Huntington’s Disease and Sleep Related Breathing Disorders

Zaburzenia oddychania w czasie snu w chorobie Huntingtona

JAKUB ANT CZAK 1/, GRZEGORZ WITKOWSKI 2/, MARIA RAKOWICZ 1/, IWONA STEPNIAK 3/, WIOLETTA KRYSA 3/, KARO LINA ZI ORA-JAKUTO W ICZ 3/, RAFAŁ ROLA 2/

1/ Department of Clinical Neurophysiology, Institute of Psychiatry and Neurology, Warsaw
2/ First Department of Neurology, Institute of Psychiatry and Neurology, Warsaw
3/ Department of Genetics, Institute of Psychiatry and Neurology, Warsaw

Introduction & aim. The sleep related breathing disorders (SRBD) cause daytime sleepiness, headache, and depression and increase the risk of hypertension and stroke. The prevalence of SRBD is increased in a number of neurodegenerative diseases. The published data concerning SRBD in Huntington’s disease (HD) include almost only presymptomatic and early symptomatic patients, who showed no increased prevalence. Here we investigated the nocturnal respiration in patients with moderate and advanced HD.

Material & methods. The studied group comprising 13 patients (seven women) with genetically confirmed HD, who were in the moderate or advanced stage of the disease, underwent the examination of the nocturnal respiration with Embletta screening device. The clinical symptoms related to SRBD were assessed with Pittsburgh Sleep Quality Index and Daytime Sleepiness Scale.

Results. The abnormal apnea hypopnea index (≥10) was found in three subjects. Additionally in another one, the significant nocturnal oxygen desaturation was observed. The questionnaires revealed poor sleep quality and excessive daytime sleepiness in six and five patients respectively.

Conclusions. This study shows for the first time that the moderate and advanced HD may be associated with higher prevalence of SRBD. The data confirm also the previously reported significant sleep disorders and excessive daytime sleepiness in HD.

Key words: Huntington’s disease, sleep related breathing disorders, daytime sleepiness, sleep quality

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Abbreviations in alphabetical order

AHI – apnea hypopnea index
BMI – body mass index
DSS – Daytime Sleepiness Scale
EDS – excessive daytime sleepiness

EHDN – European Huntington’s Disease Network
ESS – Epworth Sleepiness Scale
HD – Huntington’s disease
Mean SaO2 – mean arterial oxygen saturation during the whole recording
Minimal SaO² – minimal arterial oxygen saturation during the whole recording
ODI – oxygen desaturation index
OSAS – obstructive sleep apnea syndrome
PSQI – Pittsburgh Sleep Quality Index
REM sleep – rapid eye movement sleep
Saturation <90% – time spent with saturation under 90% (in minutes) during the whole recording
SRBD – sleep related breathing disorders
TFC – total functional capacity
UHDRSm – motor part of the Unified Huntington’s Disease Rating Scale

Introduction and Aim

Sleep related breathing disorders (SRBD) enclose a number of conditions with impaired nocturnal respiration which result in sleep fragmentation and decrease of its restorative value. The main entities are obstructive sleep apnea syndrome (OSAS), central sleep apnea with its variant – the Cheyne-Stokes respiration, upper airway resistance syndrome, nocturnal stridor and hypventilation/hypoxemia syndromes associated with sleep [1]. The main findings revealed in diagnostics with polysomnography or with screening device include apneas and hypopneas, which are recurrent cessations or limitations of the airflow in the airways. The pulse oximetry and capnometry reveal coexistent drops of the arterial oxygen saturation and increase in partial CO₂ pressure in the exhaled air [2]. SRBD cause daytime sleepiness, headache, impair cognitive and physical performance and mood and may result in cardiovascular consequences, like hypertension or stroke [3]. In general middle aged population, OSAS is the most common form of SRBD. The clinical symptoms of OSAS are found in 2% of middle aged women and 4% of middle aged men; whereas OSAS defined as apnea hypopnea index (AHI) ≥ 5 is present in 9% and 24% respectively [4].

