

REVIEW ARTICLE

Kleine–Levin syndrome: a systematic review of 186 cases in the literature

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Kleine–Levin syndrome (KLS) is a rare disorder with symptoms that include periodic hypersomnia, cognitive and behavioural disturbances. Large series of patients are lacking. In order to report on various KLS symptoms, identify risk factors and analyse treatment response, we performed a systematic review of 195 articles, written in English and non-English languages, which are available on Medline dating from 1962 to 2004. Doubtful or duplicate cases, case series without individual details and reviews ($n = 56$ articles) were excluded. In addition, the details of 186 patients from 139 articles were compiled. Primary KLS cases ($n = 168$) were found mostly in men (68%) and occurred sporadically worldwide. The median age of onset was 15 years (range 4–82 years, 81% during the second decade) and the syndrome lasted 8 years, with seven episodes of 10 days, recurring every 3.5 months (median values) with the disease lasting longer in women and in patients with less frequent episodes during the first year. It was precipitated most frequently by infections (38.2%), head trauma (9%), or alcohol consumption (5.4%). Common symptoms were hypersomnia (100%), cognitive changes (96%, including a specific feeling of derealization), eating disturbances (80%), hypersexuality (43%), compulsions (29%), and depressed mood (48%). In 75 treated patients (213 trials), somnolence decreased using stimulants (mainly amphetamines) in 40% of cases, while neuroleptics and antidepressants were of poor benefit. Only lithium (but not carbamazepine or other antiepileptics) had a higher reported response rate (41%) for stopping relapses when compared to medical abstention (19%). Secondary KLS ($n = 18$) patients were older and had more frequent and longer episodes, but had clinical symptoms and treatment responses similar to primary cases. In conclusion, KLS is a unique disease which may be more severe in female and secondary cases.

Keywords: hypersexuality; hypersomnia; Kleine–Levin syndrome; megaphagia; periodic; recurrent

Abbreviations: KLS = Kleine–Levin syndrome; REM sleep = rapid eye movement sleep

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Introduction

Kleine–Levin syndrome (KLS) is a rare disease characterized by recurrent episodes of hypersomnia and, to various degrees, behavioural or cognitive disturbances, compulsive eating behaviour and hypersexuality (American Academy of Sleep Medicine, 2005). The disease predominantly affects adolescent males. Although no population-based studies reporting on KLS prevalence are available, it is generally considered an exceptionally rare disease.

What appears to be the first case of KLS was reported by Brierre de Boismont in 1862. It is notable that this case occurred several decades prior to the 1916–1927 epidemic of encephalitis lethargica. Multiple cases of recurrent hypersomnia were first collected and reported in Frankfurt by Willi Kleine in 1925 (Kleine, 1925). Max Levin (1929, 1936) emphasized the association of periodic somnolence with morbid hunger in 1929 and 1936. Critchley (1962), reviewed

15 previously published cases, added 11 of his own personal cases, notably young marines in the British Royal Navy where he had served during World War II (Critchley and Hoffman, 1942) and gave the eponymous name to the disease, 'Kleine–Levin syndrome'. He pointed out the male predominance, the onset during adolescence, the compulsive rather than bulimic nature of the eating disorder, and the trend of the disease to spontaneously disappear.

Numerous KLS case-reports have been published since, speculating on the yet unknown cause of this condition. Psychiatrists noticed early that KLS reoccurs as endogenous depression does, and that mood stabilizing drugs occasionally benefit patients. Additionally, some patients appear depressed during episodes and temporarily hypomanic upon recovery. Psychoanalytic and psychodynamic hypotheses about KLS emerged in the seventies (Markman, 1967; Miller, 1970; Schlierf, 1975). The striking clinical features of the disease, selected reports of definite neuropathology in post-mortem cases and the high frequency of infections at disease onset led to a more organic hypothesis, most notably the possibility of a viral or post-infectious autoimmune encephalitis with primary impact on the hypothalamus. In favour of autoimmunity, a European group recently identified the human leucocyte antigen (HLA) subtype DQB1*02 as possibly being associated with the disease (Dauvilliers *et al.*, 2002).

Only a limited number of reviews have been published on KLS (Smolik and Roth, 1988; Lemire, 1993; Billiard and Carlander, 1998) and these articles have not systematically analysed all available data. Rather, these publications included only a limited number of patients or reviewed a subset of available papers in selected languages, most notably Czech, English and French. We have undertaken a careful systematic review of all published cases extensively described since 1962 with the aim of better characterizing the spectrum of the disease, risk factors and possible treatments.

