



HAL
open science

Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients.

Cyrille Vernet, Isabelle Arnulf

► **To cite this version:**

Cyrille Vernet, Isabelle Arnulf. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients.: Idiopathic hypersomnia. *Sleep*, 2009, 32 (6), pp.753-9. inserm-00392758

HAL Id: inserm-00392758

<https://inserm.hal.science/inserm-00392758>

Submitted on 15 Dec 2009

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients

Cyrille Vernet ^{1,2,3}, and Isabelle Arnulf, MD, PhD ^{1,2,3}

¹Unité des Pathologies du Sommeil, Hôpital Pitié-Salpêtrière, Paris; ²Paris 6 University, France ; ³Centre de référence national narcolepsie et hypersomnie

Submitted to: Sleep

Version: 1

Corresponding author: Isabelle Arnulf

Unité des Pathologies du Sommeil

Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital,

75651 Paris Cedex 13, France

isabelle.arnulf@psl.aphp.fr

Phone : +33 1 42 16 77 02

Fax : +33 1 42 16 77 00

Acknowledgment: the study was founded by three unrestricted grants from ANTADIR AO2006, UCB-Pharma Ltd AO2007 and CARDIF AO2007.

Abstract

Objective: To characterize the clinical, psychological, and sleep pattern of idiopathic hypersomnia with and without long sleep time, and provide normative values for 24-hour polysomnography.

Setting: University Hospital

Design: Controlled, prospective cohort

Participants: 75 consecutive patients (aged 34 ± 12 y) with idiopathic hypersomnia and 30 healthy matched controls.

Intervention: Patients and controls underwent during 48 hours a face-to face interview, questionnaires, human leukocyte antigen genotype, a night polysomnography and multiple sleep latency test (MSLT), followed by 24-hour *ad libitum* sleep monitoring.

Results: Hypersomniacs had more fatigue, higher anxiety and depression scores, and more frequent hypnagogic hallucinations (24%), sleep paralysis (28%), sleep drunkenness (36%) and un-refreshing naps (46%) than controls. They were more frequently evening types. DQB1*0602 genotype was similarly found in hypersomniacs (24.2%) and controls (19.2%). Hypersomniacs had more frequent slow wave sleep after 6 AM than controls. During 24-hour polysomnography, the 95% confidence interval for total sleep time was 493-558 min in controls, versus 672-718 min in hypersomniacs. There were 40 hypersomniacs with and 35 hypersomniacs without long (>600 min) sleep time. The hypersomniacs with long sleep time were younger (29 ± 10 vs 40 ± 13 y, $P=0.0002$), slimmer (body mass index: 26 ± 5 vs 23 ± 4 kg/m²; $P=0.005$), and had lower Horne-Ostberg scores and higher sleep efficiencies than those without long sleep time. MSLT latencies were normal (>8 min) in 71% hypersomniacs with long sleep time.

Conclusions: Hypersomnia, especially with long sleep time, is frequently associated with evening chronotype and young age. It is inadequately diagnosed using MSLT.

Keywords: hypersomnia, long sleep time, MSLT

INTRODUCTION

IDIOPATHIC HYPERSOMNIA IS CHARACTERIZED BY CHRONIC, DAILY EXCESSIVE DAYTIME SLEEPINESS DESPITE NORMAL SLEEP. The diagnosis is difficult, as more common causes of sleepiness, including sleep deprivation, use of drugs or substances, psychiatric or medical disorders and genuine sleep disorders (sleep disordered breathing, narcolepsy, periodic leg movement disorders) should be first ruled out. Since it has been distinguished from narcolepsy,¹ idiopathic hypersomnia has been defined according to small cases series, with various clinical forms. The alertness is continuously decreased during daytime, possibly culminating in irresistible needs for sleeping. Naps are either refreshing or, more typically, long and un-refreshing.² Patients may also report prolonged difficulty waking with automatic behavior, confusion, and repeated returns to sleep, a symptom named 'sleep drunkenness'. Several clinical forms have been described,³ including patients with sleepiness alone (monosymptomatic), as opposed to patients with prolonged night sleep and sleep drunkenness upon awaking (polysymptomatic). Idiopathic hypersomnia is now divided in hypersomnia with or without long (>10 h) sleep time.² The recent classification highlights the need for polygraphic criteria (in addition to the symptoms previously defined), including normal night-time sleep duration and structure, and decreased (<8 min) mean daytime sleep latency during multiple sleep latency test (MSLT), or a total sleep time typically longer than 11-12 h during long-term sleep monitoring.² Hypersomnia is idiopathic when the symptoms and polygraphic findings cannot be better explained by medical or psychiatric (mostly depression) disorders. Based on these evolving definitions, several series of patients have been published.⁴⁻¹⁴ They contain 10 to 77 patients. These series and the expert clinical opinion suggest that idiopathic hypersomnia is a rare disease, representing 8:10 to 1:10 patients with narcolepsy, with a prevalence approximating 0.005%.¹⁵ Most patients are young at disease

