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Asymptomatic Sleep Abnormalities Are a Common Early Feature in Patients with Huntington's Disease

Anna O. G. Goodman · Lorraine Rogers · Samantha Pilsworth · Catherine J. McAllister · John M. Shneerson · A. Jennifer Morton · Roger A. Barker

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Abstract Huntington's disease (HD) is a fatal neurodegenerative disease characterized by motor, cognitive, and psychiatric disturbance. In this article, we used polysomnography, actigraphy and a variety of validated questionnaires to ascertain the extent to which sleep changes are identifiable and measurable in mild stage HD, and importantly, to see whether patients are negatively impacted by the changes in their sleep. We found significant differences in sleep architecture and sleep efficiency in patients compared with controls using polysomnography. However, patient scores on the Functional Outcomes of Sleep Questionnaire, Medical Outcomes of Sleep Scale, and Epworth Sleepiness Scale were not significantly different to controls. These results suggest that although marked changes in sleep architecture are present in early HD and can be detected using polysomnography, patients do not necessarily recognize or report these abnormalities.

A. O. G. Goodman · R. A. Barker
Cambridge Centre for Brain Repair,
Department of Clinical Neurosciences, Addenbrooke's Hospital,
Hills Road,
Cambridge CB2 0QQ, United Kingdom

L. Rogers · S. Pilsworth · J. M. Shneerson
Respiratory Support and Sleep Centre, Papworth Hospital,
Papworth Everard,
Cambridge CB23 8RE, United Kingdom

C. J. McAllister · A. J. Morton
Department of Pharmacology, University of Cambridge,
Tennis Court Road,
Cambridge CB2 1PD, United Kingdom

A. O. G. Goodman (✉)
Cambridge Centre for Brain Repair,
E. D. Adrian Building, Forvie Site, Robinson Way,
Cambridge CB2 0PY, United Kingdom
e-mail: aogr2@cam.ac.uk

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Introduction

Huntington's disease (HD) is a fatal neurodegenerative disease caused by an abnormal expansion of a CAG repeat in the HD gene [1]. The disease runs a debilitating and progressive course with an average survival of around 20 years after disease onset [2]. HD patients classically develop involuntary movements including chorea, as well as progressive cognitive [3] and psychiatric disturbances [4], although a number of other features have also been reported including weight loss [5] and changes in sleep [6, 7, 8•].

Sleep studies in HD patients suggest a progressively worsening sleep disorder [6], which appears to be independent of CAG repeat length [6, 8•]. Patients have difficulty in both initiating and maintaining sleep [6, 9, 10]. Reduced sleep efficiency in mid-late stage HD [6, 10–12] was characterized by increased latency to sleep onset, frequent nocturnal awakening after sleep onset or arousals [12], and a reduced total sleep time (TST) [10]. Electroencephalographic changes have also been reported in HD, with patients with moderate disease showing more time in sleep stages 1 and 2 [6, 9], less time in rapid eye movement (REM) sleep [10, 12], and reduced slow wave sleep [12]. For a comprehensive, current review on sleep in HD, refer to Goodman and Barker [13•].

In the present study, we examined sleep in a small cohort of patients with early stage HD using a combination of polysomnography and sleep questionnaires to ascertain the extent to which sleep abnormalities are present early in the disease and their perceived impact on their life.

Subjects and Methods

Polysomnography: Subjects

Ethical approval for this study was granted by the Cambridge Research Ethics Committee. Nine HD patients with early motor manifestations of the disease were selected according to the following criteria 1) positive genetic test for HD; 2) a modified Mini-Mental State Examination (MMSE) score ≥24; 3) a Unified Huntington's Disease Rating Scale chorea score of ≤15; 4) a total functional capacity score ≥8; 5) Independence score ≥80; 6) a "healthy" body mass index (18–25 kg/m^2); and 7) Beck Depression Inventory (BDI) II score less than 20. Exclusion criteria at baseline were 1) a MMSE score of less than 24; 2) concurrent major psychiatric illness affecting function; 3) a BDI II score greater than 20; and 4) known metabolic, endocrine, or sleep disorder.