Methods

Literature searches

A Medline search was performed on December 7, 2004 using 'Kleine–Levin', 'Kleine–Levin syndrome', and 'periodic hypersomnia'. The search was limited to 1962–2004 and generated a total of 195 articles. Non-English language articles were systematically translated. An initial screening eliminated 41 articles that reported on cases published twice (including reviews or viewpoints), cases that did not meet ICD-10 diagnostic criteria for recurrent hypersomnia (Lamote de Grignon and Fernandez Alvarez, 1967; Smirne *et al.*, 1970; Plasse *et al.*, 1982; Zeitlhofer *et al.*, 1982; Cuetter, 1985; Menkes, 1992; Muller *et al.*, 1998; Sethi and Bhargava, 2002), or that had hypersomnia or hyperphagia in the context of recurrent depressive episodes (Cante and Marocchino, 1970). Cases with menstruation-linked hypersomnia were also removed (Billiard *et al.*, 1975; Lenz, 1980; Papy *et al.*, 1982; Sachs *et al.*, 1982). Abstracts of scientific meetings were not included. Finally, the large recent series of 30 patients by Dauvilliers *et al.* (2002) and 34 patients by Gadoth *et al.* (2001) were not included due to potential overlap with other published cases and insufficient individual clinical data. We thoroughly reviewed the 148 remaining articles reporting

on 186 detailed 'true' KLS cases. A list of included references and cases is posted as supplementary material at <http://brain.oxfordjournals.org>.

Data collected

A mean of four new cases/year was reported over the 40-year review period, with a tendency toward increasing values in more recent years: 1970s (2.7/year), 1980s (3.5/year) and 1990s (5.8/year). Single cases were reported in 84% of the articles, while the remaining 16% reported on 2–16 patients. The following qualitative and quantitative variables were obtained (percentage of data found indicated in parentheses) for each case: country of residence (100), sex (100), age at onset (99), familial (63) and medical history (62), indication of normal or delayed psychomotor development (67), disease duration (64), mean patient duration of KLS episodes (87), mean duration of inter-episode interval(s) (92), number of episodes (72), presence and nature of precipitating events at KLS onset (61), presence of hypersomnia (100, in at least two episodes), eating behaviour disorder (93, in at least one episode), sexual behaviour disorder (93, in at least one episode), other behavioural disorders (35), cognitive impairment (59), hallucinations, delusion and derealization (55), mood disorders (51), irritability (47). Additionally, we collected information on each case pertaining to autonomic dysfunction, measurements of blood virus titres, urinary and blood hormone levels (27), CSF measurements (42), characteristics of the EEG during and after an episode (64), sleep monitoring during (28) and after (15) an episode, brain imagery (45), and indication of first (52), second, and third treatments used, with results. Due to the unpredictable course of the disease, a treatment was considered as 'effective' when its administration was followed by a reported cessation of relapses, even if the authors did not know if the cessation was spontaneous or drug-related.

Stratification and statistics

We classified patients as primary or secondary KLS cases, depending on the absence or presence of neurological symptoms prior to KLS onset that persisted between episodes. The median disease course was calculated using a Kaplan–Meier survival curve analysis in all subjects, with 'censored data' in patients without information regarding termination of KLS included as still affected at the last time of evaluation and 'non-censored data' in patients with terminated KLS. In this analysis, the disease was considered as 'terminated' if: (i) the patient was re-evaluated and found to be free of episodes for at least twice the length of the previous mean in-between-episode interval(s), or (ii) the last observed episodes had become shorter, less frequent and with less hypersomnia, suggesting an ending to the disease. This definition does not rule out the possibility of occasional but unlikely relapses later in life for a few of these patients. Between-group comparisons were performed using Student's *t*-tests for quantitative measures, and chi-square tests for qualitative measures. Disease duration was compared between groups using the log rank test. Data are presented as median or mean \pm SD.

Results

Demographics

Of 186 reported cases, 168 were primary and 18 secondary. Patients with primary KLS were described worldwide across all continents: 34 from the Americas (27 in the United States of America, 2 in Canada, 3 in Brazil, 1 in Argentina), 75 from

Europe (22 in Germany, 12 in Great Britain, 10 in France, 7 in Czechoslovakia, 7 in Italy, 6 in Sweden, 3 in the Netherlands, 1 in Ireland, 2 in Spain, 2 in Denmark, 1 in Belgium, 1 in Croatia, 1 in Cyprus, 1 in Poland), 1 from Africa (Nigeria), 53 from Asia (27 in Israel, 10 in India, 6 in Japan, 4 in Turkey, 3 in Iran, 1 in Taiwan, 1 in China, 1 in Pakistan), and 3 from Australia. The large majority (98%) of cases were sporadic, with the exception of a family with a brother and a sister affected (Katz and Ropper, 2002), another with an uncle and nephew affected (Thacore *et al.*, 1969) and one family with two first-degree cousins affected and one uncle with narcolepsy (Janicki *et al.*, 2001).

One hundred and fifteen (68.4%) patients were male giving a 2:1 male–female ratio. The age at KLS onset was 16.9 ± 8.5 years, with a median of 15 years and a range of 4 (Zhou, 2004) to 82 years (Badino *et al.*, 1992). In 81% of cases, KLS onset occurred during the second decade (Fig. 1). Six patients had late onset (>35 years) but otherwise usual symptoms (Gallinek, 1962; Yassa and Nair, 1978; Carpenter *et al.*, 1982; Smolik and Roth, 1988; Hegarty and Merriam, 1990; Badino *et al.*, 1992; Manni *et al.*, 1993).