Idiopathic hypersomnia

onset. This is usually a lifelong disease, although recent series suggest that hypersomnia may spontaneously disappear in 14% to 25% patients.^{11, 14, 16}

These rare series highlight the lack of information about idiopathic hypersomnia. There is no published systematic interview of hypersomniacs, hence a need for determining the frequency of narcolepsy-like symptoms, fatigue, anxiety, depressive mood, and the various circadian chronotypes. The criteria of hypersomnia fluctuate from a classification of sleep disorders to another. Although several authors recognize that night-time polysomnography followed by MSLT (a more 'narcolepsy-oriented' procedure) is not sufficient to diagnose idiopathic hypersomnia, there is a lack of standardized procedure and normative data for long term sleep monitoring. Furthermore, there is no or scarce information on the sleep structure of hypersomniacs across the 24-hour period. There is still no information on the demographical and clinical differences between patients with long or normal sleep time. We characterized the clinical, sleep and typed the HLA genes DR and DQ in 75 consecutive patients with idiopathic hypersomnia (with and without long sleep time) and 30 matched controls, using a face-to-face semi-standardized questionnaire, and a 48-hour sleep monitoring. We also aimed at giving normatives for long term sleep monitoring.

METHODS

Subjects

We prospectively selected patients with idiopathic hypersomnia among all patients referred to our Sleep Disorders Unit (in a tertiary care university hospital with a biased over-recruitment of neurological cases, and recently recognized as national reference center for narcolepsy, hypersomnia and Kleine-Levin syndrome) for excessive daytime sleepiness

Idiopathic hypersomnia

between 2000 and 2007. Patients were included in the study if they met the following inclusion criteria: (1) complaining of excessive daytime sleepiness occurring daily for at least three months; (2) no improvement with an increase of the nighttime length for 15 days; (3) a mean sleep latency (MSL) during the MSLT lower than 8 minutes and no more than one sleep onset REM period, or a total sleep time > 660 min (i.e. 11/ 24 hours) on long-term sleep monitoring. Sleep monitoring and questionnaires were performed in untreated patients and controls. In the 15/75 hypersomniacs who had received stimulants (modafinil) or antidepressants in the past year, the psychotropic drugs were withdrawn for at least 10 half-lives before sleep tests. We excluded the patients with: (1) Sleep disordered breathing, defined by a respiratory disturbance index greater than 10 per hour and more than 5 apnea-hypopnea/hour (this index included apnoea, hypopnea, and respiratory effort related arousal events, the flow limitation being measured on the nasal canulae); (2) Narcolepsy defined as the presence of a definite cataplexy or MSL lower than 8 min and multiple sleep-onset REM periods during MSLT; in addition, patients with a REM sleep latency lower than 20 minutes during night-time or during daytime monitoring (at more than one nap) were excluded; (3) Hypersomnia due to a medical or psychiatric condition (e.g. Parkinson's disease, hypothyroidism, genetic disease, depression); (4) Hypersomnia due to drug or substance. We excluded thirty patients who were clinically diagnosed as idiopathic hypersomnia, but did not meet the international criteria.² They had an MSL longer than 8 min and slept between 490 and 659 min during the 24-hour monitoring. Thus, 75 patients (48 women, of whom 5 were post-menopausal, and 27 men) completed the study.

Thirty healthy, paid subjects volunteered to take part as controls after recruitment by advertisement. They were selected after a medical interview for having no sleep complaint, no excessive daytime sleepiness (defined as absence of spontaneous or elicited complain and a score at the Epworth sleepiness scale lower than 11), no chronic sleep deprivation (as checked

Idiopathic hypersomnia

using a questionnaire on sleep habit), no shift or night work, no severe medical illness, and no use of medications known to modify sleep and wakefulness. They were matched for age and sex with the patient group. Control subjects were able to comply adequately with the study requirements and signed an informed consent. The study was approved by the local ethics committee. The demographic and clinical characteristics of the participants are summarized in Table 1.

Investigations

Participants were instructed to follow a regular sleep-wake rhythm, with at least 8 hours in bed during the week preceding the 48 hour-long investigation in the Sleep Disorders Unit. They underwent a face to face interview about sleep symptoms (cataplexy, sleep drunkenness, sleep paralysis, restorative naps) and completed a standardized comprehensive sleep questionnaire including the Epworth sleepiness scale,¹⁷ the Horne-Ostberg eveningness-morningness scale,¹⁸ the Pichot fatigue scale,¹⁹ and the hospital depression and anxiety (HAD) rating scale.²⁰ The class-II human leukocyte antigen genotype was determined in all patients and controls. The sleep and wake monitoring procedure included: (i) a habituation night with sleep and respiratory monitoring from 11 PM to 6:30 AM, followed the next day by (ii) five standard sleep latency tests (MSLT) at 8 AM, 10 AM, noon, 2 PM, 4 PM, that were terminated after 20 minutes if no sleep occurred, and after 15 min asleep if sleep occurred²¹; (iii) followed the next evening by a long term (24-hour) sleep monitoring. The aim of the long term sleep monitoring was to elicit the maximum spontaneous amount of sleep in relaxed, quiet but not totally abnormal conditions, while any sleep episode, whether at night or during daytime, should never be interrupted by the technicians. Controls and patients were already hooked in the sleep unit for 24 hours. They received dinner at 7 PM. TV, computer,