Ten healthy volunteers were recruited as controls from the general public through advertisement and were matched for age, sex, race, and body mass index. Exclusion criteria included a family or personal history of HD or actively being treated for any other known neurologic, endocrine, or sleep disorder.

Assessment of Rest-Activity Phases (Actigraphy)

Participants wore Actiwatches (Cambridge Neurotechnology, Cambridge, UK) for 14 consecutive days preceding the polysomnography study. Actiwatches were worn on the nondominant wrist, except when bathing. During the recording period, participants completed a sleep diary in which they recorded the times they went to bed and the end of their overnight sleep period. Unintentional and planned naps were also recorded on the daily sleep diary, as well as caffeine and alcohol intake and subjective information on sleep quality.

Polysomnography Assessment

Sleep was formally assessed in all participants using video polysomnography (vPsg), following the 2 weeks of actigraphy. Participants were admitted to the Respiratory Support and Sleep Centre at Papworth Hospital NHS Trust and over 3 consecutive days they completed an acclimatization night (night 1), a study night with vPsg recording, followed by Multiple Sleep Latency Tests (MSLTs) on the final day.

All participants were interviewed by a qualified sleep specialist and a full sleep history was obtained. Individuals were given access to their bedroom and other facilities as part of the acclimatization period. On the first evening participants were discouraged from taking alcohol and caffeine after 19:00 hours and were prepared for bed with all electrodes and sensors attached (see "Technical detail"), as if they were having a vPsg. Electroencephalogram (EEG) recordings were not made on the first night, although video recordings were made. Throughout the study, participants were allowed to sleep and wake up at their natural time and to control the room light levels. In the evening of day 2, participants were prepared for vPsg and required to complete the Epworth Sleepiness Scale. Participants were prepared for the MSLTs on day 3 and left the facility after the final MSLT.

Statistical Analysis and Technical Detail

Significance value of $P<0.05$ was used for all studies. Data are expressed as mean ± standard deviation unless stated otherwise. A Student's t test was used to compare patients against controls where data were normally distributed or using a Mann-Whitney test in non-normally distributed populations.

Actigraphy

Actograms show physiologic movements as accelerations. The accelerometer output for multidirectional movements is sampled at 32 Hz (n=2,764,800 times each day) then integrated (to provide a positive value). A value for the sum of samples (n=960) within a 30-second epoch provides a single activity value (where no activity is equal to a value of 0).

Nonparametric analysis of the relative amplitude of these data points was used to determine four measurements, detailed below, using the Cambridge Neurotechnology Ltd, Cambridge, UK "Actiwatch Activity and Sleep Analysis Software" package, Version 5.11. The time of onset of the lowest 5 h of activity and the onset time of the maximum 10 h of activity for each 24-hour-clock period were determined and the mean of these values over the actigraphy study period was used as expressions of rest onset and activity onset. The relative amplitude of the rhythm within the rest and most active phases were used to determine the robustness of the activity rhythms of subjects. The interdaily stability (IS) was calculated from a chi-square periodogram, normalized for the number of data points, and then used to describe the 24-hour stability or strength of activity rhythm. The IS varies between 0 (Gaussian noise) and 1 (perfect stability) and is used to quantify the strength of coupling of rhythm to environmental synchronizers and behavioral routines. The intradaily variability (IV) gives an indication of the fragmentation of the rhythm and is calculated as the ratio of the mean square of the difference between all successive hours and the mean square around the grand mean [14]. For a perfect sine wave, the IV value is 0 and is 2 for a Gaussian noise (IV may be higher than 2 if an ultradian component exists). Therefore,

IV reflects the frequency and duration of the transitions between rest and activity [14].