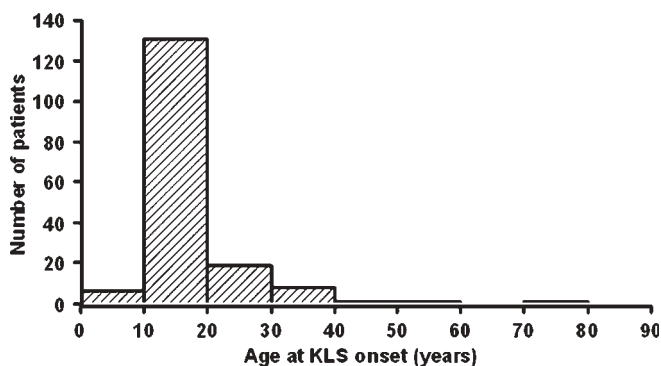


Fig. 1 Age of 168 patients at KLS onset. The y-axis displays the number of patients in each class of age.

Precipitating factors and infections

While primary KLS may develop insidiously, various precipitating factors listed in Table 1 were reported in 61% of patients. The most frequent was a trivial infection such as a flu-like illness or a non-specific fever (Lavie *et al.*, 1979; Shukla *et al.*, 1982; Reynolds *et al.*, 1984; Jensen, 1985; Visscher *et al.*, 1990; Sadeghu, 1999; Rosenow *et al.*, 2000; Katz and Ropper, 2002), an upper respiratory tract infection and tonsillitis (Fresco *et al.*, 1971; Iakhno, 1980; Goldberg, 1983; Fernandez *et al.*, 1990; Chesson *et al.*, 1991; Manni *et al.*, 1993; Salter and White, 1993; Pike and Stores, 1994; Crumley, 1997; Rosenow *et al.*, 2000; Muratori *et al.*, 2002; Poppe *et al.*, 2003), and, more rarely, a summer gastroenteritis (Gallinek, 1962; Lu *et al.*, 2000; Portilla *et al.*, 2002; Zhou, 2004) or a severe infection. Urinary or eye infections were never reported. In infection-triggered KLS, symptoms of KLS occurred shortly (between 3 and 5 days) after the onset of fever. The agents responsible for the first infection were rarely identified and included Epstein–Barr virus and varicella–zoster virus (Salter and White, 1993), Asian influenza virus (Garland *et al.*, 1965), enterovirus (Fernandez *et al.*, 1990), post-typhoid vaccine (Smolik and Roth, 1988), and *Streptococcus* in the context of a septicaemia (Gallinek, 1967), and scarlet fever (Smolik and Roth, 1988). Serum virus titres were performed and found normal in 7 of 9 patients. Similarly, there were no increases in whole blood white cell counts, except in one case. Cerebrospinal fluid was obtained through lumbar puncture during KLS episodes in 70 cases. All samples had normal white cell counts/glucose levels and negative bacterial cultures. Other triggers were more rare and variable. In a few cases, a large or first alcohol consumption or marijuana use on an evening was followed by the first episode the following morning (Wilkus and Chiles, 1975; Chiles and Wilkus, 1976; Mayer *et al.*, 1998; Janicki *et al.*, 2001; Landtblom *et al.*, 2002, 2003). Head trauma, including a knock-out during boxing (Smolik and Roth, 1988; Will *et al.*, 1988; Janicki *et al.*, 2001), physical

Table 1 Precipitating factors reported at onset and before reoccurrences of Kleine–Levin syndrome in 168 patients

Event at KLS onset	No. of patients	Frequency at KLS onset (%)	Frequency before KLS reoccurrences (%)
None reported	66	39	84
Infection or fever	72	42.8	8.9
Unspecific fever, flu-like fever	42	25	
Upper respiratory tract infection:	20	12	
Tonsillitis, sore throat, cough			
Gastro enteritis	5	3	
Identified virus/bacteria: <i>Streptococcus</i> ,	5	3	
Asian influenza, chicken pox and mononucleosis, enterovirus, post-typhoid vaccine fever			
Alcohol or marijuana	7	4.2	0.6
Head trauma	4	2.4	0
Sleep deprivation mental effort, stress	5	3	0
Menses or lactation	6	3.6	0.6
Miscellaneous: local/general anaesthesia, physical exertion, clavicle fracture	6	3.6	4.8

exertion and psychological distress (Kellett, 1977; Masi *et al.*, 2000; Arias *et al.*, 2002), surgery with general or local (dental) anaesthesia, lactation and menses (Lavie *et al.*, 1981), but not at menarche, and not as in menstruation-linked hypersomnia (Gilbert, 1964; Duffy and Davison, 1968; Papy *et al.*, 1982; Shukla *et al.*, 1982; Janicki *et al.*, 2001) were other factors occasionally reported at KLS onset.

Events triggering subsequent episodes were described in only 27 cases (Table 1) and contained a similarly high proportion of infections (fever, sore throat or zoster before each episode in five patients). Surgery with anaesthesia—one case had three episodes, each one after general anaesthesia for orthopaedic or dental surgeries (Turgman and Braham, 1977)—physical exertion or mental effort, sunstroke, alcohol, jet lag, and a bout of hemiparetic migraine were also reported as subsequent triggers for episodes.