The prevalence of SRBD is increased in a number of the neurodegenerative diseases like myotonic dystrophy [5], amyotrophic lateral sclerosis [6] and multisystem atrophy [7]. In Huntington’s disease (HD), the available studies reported no increased prevalence of SRBD [8-13]. However, they investigated mainly presymptomatic subjects or early symptomatic patients.

In this study we investigated the nocturnal respiration of HD patients in moderate and advanced stage of the disease. According to suggestions found in the literature [12, 14] we hypothesized that SRBD might be increased in this group. The main potential causes of disturbed nocturnal breathing are aspiration pneumonia which may often develop over months (silent aspiration) [15], irregularities in respiratory rhythm observed in wakefulness in HD [16, 17], dysfunction of the respiratory centre in brain stem in the course of degenerative process [18] and dysautonomia which is present in 44% of early symptomatic HD patients [19] and which is associated with SRBD in general population and – in particular – in patients with neurodegenerative diseases [20-22].

Material and methods

Studied group

We studied a convenience sample of the genetically confirmed HD patients, who were participants in the Registry 3 Project, which is conducted by the European Huntington Disease Network (EHDN). Genetic testing was performed at the Genetics Department in the Institute of Psychiatry and Neurology. The following inclusion criteria were used: the score of the motor part of the Unified Huntington’s Disease Rating Scale (UHDRSm) [23] ≥ 30 and the score of the total functional capacity (TFC) ≤ 10 [24]. Exclusion criteria were: the lack of informed consent of participant or his caregiver and severe cognitive, behavioral or mood disorder which precluded the recording of the nocturnal respiration. Additional exclusion criterion was the evening use of benzodiazepines or other substances with known impact on nocturnal respiration.

Clinical investigation

We measured the subjective sleep quality using the Pittsburgh Sleep Quality Index (PSQI) [25]. This questionnaire contains seven domains rated from 0 to 3, which sum up to the maximal score of 21, indicating the worst sleep quality. The domains evaluate the following aspects of sleep: overall sleep quality, sleep latency, duration of sleep, sleep efficiency (the ratio of the time spent asleep to the time between lights out and lights on), sleep disturbance (which evaluates the impact of specific sleep disorders like nycturia, disturbing dreams or pain during sleep), need to take medicines to improve sleep and day dysfunction due to sleepiness. The cut-off point indicating the poor sleep quality was acquired from the web page of the University of Pittsburgh (http://www.sleep.pitt.edu/includes/showFile.asp?fltype=doc&flID=2615) and it was ≥ 6. For assessment of the sleepiness as the potential consequence of SRBD, the Daytime Sleep Scale (DSS) was used. The cut off indicating the excessive daytime sleepiness (EDS) was set at ≥ 7 as advised in the seminal article [26]. The questionnaires used in the study were filled out by patients with their caregivers assistance if necessary. UHDRSm, TFC, medication regime, CAG repeats number and disease duration were acquired from the web page of the EHDN (www.euro-hd.net). (The majority of the authors are active members of EHDN).
**Investigation of nocturnal respiration**

Nocturnal respiration was recorded with the widely used screening device – the Emblettta PDS® (Embla Systems, Inc.). Recordings included the nasal air flow through nasal canula, the respiratory effort through piezoinductive bands placed around thorax and abdomen and the blood oxygen saturation with finger oximetry. The recorded period was 8 hours with the beginning about the usual patient’s bedtime. Recordings were done ambulatory except in one patient who lived in area distant to our site and was therefore admitted to the clinic. In four patients the recording was repeated due to displacement of the sensors and in one patient due to technical defect in the oximeter functioning. The analysis of the recorded signals was done visually, according to the widely accepted guidelines [2, 27]. The following disturbances in the respiratory function (respiratory events) were scored:

- **Apnea** – defined as a drop in the amplitude of the air flow signal by >90% of the baseline, for >10 seconds.
- **Hypopnea** – defined as a drop in the amplitude of the air flow signal by >30% of the baseline, for >10 seconds in association with >3% arterial oxygen desaturation.