Polysomnography

Standard electrophysiology required to stage sleep was acquired with central electroencephalography electrodes. Head (n=10) and leg (n=2 per leg) electrodes were fitted, according to standard practice. The conventional recording montage included EEG (C3-A2, C4-A1) derivations; right outer canthus (ROC-A1) and left outer canthus (LOC-A2); electrooculograms; and mental and submental chin electromyograms (EMGs). Tibialis EMG activity was monitored using surface electrodes placed on the left and right legs. Bio-calibrations confirmed optimal signals and detection of alpha rhythm with eye closure, blinks, eye movements, and movement of the legs. Respiratory airflow was monitored with a nasal cannula and connected to a pressure transducer, thoracic and abdominal respiratory effort with inductance coils, upper airway sounds from a sensor attached to the neck, and arterial oxygen saturation by finger oximetry. Digital vPsg records were acquired with Rembrandt software (Embla Ltd; Colombo, Sri Lanka).

Data from participants were analyzed by one experienced polysomnographer according to the schema of Rechtschaffen and Kales [15] using 30-second epochs. "Awakenings" were defined as a shift in EEG frequency to alpha or faster frequencies, lasting 10 s or longer. "Microarousals" were defined according to the American Sleep Disorders Association criteria. An arousal index was calculated as the total number of arousals divided by the TST in hours. Stage shifts were computed for all sleep stages and were calculated automatically after manual sleep scoring. Breathing events were scored using standard criteria according to the American Academy of Sleep [16], and periodic leg movements were scored with standard scoring criteria [17].

MSLTs followed a previously defined procedure by Littner et al. [18], which had been adapted from Carskadon et al. [19]. For the Epworth Sleepiness Scale a total score greater than 11 is used to indicate self-reported daytime sleepiness [20, 21].

Results

Patient Characteristics

The demographic characteristics of patients and controls are summarized in Table 1. Some drugs as well as psychiatric conditions such as depression can have a deleterious effect on sleep. Five patients were taking medication, some of which may cause drowsiness and affect sleep; however, none on the patients were on the same combination of medications. Medications included diazepam, dothiepin, fluoxetine, lamotrigine, lofepramine, minocycline, olanzapine, simvastatin, venlafaxine, zolmitriptan, and zopiclone.

Polysomnography in HD Patients

When sleep architecture was examined, patient hypnograms revealed that sleep cycles in the HD patients were less consolidated, more fragmented and irregular compared with controls. Sleep abnormalities were still evident in individuals who were on no medication and had no/minimal depression (Fig. 1). None of the subjects had what could be described as "normal sleep", although each of the subjects had a different repertoire of abnormalities. Table 2 compares a selection of results between patients and controls.