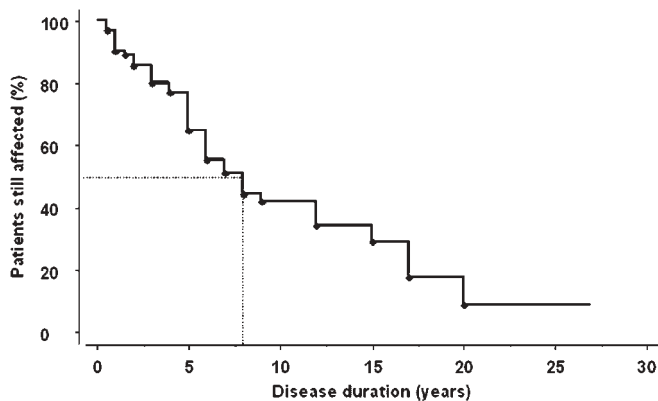


Fig. 2 Duration of KLS ($n = 110$ patients, 41% censored), presented as a Kaplan–Meier analysis. On the x -axis is the total duration of the disease (years), on the y -axis is the cumulative decreasing percentage of patients still presenting with KLS episode. The median duration of the disease (dotted line) is 8 years.

Duration of the disease, episodes and intervals in-between episodes

The duration of primary KLS was reported or could be calculated in 110 patients. It ranged from 0.5 to 41 years. Using Kaplan–Meier analysis with 41% of the data censored, KLS as a disease lasted a median of 8 years (Fig. 2). Termination was reported in 65 subjects, with 39 subjects having no more episodes for more than twice the mean inter-episode length and 26 subjects where a clear decrease in symptom severity and episode frequency was noted at the last visit. The median in the 65 cases with a known reported termination was 4 years. The mean age at the end of KLS for these 65 cases was 23 ± 12 years. There was no correlation between age at onset and disease duration ($r = -0.01$, $P = 0.95$), suggesting no preferential termination at a determined and possibly more mature age. In 33 patients with a described reported end of the disease, KLS episodes decreased in frequency, duration and intensity (less pronounced hypersomnia) prior to termination in 30 patients, while the frequency decreased but duration increased in one patient and frequency increased in two patients.

The 110 patients presented with a median of seven episodes (range: 2–130 episodes, mean \pm SD: 12 ± 15 episodes). The episodes lasted between 2.5 and 80 days, with a median of 10 days, and a mean of 12 ± 9 days (Fig. 3, left panel). Inter-episode duration ranged from 0.5 to 72 months, with a median of 3.5 months and a mean of 6 ± 10 months (Fig. 3, right panel).

Symptoms of KLS

Hypersomnia

Hypersomnia, a major clinical symptom of KLS, is mandatory for diagnosis and was present in all cases. When reported, usual sleep duration during episodes ranged from 12 to 24 h/day (mean: 18 ± 2 h, median: 18 h). Qualitative

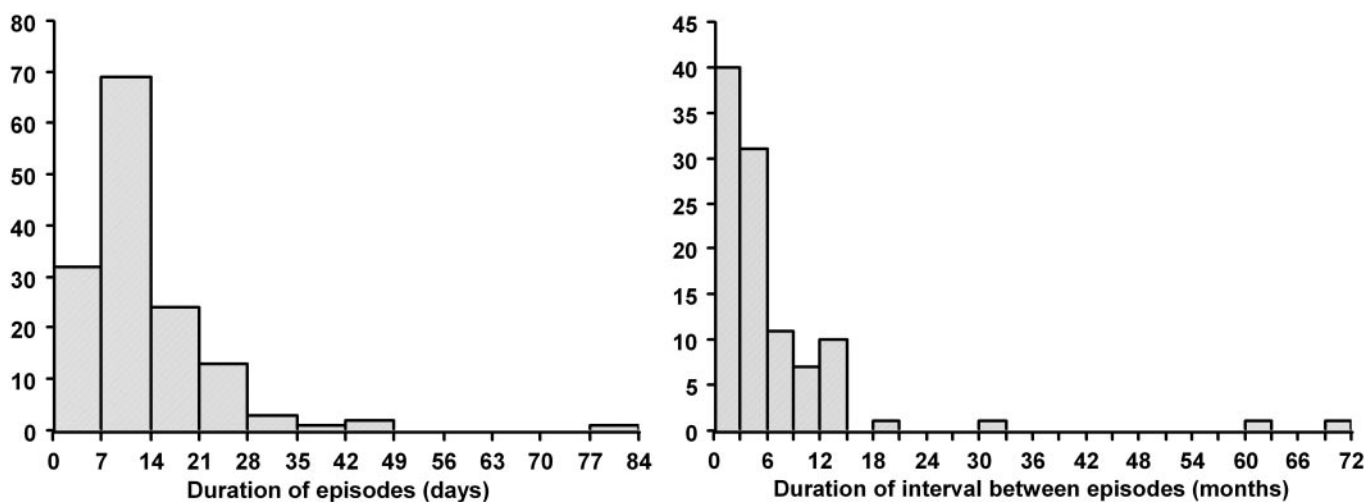


Fig. 3 Histogram of the duration of KLS episodes, in days (left panel), with a median of 10 days, and of the duration of the interval between episodes, in months (right panel), with a median of 3 months.

