

# RECURRENT HYPERMOMNIAS : A REVIEW OF 339 CASES

Michel Billiard<sup>a</sup>, Isabelle Jausset<sup>b</sup>, Yves Dauvilliers<sup>abc</sup>, Alain Besset<sup>b</sup>

<sup>a</sup> Department of Neurology, Gui de Chauliac Hospital, Montpellier, France

<sup>b</sup> INSERM U888, University of Montpellier I, Montpellier, France

<sup>c</sup> National Reference Network for Orphan Diseases (narcolepsy, idiopathic hypersomnia and Kleine-Levin syndrome, Gui de Chauliac Hospital, Montpellier, France

Michel Billiard (corresponding author) Department of Neurology, Gui de Chauliac Hospital.  
80, Avenue Augustin Fliche, 34295, Montpellier cedex 5, France

Tel : +33 (0)6 75 028 364 ; Fax : +33 (0)4 67 045 826 ; [mbilliard@wanadoo.fr](mailto:mbilliard@wanadoo.fr)

Isabelle Jausset, INSERM-U888, la Colombiere Hospital, 39, avenue Charles Flahaut. BP  
34493, 34093 Montpellier cedex 5, France

Tel : +33 (0)4 99 614 690 ; Fax : +33 (0)4 99 614 579 ; [isabelle.jausset@inserm.fr](mailto:isabelle.jausset@inserm.fr)

Yves Dauvilliers, Department of Neurology, Gui de Chauliac Hospital. 80, Avenue Augustin  
Fliche, 34295, Montpellier cedex 5, France

Tel : +33 (0)4 67 337 413 ; Fax : +33 (0)4 67 337 285 ; [ydauvilliers@yahoo.fr](mailto:ydauvilliers@yahoo.fr)

Alain Besset, INSERM-U888, la Colombiere Hospital, 39, avenue Charles Flahaut. BP  
34493, 34093 Montpellier cedex 5, France

Tel : +33 (0)4 99 614 564, Fax : +33 (0)4 99 614 579 ; [alain.besset@inserm.fr](mailto:alain.besset@inserm.fr)

Shorten version of the title : Recurrent hypersomnias

# Recurrent hypersomnias : a review of 339 cases

Michel Billiard <sup>a</sup>, Isabelle Jausse <sup>b</sup>, Yves Dauvilliers <sup>abc</sup>, Alain Besset <sup>b</sup>

<sup>a</sup> Department of Neurology, Gui de Chauliac Hospital, Montpellier, France

<sup>b</sup> INSERM U888, University of Montpellier I, Montpellier, France

<sup>c</sup> National Reference Network for Orphan Diseases (narcolepsy, idiopathic hypersomnia and Kleine-Levin syndrome, Gui de Chauliac Hospital, Montpellier, France

## KEYWORDS

Recurrent hypersomnia

Kleine-Levin syndrome

**Kleine-Levin syndrome without compulsive eating**

Menstrual related hypersomnia

Comorbidity

Atypical Kleine-Levin syndrome

**Summary :** Based on 339 cases of recurrent hypersomnia this review identifies, quantifies and compares 4 clinical forms of it (1) Kleine-Levin syndrome (KLS) (239 cases), (2) Kleine-Levin syndrome without compulsive eating (KLS w/o comp. eat.) (54 cases), (3) Menstrual related hypersomnia (MRH) (18 cases) and Recurrent hypersomnia with comorbidity (RHC) (27 cases). A second part of the review considers the main current issues on recurrent hypersomnia: the predisposing factors, including a window on family cases; the pathophysiology based on clinical patterns, neuroimaging data, neuropathological examinations and CSF hypocretin-1 measurements; the issues of recurrence and of a possible disruption of the circadian timing system; the relationships between recurrent hypersomnia and mood disorders; and a note on the atypical Kleine-Levin syndrome. The main outcomes of this study are a clear nosologic distinction of the different forms of recurrent hypersomnia, the finding that the prevalence of familial cases of KLS is in the same range as in narcolepsy, the suggestion of the possible involvement of a large set of cortical and subcortical structures in recurrent hypersomnias and some clues in favor of a relationship between recurrent hypersomnias and mood disorders.

