>13 (21)</td>
</tr>
<tr>
<td>REM sleep</td>
<td>164 (85) c</td>
<td>107 (65)</td>
<td>.01</td>
<td>57 (44)</td>
</tr>
<tr>
<td>Sleep stage duration, % total sleep time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>9 (7)</td>
<td>6 (5)</td>
<td>.03</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>53 (12)</td>
<td>50 (14)</td>
<td>.38</td>
<td>50 (10)</td>
</tr>
<tr>
<td>Stages 3-4</td>
<td>23 (13)</td>
<td>24 (13)</td>
<td>.82</td>
<td>21 (12)</td>
</tr>
<tr>
<td>REM sleep</td>
<td>14 (6) c</td>
<td>19 (6)</td>
<td>.002</td>
<td>21 (8)</td>
</tr>
<tr>
<td>Increased muscle tone, % of REM sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chin</td>
<td>2.3 (8.1)</td>
<td>1.8 (2.6)</td>
<td>.77</td>
<td>3.4 (5.6)</td>
</tr>
<tr>
<td>Legs</td>
<td>3.1 (14.3)</td>
<td>1.0 (1.3)</td>
<td>.50</td>
<td>1.8 (2.6)</td>
</tr>
<tr>
<td>Sleep fragmentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arousals, No./h</td>
<td>16 (12)</td>
<td>14 (17)</td>
<td>.74</td>
<td>24 (30)</td>
</tr>
<tr>
<td>Periodic leg movements, No./h</td>
<td>9 (11)</td>
<td>2 (5)</td>
<td>.007</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Periodic leg movement arousals, No./h</td>
<td>2.2 (3.2)</td>
<td>0.4 (1.7)</td>
<td>.02</td>
<td>1.7 (2.3)</td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
<td>5 (7)</td>
<td>10 (18)</td>
<td>.21</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Daytime sleepiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean sleep latency, min</td>
<td>14.3 (5.9) c</td>
<td>NP</td>
<td>NA</td>
<td>4.3 (3.1)</td>
</tr>
<tr>
<td>Less than 8 min, No. (%) of patients</td>
<td>4 (16) c</td>
<td>NP</td>
<td>NA</td>
<td>23 (92)</td>
</tr>
<tr>
<td>Multiple sleep onset in REM periods, No. (%) of patients</td>
<td>0 c</td>
<td>NP</td>
<td>NA</td>
<td>22 (88)</td>
</tr>
</tbody>
</table>

Abbreviations: HD, Huntington disease; NA, not applicable; NP, not performed; REM, rapid eye movement.

a Unless otherwise indicated, data are expressed as mean (SD).

b Indicates comparison between HD patients and controls.

c Patients with HD were significantly different from patients with narcolepsy or cataplexy (P < .05).
tinuous positive airway pressure. However, their adherence to a regimen of using the device was poor. Apneahypopnea index values were also greater than 30 in 2 patients with narcolepsy and in 2 controls. We could not find any correlation between CAG repeat length and any sleep measure.

REM SLEEP ABNORMALITIES

The HD patients had longer REM sleep latencies and shorter REM sleep percentages than did controls. Percentages of REM sleep were abnormal in 1 of the 2 premanifest carriers (14% and 20%, respectively) and in 4 patients with very mild HD. This difference was still present after adjustment for the presence of psychotropic drugs (neuroleptics, benzodiazepines, and antidepressants) liable to affect REM sleep duration and latency. Percentages of REM sleep (but not latencies) decreased with disease severity; the mean percentage of REM sleep was 16.3% (3.9%) in the premanifest/very mild HD group, 16.4% (3.7%) in the mild HD group, and 9.7% (5.7%) in the moderate HD group (P=.02). There was no correlation between CAG repeat length and REM sleep percentage, REM sleep duration, and REM sleep latency. In the HD group, there was a strong and significant (r=0.54; P=.005) correlation between REM sleep duration and total sleep time. Overall, enhanced muscle tone activity during REM sleep was not different between groups. However, 1 HD patient and 1 patient with narcolepsy had percentages of enhanced chin muscle tone greater than 20% of REM sleep, a criterion often used to characterize REM sleep without atonia.8 According to our findings after video monitoring during REM sleep, 2 women and 1 man with HD (12% of the HD sample) had REM sleep behavior disorders. These consisted of complex movements of the lips (such as speaking without sound), head, trunk, and right hand and arm (such as grasping invisible objects or kicking) (a video of 1 of these HD patients during REM sleep [infrared video and sleep monitoring] is available online at http://www.archneurol.com and shows purposeful movements of both hands, the arms, and the trunk corresponding to REM sleep behavior disorder). The 3 patients with REM sleep behavior disorders were aged 41, 45, and 64 years. One had mild HD and 2 had moderate HD, with 39, 45, and 46 CAG repeats. They were not taking any antidepressant drugs.

