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NEUROLOGICAL DISORDERS

Hypocretin-1 Levels Associate with Fragmented Sleep in Patients with Narcolepsy Type 1

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Study Objectives: We aimed to analyze nocturnal sleep characteristics of patients with narcolepsy type 1 (narcolepsy with cataplexy) measured by actigraphy in respect to cerebrospinal fluid hypocretin-1 levels of the same patients.
Methods: Actigraphy recording of 1−2 w and hypocretin-1 concentration analysis were done to thirty-six unmedicated patients, aged 7 to 63 y, 50% female. Twenty-six of them had hypocretin-1 levels under 30 pg/mL and the rest had levels of 31−79 pg/mL.
Results: According to actigraphy, patients with very low hypocretin levels had statistically significantly longer sleep latency (P = 0.033) and more fragmented sleep, indicated by both the number of immobile phases of 1 min (P = 0.020) and movement + fragmentation index (P = 0.049). There were no statistically significant differences in the actual sleep time or circadian rhythm parameters measured by actigraphy.
Conclusions: Actigraphy gives additional information about the stabilization of sleep in patients with narcolepsy type 1. Very low hypocretin levels associate with more wake intruding into sleep.
Keywords: actigraphy, disrupted sleep, hypocretin, narcolepsy, sleep fragmentation
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Significance
Narcolepsy type 1 patients have excessive daytime sleepiness, cataplexy, and disturbed sleep together with absent or decreased hypocretin-1 concentration in the cerebrospinal fluid. In this study, actigraphy recordings of 1−2 w showed that patients with extremely low hypocretin levels had more fragmented sleep than patients with slightly higher hypocretin levels. Our results suggest that an absolute hypocretin deficiency strongly affects the sleep-wake switch, leading to poor quality of nocturnal sleep. Sleep disruption in narcolepsy type 1 can be easily demonstrated by actigraphy recordings. Objective demonstration of sleep fragmentation might be useful in order to choose the best medication for the patient and to follow its effect.

INTRODUCTION

Narcolepsy type 1 (NT1), formerly known as narcolepsy-cataplexy, is a distinct sleep disorder caused by loss of hypocretin-producing neurons in hypothalamus. Patients with NT1 have symptoms both daytime and nighttime: excessive daytime sleepiness, cataplexy, disturbed sleep, and often also sleep paralyses and hallucinations during sleep-wake transitions. Main diagnostic tools are Multiple Sleep Latency Test (MSLT) preceded by polysomnography (PSG), and the analysis of hypocretin-1 concentration in the cerebrospinal fluid (CSF).[1]

In 2014, the International Classification of Sleep Disorders, Third Edition raised actigraphy (ACT) to a major role for the objective monitoring of sleep duration, quality, and schedule prior to MSLT in order to objectively rule out delayed sleep phase syndrome and behaviorally induced insufficient sleep, both of which are common causes of daytime somnolence[1]. There are few studies on actigraphy in narcolepsy. A pioneer work showed differences in diurnal and nocturnal motor activity between narcoleptics and matched controls.[2] Two groups have shown effects of narcolepsy medication on sleep quality measured by ACT.[3,4]

Quite recently, Filardi and coworkers compared patients with NT1, those with idiopathic hypersomnia, and controls with an ACT recording of 1 w.[5] They noticed that patients with NT1 had less sleep, lower sleep efficiency, and more wake epochs during the night than the other subjects. In addition, individuals with narcolepsy had less motor activity and longer naps during the day. They did not analyze these results with respect to hypocretin-1 levels.

The goal of the current study was to analyze the actigraphic characteristics of nocturnal sleep among patients with NT1 with different hypocretin levels.

METHODS

This study has been approved by the Institutional Review Board of the National Institute for Health and Welfare (THL). A written informed consent was received from all patients for use of their data and for a minority of tests that were not part of the diagnostic procedure. Parents signed the written informed consent on behalf of the children involved in the current study.

Thirty-six drug-naïve patients with narcolepsy from Helsinki Sleep Clinic, Vitalmed Research Centre with the available data both from an ACT recording and a CSF hypocretin-1 level analysis were included in this study. All patients had daily symptoms and a CSF hypocretin-1 level < 110 pg/mL, i.e., they had NT1.[1] Analysis of CSF hypocretin-1 concentration was measured in Rinnekoti Research Laboratory using human orexin-A RIA Kit (Phoenix Pharmaceutical, Inc., Belmont, CA, USA) with Stanford reference sample.

ACT recordings lasting for 1 w or a fortnight and analyses were done using Actiwatch (Cambridge Neurotechnology Ltd, Cambridgeshire, UK). The recording was always combined to a sleep log filled by the patients or their parents. The epoch length was 1 min and the sensitivity of the algorithm for wake threshold was set to the medium sensitivity. The definitions of the used ACT parameters were described in detail previously.[6] Very briefly, sleep efficiency, number of immobile phases of 1 min and movement + fragmentation index are comparable

Table 1—Characteristics of study patients.