information such as ‘the patient spent most of the night and the day asleep’ was reported in other cases. Prodromic symptoms included sudden overwhelming tiredness, i.e. ‘feeling drawn towards his bed’, or ‘reluctant to get up in the morning’ (Prabhakaran *et al.*, 1970). Several authors noted that their patients remained arousable, waking up spontaneously to void and eat, but were irritable or aggressive when awakened or prevented from sleep. The need for sleep was so intense that a male teenager ‘was found sleeping under a neighbour’s porch’ (Powers and Gunderman, 1978), another ‘left his classroom during a lesson, lay down on the floor of the corridor and fell asleep’ (Frank *et al.*, 1974), while an adult patient was ‘found asleep on the pavement of the street’ (Prabhakaran *et al.*, 1970). At the end of an episode, a short-lasting insomnia was noted in three cases (Gallinek, 1967; Frösher *et al.*, 1991; Russell and Grunstein, 1992). Sleep symptoms changed from frank hypersomnia during the first episodes to a heavy fatigue accompanied by a feeling ‘as if in twilight between sleep and waking’ during later episodes. Cataplexy and sleep paralysis were never mentioned as co-morbid symptoms.

Sleep was monitored during an episode in 40 patients, using daytime nap ($n = 5$), nocturnal sleep ($n = 19$), multiple sleep latency tests ($n = 7$, mean sleep latency: 3.6 ± 1.1 min), and 24–72 h continuous recordings ($n = 10$). Mean total sleep time was 445 ± 122 min during the night (Stage 1, $6 \pm 4\%$; Stage 2, $56 \pm 9\%$; Stage 3–4, $19 \pm 11\%$; REM sleep, $19 \pm 6\%$) and 838 ± 288 min on a 24 h basis. REM sleep was commonly reported during daytime sleep recordings or multiple sleep latency tests, with six of 19 patients (21%) having a narcolepsy-like pattern (≥ 2 sleep onset in REM periods). In other cases, the duration of sleep stages during daytime sleep contained an excess of Stages 1–2. Only two patients had a moderately decreased nocturnal sleep efficiency (Reynolds *et al.*, 1980; Gadoth *et al.*, 1987) but they were not monitored during the daytime. Rare sleep abnormalities such as an absence of REM sleep in one patient (Striano *et al.*, 1986), an absence of slow wave sleep in one patient (Reynolds *et al.*, 1980), and recurrent interruption of Stage 2 by fear and stereotypical movements in one patient (Striano *et al.*, 1986), were also found. Mean polysomnographic recording results in 29 subjects were similar and not statistically different from those reported in similar independent samples (Gadoth *et al.*, 2001; Dauvilliers *et al.*, 2002).

Cognitive disturbances

Almost all patients had cognitive disturbances such as confusion, concentration, attention and memory defects. These were evident when interviewed during episodes (such as abnormal responses to question), or reported on subsequent interviews, as a recall of a previous episode (Table 2).

Abnormal speech was reported in two-thirds of cases. This included being mute ($n = 5$), without spontaneous speech ($n = 6$), using monosyllabic or short sentences with limited vocabulary ($n = 9$), having slurred, muddled, incoherent ($n = 6$), or childish ($n = 1$) stereotypical language, slow to

Table 2 Frequency of symptoms during episodes of Kleine–Levin syndrome

Symptoms	Patients with the symptom/total	Percentage
Hypersomnia	168/168	100
Cognitive disorders	98/102	96
Abnormal speech	35/58	60
Confusion	24/47	51
Amnesia	24/50	48
Derealization	22/93	24
Hallucinations	13/93	14
Delusions	15/93	16
Eating behaviour disorders	125/157	80
Megaphagia	97/125	78
Craving for sweets	15/125	12
Increased drinking	10/125	8
Binge eating	7/125	6
Decreased appetite	6/125	5
Food utilization behaviour	5/125	4
Depression	41/86	48
Irritability	79/86	92
Other behavioural disorders		
Hypersexuality	67/155	43
Compulsions to sing, write, pace	17/59	29

speak and to comprehend ($n = 13$), with verbal perseverations (such as answering with the time at each question) or echoing questions ($n = 4$). Formal cognitive and memory tests were rarely used and when they were, their validity was questionable in uncooperative, irritable, sleepy, and inattentive subjects (Malhotra *et al.*, 1997; Landtblom *et al.*, 2002, 2003). In one report it was determined that a teenager had an intelligence quotient of 66 during an episode and 88 thereafter (Fresco *et al.*, 1971). This state of mental ‘viscosity/slowness’ was qualitatively described by some patients as a ‘struggle to follow a thought’ (Chesson *et al.*, 1991) requiring ‘too much energy with racing thoughts’, while ‘everything was going fast’ (Crumley, 1997). A 13-year-old girl found multiple simultaneous stimuli ‘overwhelming’, while her brother compared his way of thinking during an episode to ‘a single-channel TV versus a 100-channel TV between episodes’ (Katz and Ropper, 2002). In addition, a 16-year-old boy did not know how to eat a steak with cutlery (Rosenow *et al.*, 2000), suggesting apraxia. Many patients reported amnesia of the events that occurred during an attack. Between episodes, 96.4% patients were described as totally normal. In a few cases (8/168), however, patients reported academic decline and a mild, long-lasting memory dysfunction between episodes (Fresco *et al.*, 1971; Sagar *et al.*, 1990; Masi *et al.*, 2000). The possibility of residual dysfunction after KLS termination was also reported in three cases (Smolik and Roth, 1988; Landtblom *et al.*, 2003).