## Introduction

The first descriptions of recurrent hypersomnia date back to Kleine,<sup>1</sup> Lewis,<sup>2</sup> Levin,<sup>3-4</sup> and Lhermitte and Kyriaco,<sup>5</sup> although anterior cases have been later found as early as in the eighteenth century literature,<sup>6</sup>

According to the International classification of sleep disorders, 2<sup>nd</sup> edition, (ICSD-2) <sup>7</sup> the diagnostic criteria of recurrent hypersomnia are:

- A. The patient experiences recurrent episodes of excessive sleepiness of two days' to four weeks' duration
- B. Episodes recur at least once a year
- C. The patient has normal alertness, cognitive functioning and behavior between attacks
- D. The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder

Up to now a number of case reports have been published as well as some reviews,<sup>8-19</sup> and a recent cross-sectional, systematic evaluation of 108 new cases and comparison with matched control subjects.<sup>20</sup> Most reviews have focused on the most typical form of recurrent hypersomnia, e.g. KLS in which recurrent episodes of hypersomnia are associated with behavioral and cognitive abnormalities,<sup>8, 10-15,17-19</sup> while two reviews have considered several forms of recurrent hypersomnia.<sup>9,16</sup>

The aim of this study was not to perform a further detailed review of KLS including its symptoms, physical signs, laboratory tests and treatments, recently and remarkably carried out in a review <sup>19</sup> and in a controlled study <sup>20</sup> and, concerning the treatment only, in a recent Cochrane database systematic review,<sup>21</sup> but first to identify, quantify and compare the main subtypes of recurrent hypersomnia, and second to consider the main current issues on recurrent hypersomnia: the predisposing factors, including a window on family cases; the pathophysiology based on clinical patterns, neuroimaging data, neuropathological examinations and CSF hypocretin-1 measurements; the issues of recurrence and of a possible disruption of the circadian timing system; the relationships between recurrent hypersomnia and mood disorders; and a note on the atypical Kleine-Levin syndrome.

## Methodology

### Population

Our study was based on a review of 339 cases of recurrent hypersomnia including 296 cases collected in 223 articles of the world literature (references available on the journal site), 21 cases collected in one university thesis<sup>16</sup> and in three medical theses,<sup>22-24</sup> and 22 cases from our own population in Montpellier. Cases from large reviews without sufficient individual clinical and laboratory data were not included.

This population consisted of 198 cases from Europe (59 from France, 28 from UK, 25 from Germany, 21 from Italy, 9 from Sweden, 8 from Spain and Turkey, 7 from the Czech Republic, 5 from the Netherlands and Poland, 4 from Russia, Serbia and Switzerland, 3 from Denmark, 2 from Austria and 1 from Belgium, Croatia, Cyprus, Hungary, Ireland and Romania); 79 cases from Asia (21 from India, 19 from Japan, 12 from Israel, 12 from Taiwan, 6 from Saudi Arabia, 3 from Iran, 2 from Pakistan and 1 from China, Hong-Kong, Lebanon and South-Korea); 48 cases from North America (38 from the USA and 10 from Canada); 10 cases from Latin America (7 from Brazil and 3 from Argentina); 3 cases from Oceania (2 from Australia and 1 from New-Zealand); and 1 case from Africa (Nigeria).

With a few exceptions only, all these cases were seen and investigated in departments of neurology or psychiatry. The quality of the reports was heterogeneous, but almost as a rule, the older the case reports, the more detailed the clinical descriptions were, and the most recent the case reports the less emphasis was laid on clinical aspects and the more on laboratory tests.

## Data collection

The following qualitative and quantitative parameters were looked for in the different forms of recurrent hypersomnia: familial and personal psychiatric past-history, familial history of recurrent hypersomnia, comorbidity, events at onset of the first episode and events at onset of subsequent episodes, season of onset when available, age of onset, delay of diagnosis, behavioral symptoms (compulsive eating, sexual disinhibition, odd behavior), clusters of behavioral symptoms, major cognitive symptoms (confusion, feeling of unreality, delusions/hallucinations), mental symptoms (depression, anxiety), physical signs (dysautonomic features, weight gain), transient symptoms at the end of episodes (amnesia, depression, elation, insomnia), duration (in days), cycle length (time from onset of one episode to the onset of the next episode, in days) and frequency of episodes (per year), duration of the condition when the follow-up after the last episode was less than one year and more than one year, duration of the condition with and without a prophylactic treatment, decrease or not of

frequency, severity and duration of hypersomniac episodes throughout the course of the condition, neuroimaging data and CSF hypocretin-1 measurements.

Note that for a large number of variables the answer could be yes, no or missing data. This is important to have in mind as missing data cannot be equated with no data, and any generalization in the absence of data may be hazardous. Thus all our results were expressed as yes, no or missing data.

## Statistics

The characteristics of the population were described using median values and ranges for quantitative variables, and proportions for categorical variables. For continuous variables, the distributions were tested with the Shapiro-Wilk test and were mostly skewed. We therefore used non-parametric tests. Chi square or Fisher tests were used to compare categorical variables between the two groups and the Mann-Whitney test was used for continuous variables. Spearman's rank-order correlations were used to measure the association between two continuous variables. For all comparisons, significance was set at  $p \leq 0.05$ . Statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC, USA).