The apneas were further divided into three types:

- **Obstructive apneas**, characterized by the presence of the respiratory effort i.e. presence of the respiratory movements (recorded by piezoinductive bands) throughout the entire period of absent (i.e. decreased by >90% as stated above) airflow.
- **Central apneas**, characterized by the absence of the respiratory effort throughout the entire period of absent (i.e. decreased by >90% as stated above) airflow.
- **Mixed apneas**, characterized by the absence of the respiratory effort in the initial part of the apnea and its reappearance before the resumption of the airflow.

Hypopneas were not divided into subtypes.

From the recorded signals and the scored events the following parameters were derived:

- **Apnea Hypopnea Index (AHI)** – the number of apneas and hypopneas per hour of the recording
- **Oxygen desaturation index (ODI)** – the number of the ≥3% arterial oxygen desaturations per hour of the recording
- **Mean SaO2** – mean arterial oxygen saturation during the whole recording
- **Minimal SaO2** – minimal arterial oxygen saturation during the whole recording
- **Saturation <90%** – time spent with saturation under 90% (in minutes) during the whole recording

The cut-off values of AHI for light and moderate sleep apnea syndrome were 5 and 15 respectively [28].

In patients with significant AHI, the type of the apnea syndrome (obstructive, central or mixed) was defined according to prevailing type of the scored apneas.

The data were analyzed only descriptively. They are presented as mean, standard deviation and the range.

The study was performed according to the Declaration of Helsinki of 1975 for Human Research and the protocol was approved by a local Ethics Committee. All subjects gave their informed consent prior to inclusion.

**Results**

**Demographic and clinical data**

We included 13 patients (seven women, aged 54.9±19.3 range 22-78), who scored 54.2±18.3 range 30-87 in UHDRSm and 6.2±2.5 range 3-10 in TFC. According to the grading system of Shoulson and Fahn [24] which is based on the TFC score, five of our patients were in stage two and eight in stage three of the disease progression. The mean BMI was 23.5±4.3 range 18.3-31.2 with one patient being obese and four overweight. The demographic and clinical data of particular subjects are listed in the table I.

**Table I. Demographic and clinical data**

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TFC – total functional capacity. Dis. stage – stage of the disease advancement according to Shoulson and Fahn (1979), BMI – body mass index, UHDRSm – the motor part of the Unified Huntington’s Disease Rating Scale, Dis. duration – duration of the disease in years.

The medication for sleep was taken by five patients but it did not include the benzodiazepines. Involuntary movements were treated pharmacologically in ten patients with tiapride, tetrabenazine, carbamazepine and haloperidol. Two patients received levodopa for rigidity. Four patients received antidepressives. The detailed medication regimens are shown in the table II.
Assessment of sleep and daytime sleepiness

Assessment with PSQI revealed poor sleep quality in 6 subjects. The worst rating concerned the domain of the sleep onset latency. The DSS revealed EDS in 5 subjects. The detailed PSQI and DSS scores are presented in the table III.

Nocturnal respiration

Three patients showed an abnormally high AHI. In the first one it indicated a light apnea syndrome, predominantly with central events (number 3 in all tables). In the second one, the AHI was of moderate severity with obstructive events prevailing (number 10). Third patient showed a moderate sleep apnea syndrome with central and obstructive events balanced (number 11). There was another patient (number 9) whose AHI remained in normal range, but who showed a slightly elevated ODI and who spent 89 min with saturation <90%. This may be indicative of a significant nocturnal hypoxemia. The results of the screening of the nocturnal respiration are presented in the table IV.

Discussion

Significant abnormalities of the nocturnal respiration were observed in four of thirteen (30.7%) investigated patients. According to our best knowledge, this is the first study reporting the relatively high prevalence of SRBD in moderate and advanced HD.