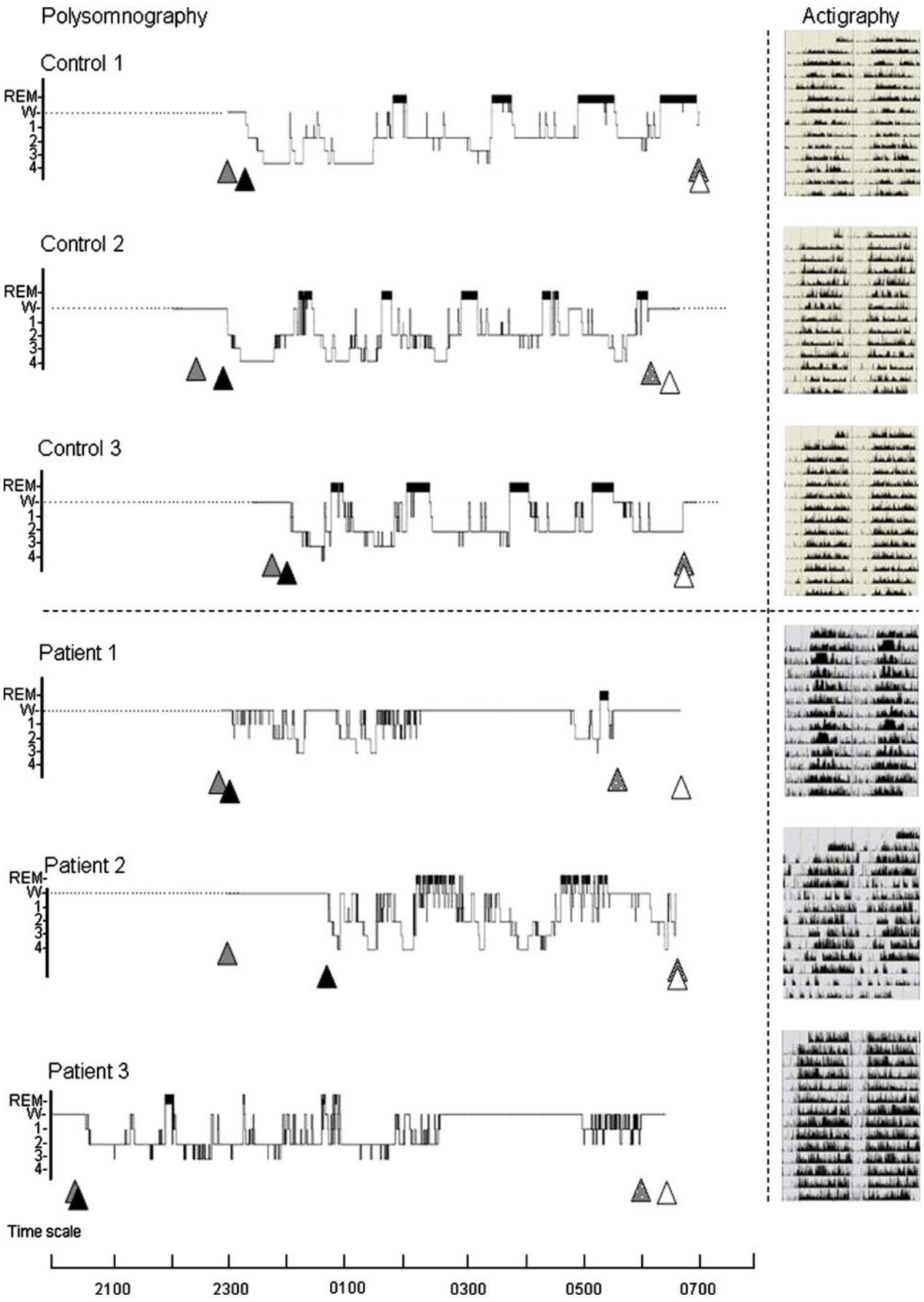
Patients spent significantly longer in bed (544.2± 64.4 min) compared with controls (471.1±55.1 min; $P<$ 0.03), although the TST was significantly less and therefore sleep efficiency (%; TST/time in bed) was reduced in patients (62.9%±19.2%) compared with controls (81.6%± 8.2%; $P<0.05$).

Patients had an altered proportion and distribution of sleep stages. During the sleep period time, patients spent significantly more time awake (28.3%±17.7%) compared with controls (14.3%±8.2%). Three patients had a total absence of the stage 4 sleep and one patient spent only 0.1% of the TST in stage 4 sleep, although differences between groups did not reach statistical significance ($P=$ 0.09). However, REM sleep was significantly different in patients compared with controls (patients: 10.9%±6.5%, vs controls: 17.6%±4.4%; $P<0.05$).