## Results

### Diagnostic categories

Four forms of recurrent hypersomnia were considered, (1) KLS characterized by recurrent episodes of hypersomnia clearly associated, at least during some episodes, with compulsive eating, plus or minus other behavioral abnormalities such as sexual disinhibition and/or odd behaviors, cognitive abnormalities such as feeling of unreality, confusion, delusions/hallucinations and psychiatric symptoms such as depression and/or anxiety. This definition complies with Critchley's definition of Kleine-Levin syndrome, "a syndrome composed of recurring episodes of undue sleepiness lasting some days, associated with an inordinate intake of food, and often with abnormal behavior (2) KLS w-o comp. eat. on the model of narcolepsy without cataplexy, to single out those cases lacking one of the two main symptoms of KLS, e.g. compulsive eating, on the grounds of Critchley's definition of KLS and of our own findings (below) that other symptoms are found in 50% or less of cases of KLS. (3) MRH characterized by recurrent episodes of hypersomnia, plus or minus other

symptoms of KLS, associated with menstruation and/or puerperium. (4) RHC characterized by recurrent episodes of hypersomnia plus or minus other symptoms of KLS, in patients diagnosed with a physical or mental disorder.

#### Men/women ratio

The men/women ratio was maximum in KLS, 4.08, and lower in the other forms of recurrent hypersomnia: 2.85 in KLS w/o comp. eat. and 2.50 in RHC . However this men/women ratio did not differ significantly across the different forms.

#### Age of onset and delay of diagnosis

The median age of onset did not differ between men and women in the different forms of recurrent hypersomnia, except in KLS w/o comp. eat. in which the age of onset was slightly

Table 1 about here

greater in women than in men (table 1). Only 9 patients with KLS (3.7%) started their condition before the age of 10 and 16 (6.7%) after the age of 30. The mean delay of diagnosis was 2 or 2.5 years, except in women with KLS w/o comp. eat. in whom it was significantly longer. However the range of age was wide, whatever the form of recurrent hypersomnia, underlining the fact that this rare condition is still largely ignored from the medical community.

#### Familial and personal psychiatric past-history

A familial psychiatric past-history was found in a limited number of cases: a mood disorder in 16 cases (6.4%) and schizophrenia or another psychotic disorder in 5 cases (2.0%) of KLS, a mood disorder in 5 cases (11.9%) of KLS w/o comp. eat., in 1 case (6%) of MRH and in 3 cases (10.6%) of RHC.

A personal psychiatric past-history was even less frequent: a mood disorder in 5 cases (2%) and schizophrenia or another psychotic disorder in 4 cases (1.6%) of KLS, a mood disorder in 1 case (2.3%) and an undetermined psychiatric condition in 1 case (2.3%) of KLS w/o comp.

eat., a mood disorder in 1 case (5.8%) of MRH, and a mood disorder in 1 case (3.5%) and a pervasive development disorder in 4 cases (14.2%) of RHC.

Events at onset of the first episode and of subsequent episodes

In the case of KLS, events at onset were in the same range of frequency (66.5% of cases) as in previous reviews (43.7 to 77% of cases<sup>17-19</sup> (table 2). They were equally frequent in KLS and in KLS w/o comp. eat. As in previous reviews an infectious condition was the most frequent

Table 2 about here

trigger. Events at the onset of subsequent episodes were found in fewer cases and only at the onset of some episodes. In the case of MRH, events at onset were systematic. They included menarche, menstruation alone or with an additional trigger (influenza, girl scout outing, exposure to alcohol, etc..) and puerperium. Of note, symptomatic episodes were always accompanied by one of the above referred events, but did not occur systematically with each menstruation or puerperium. Finally, in the case of RHC, the recurrent hypersomnia was presumably secondary to a central nervous system insult in 11 cases only (39.2%)<sup>5, 25-34</sup> (table 3), based on several of the following features, late age of onset, initial severe head injury, stroke or tumor, neurological signs persisting in between episodes, abnormal neuroimaging,

Table 3 about here

unfavourable outcome. In the other 17 cases where recurrent hypersomnia was associated with a genetic disorder (Prader-Willy syndrome, Robert's syndrome, incontinentia pigmenti), a pervasive developmental disorder (Asperger's disorder, autistic disorder), a severe infectious encephalitis, a head traumatism with no obvious anatomical consequence, a causal relationship could not be ascertained.