MEASURES OF DAYTIME SLEEPINESS

Multiple sleep latency tests were performed only in the HD patients and those with narcolepsy. The HD patients had much longer mean sleep latencies during daytime and fewer sleep-onset REM periods (0.2 [0.5]) than did those with narcolepsy (3.2 [1.5]; P<.001). In the HD group, there was no correlation between mean daytime sleep latencies and severity of the disease or the CAG repeat length. However, 4 HD patients (16%) had abnormally short (<8 minutes) mean daytime sleep latencies. All patients had fewer than 2 sleep-onset REM periods; thus, none met the criteria for narcolepsy without cataplexy.10 In the HD group, the correlation between subjective (Epworth Sleepiness Scale score) and objective (mean daytime sleep latencies) sleepiness was poor (r=0.08) and not significant (P=.73).

In addition, there was no significant correlation between mean daytime sleep latencies and nighttime total sleep times (r=0.001; P=.99) or arousal indices (r=0.25; P=.27). Patients who reported insomnia had longer mean daytime sleep latencies (16.1 [4.6] minutes) than those who did not (11.1 [7.0] minutes; P=.05).

In this large series of HD patients, insomnia, advanced sleep phase, REM sleep abnormalities, and increased motor activity during sleep were frequent. These sleep abnormalities were present in very mild and even premanifest HD.

The HD patients mainly had sleep maintenance insomnia, with no major problems falling asleep and no compensatory daytime sleepiness. On the contrary, the patients reporting insomnia had longer daytime sleep latencies than did those who did not. This pattern is more consistent with models of hyperarousal than with disruption of circadian rhythm patterns. Hyperarousal may be caused by the anxiety disorder often reported in other HD groups20 or by loss of some sleep-promoting neurons, such as the ventrolateral preoptic group in the anterior hypothalamus,21 as yet unstudied in HD. A complete disintegration of circadian behavior is evident in the transgenic model of HD (R6/2 mice), in which daytime activity increases and nocturnal activity falls, mirroring the disrupted night-day activity patterns observed in a small group of HD patients.8 Although we found that the HD patients (regardless of whether they had insomnia) fell asleep earlier than did the controls, circadian factors and their contribution to insomnia still need to be studied more carefully in HD patients, using a morningness-eveningness scale,22 actigraphy, and central body temperature monitoring. Sleep homeostasis was not specifically studied herein, but indirect measures (normal duration of slow wave sleep) suggest that it is unaltered in HD patients.

The reduction (and sometimes absence) and delay of REM sleep has already been observed in 2 previous studies of 7 and 6 HD patients24 but never in premanifest and very mild HD patients, as in this study. This REM sleep dysfunction seems to be an early marker of the disease, which progresses with disease duration. In 1 study,2 these abnormalities were correlated with the presence and severity of cognitive but not motor symptoms. The reduction of REM sleep, together with decreased eye movement density during REM sleep found in other groups,2,23 and with imperfect REM sleep atonia during REM sleep in 3 patients, suggests that the executive systems of REM sleep, mainly located in the brainstem, are vulnerable to the pathological effect of mutant huntingtin. In addition, REM sleep mechanisms are highly dependent on oxygen supply and cerebral metabolic rate,24 which may be impaired in HD. Recently, a reduced oxygen consumption rate has been demonstrated in the mitochondria of the HD mouse brain.25 Reduced REM sleep contributes to the decrease in total sleep time observed in our series.

COMMENT

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but not to insomnia. No sleep complaint or measure correlated with CAG repeat length. Our study, which is mainly descriptive, may lack sufficient power to correlate genotype variations with sleep phenotype. Nevertheless, in larger groups, CAG repeat length correlates with HD age at onset but not with pivotal clinical symptoms (ie, chorea, psychosis, depression, dementia, and rigidity).26