Idiopathic hypersomnia

and visit from friends were forbidden, but books, newspapers, watches and daylight were allowed. The participants were then free to determine when they wanted to sleep and switch lights off in the evening, with a spontaneous awakening (and lights on) the next day. In addition, all subjects were proposed two naps during the morning and the afternoon, lying in the dark. The nap attempts were discontinued by the subjects after 30 min if they could not sleep, and were *ad libitum* continued when they fell asleep. Tests were stopped at 5 PM. All in all, this procedure provided a 20 hours long opportunity to sleep for all subjects. Subjects received a breakfast after waking up, and a lunch if they woke up for. This procedure was highly recommended in diagnosis criteria for idiopathic hypersomnia,^{2, 15} but lacked of standardized values in healthy subjects. We determined normative values here.

Polysomnographic recordings included an electroencephalography (Fp1-A2, C3-A2, O1-A2), left and right electro-oculograms, levator menti and bilateral tibialis anterior surface electromyography, nasal pressure trough cannulae, respiratory efforts using thoracic and abdominal belts, position, tracheal sounds, pulse rate and transcutaneous oximetry (Medatec Ltd France) during the first night. The respiratory sensors were removed during the MSLT and the 24-hour sleep monitoring. Sleep stages, arousals, periodic leg movements, and respiratory events were scored visually according to standard criteria.²²⁻²⁵ Total sleep time, total sleep period, sleep and REM sleep latencies, the durations and percentages of non REM sleep stage 1, 2, 3-4, and REM sleep were determined during Night 1 and Night 2, and during the 24-hour monitoring procedure. The indexes of sleep fragmentation (arousal index, periodic leg movements, periodic leg movement-associated arousal index, apnea-hypopnea index), and minimal oxygen saturation during sleep were measured during Night 1. In order to look if it was correlated with sleep drunkenness, we noted the time of offset of the last slow wave sleep (SWS) episode longer than 5 minutes during the second night sleep.

Statistical analysis

The patients with hypersomnia were first compared as a group to the control group. In a second analysis, the hypersomniac patients with long sleep time (defined as a nighttime sleep greater than 600 min during Night 2) were compared to the patients without long sleep time. After having checked the Gaussian distribution of variables, we analyzed between-groups dichotomous variables using chi-square test, and continuous variables using analysis of variance (Statistica 7.1, Stat Soft Inc, Tulsa, OK). A P value lower than 0.05 was considered as significant (with corrections for repeated measures). Values are presented as mean \pm SD (otherwise specified). For normative values, we determined the 95% confidence interval in controls.

RESULTS

Clinical differences between hypersomniacs and controls

As expected by matching, patients and controls did not differ for age, sex ratio (Table 1). The body mass indexes were remarkably similar in hypersomniacs and controls. Patients with hypersomnia had higher Epworth sleepiness scores than controls. In the hypersomniac group, 89% patients had a score greater than 10, and 42% had a score greater than 15. They had no cataplexy and no more hallucinations than controls, but 28% hypersomniacs had sleep paralysis, 36% had sleep drunkenness and 46% had un-refreshing naps. All these symptoms were, in contrast, infrequent in normal controls (especially for sleep drunkenness, that was never found in controls), suggesting they were poorly sensitive but highly specific.

Idiopathic hypersomnia

Hypersomniacs had higher fatigue scores than controls. In the patient group, there were no correlation between the subjective sleepiness (Epworth sleepiness score) and the MSL ($r=-0.02$, $P=0.91$) or the Pichot fatigue score ($r=0.15$, $P=0.44$). Using the HAD rating scale, patients scored themselves as slightly more anxious and depressed than controls, while 22% patients had abnormal scores (greater than 11) for anxiety (vs 10% in controls, $P=0.3$), and 19% had abnormal score (greater than 11) for depression (vs 3%, $P=0.06$). As for the chronotype, patients had lower Horne-Ostberg scores than controls, indicating a delayed sleep phase.

HLA genotyping

The HLA DQB1*0602 genotype was found equally in hypersomniacs (24.2%) and controls (19.2%, $P=0.6$). There were no difference for the frequency of the 122 various alleles of HLA DRB1 and DQB1 tested in patients (Table 2), compared to the 60 alleles tested in controls, except for the HLA DRB1*11, which was found at a twice lower frequency in patients than in controls than ($p=0.05$), leading to an odd-ratio of 0.48. No specific haplotype could be identified, for the sample was too small to reach significance.