	Hypocretin < 30 pg/mL	Hypocretin ≥ 30 pg/mL	P
n	26	10	
CSF hypocretin-1 (pg/mL)	**0.0 (0–27)**	**54 (31–79)**	**< 0.001***
Females (%)	42.3	57.7	0.137†
Age	18.0 (7.9–63.2)	24.9 (17.1–39.1)	0.219*
Sleep latency in ACT (min)	**10.4 (0.3–72.0)**	**2.0 (0.0–63.0)**	**0.033***
Actual sleep time in ACT (h)	6.4 (3.8–8.6)	6.4 (4.6–7.3)	0.508*
Sleep efficiency in ACT (%)	72.4 (49.0–85.7)	79.2 (55.5–92.9)	0.074*
Sleep efficiency under 85% (%)	**96.2**	**70.0**	**0.025†**
Number of immobile phases of 1 min	**16 (5–35)**	**9 (3–18)**	**0.020***
Movement + fragmentation index	**44.5 (23.2–99.6)**	**37.3 (19.9–63.1)**	**0.049***
Cosine peak (hh:mm)	15:09 (11:54–17:48)	15:27 (13:48–19:16)	0.454*
L5 onset (hh:mm)	00:30 (23:00–06:00)	02:30 (24:00–05:00)	0.053*
M10 onset (hh:mm)	10:00 (06:00–12:00)	12:00 (07:00–16:00)	0.080*
Interdaily stability	0.39 (0.22–0.54)	0.41 (0.26–0.66)	0.611*

Data expressed as the median (range). P shows the statistical significance between patients with undetectable and detectable hypocretin-1 levels. *Mann-Whitney U test, †Pearson's chi-squared test. Statistically significant differences between the groups in bold. CSF, cerebrospinal fluid; ACT, actigraphy; L5, lowest 5 [hours of activity, see[6] for more details]; M10, maximal 10 [hours of activity].

to the quality of sleep and sleep fragmentation, whereas actual sleep time is analogous to the quantity of sleep. Cosine peak, L5 onset, and M10 onset describe the circadian sleep-wake rhythm and interdaily stability describes the circadian regularity.[7]

Patients fulfilled the modified Nordic Basic Sleep Questionnaire.[8] In this study, the questions about napping, caffeine consumption, and symptoms related to rapid eye movement sleep behavioral disorder (RBD) or restless legs syndrome (RLS) were relevant.

Statistical analyses were performed with a computerized statistical package (IBM SPSS Statistics 22.0, Armonk, NY, USA). For statistical comparisons of the continuous variables, nonparametric methods (Mann-Whitney *U* test) were used due to the slight abnormality of distributions, which was verified by skewness and kurtosis. For categorical variables, Pearson chi-squared test was used. All P values are two-sided, and the significance level is set at 0.05 throughout. For descriptive purposes, we report values as medians and range. Figure S1 (supplemental material) was made using STATA version 13.1 (Stata Corporation, College Station, TX, USA).

RESULTS

The age of the patients with NT1 in our study varied from 7 to 63 y, and 18 (50%) of them were female. CSF hypocretin-1 levels varied from 0 to 79 pg/mL. As the values less than 30 pg/mL might not be absolutely accurate, we used 30 pg/mL as the detection limit. The concentration was 0 pg/mL in 18 patients, and less than 30 pg/mL in 26 patients. The results with the hypocretin 30 pg/mL as the detection limit are shown in Table 1. Because we have the exact values for each patient, the results with the hypocretin level of 0 pg/mL as the limit are shown in Table S1 (supplemental material).

Patients with undetectable or extremely low hypocretin levels had statistically significantly longer sleep latency according to ACT (Table 1). They also had statistically significantly more fragmented sleep, indicated by both the number of immobile phases of 1 min and movement + fragmentation index. There were no statistically significant differences in the actual sleep time or sleep efficiency measured by ACT (Table 1). Based on the clinical experience and the comparability to PSG results, the sleep efficiency of less than 85% in ACT can be considered abnormally low. There were more patients with abnormal sleep efficiency in the very low hypocretin group, and the difference was statistically significant (Table 1).

The scatterplot and linear regression line with 95% confidence intervals showing the relation of hypocretin-1 levels and the number of immobile phases of 1 minute in ACT are seen in Figure S1. Above the number 17.5 of immobile phases of 1 min, 100% of the patients had hypocretin-1 levels less than 30 pg/mL.

Circadian phase parameters measured by ACT were not statistically significantly different between the groups (Table 1), but there were, however, some trends toward somewhat earlier sleep-wake rhythm in the very low hypocretin group. Circadian rhythm regularity, measured by interdaily stability, was similar in the two groups (Table 1).