In the report of Banno et al. [29] a HD case was described who suffered from moderate SRBD and whose nocturnal respiration was successfully normalized under noninvasive ventilation therapy with subsequent improvement of memory deficits and other cognitive impairment. Thus, our data indicates that many patients in moderate and advanced HD stage suffer from coexistent SRBD, which may be effectively treated with benefit for HD-related symptoms.

Studied group

Our definition of the moderately and severely advanced HD allowed one point more in TFC than in the study of Arnulf et al. [11] (≤10 vs. ≤9) but required more points in UHDRS (≥30 vs. ≥26). We set more impact on UHDRS because the motor symptoms include also dysphagia (with aspiration pneumonia and pulmonary restriction) and irregularities in respiration pattern and therefore are more closely related to SRBD than the functional capacity.

Three of our patients used sleep promoting medication, which were melatonin, hydroxyzine and mianserine. These substances do not influence the nocturnal respiration and the results of examination with Embletta were in these patients normal. Another patient used clonazepam which is known to induce or aggravate sleep apnea and his AHI was increased. The medication was however taken in the morning and in the relatively low dose (0.5 mg). This allows assuming that this medication did not contribute to registered apnea significantly.
The DSS was abnormal in 5 out of 13 (38.5%) patients. This means a high prevalence of EDS and is in line with the report of Videnovic et al. [30] who observed it in 50% of their HD patients. By contrast, Aziz et al. [31] and Arnulf et al. [11] found no higher prevalence of EDS in HD patients than in controls. These discrepancies are hardly to explain. There are three factors that differentiate our patients from the cohorts mentioned above and which may account for higher prevalence of EDS in our group than in the studies of Aziz et al. and Arnulf et al. The first one is the more advanced stage of the disease of our patients, which may result in more widespread neurodegeneration affecting the wakefulness promoting areas and regions responsible for the circadian rhythm. The second is the different tool used to assess the EDS. While other authors used the Epworth Sleepiness Scale (ESS) [32] and the multiple sleep latency test (in the study of Arnulf et al. [11]) we used the DSS, which was initially designed for patients with myotonic dystrophy [26]. The reason for our choice was the last of the seven items of the ESS, which asks the patient about the chance of dosing while driving a car and stopping in a traffic. In the studied group of our patients, there was only one who occasionally drove. Therefore the ESS was generally inapplicable. Considering the findings of Beglinger et al. [33] that driving is one of the earliest impaired activities in HD, the suggestion arises that some of the patients investigated previously with ESS also did not drive or did it occasionally and for short distances. This might bias the ESS score towards decreased prevalence of the EDS in the previous studies. Similar possibility exists for the ESS subitems number three and four which ask about a chance of dosing while being in a car as a passenger or sitting inactively in a public place e.g. a theater or a meeting. Symptomatic HD patients stay mostly at home, which is due to invalidism but also regretfully to the social stigma [34]. This may further bias the ESS score downwards. The DSS is based on the activities and situations at home and therefore may be more suitable for HD patients.

The great number of sleepiness inducing medicines used by our patients can further account for the differences between our data and of two mentioned studies [11, 31]. Beside the patient who took Clonazepam, the other ten patients took preparates, which are likely to induce sleepiness. These preparates included: tetrabenazine, tiapride, haloperidol, perezina, antihistaminica and risperidone. The patients investigated by Arnulf et al. [11] and Aziz et al. [31] used considerably less medication potentially causing EDS and the early stage of HD is the most probable reason for this.

**Subjective sleep quality**

Six out of thirteen (46.2%) subjects complained of the poor sleep quality. The most frequently reported problem was the prolonged sleep latency, which had been observed previously [8, 11, 12, 31] and is attributed to impaired circadian regulation in HD [35, 36]. Contrary to daytime sleepiness, our data on sleep quality are in line with the most previous reports. These described increased prevalence of sleep disorders, even in the early stage of the disease [12, 30, 37, 38].