Clinical differences between hypersomniacs with and without long sleep time

There were 40 patients (53% of hypersomniacs) with long sleep time and 35 patients (47%) without long sleep time (i.e. with a total sleep time lower than 600 min and MSL lower than 8 min). The patients with long sleep time were younger than the patients without long sleep time (29 ± 10 y vs 40 ± 13 y, $P=0.0002$) and had lower body mass indexes (23 ± 4 vs 26 ± 5 kg/m²; $P=0.005$) than those without long sleep time, with no gender difference (Table

Idiopathic hypersomnia

3). As for the clinical symptoms (sleep drunkenness, sleepiness and fatigue scores) there was no difference between the patients with long and normal sleep time, except for lower Horne and Ostberg scores (44.0 ± 13.8 vs 52.7 ± 10.2 , $P=0.04$) in patients with vs without long sleep time. The frequency of HLA DQB1*0602 genotype was not different (26% and 22%, $P=0.78$) between these two groups.

Normative measures during *ad libitum* sleep in healthy subjects

The controls slept 491 ± 77 min (range 265-642 min), during night-time and 525 ± 87 min (range 286-690 min) during the 24-hour monitoring (Table 4). The median value for nighttime sleep was 491 min, with a 95% confidence interval of 462-520 min. During the 24-hour period, the median sleep duration in controls was 522 min, with a 95% confidence interval of 493-558 min. Thereby, sleep amounts greater than 558 min (9.3 h) on a continuous 24-hour monitoring may be considered as abnormal.

Polysomnographic differences between hypersomniacs and controls during *ad libitum* sleep monitoring

During the second night, patients had a longer total sleep time than controls but normal sleep efficiency, and sleep onset and REM sleep latencies (Table 4). While healthy volunteers were asleep 44% of the time recorded on a 24-hour long basis, hypersomniacs slept 58% of the time ($P<0.0001$). There was a weak ($r=-0.06$) but significant ($P=0.03$) negative correlation between the age of hypersomniacs and the time slept both at night and during 24 hours. As for sleep structure, there were no between-groups differences for non REM sleep stage 1-2 percentages. The SWS percentages were lower in hypersomniacs, a

Idiopathic hypersomnia

difference that disappeared when considering the raw duration of SWS (120 ± 51 min in hypersomniacs vs 121 ± 34 min in controls, $P=0.89$). The REM sleep percentages and times during night-time were higher in hypersomniacs than in controls. Hypersomniacs had more frequent SWS episodes at the end of the night, as 61% hypersomniacs had a SWS episode after 6 AM, vs 37% in controls. The time of the last SWS episode was $8:44 \pm 1:40$ AM in the hypersomniacs vs $6:11 \pm 1:45$ AM in the controls. While the duration of sleep cycles was similar in patients (102 ± 28 min) and in controls (93 ± 12 min, $P=0.11$), patients had more sleep cycles (6.0 ± 0.8) than controls (5.5 ± 0.9 , $P=0.02$). There were no differences between groups for periodic legs movements and their related arousals. Fifteen percent patients had a periodic legs movement indexes greater than 15 (a value considered as abnormal in adults), vs 7% controls ($P=0.30$). As for sleep-disordered breathing, there were no differences between groups regarding apnea-hypopnea index, apnea index, respiratory disturbance index and minimal SpO₂ (data not shown).

During daytime, hypersomniacs slept longer (116 ± 57 min) than controls (35 ± 33 min, $P<0.0001$). They had higher REM sleep percentages (12.1 ± 12.3 % vs 4.2 ± 10.0 %, $P=0.003$) and SWS percentages (13.3 ± 12.4 % vs 5.4 ± 10.0 %; $P=0.002$) than controls. When considering the amount sleep during a 24-hour period, hypersomniacs had much longer total sleep time than controls, with higher sleep stages 1-2 and REM sleep durations, and higher sleep stage 1-2 percentage (Table 4).

Polygraphic differences between hypersomniac patients with and without long sleep time

By definition, the patients with long sleep time had longer total sleep time during Night 2 (Table 5). Compared to the patients without long sleep time, they had higher sleep efficiency (92.3 ± 5.6 % vs 89.3 ± 6.7 %, $P=0.04$) during the night, and later SWS episode ($9:27 \pm 1:40$ AM vs $8:08 \pm 1:26$ AM, $p=0.02$), with no other difference in sleep structure.

Idiopathic hypersomnia

Daytime sleep was also not different between groups. Total sleep time during the 24-hour monitoring was higher (747 ± 82 min) in the group with long sleep time than without (635 ± 82 min, $P < 0.0001$).