We also looked at the season of onset of the condition. Unfortunately data were found in only 94 patients out of 239 in KLS and in only 13 patients out of 54 in KLS w-o comp. eat. Moreover, if a predominance of Winter and Summer was observed in KLS, 35.1% in Winter, 30.8% in Summer, 20.2% in Spring and 13.8% in Autumn, it was not the case in KLS w/o comp. eat., 46.1% in Spring, 38.4% in Winter, 30.0% in Autumn and none in Summer, making any conclusion hazardous.

## Symptoms (table 4)

Symptoms were looked for in the various diagnostic categories to assess the frequency of compulsive eating versus the other symptoms in KLS and to explore the presence or not of compulsive eating and/or other symptoms of KLS in the other diagnostic categories

### 1. Behavioral symptoms

Hypersomnia was by definition present in the four forms of recurrent hypersomnia. However this symptom requires some qualification. Indeed hypersomnia is purely behavioral and one cannot rule out clinophilia in the case of depression, all the more as the results of either electroencephalogram or sleep monitoring are extremely heterogeneous.<sup>19</sup>

Compulsive eating was present in 100% of men and women with KLS, sometimes systematically from the first to the last episode, but more often during some episodes only. This result is in agreement with Cricley's definition of KLS<sup>8</sup> (above) and at variance with those of previous reviews, 65.6%,<sup>17</sup> 56.6%,<sup>18</sup> 80%,<sup>19</sup> in which cases of KLS w-o comp. eat. were merged with cases of KLS.

Sexual disinhibition was significantly more frequently reported in men with KLS (50.7%) than in women (29.1%) ( $p = 0.0026$ ). However, sexual disinhibition in women could assume a less visible expression such as fantasy of being chatted up by men or experiencing love affairs..

Table 4 about here

In addition to hypersomnia, compulsive eating and/or sexual disinhibition, odd behaviours were observed in all forms of recurrent hypersomnia, specially in men (30%) and women (35%) with KLS. These odd behaviors were of three different types: 1) incoherence, non respect of social rules, discrepancy between the observed behavior and the expected one in the social context; 2) motor stereotypes or anomalies of posture; 3) childish behaviour. Due to their very special semiology we propose this symptom to be considered as a behavioral symptom of recurrent hypersomnia.



On the other hand, in most cases, irritability or aggressiveness were only a consequence of the patient being prevented from sleeping, eating compulsively or having inappropriate sexual behavior.

Noteworthy, only 34 patients (14.2%) with KLS experienced the four behavioral symptoms, hypersomnia, compulsive eating, sexual disinhibition and odd behaviors, at least during one episode, and 73 patients (30.5%) the first three behavioral symptoms.

## 2. Cognitive symptoms

As recently emphasized in the systematic study of 108 patients, a majority of patients with KLS are affected with impaired speech, impaired concentration, impaired reading, inability to make a decision, impairment of memory, apathy.<sup>20</sup> However, due to the variety of terms used by the different authors and the need for cognitive tests for an exact evaluation of some of these symptoms, an exact quantification was not attempted in this retrospective study. On the other hand, due to their more dramatic expression, confusion, feeling of unreality and delusions /hallucinations were more accessible to quantification, and in no case identified in more than 50% of the patients whatever the diagnostic category.

## 3. Mental symptoms

Depression was more frequently reported in women than in men. However, due to the number of missing data, statistics were not applicable. Anxiety was generally less frequently reported than depression.

## 4. Physical signs

Dysautonomic features were identified in 10 to 25% of patients with KLS, KLS w/o comp. eat. and MRH. In KLS, profuse sweating was observed in 21 patients (8.5%), reddish, flushed, congestive or puffy face in 15 patients (6.0%), hypotension and/or bradycardia in 5 patients (2.0%), nauseating body, hair or urine in 5 patients (2.0%). These symptoms are of interest in support of an altered diencephalic function. Weight gain was significantly more frequent in women than in men ( $p < 0.0001$ ) with KLS, and equally frequent in women with KLS or MRH

## 5. Transient symptoms at the end of episodes

Termination of episodes could be marked by transient symptoms, for 24 h or more, most frequently amnesia, in up to 30% of cases in KLS. Elation was more frequent in men than in women whatever the form of recurrent hypersomnia, but not significantly, in relation with the number of missing data.

