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Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients Cyril Vernet and Isabelle Arnulf Et oui voici mon premier papier accepté dans le revue SLEEP

Objectif : Le but de cet article est de comparer les deux groupes de patients atteints d'hypersomnie idiopathique qui ont ou non un temps de sommeil allongé (plus de 11 heures). **Sujets :** 75 patients atteints d'hypersomnie idiopathique, d'âge moyen 34 ± 12 ans, ont été inclus dans cet étude ainsi que 30 témoins appariés. **interventions :** Les patients et les témoins ont bénéficié d'un interrogatoire face à face, d'un génotypage HLA et d'un enregistrement polysomnographique de 48 heures incluant les tests itératifs de latence d'endormissement (TILE) et un enregistrement de longue durée.

Analyse : Les résultats cliniques et polysomnographiques sont comparés à ceux d'un groupe de témoins sains. C'est une nouveauté puisqu'habituellement les comparaisons sont faites entre patients (hypersomnie idiopathique, narcolepsie...).

Résultats : Par rapport aux témoins sains, les patients atteints d'hypersomnie idiopathique étaient plus fatigués, avaient un score d'anxiété et de dépression supérieur, avaient plus souvent des hallucinations hypnagogiques (24%), des paralysies du sommeil (28%), de l'ivresse de sommeil (36%) et des siestes non récupératrices (46%) que les témoins. Les patients étaient plus souvent du soir. Le génotype HLA DQB1*0602 était aussi fréquent chez les hypersomniaques (24.2%) que chez les contrôles (19.2%). Les patients atteints d'hypersomnie idiopathique avaient plus souvent du sommeil lent profond après 6 heures du matin que les contrôles. Pendant la polysomnographie de longue durée (24 heures), l'intervalle de confiance à 95% du temps de sommeil total était de 493-558 min chez les contrôles contre 672-718 min chez les hypersomniaques.

Il y avait 40 hypersomniaques avec et 35 hypersomniaques sans long (>600 min) temps de sommeil. Les patients souffrant d'hypersomnie idiopathique avec long temps de sommeil étaient plus jeunes (29 ± 10 vs 40 ± 13 y, $P=0.0002$), maigres (indice de masse corporelle: 26 ± 5 vs 23 ± 4 kg/m²; $P=0.005$), avaient un score de Horne-Ostberg plus bas et de plus grandes efficacités de sommeil que les patients souffrants d'hypersomnie idiopathique sans allongement du temps de sommeil. Les latences moyennes d'endormissement aux TILE étaient normales (>8 min) chez 71% des hypersomniaques avec temps de sommeil allongé.

Conclusions : L'hypersomnie idiopathique, et spécifiquement avec un temps de sommeil allongé, est fréquemment associée avec un chronotype du soir et un âge jeune. L'hypersomnie est mal diagnostiquée avec le TILE.

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Commentaires personnels :

La classification actuelle (avec ou sans allongement du temps de sommeil) n'a pas d'utilité ni clinique ni en recherche en dehors de montrer l'existence de deux formes de la maladie. Mais en réalité ces 2 formes sont les extrêmes d'un spectre continu de phénotypes hypersomniaques allant du patient somnolent jusqu'au patient non somnolent mais avec une durée de sommeil très longue associée à une ivresse de sommeil.

Résumé en anglais

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.