Multiple sleep latency tests in hypersomniacs

As a group, hypersomniacs had twice shorter MSL than controls (Table 6), but the dynamic profile over time in the five tests was similar (not shown). Of note, MSL was 4.6 min in one healthy volunteer, in spite of normal Epworth sleepiness score of 7/24 and normal total sleep time over 24 hours. As many as 39% hypersomniacs had normal MSL (greater than 8 min), while 30% had MSL greater than 10 min (still above the 'gray zone' of 8-10 min). The number of sleep onset REM periods was similar in hypersomniacs and in controls. In hypersomniacs, longer MSL were associated with longer sleep durations during night-time ($r=0.12$, $P=0.005$) and during a 24-hour period ($r=0.12$, $P=0.006$). In hypersomniacs, the MSL was higher in the group with long sleep time than without (Table 6). In the subgroup of 40 patients with long sleep time, 71% had an MSL greater than 8 min (vs 0% in the group without long sleep time, $P=0.0001$), while 54% had an MSL greater than 10 min (Table 6).

DISCUSSION

This is a large, prospective, controlled series of patients with idiopathic hypersomnia, bringing new information on several aspects of this rare disease. This includes clinical symptoms (particularly chronotype and psychological aspects in hypersomnia), differences

Idiopathic hypersomnia

between hypersomniacs with and without long sleep time, sensitivity of the MSLT and suggestion of normative data during long term sleep monitoring.

Clinical features in hypersomniacs

Notably, hypersomniacs are not overweighted in our series, suggesting a major difference with the overweight and even obesity described in around one third of patients with narcolepsy.²⁶ It suggests that the hypothalamic area responsible for eating behavior and metabolism (including the orexin/hyocretin neurons) are not dysfunctional in hypersomnia. In addition, it suggests that oversleeping (and possibly being less active due to hypersomnolence) does not result, per se, in an increased weight. On the contrary, patients with long sleep time have a lower body mass index than those without long sleep time. The classical symptoms of hypersomnia (sleep drunkenness and unrefreshing naps) are found in only 36 and 54% patients, respectively, but almost never in controls, suggesting a poor sensitivity but a high specificity. The higher fatigue score and the slightly higher anxiety and depression scores in hypersomniacs could be a consequence of the difficulties of adapt to this disabling condition. Of interest, there are here several indications of delayed sleep phase in idiopathic hypersomnia, as Horne-Ostberg scores are lower than in controls, and hypersomniacs are more evening types. The sleep phase delay cannot be attributed to young age, as controls are matched with patients for age, but could be a long-term consequence of prolonged sleep in the morning/afternoon. In a single study, a delayed secretion of melatonin and cortisol was observed in 15 patients with idiopathic hypersomnia,²⁷ also supporting a longer circadian period in these patients. If proved to be exact, this finding could support the evening use of melatonin in hypersomniacs, in order to advance the sleep phase.

Differences between hypersomniac patients with and without long sleep time

The distinction of hypersomnia with and without long sleep time is recent. As a result, there is no characterization of these two groups, to our knowledge. In our series, patients with long sleep time are younger, slimmer, have lower Horne-Ostberg scores, and would sleep longer on a 24-hour basis, with higher sleep efficiency, than patients without long sleep time. We could not identify psychological profiles, symptoms, and sleep structure specific to this subgroup. As many as 71% patients with long sleep time have normal MSL during MSLT, reinforcing the idea that the latter test is poorly sensitive for diagnosing hypersomnia.^{11, 15} As these patients are younger, they may suffer from a juvenile form of the same disease, later evolving toward less night-time sleep. In favor of this hypothesis, total sleep time during night-time and during 24 hours slightly decreases with increasing age at diagnosis time. A longitudinal follow-up of these patients using the same monitoring procedure would help to support this hypothesis.

MSLT vs 24-hour sleep monitoring for diagnosing hypersomnia

This study highlights the MSLT limitations for the diagnosis of hypersomnia, compared to the sensitivity of 24-hour monitoring. Indeed, although several authors point on normal or subnormal MSLT in hypersomniacs (nicely illustrated by the single case-report of a man sleeping 19 hours over 24 hours despite a normal MSL of 11 min),^{15, 28} they also underline the absence of standardization and normative values for 24-hour *ad libitum* monitoring.¹⁵ Here we provide for the first time normative values for the duration of sleep during an *ad libitum* 24-hour continuous monitoring in 30 healthy volunteers. We followed the recommendations developed by Billiard and Dauvilliers and reported in the International

Idiopathic hypersomnia

Classification of Sleep disorders-2005 revised. These recommendations specify to monitor patients after a night-time sleep monitoring followed by MSLT, and to allow the patients the opportunity to develop extended, uninterrupted sleep. The subjects receive the instruction of not fighting against sleep, and the technician of not interrupting sleep for whatever reason. Following these instructions, healthy volunteers sleep from 286 to 690 min (i.e. a maximum of 11.5 h), while the 95% confidence interval upper threshold is 558 min (9.3 h). This suggests that a longer time asleep is abnormal. These normative limits could be useful in the future for diagnosing hypersomniacs with normal MSLT, which is the case here in 71% hypersomniacs with long sleep time. Even the assertion that MSL may be in the 'gray zone' of 8-10 min in central hypersomnia is not founded here, as more than half of the patients with long sleep time had MSL above 10 min. On the contrary, the patients who sleep longer at nighttime have longer sleep latencies during MSLT in our series. These results support the idea that hypersomniacs would not fall asleep as quickly as narcoleptic patients, i.e. without rapid shift from wakefulness to sleep. In contrast, they would have difficulties to wake up spontaneously after sleep, i.e. difficulties to shift from sleep to wake, a disability which could result in severe cases in sleep drunkenness.