## 6. Temporal patterns of recurrent hypersomnia

The median duration of episodes was not significantly different between men and women whatever the form of recurrent hypersomnia, but there was a major interindividual variability up to 1-180 days in men and 1-60 days in women with KLS (table 5), as well as an intraindividual variability in some case reports, 7 to 14 days,<sup>35</sup> 7 to 30 days,<sup>36</sup> 14 to 84 days,<sup>2</sup> and 60 to 300 days.<sup>37</sup>

Table 5 about here

The cycle length was measured during the time when it was relatively regular, that is by and large during the first months or years of the condition. It was longer in men than in women with KLS ( $p = 0.0364$ ) and longer in women than in men with KLS w/o comp. eat. ( $p = 0.0472$ ). However, as it was the case with the duration of episodes, there was a major interindividual variability of up to 14-1095 days in men and 4-1460 days in women with KLS. Moreover, in several patients, there were symptom-free years between a first and a second period with recurrent episodes,<sup>1, 8, 23, 38- 42</sup> or an alternation of periods with recurrent episodes and symptom-free periods.<sup>33, 43</sup> **These results invalidate diagnostic criterion B of ICSD-2 that episodes recur at least once a year.** A correlation was not evidenced between the cycle length and the age of patients with KLS, unlike in patients with KLS w/o comp.eat. ( $r = 0.43$ ,  $p = 0.02$ ). Note that in a few patients the duration and the cycle length of episodes tended to decrease<sup>8,44</sup> or to increase.<sup>36</sup>

The median frequency of episodes per year was significantly higher in women than in men with KLS ( $p = 0.0171$ ) and maximum in women with MRH.

## 7. Duration of the condition

The total duration of the condition could be measured with some certainty only in those cases when the duration of the follow-up was at least 1 year after the last episode, although this cut-off is arbitrary and does not rule out the possibility of one or several later relapses. Eventually the duration could be measured in 125 patients (52.3%) with KLS, 25 (46.2%) with KLS w/o comp. eat., 6 (33.3%) with MRH and 7 (25.%) with RHC (table 6). In the first two forms of recurrent hypersomnia there was a nonsignificant difference in the duration of the condition in men and women but the range of years was extremely large, up to 33 years in men with KLS.

Table 6 about here

Interestingly, the duration of the condition, when the follow-up was greater or equal to one year, tended to be shorter (median 800 days, range 15-10585 days) in patients with a prophylactic treatment than in those without (median 1460 days, range 60-12045 days) ( $p=0.0836$ ), in favour of the efficacy of a prophylactic treatment in some patients. However, that was not the case in other forms of recurrent hypersomnia

#### 8. Decrease of frequency, severity and duration of episodes

Although it is commonly assumed that the episodes of recurrent hypersomnia decrease in frequency, severity and duration with time before fading out, it was clearly evidenced only in a limited number of cases : decrease of frequency in 62 cases (25.9%) of KLS and 9 cases (16.6%) of KLS w/o comp. eat., decrease of severity in 51 cases (21.3%) of KLS and 6 cases (11.1%) of KLS w/o comp. eat., and decrease of duration in 38 cases (15.9%) of KLS and 5 cases (9.2%) of KLS w/o comp. eat.

### **Special issues**

#### Predisposing factors

Predisposing factors are unknown. However, by analogy with narcolepsy, an association with HLA-DR2 has been looked for as early as 1990 in two boys affected with KLS.<sup>45</sup> Neither of the two were DR2 positive. Later on, a multicenter study based on the analysis of gene polymorphism of HLA-DQB1, tryptophan hydroxylase (TpH) and catechol-o-methyltransferase (COMT) in 30 unrelated patients with KLS (25 with a typical form and 5

with KLS w/o comp. eat.) and their relatives, found a HLA-DQB1\*0201 allele frequency of 28.3% in patients and 12.5% in controls ( $X^2 = 4.82$ ),  $p < 0.03$ , but no allele or genotype association between KLS and TpH or COMT gene polymorphism.<sup>18</sup> However, in a more recent study based on HLA-DQB1 typing performed in 108 patients, HLA DR and DQ alleles did not differ between cases and control subjects.<sup>20</sup> Interestingly, in the latter paper based on a systematic study of 108 patients and 108 matched controls, 25% of patients reported problems at birth versus 7.4% in controls.<sup>20</sup> In our retrospective study a problem at birth was only reported in 7.6% of patients.

### Familial patterns

In our 239 patients with KLS, 9 cases (3.7%) of familial KLS have been identified<sup>18, 46-53</sup> (table 7), but none in patients with KLS w/o comp. eat., MRH and RHC. This figure is in the range of what is observed for narcolepsy with cataplexy. Among these 8 families, only 2 included more than 2 affected relatives. In the first family, the paternal grand-mother, the father and two of the eight children were affected, in favour of an autosomal dominant mode of inheritance.<sup>47</sup> In the second family, the father and five out of ten children were affected, but the father and the mother were close relatives, in favour of an autosomal recessive mode of inheritance.<sup>52</sup> Apparently these familial cases did not differ from sporadic cases. Indeed, the

Table 7 about here

age of onset of the condition in the probands (median 16 years, range 11-18), the duration of episodes (median 8 days, range 4-15) and their frequency (median 4.6 / year, range 1-11.75), did not differ from those in sporadic cases. Three further familial cases have been recently reported, but without any suggestion regarding the mode of inheritance.<sup>20</sup> Given the existence of these two multiplex families, genome-wide mapping studies should be performed to search for potential linkage. No case of twins affected with KLS or another form of recurrent hypersomnia and no case of adoption have been reported so far.