Derealization, hallucination and delusion

A feeling of unreality (surroundings seemed wrong, distorted or unreal, as in a dream) or of disconnected thinking during

episodes was reported by most patients and felt to be the most specific symptom of the syndrome (Table 2). Five patients discussing together agreed that it was the most important and disabling symptom (Landtblom *et al.*, 2003). Altered perception was expressed qualitatively as feeling ‘strange’, ‘detached’ or ‘different’ (Thacore *et al.*, 1969; George, 1970; Papacostas, 2003). Objects were perceived to be a long way off and voices to be distant—one patient’s own voice appearing strange to himself (Kellett, 1977; Mayer *et al.*, 1998; Masi *et al.*, 2000)—with an ‘unpleasant perception, bizarre and wrong’, ‘with a nightmarish sense of the surroundings’ (Katz and Ropper, 2002) or ‘with the feeling of being almost in a dream’ (Green and Cracco, 1970; Mukaddes *et al.*, 1999a). This feeling also included depersonalization, anguish, a belief of splitting between mind and body (Mukaddes *et al.*, 1999a) and ‘a persistent sense of unreality and disconnection’ from the environment, like being ‘underwater’ (Katz and Ropper, 2002). Other more unusual changes included a blurred vision and the eyes being ‘dull’ or ‘glassy’ (Roth *et al.*, 1980).

Aside from this feeling of unreality, some patients experienced visual or auditory hallucinations and paranoid or paranoid delusions. Patients reported seeing ‘scary snakes on TV’ (Fresco *et al.*, 1971); seeing ‘distorted faces, including Jesus’; seeing ‘the dead bodies of her parents’ (Duffy and Davison, 1968). Another girl felt that someone was trying to eat her, and that she was being filmed during the night (Overweg, 1971). One teenager was afraid of people trying to kill him, heard threatening voices (mostly at night), and took his razor to the nurse’s desk to prevent people from killing him (Powers and Gunderman, 1978). Another patient believed his wife was trying to poison him and that neighbours would steal from him. He changed his lock five times and stopped eating for fear of being poisoned (Carpenter *et al.*, 1982).

Eating behaviour disorders

Three quarters of the patients had changes in eating behaviours during episodes (Table 2). The majority typically ate larger amounts of food (megaphagia). Increased food intake ranged from a mild increase to ‘three times his usual diet’ (Shukla *et al.*, 1982) or ‘6–8 meals a day’ (Hart, 1985) with a 7–30 lb (3.2–13.6 kg) weight gain. A patient was hospitalized for breathlessness caused by a distended abdomen, due to recent enormous meals (Prabhakaran *et al.*, 1970). Increased drinking of water and juice was also occasionally present, but was never observed alone. A minority of patients (5%) had an aversion to food or ate less during one or several episodes, but would overeat during other episodes (Kellett, 1977; Manni *et al.*, 1993; Portilla *et al.*, 2002; Poppe *et al.*, 2003). Several authors noted that the symptoms were distinct from bulimia, since patients never alternated with periods of self-induced vomiting and voluntary fasting. Food cravings and megaphagia were the most critical elements. Some patients stole food in shops or off the plates of other patients in the hospital (George, 1970; Prabhakaran *et al.*, 1970; Rosenow *et al.*, 2000), searched for food in dustbins (Prabhakaran *et al.*, 1970) and

stuffed food in their mouths with both hands (Duffy and Davison, 1968). Five other patients (4% of the group) had an inability to restrain themselves from eating in the presence of food, reminiscent of the general behaviour of utilization described in frontal syndrome. One patient ‘ate anything within reach’ (Hegarty and Merriam, 1990), and another was offered ‘multiple second servings shortly after he had eaten his regular meal, which he also finished’ (Elian, 1968). Two patients would ‘grab any food in sight’ (Sagar *et al.*, 1990), while another would ‘eat mechanically, finishing whatever amount was given’ (Katz and Ropper, 2002). The food craving could be specifically directed toward sweets; patients added eight teaspoons of sugar to cereal (Chiles and Wilkus, 1976), ate ‘six bowls of desserts, six chocolate bars in a semi-automatic manner’ (Russell and Grunstein, 1992) or drank several bottles per day of pure chocolate or blackberry syrup (Garland *et al.*, 1965; Haberland and Weissman, 1968). Interestingly, some patients would eat things they would have refused in the past, such as a Turkish girl who ate watermelon rinds (Mukaddes *et al.*, 1999a) or a vegetarian Indian who ate non-vegetarian food (Shukla *et al.*, 1982).

Mood disorders and irritability

Half of the patients had a depressive mood during episodes (Table 2). Fifteen percent of the patients reported suicidal thoughts and two patients attempted suicide (Gallinek, 1962; Vlach, 1962). In most cases, the depressed mood resolved at the end of each episode, although in rare cases it persisted longer. A few cases (8%) reported to be hypomanic for a couple of days at the end of a KLS episode (Reynolds *et al.*, 1980; Goldberg, 1983). Another 8% had a flattened affect, and 7% were anxious, with two of them panicking when left alone.