Here, *ad libitum* night and day sleep is monitored after a habituation night followed by clinical MSLT. Despite this procedure was recommended,² one may object that the amount of sleep obtained during the five MSLT naps may hamper subsequent sleep by consuming processus S (homeostatic sleep drive) in patients, while it would not be the case in controls (who usually sleep less often during the MSLT). In our procedure, the habituation night is however stopped at 6:30 AM, mostly by forced awakening in these young subjects with frequently delayed sleep. This sleep curtailment may be compensated in part during the MSLT naps. Furthermore, shorter MSL are not associated with shorter night time sleep duration, while they are on the contrary associated with longer sleep duration on a 24-hour

Idiopathic hypersomnia

basis. Eventually, each nap lasts 15 minutes, whatever the sleep onset latency, normalizing the total time slept during the MSLT naps. Another potential limitation during *ad libitum* procedure is the presence of *zeitgebers* (watches, daylight during lunch, meals), and the possibility to briefly walk at breakfast and lunch. We think however that these conditions are closer to the patient usual life when they are free of schedules and work (e.g. during vacations) than other artificial procedures (continuous bed rest, continuous darkness, absence of clock). These practical conditions are also easier to adapt in routine, clinical sleep disorders unit settings, allowing our normative data to be used by others.

Idiopathic hypersomnia

Table 1 Clinical and biological characteristics of 75 patients with idiopathic hypersomnia and 30 matched controls

Clinical characteristics	Patients	Controls	P
Number	75	30	
Age, y	34.0 ± 12.5	38.6 ± 15.2	0.15
BMI, kg/m ²	24.4 ± 5.0	24.4 ± 4.6	0.97
Women, %	64.0	50.0	0.19
Hypnagogic hallucinations, %	24.1	8.7	0.09
Sleep paralysis, %	27.6	4.3	0.01
Non refreshing naps, %	46.3	5.0	0.001
Sleep drunkenness, %	36.5	0.0	< 0.0001
Epworth sleepiness score (0-24)	15.0 ± 4.2	5.4 ± 2.5	< 0.0001
Pichot fatigue score (0-32)	26.4 ± 8.3	10.6 ± 3.0	< 0.0001
HAD anxiety (0-21)	8.7 ± 4.0	6.1 ± 3.6	0.006
HAD depression (0-21)	7.1 ± 5.0	4.0 ± 3.0	0.003
Horne-Ostberg score	47.8 ± 13.0	55.2 ± 8.8	0.007
HLA DQB1*0602 positive, %	24.2	19.2	0.60

HAD: Hospital Anxiety and Depression Rating Scale; HLA: Human Leukocyte Antigen.

Idiopathic hypersomnia

Table 2 Frequency of the DQB1 and DRB1 HLA alleles (low resolution) in 61 patients with idiopathic hypersomnia and in 30 controls.

Subtype	Patients	Controls	P
Number of alleles	122	60	
HLA DRB1* allele, %			
DRB1*01	9	12	0.6
DRB1*03	12	9	0.4
DRB1*04	13	9	0.4
DRB1*07	14	21	0.3
DRB1*08	2	2	1.0
DRB1*09	2	2	1.0
DRB1*10	3	0	0.2
DRB1*11	10	21	0.05
DRB1*12	2	2	1.0
DRB1*13	12	14	0.8
DRB1*14	2	0	0.2
DRB1*15	14	9	0.3
DRB1*16	2	2	1.0
HLA DQB1* allele, %			
DQB1*02	26	28	0.8
DQB1*03	32	38	0.4
DQB1*04	2	2	1.0
DQB1*05	15	15	1.0
DQB1*06	25	17	0.3

RR: relative risk.

Idiopathic hypersomnia

Table 3 Clinical and biological characteristics of hypersomniacs with and without long sleep time

Clinical characteristics	Patients without long sleep time	Patients with long sleep time	P
Number	35	40	
Age, y	39.7 ± 13.0	29.1 ± 9.7	0.0002
BMI, kg/m ²	26.1 ± 5.3	22.8 ± 4.1	0.005
Women, %	60.0	67.5	0.63
Hypnagogic hallucinations, %	25.0	23.3	0.88
Sleep paralysis, %	28.6	26.7	0.87
Non refreshing naps, %	45.0	47.6	0.87
Sleep drunkenness, %	23.1	50.0	0.08
Epworth sleepiness score (0-24)	15.0 ± 4.1	14.9 ± 4.3	0.91
Pichot fatigue score (0-32)	26.9 ± 7.9	26.0 ± 8.8	0.75
HAD anxiety (0-21)	9.6 ± 4.1	8.1 ± 4.0	0.29
HAD depression (0-21)	7.5 ± 4.6	6.8 ± 5.4	0.66
Horne-Ostberg score	52.7 ± 10.2	44.0 ± 13.8	0.04
HLA DQB1*0602 positive, %	21.9	26.5	0.78

HAD: Hospital Anxiety and Depression Rating Scale; HLA: Human Leukocyte Antigen.