Table 1 Demographic data for participants

	Sex	Mean age, *y* ± SD (range)	TFC score	TFA score	UHDRS motor score	UHDRS chorea score
Controls	5 M, 5 F	54.9±9.63 (38–68)	–	–	–	–
Patients	5 M, 4 F	54.7±7.1 (47–66)	9.8±0.61 (8–13)	28.1±2.4 (25–32)	19.9±6.9 (12–32)	6.8±3.7 (3–14)

F female, *M* male, *SD* standard deviation, *TFA* total functional assessment, *TFC* total functional capacity, *UHDRS* Unified Huntington's Disease Rating Scale


Polysomnography
Actigraphy
Control 1
Control 2
Control 3
Patient 1
Patient 2
Patient 3
REM
W
1
2
3
4
Time scale
2100
2300
0100
0300
0500
0700

◀ **Fig. 1** Polysomnography results showing normal, standard hypnograms from three control examples compared with three example patient hypnograms. Patients 1 and 3 were not on any medication and had no/minimal depression; Beck Depression Inventory scores were 5, 1, and 3 for Patients 1 to 3, respectively (scores < 12 represent no/minimal depression). Hypnograms are set above a time scale from 20.00 hours to 08.00 hours. The *dark gray triangles* on the left of the hypnograms show the time of "lights off," the *black triangles* show "sleep onset," the *gray-shaded triangles* on the right side of the hypnogram represent "end of sleep," and the *white triangles* represent "lights on." Associated actograms are located on the right-hand side of the figure. The recording made over 14 days is shown. Activity is double-plotted. *Black vertical lines* indicate levels of activity. REM—rapid eye movement; W—wake; 1—stage 1 sleep; 2—stage 2 sleep; 3—stage 3 sleep; 4—stage 4 sleep

Disturbances in the patients' polysomnography hypnograms were also seen in the actograms, which revealed an overall loss of form and definition, suggesting deterioration of circadian timing (Fig. 1).

Despite the striking abnormalities in their sleep architecture, none of the patients reported suffering from excessive daytime sleepiness. Using the Epworth Sleepiness Scale where "daytime sleepiness" is defined as present when there is a score of 11 or greater, patients scored a mean of 3.0±3.2 arbitrary units (range 0–10), compared with controls 5.1±2.8 and the published normal value of 5.9±2.2 [20, 21]. Scores on the Functional Outcomes of Sleep Questionnaire and the Medical Outcomes Study Scale, which contains subsections on sleep quality, were also not significantly different between groups.

Discussion

HD is typically considered to be a movement disorder with cognitive and psychiatric abnormalities. However, a variety of other features have been described including endocrine, metabolic, sleep and circadian rhythms abnormalities, most often in moderate disease.

We found that in early stage HD, patients have alterations in rest-activity cycles similar to that previously described in more advanced disease, which suggests that abnormalities of sleep start early in the disease course and may offer a potentially important therapeutic target. Although actigraphy is a useful measure of sleep-wake and thus circadian behavior, it can only give an indirect, crude measure of sleep. Therefore, we used polysomnography studies to study sleep directly. Polysomnography revealed that each of our

Table 2 Sleep parameter results from video PSG in patients and controls

		Controls PSG	Patients PSG	Significance
PSG				
	TIB, *min*	471.1±55.10	544.2±64.4	0.02[d]
	Total time sleep, *min*	384.0±56.8	342.3±109.9	0.31
	Sleep latency, *min*	12.8±8.1	32.3±33.1	0.05[d]
	REM latency, *min*	63.7±41.7	133.9±109.7	0.01[d]
	Arousal Index (SPT)[a]	23.2±7.3	19.0±9.5	0.24
	Sleep efficiency, %	81.6±8.2	62.9±19.2	0.03[d]
	Apnea-Hypopnea Index[b]	6.0±4.2	8.3±9.4	1.0
Sleep period time	Wake, %	14.3±8.2	28.3±17.7	0.04[d]
	Stage 1, %	6.5±3.1	10.5±6.2	0.18
	Stage 2, %	44.6±7.1	36.3±13.1	0.11
	Stage 3, %	8.1±2.5	6.3±3.8	0.16
	Stage 4, %	9.6±7.4	4.8±5.6	0.09
	SWS, %	17.7±8.4	11.1±7.7	0.16
	REM, %	16.8±3.9	10.9±6.5	0.05[d]
	Sleep stage shifts, *n*	173.9±48.0	196.7±87.9	0.78
	Desaturation Index (TIB)[c]	1.0±1.0	11.0±15.03	0.18
Questionnaires				
	Epworth Sleepiness Scale	5.1±2.8	3.0±3.2	0.09
	Horne Ostberg	57.6±8.0	63.4±6.1	0.11
	Functional Outcomes of Sleep	17.8±3.3	17.3±2.4	0.49
MOS	Sleep Disturbance	16.8±19.0	37.2±30.3	0.19
	Sleep Problems Index I	18.5±15.0	25.9±20.1	0.55
	Sleep Problems Index II	19.1±14.7	26.6±19.9	0.67