### Pathophysiology

For years the symptoms observed in recurrent hypersomnia have been hypothesized to be of hypothalamic origin. Today various arguments speak in favour of a more complex anatomical

basis. 1) Patients with RHC in whom recurrent hypersomnia is assumed to be secondary to the comorbid disease may present a frontal lobe syndrome,<sup>5,28</sup> a thalamic syndrome,<sup>29</sup> a peduncular syndrome.<sup>31</sup> 2) Pneumoencephalography, computerized tomography and magnetic resonance imaging, are normal or almost normal in all primary cases of recurrent hypersomnia.<sup>19</sup> On the other hand, in the case of RHC assumed to be secondary to the associated disease, lesions have been found in the floor of the 3<sup>rd</sup> ventricle,<sup>27</sup> in the frontal lobe,<sup>28</sup> in the occipital lobe, hippocampus, uncus and amygdaloid body,<sup>29</sup> in the thalamus,<sup>30</sup> and in the hypothalamus and temporal lobe.<sup>32</sup> 3) SPECT studies performed during symptomatic periods and/or asymptomatic intervals have evidenced decreased tracer perfusion in as many regions as basal ganglia, thalamus, frontal, parietal, temporal or occipital lobes, during symptomatic periods and a partial normalization during asymptomatic intervals (table 8).<sup>24, 36, 54-62</sup> These regions have extensive connectivity to each other and to limbic

Table 8 about here

structures through neuroanatomical circuits that are organized in parallel, so that lesions in one part can result in a malfunction in other areas. 4) Finally neuropathological examinations have been performed in four cases of KLS and have shown various abnormalities: perivascular infiltrates in the temporal cortex, amygdala and hypothalamus in a 50 year old woman who died as a consequence of uterine carcinoma;<sup>26</sup> infiltrates of inflammatory cells with microglial proliferation in the thalamus and hypothalamus in a 46 year-old man who died of cardiopulmonary arrest;<sup>63</sup> perivascular lympho-monocyte infiltrate in the thalamus, hypothalamus and floor of the third ventricle in an 8 year-old girl who died of pulmonary embolism;<sup>31</sup> and mildly depigmented substantia nigra and locus coeruleus in a 17 year old adolescent who died of cardiopulmonary arrest.<sup>64</sup> Altogether these data suggest the functional involvement of a larger set of brain structures, both cortical and subcortical, than formerly suggested. In this context, given the role of hypocretin neuropeptides in both sleep-wake regulation and feeding, hypocretins seem good candidates to be involved in the functional abnormality of recurrent hypersomnia. **Hence the assessment of CSF hypocretin-1 performed in a few patients with recurrent hypersomnia. Up to now, 11 patients with KLS and none with KLS w/o comp. eat., MRH or RHC, have been investigated, 4 during symptomatic periods only,<sup>49, 61 65-66,</sup> 5 during asymptomatic intervals only,<sup>65,67</sup> and 2 during both symptomatic periods and asymptomatic intervals.<sup>67-68</sup> In the patients investigated during symptomatic periods CSF hypocretin-1 levels were normal (> 200 pg/mL) in 3 patients<sup>49, 61, 66</sup> and**

intermediate ( $> 110$  pg/mL,  $\leq 200$  pg/mL) in 1.<sup>65</sup> In the patients investigated during asymptomatic intervals CSF hypocretin-1 levels were normal in all cases ( $> 200$  pg/mL). Finally, in the first patient investigated during both a symptomatic period and an asymptomatic interval, a male patient with typical KLS also affected with Prader-Willy syndrome, there was a decrease from a normal level (221 pg/ml) during an asymptomatic interval to an intermediate level (111 pg/ml) during a symptomatic period (a decrease of 50.2%)<sup>67</sup> and in the second patient, a female patient with typical KLS, there was a decrease from a normal level (581 pg/ml) during an asymptomatic interval to a normal level (282 pg/ml) during a symptomatic period (a reduction of 48.5%).<sup>68</sup> A more recent paper refers to the hypocretin-1 concentrations as measured in unextracted lumbar CSF of 8 patients, with 6 normal ( $> 200$  pg/ml) and 2 intermediate (110-200 pg/ml), but with no clear indication on the origin of the samples and the conditions of collection, during a symptomatic period or during an asymptomatic interval.<sup>69</sup> Although of potential interest these results are far too limited to draw any conclusion.