Idiopathic hypersomnia

Table 4 Polysomnographic characteristics of 75 patients with idiopathic hypersomnia and 30 matched controls

Sleep measures	Patients	Controls	P
Number	75	30	
Night-time sleep			
Total sleep time, min	579 ± 90	491 ± 77	< 0.0001
Sleep efficiency, %	90.9 ± 6.3	88.8 ± 7.3	0.18
Latency to, min			
Sleep onset	31.2 ± 41.6	32.0 ± 20.9	0.90
REM sleep	81.5 ± 48.0	84.2 ± 43.7	0.79
Sleep stages, % total			
stages 1-2	55.4 ± 9.1	53.8 ± 7.8	0.38
stages 3-4	20.8 ± 8.2	24.9 ± 6.5	0.01
REM sleep	23.7 ± 6.5	21.1 ± 4.6	0.02
Sleep fragmentation			
Arousals, n/h	8.7 ± 5.8	18.0 ± 8.9	< 0.0001
Periodic legs movements, n/h	8.5 ± 12.5	5.9 ± 20.7	0.54
Apnea/hypopnea, n/h	2.3 ± 3.7	4.4 ± 5.4	0.05
End of the night			
SWS after 6 AM, % patients	60.6	36.7	0.03
Time of last SWS episode	8:44 ± 1:40	6:11 ± 1:45	< 0.0001
Sleep fragmentation			
Arousals, n/h	8.7 ± 5.8	18.0 ± 8.9	< 0.0001
Periodic legs movements, n/h	8.5 ± 12.5	5.9 ± 20.7	0.54
Apnea/hypopnea, n/h	2.3 ± 3.7	4.4 ± 5.4	0.05
Sleep during 24-hour monitoring			
Total sleep time, min	695 ± 99	525 ± 87	< 0.0001
Sleep stages, % total			
stages 1-2	58.2 ± 9.0	55.8 ± 7.4	0.17
stages 3-4	19.7 ± 7.9	26.1 ± 8.5	0.0008
REM sleep	22.1 ± 6.0	20.0 ± 4.3	0.06

Table 5 Polysomnographic characteristics of hypersomniacs with and without long sleep time

Sleep measures	Patients without long sleep time	Patients with long sleep time	P
Number	35	40	
Night-time sleep			
Total sleep time, min	517 ± 60	633 ± 76	< 0.0001
Sleep efficiency, %	89.3 ± 6.7	92.3 ± 5.6	0.04
Latency to, min			
Sleep onset	26.7 ± 26.5	35.1 ± 51.3	0.37
REM sleep	82.8 ± 53.2	80.5 ± 43.5	0.84
Sleep stages, % total			
stages 1-2	56.0 ± 9.4	54.8 ± 9.2	0.59
stages 3-4	20.8 ± 7.9	20.8 ± 8.6	0.97
REM sleep	23.1 ± 5.4	24.3 ± 7.3	0.41
Sleep fragmentation			
Arousals, n/h	10.3 ± 7.1	7.3 ± 4.1	0.15
Periodic legs movements, n/h	10.8 ± 14.7	5.4 ± 8.2	0.13
Apnea/hypopnea, n/h	3.4 ± 4.5	0.9 ± 1.3	0.004
End of the night			
SWS after 6 AM, % patients	59.4	61.8	0.88
Time of last SWS episode	8:08 ± 1:26	9:27 ± 1:40	0.02
Sleep fragmentation			
Arousals, n/h	10.3 ± 7.1	7.3 ± 4.1	0.15
Periodic legs movements, n/h	10.8 ± 14.7	5.4 ± 8.2	0.13
Apnea/hypopnea, n/h	3.4 ± 4.5	0.9 ± 1.3	0.004
Sleep during 24-hour monitoring			
Total sleep time, min	635 ± 82	747 ± 82	< 0.0001
Sleep stages, % total			
stages 1-2	58.9 ± 8.5	57.5 ± 9.5	0.52
stages 3-4	19.3 ± 7.2	20.0 ± 8.6	0.68
REM sleep	21.6 ± 5.3	22.5 ± 6.7	0.55

Idiopathic hypersomnia

Table 6 Mean sleep onset latency during multiple sleep latency tests in the various studied groups.