The HD patients had increased motor activity during sleep, including periodic leg movements and REM sleep behavior disorders. The leg movements were not associated with restless legs syndrome and did not cause insomnia or significant arousals; they reflect disinhibition of the descending motor pathways, possibly the A11 projections to the spinal cord.27 Three HD patients presented with REM sleep behavior disorder. Because none of them took drugs (including antidepressants) liable to induce REM sleep behavior disorders, this finding may be specific. Clinical REM sleep behavior disorder is rare (0.5%) in the general population28 but can precede and accompany narcolepsy and synucleopathies (with a prevalence of 30%-100%).7,29 Spinocerebellar ataxia, also a genetic polyglutamine disease, is similarly associated with REM sleep behavior disorder. Rapid eye movement sleep behavior disorder and its preclinical form (REM sleep without atonia) were identified in 30% to 44% of patients with spinocerebellar ataxia subtypes 1 and 3 (Machado-Joseph disease).5,6,30 The newly identified association of REM sleep behavior disorders in 12% of HD patients is an important specific finding because it extends the idea that pathologic involvement of REM sleep atonia--generating structures is common to a number of neurodegenerative movement disorders, regardless of molecular abnormalities. This association also suggests that mutant huntingtin may accumulate in neurons controlling muscle atonia during REM sleep. Although incompletely identified, these neurons include mainly the ventral sublaterodorsal nucleus in the pons (also called locus subcoeruleus in humans), and possibly the magnocellular reticular formation in the medulla, the pedunculopontine area and the hypothalamus.7 Previous studies in HD have found some neuronal loss in the locus coeruleus31 and in the hypothalamus,32 but studies of specific areas involved in regulating REM sleep have not yet been performed. The clinical outcome of these behaviors is the risk of injury; hence, a systematic interview about nocturnal violence in HD caregivers could be useful, along with securing the bed environment, avoiding antidepressant use (especially venlafaxine), and possibly testing melatonin use at bedtime (rather than clonazepam, another efficacious treatment of REM sleep behavior disorders that may not be well tolerated in HD patients).33

In contrast, we did not find any pattern of secondary narcolepsy, with or without cataplexy, whether clinical or polygraphical. In addition, although narcolepsy is associated with shortened REM sleep latency,10 our group of HD patients, conversely, had delayed REM sleep. These results do not support a major functional role for reduction of hypocretin levels in human HD. Nevertheless, some HD patients may experience abnormal daytime sleepiness, with frequencies varying from 16% to 32%, depending on the measure used (eg, patient report, Epworth Sleepiness Scale score, or multiple sleep latency tests). In our study, however, these frequencies in the HD group were no higher than those in the control group and were never as severe as the major daytime sleepiness of patients with narcolepsy. Furthermore, there are too many discrepancies between objective and subjective measures in HD to support a model of a central disorder of arousal.

Despite this being, to our knowledge, the largest such study, a significant limitation is the restricted number of patients (making subgroup comparisons less reliable). This limitation and the mainly descriptive design of the study are balanced by the use of complex measures (eg, videopolysomnography and multiple sleep latency tests) that cannot be obtained easily in larger groups. We hope that further focused studies will give a greater insight into the epidemiology and pathological substrates of the sleep abnormalities we have observed in HD.

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Additional Information: The video is available online at http://www.archneurol.com.
REFERENCES

the inversion due to the high level of linkage disequilibrium but, outside the inversion, they become highly variable, with no identifiable pattern. This is also supported by the constant level of association that drops off at the boundaries of the inversion. The inversion is likely a recent event because it is found only in white populations. Although a specific cause cannot be determined, something in the inversion is likely affecting expression of the tau gene and, ultimately, disease status. The inversion, or, more specifically, the H2 haplotype, seems to offer some protection against PSP and CBD.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Miller and Wilhelmsen. Acquisition of data: Webb, Miller, Bonasera, Boxer, and Karydas. Analysis and interpretation of data: Webb and Wilhelmsen. Drafting of the manuscript: Webb. Critical revision of the manuscript for important intellectual content: Miller, Bonasera, Boxer, Karydas, and Wilhelmsen. Statistical analysis: Wilhelmsen. Obtained funding: Miller and Wilhelmsen. Administrative, technical, and material support: Miller, Boxer, and Wilhelmsen. Study supervision: Wilhelmsen.

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REFERENCES


Correction

Errors in Byline, Author Affiliations, and Author Contributions. In the Original Contribution titled “Rapid Eye Movement Sleep Disturbances in Huntington Disease” by Arnulf et al, published in the April issue of the Archives (2008;65[4]:482-488), the fourth author’s name was misspelled in the byline on page 482, where it should have appeared as “Johannes Schiefer, MD.” As a result, that author’s name was also misspelled in the “Author Affiliations” and “Author Contributions” sections of the Acknowledgments on page 487, where it should have been given as “Schiefer.”