Contrasting with the high frequency of siblings affected in patients with bipolar disorders, a familial history of severe depression was found in only six KLS patients, parental alcoholism in seven patients, and parental schizophrenia in only two patients. Irritability was present in almost all patients, especially when sleep, sexual or food drive were prohibited. It culminated in rare but severe aggressive behaviour. A child beat his grandmother (Powers and Gunderman, 1978), an adult patient beat his dog (Yassa and Nair, 1978), another child bit his father (Bouchard and Lévasséur, 2001), one teenager spat in the face in his physician (Mukaddes *et al.*, 1999b), one young man threw stones and was caught by the police (Prabhakaran *et al.*, 1970), while another teenager had such a rage outburst at school that the police evacuated the classroom (Crumley, 1997).

Hypersexuality and other compulsive behaviours

Nearly half of the patients had symptoms consistent with hypersexuality during episodes. In males, these included increased/overt masturbation, exposing oneself, obscene

language, fondling genitalia and making unwanted sexual advances. Inappropriate sexual advances included the assaulting of female nursing staff, female visitors, patient's sisters, daughter or other female relatives, and in three cases another man (Garland *et al.*, 1965; Fresco *et al.*, 1971; Yassa and Nair, 1978). Of interest, these symptoms were also reported, although more rarely, in women (Duffy and Davison, 1968; Hart, 1985; Kesler *et al.*, 2000) and in three pre-pubescent children (Sagar *et al.*, 1990; Salter and White, 1993; Pike and Stores, 1994). The plasma levels of sex hormones (testosterone, luteinizing hormone, follicle-stimulating hormone) were normal in 14 patients and mildly decreased in two patients. Interestingly, no increase in testosterone has been found in KLS patients during KLS episodes.

Other compulsions that occurred during the episodes included inappropriate and compulsive singing in eight patients (Garland *et al.*, 1965; Chiles and Wilkus, 1976; Ferguson, 1986; Malhotra *et al.*, 1997; Sadeghu, 1999; Muratori *et al.*, 2002), body rocking (Green and Cracco, 1970; Papacostas and Hadjivasilis, 2000), chewing lips (Thacore *et al.*, 1969), compulsive writing on walls (or on the sole of the patient's foot in two patients) and stripping down wallpaper in two other patients (Will *et al.*, 1988; Mukaddes *et al.*, 1999b), continuously switching lights on and off (Jensen, 1985), pacing, wringing hands and tearing out hair (Duffy and Davison, 1968) and the compulsion to set fire in one patient (Powers and Gunderman, 1978).

Medical examinations and tests

Clinical examination was unremarkable in all cases with primary KLS. In particular, the absence of neurological signs indicative of a focal lesion or of meningitis was notable. Signs of autonomic dysfunction were rare and included a flushed face (Russell and Grunstein, 1992), thermoregulatory changes (Smolik and Roth, 1988), hyperventilation (Fukunishi and Hosokawa, 1989), short episodes of flushes, profuse sweating, excessive salivation, hypertension and tachycardia (Hegarty and Merriam, 1990), hypotension and bradycardia (Koerber *et al.*, 1984; Domzal-Stryga *et al.*, 1986; Gillberg, 1987; Manni *et al.*, 1993; Muratori *et al.*, 2002). One patient died of cardio-respiratory arrest following an ataxic respiratory pattern. There was no evidence of neuronal damage in his hypothalamus.

The medical tests in KLS patients were mainly aimed at eliminating epilepsy (EEG), focal brain lesions (brain imaging), and meningitis or encephalitis (CSF analysis) as potential causes. Many, if not most, were conducted during episodes.

Cerebrospinal fluid analysis

CSF white cell counts and protein levels were normal in all patients, ruling out infectious meningitis. Immunoelectrophoresis of the CSF was performed and found to be normal in four patients. This excludes the possibility of frequent oligoclonal secretion of antibodies as observed in

multiple sclerosis, another remittent neurological disease (Billard *et al.*, 1978; Powers and Gunderman, 1978; Da Silveira Neto and Da Silveira, 1991; Pike and Stores, 1994). CSF levels of serotonin and a serotonin metabolite were increased (five times and twice the normal values, respectively) in one patient (Koerber *et al.*, 1984), but not in four other patients, as were dopamine and norepinephrine metabolite levels (Carpenter *et al.*, 1982; Hart, 1985; Hasegawa *et al.*, 1998; Landtblom *et al.*, 2002). The CSF levels of hypocretin-1, a hypothalamic peptide that has been shown to be deficient in narcolepsy, were found within normal ranges in five KLS patients but slightly decreased (111 and 137 pmol·l⁻¹) in two patients during an episode (Katz and Ropper, 2002; Mignot *et al.*, 2002; Dauvilliers *et al.*, 2003).