MOS Medical Outcomes Study, *PSG* polysomnography, *REM* rapid eye movement, *SD* standard deviation, *SPT* sleep period time, *SWS* slow wave sleep, *TIB* time in bed

[a] The Arousal Index was calculated as the total number of arousals divided by the total sleep time in hours

[b] The Apnea-Hypopnea Index was calculated as the number of apneas or hypopneas per hour

[c] The Desaturation Index was calculated as the number of decreases in oxygen by 4% per hour of TIB

[d] $P<0.05$

early stage HD patients had altered sleep architecture. These abnormalities were characterized by poorly consolidated, fragmented and irregular sleep stages with no clear stage progression of sleep cycles and extended periods of wakefulness. Furthermore, multiple sleep stage shifts were apparent in the majority of patients so that extended periods of uninterrupted time spent in a single stage were rarely observed.

Although this study has shown that there are significant problems of sleep and rest-activity patterns in early stage HD, it has a number of limitations. First, the cohort size was small; nevertheless, all nine patients showed marked abnormalities in hypnograms. Because eventually sleep disturbances become a serious problem for most HD patients [6, 9, 10, 12], we think it is likely that our data reflects the situation in early HD. Second, actigraphy is solely reliant on movement, a measure that only indirectly reflects measures of sleep. Because HD is a movement disorder, actigraphy data could be misinterpreted. We think it is unlikely that the rest-activity changes we described were artefacts of the collection method, since the polysomnography data (which is not dependent on movement) confirmed the actigraphy findings. Finally, as is typical of HD patients at this stage of disease, most (5/9) were taking medication, and four had mild depression. Because both drugs and depression cause abnormalities in sleep architecture, we cannot exclude the possibility that they caused the sleep abnormalities we report. However, we have shown that patients on no medication and with no/minimal depression have clear sleep abnormalities. Furthermore, none of the patients were on the same drug regimen, and only four of the patients were mildly depressed (none were moderately or severely depressed), yet all nine of the patients we studied had some degree of sleep disturbance, none had "normal" sleep, and the depressed patients did not have worse sleep results than those who were not depressed.

The sleep deficits we saw in this study may be especially important because there is considerable circumstantial evidence to suggest a link between some of the symptoms seen in HD and sleep deprivation. HD has a complex and insidious progression, and apart from chorea, has no one defining symptom that characterizes it. In the early stages HD has a cluster of symptoms that may include a loss of fine motor control, irritability, impulsiveness, depression, and mild cognitive impairment. Interestingly, sleep deprivation has been implicated in many of the same repertoire of symptoms, with several studies clearly showing that sleep deprivation can have profound effects on cognitive and motor function [22–24] as well as on metabolism [25–29]. Furthermore, two studies in the R6/2 mouse model of HD have shown that manipulating sleep (circadian rhythm abnormalities) can restore cognitive deficits [30, 31•], suggesting that treating this aspect of HD may have effects well beyond sleep.

Conclusions

We have shown in this small study in early HD that asymptomatic abnormalities in sleep are present, which may contribute to some of the problems of early disease. However, more work is needed to ascertain whether or not they progress over time or occur ahead of overt motor manifestations of the disease. Because sleep abnormalities may exacerbate or even cause the behavioral, cognitive, and motor aspects of the disease, the potential for treating the sleep disorder in HD should be investigated directly.

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