There were no statistically significant differences between male and female patients or between adult and underaged patients in any of the measured parameters. The patients with lower hypocretin levels did not have more symptoms related to RBD or RLS than the other patients with NT1 in our study. They did not consume more caffeine or take more naps during the day according to their own reports, either.

DISCUSSION

Patients with NT1 in the current study had rather low quality of sleep according to ACT recordings. Sleep latency was usually not prolonged but sleep efficiency was low, suggesting an increased amount of wake after sleep onset. In particular, sleep of almost all the patients was fragmented or disrupted. Our results

are in line with those of Filardi and coworkers.[5] Unfortunately, different ACT programs produce dissimilar parameters that cannot be directly compared, but their results showed reduced sleep efficiency and elevated motor activity during sleep, just like ours. Our current findings are also coherent with polysomnographic measurements showing frequent arousals and awakenings, elevated wake time after sleep onset, and reduced sleep efficiency among both unmedicated and medicated narcolepsy patients and especially patients with NT1.[9–11]

As far as we know, this is the first study to look at the sleep characteristics with ACT in respect to hypocretin levels among patients with NT1. We found some interesting associations between hypocretin levels and quite a few sleep characteristics. Patients with less hypocretin had more fragmented sleep, more abnormal sleep efficiency, and longer sleep latency measured by ACT. Both sleep efficiency and sleep latency could be affected by someone going to bed well before their usual sleep onset (or lingering in bed after their usual sleep offset, affecting sleep efficiency only). We find it very unlikely, though, as every patient got the same instructions to go to bed only when sleepy and not to stay in bed excessively in the morning. The ACT parameters related to sleep fragmentation are not affected by this possibility but indicate the actual restlessness of sleep. As interdaily stability did not differ between the subgroups, circadian dysfunction seems not to be the underlying factor for larger sleep fragmentation among patients with very low hypocretin levels.

Hypocretin neurons are thought to act as main stabilizers of sleep-wake transitions through excitatory projections to several wake-promoting nuclei, and destabilizing the sleep-wake switch also results in more frequent awakenings.[12,13] An absolute hypocretin deficiency or very low hypocretin concentrations in some of our patients with NT1 may cause more wake to intrude on sleep, as shown objectively here. Possibly very low hypocretin levels also cause more sleep to intrude on wake, resulting in more irresistible attacks of falling asleep, although not shown in the current study.

In our current material, patients with hypocretin levels lower than 30 pg/mL were slightly, albeit insignificantly, younger than the other patients with NT1. In our very recent study, we noticed shorter diagnostic delays for patients with NT1 with very low hypocretin levels compared to those with slightly higher levels.[14] Perhaps symptoms show up earlier and the diagnosis is set quicker if the hypocretin levels descend to the minimum. We did not notice prominent differences in the clinical picture between patients with NT1 with diverse hypocretin-1 levels.[14] Apparently, hypocretin levels do not explain all the differences in the symptoms or actigraphic findings of the patients with NT1. We hypothesize that also other neural networks than hypocretin, e.g., histamine, contribute to the severity of symptoms and the ability to cope with poor quality of sleep.[15,16] Nonetheless, our results support the hypothesis that the hypocretin network has a major role in the stabilization of the flip-flop switch between wake and sleep.[12,13]

It is important to notice here that ACT measures activity, not sleep stages. Therefore, rapid eye movement sleep without muscle atonia (RWA), and thus with minor or major activity, would have been scored as wake in ACT. The findings presented here may also indicate that patients with NT1 with very low hypocretin levels have more RWA or RBD than the rest of the patients with NT1.[17] They might even have a sleep onset RWA in the very beginning of their sleep that could contribute to longer sleep latencies measured by ACT, as we noticed in this study. In addition, narcolepsy patients have more high-frequency leg movements and periodic leg movements during sleep than healthy controls, but it is not known whether these phenomena associate with hypocretin levels.[18,19] There were no differences in the RBD-type or RLS-type symptoms between our patients with extremely low or slightly higher hypocretin levels, however.

Our study has certain limitations. With ACT recordings, we did not look at daytime motor activity or naps. PSG was performed to all patients, but the data cannot be directly compared, as they were collected at different time points than ACT recordings. MSLT was not performed in 5 of 36 patients, because the diagnostic criteria of NT1 were already fulfilled with the combination of clinical picture and CSF hypocretin-1 concentration analysis.

CONCLUSIONS

Actigraphy can be used to objectively document the sleep disruption patients with NT1 often complain about. Objective demonstration of fragmentation might be useful in order to choose the best medication for the patient and to follow its effect. Our results suggest that an absolute hypocretin deficiency strongly affects the sleep-wake switch, leading to poor quality of nocturnal sleep.

ABBREVIATIONS

ACT, actigraphy
CSF, cerebrospinal fluid
MSLT, Multiple Sleep Latency Test
NT1, narcolepsy type 1
PSG, polysomnography
RBD, REM sleep behavioral disorder
RLS, restless legs syndrome
RWA, REM sleep without atonia

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