**SRBD**

Our examination revealed disturbed nocturnal respiration in four out of 13 (30.7%) patients. This result indicates that the prevalence of SRBD in moderate and advanced HD may be higher than in the general population. Considering that the increased BMI is the strongest risk factor of SRBD [40] and that it is lower among HD patients than in the general population [11, 39], our data suggest that the moderate and advanced HD may be a significant, independent risk factor for SRBD.

Moreover our results indicate, that in HD, OSAS may not be the predominant form of SRBD as it is in the general population. The progressing degeneration of the brain stem and pulmonary restriction due to aspiration or failure of the respiratory pump may induce central apneas and hypoxemia in a significant number of patients.
Finally, our results are in contrast with the previous studies, which reported no increased prevalence of SRBD in HD. The most probable explanation is the more advanced stage of the disease among our patients. The cohorts studied by Wiegand et al. and Cuturic et al. [10, 12] included only presymptomatic and early symptomatic patients. Hansotia et al. [8] included five patients described as moderately advanced, who were however rated according to a battery of cognitive and fine motorics tests and not to TFC or UHDRSm. Therefore the comparison with other studies is difficult. Bollen et al. [9] included five patients in the second stage of HD progression, five patients in the third stage and two patients in the fourth stage [24]. They monitored however only three hours of sleep in the morning, which followed a whole night of total sleep deprivation. The mean time spent asleep by patients during this observation was only 50 min, with negligible amounts of slow wave and REM sleep. This study as well as the study of Hansotia et al. [8] lacked also the SaO measurement, which precluded the diagnosis of hypoventilation. Finally, Arnulf et al. [11] investigated sleep of 25 HD patients of whom 10 were in moderate stage, with mean TFC slightly higher (6.3±3.1 range 3-13) and UHDRSm slightly lower (45.9±15.6 range 28-66) than in our group. The results of polysomnography were however shown for all 25 HD patients. In the comment, there was information that two oldest patients showed AHI over 30. It is likely that these patients belonged to the moderately advanced group and thus it is likely that the results of Arnulf et al. [11] did not contradict the association of SRBD with moderate and advanced HD.

Our group was characterized by high prevalence of SRBD and of sleep disorders and EDS. It may suggest that SRBD have an influence on sleep and alertness in HD. In regard to small number of subjects it was not possible to investigate if these disturbances are related to each other.

Study limitations

The limitation of the present study was the use of screening device instead of the full nocturnal polysomnography. The signals obtained did not allow scoring the respiratory effort related arousals, which are significant events, additional to apneas and hypopneas. Moreover, we were only able to evaluate the number of respiratory events per hour of recording and not per hour of sleep. Generally, this could bias our data towards decreased sensitivity i.e. falsely decrease the number of respiratory events and the severity of SRBD [41].

It should be however stressed that our study contains the greatest number of the recordings of the nocturnal respiration among moderate and advanced HD patients until now. The reason for this are the significant difficulties which accompany the sleep recording in manifested Huntington’s disease. These difficulties include personality changes and anxiety, which can make the patient unwilling to stay in the sleep laboratory. Further, the cognitive impairment limits the patient’s cooperation during mounting the big set of sensors required for full polysomnography. Finally, the involuntary movements, which arise during time spent awake require repetitive correction of the sensors’ adhesion and placement. According to the guidelines of the American Academy of Sleep Medicine these difficulties justify the use of the screening device instead of polysomnography [41].

Another limitation is the lack of the control group. We therefore make our conclusions with caution and with awareness that they should be confirmed in a more extended study.

Conclusions

Our study indicates that the prevalence of SRBD in moderate and advanced HD is high and that HD in this stage may be a risk factor for SRBD. OSAS may not be a predominant form of SRBD in this patients’ group. Further, our data confirm the previously found prolonged sleep onset latency and decreased sleep quality in HD. The excessive daytime sleepiness may be more frequent in moderate and advanced HD. Finally, the use of the ESS-questionnaire in HD patients should be reconsidered.

Piśmiennictwo / References