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Article complet en anglais

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 unrefreshing. 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 >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 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-h period. There is still no information on the demographic 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-h sleep monitoring. We also aimed to provide normative values 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 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 >=3 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 >10 per hour or apnea-hypopnea index >5/hour (this index included apnea, hypopnea, and respiratory effort related arousal events, the flow limitation being measured on the nasal cannulae); (2) narcolepsy defined as the presence of a definite cataplexy or MSL <8 min and multiple sleep-onset REM periods during MSLT; in addition, patients with a REM sleep latency <20 min during nighttime or daytime monitoring (at more than one nap) were excluded; (3) hypersomnia due to a medical or psychiatric condition (e.g., Parkinson disease, hypothyroidism, genetic disease, depression); (4) hypersomnia due to drug or substance. We excluded 30 patients with clinical diagnoses of idiopathic hypersomnia, but who did not meet the international criteria.² They had MSLs >8 min and slept between 490 and 659 min during the 24-h 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 <11), no chronic sleep deprivation (as checked 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. Thus, 30 healthy subjects (15 women, of whom 2 were post-menopausal, and 15 men) completed the study. 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 ≤8 h in bed during the week preceding the 48-h 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 23:00 to 06:30, followed the next day by (ii) 5 standard sleep latency tests (MSLT) at 08:00, 10:00, 12:00, 14:00, and 16:00, which were terminated after 20 minutes if no sleep occurred, and after 15 min asleep if sleep occurred;²¹ (iii) followed the next evening by a long term (24-h) sleep monitoring. The aim of 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 19:00. TV, computer, 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 17:00. This procedure provided a 20-h opportunity for sleep. Subjects received a breakfast after waking up, and a lunch if they woke for it. 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 electroculograms, 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-h 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 NREM sleep stage 1,2, 3-4, and REM sleep were determined during Night 1 and Night 2, and during the 24-h 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 >5 min 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 nighttime sleep >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 in age or sex distribution (Table 1). The body mass indexes were remarkably similar in hypersomniacs and controls. Patients with hypersomnia had higher Epworth Sleepiness Scale scores than controls. In the hypersomniac group, 89% patients had scores >10, and 42% had scores >15. They had no cataplexy and no more hallucinations than controls, but 28% of hypersomniacs had sleep paralysis, 36% had sleep drunkenness, and 46% had unrefreshing naps. All these symptoms were infrequent in normal controls (especially sleep drunkenness, which was never found in controls), suggesting they were poorly sensitive but highly specific. Hypersomniacs had higher fatigue scores than controls. In the patient group, there were no correlation between the subjective sleepiness (Epworth 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 (>11) for anxiety (vs 10% in controls, $P = 0.3$), and 19% had abnormal score (>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 <600 min and MSL <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 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 nighttime and 525 ± 87 min (range 286–690 min) during 24-h monitoring (Table 4). The median value for nighttime sleep was 491 min, with a 95% confidence interval of 462–520 min. During the 24-h period, the median sleep duration in controls was 522 min, with a 95% confidence interval of 493–558 min. Thus, sleep duration >558 min (9.3 h) on continuous 24-h 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-h 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 NREM sleep stage 1-2 percentages. The SWS percentages were lower in hypersomniacs, a 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 06:00, vs 37% in controls. The time of the last SWS episode was $08:44 \pm 1:40$ in the hypersomniacs vs $06:11 \pm 1:45$ 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. Among hypersomniacs, 15% had periodic leg movement indexes >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 ($12.1\% \pm 12.3\%$ vs $4.2\% \pm 10.0\%$, $P = 0.003$) and SWS percentages ($13.3\% \pm 12.4\%$ vs $5.4\% \pm 10.0\%$; $P = 0.002$) than controls. When considering the amount sleep during a 24-h 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 ($92.3\% \pm 5.6\%$ vs $89.3\% \pm 6.7\%$, $P = 0.04$) during the night, and later SWS episode ($09:27 \pm 1:40$ vs $08:08 \pm 1:26$, $P = 0.02$), with no other difference in sleep structure. Daytime sleep was also not different between groups. Total sleep time during the 24-h 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 5 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 >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 nighttime ($r = 0.12$, $P = 0.005$) and during a 24-h 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 >8 min (vs 0% in the group without long sleep time, $P = 0.0001$), while 54% had an MSL >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 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/hypocretin 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-h basis, with higher sleep efficiency, than patients without long sleep time. We could not identify psychological profiles, symptoms, or 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 nighttime sleep. In favor of this hypothesis, total sleep time during nighttime 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-h continuous monitoring in 30 healthy volunteers. We followed the recommendations developed by Billiard and Dauvilliers and reported in the ICSD-2 International Classification of Sleep disorders-2005 revised. These recommendations specify to monitor patients after nighttime 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 >10 min. On the contrary, the patients who have longer nighttime sleep 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 difficulty waking spontaneously after sleep (i.e., difficulty shifting from sleep to wake), 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 5 MSLT naps may hamper subsequent sleep by consuming process 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 06:30, 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 nighttime sleep duration, while they are on the contrary associated with longer sleep duration on a 24-h 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.

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