Supporting information

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Appendix S1. Introduction, Methods, Results, Discussion, and Tables.

Appendix S2. Details of variables used in this analysis.

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Received 18 November 2020; revised 18 January 2021; accepted 22 January 2021.

Evaluation of pathological sleepiness by Multiple Sleep Latency Test and 24-hour polysomnography in patients suspected of idiopathic hypersomnia

doi:10.1111/pcn.13196

Sleepiness is considered not to be unidimensional. The *International Classification of Sleep Disorders*, 3rd edition (ICSD-3) employs two criteria for 'pathological sleepiness' for idiopathic hypersomnia: (i) sleep prolongation with a 24-h total sleep time (TST) ≥ 660 min, measured either by 24-h polysomnography (24-h PSG) or by wrist-actigraphy-based sleep time averaged for at least 7 days; and high sleep propensity with a mean sleep latency (mSL) of ≤8 min on the Multiple Sleep Latency Test (MSLT).[1] The MSLT evaluates the tendency to fall asleep during daytime nap opportunities and serves as the gold standard for the diagnosis of central disorders of hypersomnolence. However, recent studies indicate that the MSLT is inadequate to delineate hypersomnia other than narcolepsy type 1.[2–4] Although several attempts using continuous PSG monitoring have been performed,[5–7] appropriate markers for idiopathic hypersomnia have not been established.[8] We performed 24-h PSG, standard PSG, and MSLT to understand the difference between the two aspects of sleepiness. This study was approved by the Ethics Committees of the Institute of Neuropsychiatry and Tokyo Metropolitan Institute of Medical Science. All patients gave written informed consent.

Forty consecutive patients visiting Seiwa Hospital with suspected idiopathic hypersomnia with long sleep time were evaluated by 3-day sleep studies – unattended 24-h PSG, followed by PSG and MSLT – from January 2017 to June 2019. Clinical and PSG variables from 35 eligible patients were compared to search for markers of pathological sleepiness. Our patients turned out to share clinical symptoms characteristic of idiopathic hypersomnia. (Detailed methods and characteristics of our patients are provided in Supplementary Information, Table S1.)

Twenty-nine of 35 patients were confirmed to have pathological sleepiness as determined either with 24-h PSG TST ≥ 660 min (27 patients) or MSLT mSL ≤ 8 min (six patients). Only four patients met both criteria, indicating that pathological sleepiness determined with 24-h PSG and MSLT reflected different aspects of sleepiness (see Supplementary Fig. S1).

We next searched for markers characteristic of patients with sleep prolongation or high sleep propensity. There were no differences in demographic data, self-reported measures, or clinical symptoms except for higher percentage of 'always unrefreshed nap' in those with sleep prolongation and higher percentage of 'experience of sleep attack' and lower percentage of 'long nap' in those with high sleep propensity (Table S1). As expected, we confirmed shorter MSLT mSL in the high-sleep-propensity group and longer 24-h PSG TST in the sleep-prolongation group (Table 1). No conventional PSG variables predicted sleep prolongation. Some sleep variables on 24-h PSG were identified as possible markers for sleep prolongation: shortened REM latency (P = 0.026), lower 24-h PSG_N3 (%TST; P = 0.020), more non rapid eye movement (NREM)-REM cycle counts (P = 0.0002), and shorter NREM-REM cycle duration (P = 0.046). Binary logistic regression analyses confirmed that a symptom of 'always unrefreshed upon waking' (odds ratio [OR] 44.1, P = 0.021), 24-h PSG REM latency (OR 1.009, P = 0.027), and 24-h PSG NREM-REM cycle duration (OR 1.07, P = 0.06) were independent predictors of pathological sleep prolongation. Similar analyses revealed that a symptom of 'experience of sleep attack' was independently associated with high sleep propensity (OR 0.11, P = 0.023). (See Table S2. Detailed description for Table 1 and S2 are provided in Supplementary Information.)

Twenty-five of the 35 patients fulfilled the ICSD-3 criteria for idiopathic hypersomnia, two with narcolepsy type 2, two with pathological sleepiness without a diagnosis (sleep prolongation with multiple sleep-onset REM periods [SOREMP]), and six with non-hypersomnia. The sensitivity, specificity, and accuracy of two tests for the diagnosis of ICSD-3-defined idiopathic hypersomnia were calculated. Test sensitivity was 12% with MSLT and 92% with 24-h PSG, test specificity was 80% and 60%, and accuracy was 34% and 83%, respectively (Table S3). The low sensitivity and accuracy of MSLT may be partly due to the sampling bias because we performed 24-h PSG only for those with habitually long self-reported sleep time. However, our results indicated that 79% (23/29) of our patients with pathological sleepiness would be overlooked if they were evaluated with MSLT alone, replicating that idiopathic hypersomnia patients often fail to show high sleep propensity.[1, 6, 9, 10] Although the presence of multiple SOREMP reflects the pathophysiology of narcolepsy, there is no evidence that their absence is related to the pathophysiology of idiopathic hypersomnia. In this study, four of 27 (14.8%) patients with pathological sleep prolongation showed multiple SOREMP on MSLT. Further studies with larger sample sizes are required to clarify the significance of SOREMP and other REM abnormalities in those with sleep prolongation. (REM abnormality and limitations of this study are described in detail in Supplementary Information.)