Subjects	Controls	Patients with idiopathic hypersomnia	P	Hypersomniacs without long sleep time	Hypersomniacs with long sleep time	P
No.	30	75		35	40	
Mean sleep latency (MSL) ± SE, min	15.8 ± 0.7	7.8 ± 0.5	< 0.0001	5.6 ± 0.3	9.6 ± 0.7	< 0.0001
Subjects with (%)						
MSL <8min	3.3	60.9	< 0.0001	100	28.6	< 0.0001
MSL between 8 and 10 min	0.0	9.4	< 0.0001	0.0	17	< 0.0001
MSL >10 min	96.6	29.7	< 0.0001	0.0	54	< 0.0001

Idiopathic hypersomnia

References

1. Roth B, Nevsimalova S, Rechtschaffen A. Hypersomnia with "sleep drunkenness". *Arch Gen Psychiatry* 1972;26(5):456-62.
2. AASM. The International Classification of Sleep Disorders : Diagnostic and Coding manual. 2005.
3. Roth B. Idiopathic hypersomnia: a study of 187 personally observed cases. *Int J Neurol* 1981;15(1-2):108-18.
4. Vgontzas AN, Bixler EO, Kales A, Criley C, Vela-Bueno A. Differences in nocturnal and daytime sleep between primary and psychiatric hypersomnia: diagnostic and treatment implications. *Psychosom Med* 2000;62(2):220-6.
5. Aldrich MS. The clinical spectrum of narcolepsy and idiopathic hypersomnia. *Neurology* 1996;46(2):393-401.
6. Bassetti C, Aldrich M. Idiopathic hypersomnia. A series of 42 patients. *Brain* 1997;120(8):1423-35.
7. Coleman RM, Roffwarg HP, Kennedy SJ, et al. Sleep-wake disorders based on a polysomnographic diagnosis. A national cooperative study. *JAMA* 1982;247(7):997-1003.
8. Baker TL, Guilleminault C, Nino-Murcia G, Dement WC. Comparative polysomnographic study of narcolepsy and idiopathic central nervous system hypersomnia. *Sleep* 1986;9(1 Pt 2):232-42.
9. Billiard M, Merle C, Carlander B, Ondze B, Alvarez D, Besset A. Idiopathic hypersomnia. *Psychiatry Clin Neurosci* 1998;52(2):125-9.
10. Komada Y, Inoue Y, Mukai J, Shirakawa S, Takahashi K, Honda Y. Difference in the characteristics of subjective and objective sleepiness between narcolepsy and essential hypersomnia. *Psychiatry Clin Neurosci* 2005;59(2):194-9.
11. Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. *Sleep* 2007;30(10):1274-81.
12. Bove A, Culebras A, Moore JT, Westlake RE. Relationship between sleep spindles and hypersomnia. *Sleep* 1994;17(5):449-55.
13. Sforza E, Gaudreau H, Petit D, Montplaisir J. Homeostatic sleep regulation in patients with idiopathic hypersomnia. *Clin Neurophysiol* 2000;111(2):277-82.
14. Bruck D, Parkes JD. A comparison of idiopathic hypersomnia and narcolepsy-cataplexy using self report measures and sleep diary data. *J Neurol Neurosurg Psychiatry* 1996;60(5):576-8.
15. Billiard M, Dauvilliers Y. Idiopathic Hypersomnia. *Sleep Med Rev* 2001;5(5):349-58.
16. Billiard M. Idiopathic hypersomnia. *Neurol Clin* 1996;14(3):573-82.
17. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540-5.
18. Horne J, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* 1976;4:97-110.
19. Pichot P, Brun JP. [Brief self-evaluation questionnaire for depressive, asthenic and anxious dimensions]. *Ann Med Psychol (Paris)* 1984;142(6):862-5.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361-70.
21. Carskadon MA, Mitler MM, Roth T. Guidelines for the Multiple Sleep Latency Test (MSLT) : a standard measure of sleepiness. *Sleep* 1986;9:519-24.
22. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles: UCLA Brain Information Service/Brain Research Institute., 1968.

Idiopathic hypersomnia

23. American Sleep Disorders Association. EEG arousals: Scoring rules and examples. *Sleep* 1992;15:174-84.
24. American Sleep Disorders Association. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. *Sleep* 1995;18:511-3.
25. American Sleep Disorders Association Atlas Task Force. Recording and scoring leg movements. *Sleep* 1993;16:749-59.
26. Okun ML, Lin L, Pelin Z, Hong S, Mignot E. Clinical aspects of narcolepsy-cataplexy across ethnic groups. *Sleep* 2002;25(1):27-35.
27. Nevsimalova S, Blazejova K, Illnerova H, et al. A contribution to pathophysiology of idiopathic hypersomnia. *Suppl Clin Neurophysiol* 2000;53:366-70.
28. Voderholzer U, Backhaus J, Hornyak M, Hohagen F, Berger M, Riemann D. A 19-h spontaneous sleep period in idiopathic central nervous system hypersomnia. *J Sleep Res* 1998;7(2):101-3.