## Recurrence

Surprisingly enough, the issue of recurrence of pathological episodes has only been recently considered. Based on the generally young age of onset, the recurrence of symptoms, the frequent infectious trigger and a significantly increased frequency of the HLA-DQB1\*0201 allele in a multicenter group of 30 unrelated patients with KLS, an autoimmune etiology for KLS has been suggested.<sup>18</sup> However, as indicated above, a later study did not confirm an association with HLA<sup>20</sup> and no direct evidence for this putative autoimmune process has so far been found. Thus screening the CSF of patients with recurrent hypersomnia for the presence of autoantibodies against neurons in the above suggested neuroanatomical regions is warranted.

## Abnormal circadian rhythm?

It is now well known that circadian gene mutations are associated with circadian rhythm sleep disorders. For example a *PER 2* gene mutation (serine/glycine) on chromosome 2q has been found to be responsible for a familial form of the advanced sleep phase syndrome<sup>70</sup> and a *PER 3* gene polymorphism is associated with the delayed sleep phase syndrome.<sup>71</sup> Accordingly, several authors have looked for a circadian rhythm disruption in KLS patients.

Up to now conflicting results have been obtained. Neuroendocrine rhythms have been investigated in a 17 year old adolescent boy with KLS, during an attack and three weeks after recovery.<sup>72</sup> During the attack a normal 24-hour pattern of melatonin, cortisol and prolactin secretion was evidenced, against a gross dysfunction of the biological clock. Sleep time and body temperature before, during and after a symptomatic period, were monitored in a 39 year old man suffering from typical KLS for 17 years, with an interruption of 10 years.<sup>44</sup> During an asymptomatic interval body temperature varied between 36°2 and 37°7 with a normal well-entrained sleep-wakefulness rhythm. On the contrary, during a symptomatic period, body temperature varied by less than 0.8 ° C and the normal nycthemeral variation was replaced by a 28-hour peak to peak rhythm. At the end of the episode the peak to peak rhythm gradually shortened and came back to normal shortly after the attack ended. The recovery process was interpreted as a phase advance of the termination of sleep with a relatively constant nocturnal sleep onset. **24-Hour hormone profile of growth hormone, melatonin, TSH, cortisol and FSH (in the woman only) were assessed in five patients, 4 men and 1 woman, with KLS. Findings did not support an underlying circadian disorder in KLS.**<sup>73</sup> Finally a 2-hour delay was observed in the melatonin secretory pattern and a 90-minute delay in the sleep pattern of a 28-year-old man who had KLS since the age of 9.<sup>74</sup> At this point it would be extremely hazardous to draw any conclusion.

#### Recurrent hypersomnia and mood disorders

Attention has been drawn for many years on some analogies between recurrent hypersomnia and mood disorders, even if they seem to differ by the sudden occurrence, the transient duration and the overnight disappearance of the former. A history of familial mood disorder has been reported in only 5 to 10% of the patients with the different forms of recurrent hypersomnia (cf above). A few cases of recurrent hypersomnia are remarkable for an alternation between hypersomniac episodes and manic-depressive episodes.<sup>75-76</sup> Odd behaviors have a distinct psychiatric flavour, frequently in the direction of manic symptoms. Depression, sometimes with suicidal thoughts, is a symptom of hypersomniac episodes in a substantial percentage of patients, up to 40.4% of women with KLS and 35.3% of women with MRH. Elation occurs in 13.5% or more of men upon emergence from hypersomniac episodes. Mood stabilizers such as carbamazepine, lithium and depakine are prophylactic against the recurrence of episodes in some patients. Moreover there are similarities between recurrent hypersomnia and two mood disorders specifiers, (e.g. instructions providing an

opportunity to define a more homogeneous subgrouping of individuals with a mood disorder):<sup>77</sup> the first one is depression with atypical features, a current or most recent episode specifier of mood disorders, characterized by mood reactivity and two or more of the following features (1) significant weight gain or increase in appetite, (2) hypersomnia, (3) leaden paralysis and (4) long-standing pattern of interpersonal rejection sensitivity; the second one is seasonal affective disorder, a course specifier in which major depressive episodes are often accompanied by anergy, hypersomnia, hyperphagia, weight gain, increased appetite for carbohydrates and loss of concentration.<sup>77</sup> Note that in both recurrent hypersomnia and the two indicated mood disorders specifiers, hypersomnia is essentially behavioral and still lacks objective criterion. Finally, based on the above reviewed clinical, neuroimaging and SPECT data, there might be some congruence, between the neuroanatomical circuits of recurrent hypersomnia and of mood disorders.<sup>78</sup>