Our study indicates that the two aspects of sleepiness, sleep prolongation and high sleep propensity, are fundamentally different, and that 24-h PSG should be used as a first-line diagnostic tool for idiopathic hypersomnia with long sleep time.

Acknowledgments

We would like to thank all the patients who participated in this study. We would also like to thank the nursing staff at Seiwa Hospital for handling blood samples and Ms Megumi Hazumi for obtaining informed consent.

Disclosure statement

Dr Honda has received consultant fees from Takeda Pharmaceutical Company, Alfresa Pharma Corporation, Ono Pharmaceutical Company, and

Table 1. PSG variables and comparison between those with and without pathological sleepiness

			Sleep prolongation by 24-h PSG			Sleep propensity by MSLT		
			Pathological sleepiness		*t*-test	Pathological sleepiness		*t*-test
	Total (n = 35)	Range	+ (n = 27) TST > 660 min	− (n = 8) TST < 660 min	*P*	+ (n = 6) mSL < 8 min	− (n = 29) mSL > 8 min	*P*
PSG and MSLT sleep variables								
TST (min)	458.0 ± 53.6	[336, 546.5]	456.4 ± 52.9	463.2 ± 59.1	NS	491.7 ± 25.6	451.0 ± 55.4	NS
SE (%)	84.2 ± 10.4	[57.1, 96.3]	83.6 ± 10.6	86.3 ± 9.8	NS	91.3 ± 4.5	82.7 ± 10.7	NS
SL (min)	29.8 ± 28.3	[3, 136]	29.6 ± 29.4	30.5 ± 26.2	NS	15.5 ± 10.6	32.8 ± 30.0	NS
REML (min)	90.0 ± 42.9	[47, 236.5]	85.3 ± 44.7	105.8 ± 34.1	NS	94.7 ± 30.2	89.0 ± 45.5	NS
ArI	10.4 ± 2.8	[5.5, 16.1]	10.5 ± 2.6	9.8 ± 3.5	NS	10.2 ± 3.1	10.4 ± 2.8	NS
REM (%TST)	21.2 ± 5.1	[10.7, 30.7]	20.8 ± 5.3	22.4 ± 4.3	NS	22.2 ± 2.6	21.0 ± 5.5	NS
N1 (%TST)	8.5 ± 3.6	[2.3, 18.4]	8.8 ± 3.7	7.6 ± 3.2	NS	8.9 ± 3.9	8.5 ± 3.6	NS
N2 (%TST)	52.8 ± 7.8	[36.0, 67.2]	53.2 ± 51.5	51.5 ± 7.5	NS	55.1 ± 7.7	52.4 ± 7.9	NS
N3 (%TST)	16.9 ± 8.8	[2.1, 44.0]	17.1 ± 8.9	16.2 ± 9.1	NS	13.8 ± 6.5	17.6 ± 9.2	NS
REM cycle count	4.4 ± 0.9	[3, 6]	4.4 ± 0.9	4.3 ± 1.2	NS	4.2 ± 0.8	4.4 ± 1.0	NS
MSLT mSL (min)	12.8 ± 4.4	[3.9, 19.0]	13.1 ± 3.8	11.9 ± 6.2	NS	5.8 ± 1.8	14.3 ± 3.2	4E-07
MSLT SOREMP number	0.40 ± 0.85	[0, 3]	0.48 ± 0.94	0.13 ± 0.35	NS	1.0 ± 1.5	0.3 ± 0.6	NS
24-h PSG sleep variables								
24-hPSG_TST (min)	799.8 ± 170.7	[504, 1171.5]	865.6 ± 133.1	577.7 ± 51.4	3.0E-10	757.8 ± 159.5	808.4 ± 174.3	NS
24-hPSG_SL (min)	103.7 ± 123.8	[13.5, 525]	71.6 ± 71.1	212.3 ± 195.7	NS	58.3 ± 35.3	113.2 ± 133.7	NS
24-hPSG_REML (min)	152.9 ± 154.2	[1.5, 576]	106.8 ± 101.4	308.7 ± 203.4	0.0265	201.1 ± 196.1	143.0 ± 146.3	NS
24-hPSG_ArI	10.4 ± 2.8	[5.9, 20.6]	10.1 ± 2.4	11.3 ± 4.0	NS	10.5 ± 2.4	10.4 ± 3.0	NS
24-hPSG_REM (%TST)	24.1 ± 4.9	[14.8, 35.5]	24.5 ± 4.6	22.8 ± 5.8	NS	21.2 ± 5.1	24.7 ± 4.7	NS
24-hPSG_N1 (%TST)	10.1 ± 3.6	[6.0, 23.4]	10.4 ± 3.7	9.4 ± 3.3	NS	9.7 ± 2.6	10.2 ± 3.8	NS
24-hPSG_N2 (%TST)	50.9 ± 10.4	[10.7, 68.0]	51.6 ± 10.0	48.4 ± 12.0	NS	46.2 ± 19.3	51.9 ± 7.7	NS
24-hPSG_N3 (%TST)	13.2 ± 8.7	[0.2, 32.9]	11.4 ± 7.0	19.4 ± 11.0	0.020	13.6 ± 11.8	13.2 ± 8.2	NS
24-hPSG_REM cycle count	8.0 ± 3.0	[3, 16]	8.9 ± 2.7	4.9 ± 1.2	2.3E-04	6.7 ± 3.2	8.3 ± 2.9	NS
24-hPSG REM cycle duration (min)	99.7 ± 17.2	[70.5, 158.0]	96.6 ± 13.8	110.2 ± 23.7	0.046	101.1 ± 13.6	99.4 ± 18.0	NS

Sleep variables on PSG, MSLT, and 24-h PSG were summarized. To find markers characteristic of those with pathological sleep prolongation or high sleep propensity, we examined the differences between those with and without pathological sleepiness determined either by 24-h PSG or by MSLT. Several PSG variables showed significant difference in those with sleep prolongation, but none showed differences in those with high sleep propensity.
ArI, arousal index; mSL, mean sleep latency; MSLT, Multiple Sleep Latency Test; NS, not significant; PSG, polysomnography; REML, REM latency; SE, sleep efficiency; SL, sleep latency; SOREMP, sleep-onset REM period; TST, total sleep time.

Fujifilm Toyama Chemical Company for work completely outside this research. None of the other authors have any potential conflicts of interest to disclose. This study was supported by operating expenses of Tokyo Metropolitan Institute of Medical Sciences and did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Supporting information

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Supplementary Information S1. Detailed methods, characteristics of our subjects, markers for the pathological sleepiness, REM abnormality in those with sleep prolongation, limitation and references.

Figure S1. Representative 24-h polysomnography (PSG) hypnograms of patients in the three subtypes. Representative 24-h PSG hypnograms are shown with the time series variation of position sensors. L, S, R, and U in the position sensor indicated that the patients were in left lateral

decubitus, supine, right lateral decubitus, and upright positions, respectively. The bottom line in the position sensor (U) indicates that the participant was in the upright position.

Table S1. Clinical characteristics of patients. Demographic data, self-reported measures, HLA-DQB1 status, and frequency of clinical symptoms related to idiopathic hypersomnia are listed. A higher percentage of those with sleep prolongation experienced a symptom of 'always unrefreshed upon waking (unrefreshed nap),' and a higher percentage of those with high sleep propensity had experience of a symptom of 'sleep attack.'

Table S2. Logistic regression models. Table S2A: Logistic regression model for sleep prolongation. Binary logistic regression using a backward elimination approach was performed to identify predictors of sleep prolongation. The initial model included age, sex, BMI, and candidate variables identified in the bivariate analyses. Those with 'always unrefreshed upon waking from naps' had a 44-fold higher risk for pathological sleep prolongation. This final model had good Nagelkerke's *R* square value. Table S2B: Logistic regression model for high sleep propensity. Similar logistic regression analysis was performed to identify predictors of high sleep propensity. The initial model included age, sex, BMI, and two symptoms: long nap >30min and the experience of sleep attack. Those with the experience of sleep attack had a 0.104-fold lower risk (that is, a 9.6-fold higher risk) for high sleep propensity. Only sleep attack remained in the final model with low Nagelkerke's *R* square value.

Table S3. Sensitivity, specificity, and accuracy of Multiple Sleep Latency Test (MSLT) and 24-h polysomnography (PSG) for the diagnosis of idiopathic hypersomnia. The results of total sleep time (TST) on 24-h PSG and mean sleep latency (mSL) on MSLT, a marker for pathological sleepiness, were tabulated against the final diagnosis of idiopathic hypersomnia according to the *International Classification of Sleep Disorders*, 3rd edition (ICSD-3) criteria. Test sensitivity and accuracy were higher with 24-h PSG, indicating that 24-h PSG was a better diagnostic tool for our patients, who were suspected of idiopathic hypersomnia with long sleep time.

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Received 14 December 2020; revised 24 December 2020; accepted 11 January 2021.