### Atypical Kleine-Levin syndrome

Czech authors have defined as atypical KLS a form of recurrent disorder in which hypersomnia and/or compulsive eating are systematically replaced by its or their opposite(s), insomnia and anorexia.<sup>16</sup> We found 17 such cases (not included in this review of 339 cases), 11 of which in the same publication.<sup>79</sup> In 3 cases the atypical symptom was insomnia,<sup>75, 79-80,</sup> in 11 cases the atypical symptom was anorexia up to an aversion for food,<sup>16, 23, 79, 81</sup> and in 3 cases insomnia and anorexia.<sup>79</sup> Apart from these atypical features all patients with atypical KLS were comparable to patients affected with KLS. Median age of onset was 16, range 11 to 52. Circumstances at onset were found in 12 patients (70.5%) and all patients were completely free of symptoms between episodes. These cases are rare but of potential pathophysiological interest. Worth mentioning that it is not exceptional, in otherwise typical KLS, that during one or a few episodes hypersomnia may be replaced by insomnia or compulsive eating by anorexia.

### Limitations

This is a retrospective study. However, it was the only possibility to gather a sizeable number of cases of KLS w/o comp. eat., MRH and RHC. The quality of the reports was highly variable and there were a lot of missing data. We used unpublished case reports from thesis and from our own population. Yet these cases contained often more data, especially more



clinical data, than many already published cases. Statistics were hampered by the unequal number of patients in each form of recurrent hypersomnia, from 239 with KLS to 18 with MRH. Finally, in spite of being the largest series of recurrent hypersomnia ever published, this article does not claim to have any epidemiological value, given the wide variety of the number of cases published in each country.

## **Conclusion**

This review differentiates four major forms of recurrent hypersomnia. It comes back to the initial definition of KLS by Critchley of “a syndrome composed of recurring episodes of undue sleepiness lasting some days, associated with an inordinate intake of food, and often with abnormal behaviour”. It singles out KLS without compulsive eating on the model of narcolepsy without cataplexy, on the grounds of likely different pathophysiology . It shows that menstrual related hypersomnia may extend to puerperium. Finally it emphasizes that only some of recurrent hypersomnias with comorbidity may be secondary to the associated condition.

In addition, it evaluates the frequency of the various symptoms and physical signs of KLS in the various forms of recurrent hypersomnia. It collects the available published cases of familial KLS and shows that the prevalence of familial cases is in the same range as in narcolepsy. Based on clinical symptoms, physical signs and brain imagery, it suggests the possible functional involvement of a large set of cortical and subcortical structures in recurrent hypersomnia. It makes the point on a possible circadian impairment. Eventually, it brings some cues in favour of a relationship between recurrent hypersomnia and depression.

Yet this review leaves a lot of pending questions. Why do behavioral, cognitive, mental symptoms and physical signs vary in number and severity from one episode to the other in a single individual? What are the respective roles of genetic and environmental factors in the occurrence of recurrent hypersomnias. What is the neuroanatomical circuitry supporting such a variety of symptoms? What is the origin of the ultimate fading out of these different forms of recurrent hypersomnia?

## **Acknowledgements**

The authors wish to thank Lucile André, Annick Billiard, Jan Brands, Bertrand Carlander, Lara Moussine-Pouchkine, Paatchi Popova, Mieko Saipo, Karel Sonka, Maria Brismontier and Sabine Stolz for translating articles written in Spanish, Portuguese, Italian, Dutch, Danish, Swedish, Russian, Serbo-Croatian, Japanese, Czech, German and Polish.

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## **Practice points**

1. The name Kleine-Levin syndrome applies only to those patients affected with recurrent hypersomnia, associated with compulsive eating, at least during some episodes
2. Kleine-Levin syndrome should be differentiated from Kleine-Levin syndrome w/o compulsive eating
3. Menstrual related hypersomnia is a rare condition. It is very similar to the Kleine-Levin in women except for events at onset
4. Only some cases of recurrent hypersomnia with comorbidity deserve to be considered as secondary to the associated condition
5. Odd behavior should be considered as a behavioral symptom of recurrent hypersomnia

## **Research agenda**

1. Genome-wide mapping studies should be conducted in multiplex families to search for potential linkage
2. Future SPECT studies should be performed in strictly comparable conditions of sleep and wakefulness
3. CSF-hypocretin 1 measurements should be performed during both symptomatic periods and asymptomatic intervals in patients with recurrent hypersomnia
4. In view of the autoimmune hypothesis, screening the CSF of patients with recurrent hypersomnia for the presence of autoantibodies against neurons in possibly affected neuroanatomical regions should be performed
5. Circadian clock genes should be investigated in patients with recurrent hypersomnia