Electroencephalograms and brain imaging

One fourth of the patients had a normal EEG during episodes. In 70% of the patients, a non-specific diffuse slowing of background EEG activity, such as the alpha frequency band being slowed toward 7–8 Hz, was observed. Less often, low frequency high amplitude waves (delta or theta) occurred in isolation or in sequence, mainly in the bilateral temporal or temporofrontal areas. A remarkable finding was the ubiquitous absence of epileptic activity; an intra-cerebral sphenoid electrode was even recorded in a few patients. Rarely, isolated spike discharges (Elian, 1968), self-limited photo-paroxysmal response (Papacostas, 2003) or sharp waves (Malhotra *et al.*, 1997) were observed, but were considered of no clinical significance.

Brain computerized tomography and magnetic resonance imaging were normal in all cases. Functional imaging measuring cerebral blood flow by single photoemission tomography was performed in nine patients aged 13–27 years. Cerebral blood flow was normal in four patients and reduced in five patients. The reduction occurred in the temporal or temporofrontal areas of either or both sides (Yassa and Nair, 1978; Argentino and Sideri, 1980; Lu *et al.*, 2000; Arias *et al.*, 2002; Landtblom *et al.*, 2002, 2003; Portilla *et al.*, 2002) and in the basal ganglia (Lu *et al.*, 2000). Brain neuropathological examinations (Table 3) were performed after the death of two patients with primary KLS (Carpenter *et al.*, 1982; Koerber *et al.*, 1984) and in two patients with secondary KLS. The cortex was intact in all but one patient (a patient with paraneoplastic syndrome). There were intense signs of inflammatory encephalitis within the hypothalamus in two patients, mild inflammation in one patient and none in the last patient.

Hormonal tests

Changes in levels of pituitary hormones were only rarely found in KLS patients. Hormonal measurements were performed during episodes in 45 patients. The pituitary axis was considered 'normal' without published details in seven cases. The plasma levels of thyroid-stimulating hormone (TSH, 21 patients), cortisol at 8 a.m. and 4 p.m. (20 patients) and adrenocorticotrophic hormone (ACTH, 4 patients) were always

Table 3 Neuropathological findings in 4 cases with Kleine–Levin syndrome (KLS)

	Primary KLS		Secondary KLS	
	Carpenter <i>et al.</i> , 1982	Koerber <i>et al.</i> , 1984	Takrani <i>et al.</i> , 1976	Fenzi <i>et al.</i> , 1993
Patient	Male, 46 years	Male, 17 years	Female, 50 years	Female, 6 years
Typical signs	Hypersomnia, megaphagia, sexual disinhibition, seven attacks	Hypersomnia, megaphagia, masturbation, several attacks	Hypersomnia, megaphagia, aggressivity, four attacks	Hypersomnia, megaphagia, agitation, two attacks
Atypical signs	Late onset, some attacks lasted 3 months	Autonomic dysfunction, muscle weakness	Late onset, Uterine carcinoma	Upward-gaze palsy, mild ptosis
Cause of death	Aspiration pneumonia (due to megaphagia)	Cardiopulmonary arrest	Complications of cancer	Pulmonary embolism after a bone fracture when agitated during an episode
Lesions				
Cortex	Normal	Normal	Perivascular temporal infiltrate	Normal
Amygdala	Normal	Normal	Perivascular infiltrate	Normal
Thalamus (medial and intralaminar)	Major new and old lesions of the thalamus: abundant infiltrates of inflammatory cells, with microglial proliferation. Cuffing of veins with monocytes and lymphocytes	Normal	Normal	Perivascular lympho-monocyte infiltrate in the thalamus: scattered foci of cellular infiltrates with parenchymal nodular-microglial proliferation
Hypothalamus	Very mild proliferation of subependymal astrocytes on the third ventricle wall, small amounts of lymphocytic cuffing in the lateral hypothalamus	Normal	Perivascular infiltrate	Perivascular lympho-monocyte infiltrate in the hypothalamus, and floor of the third ventricle
Brainstem	Normal	Mildly depigmented substantia nigra and locus coeruleus, no Lewy bodies or tangles		Microglial nodule in the peri-aqueductal grey region and in the oculomotor nerve nuclei

normal, while those of growth hormone (GH) were either normal (10 of 12 patients), increased (1 of 12 patients, Rosenow *et al.*, 2000) or decreased (1 of 12 patients, Chesson *et al.*, 1991). The diurnal profiles of secretion of GH, melatonin, TSH and cortisol were unchanged during and after episodes in five of five patients (Mayer *et al.*, 1998) suggesting that circadian systems were basically intact. The dynamic testing of hypothalamic functioning was rarely done (three patients) and yielded inconsistent results. The TSH response to thyroid-releasing hormone (TRH) and cortisol and ACTH responses to hypoglycaemic stimulation were abolished (Fernandez *et al.*, 1990) or blunted (Malhotra *et al.*, 1997) during an episode and normalized thereafter in two patients. A patient had a paradoxical GH response to TRH (Gadoth *et al.*, 1987), while another had a normal GH in response to hypoglycaemia (Malhotra *et al.*, 1997).

Therapeutic attempts

In 75 patients, one or several drug therapies were attempted, constituting a total of 213 open-labelled trials (Table 4). The results obtained with these therapies were compared to natural evolution, as reported in a group of 26 patients who

did not receive drug treatment. Among stimulants, only amphetamines significantly reduced sleepiness in patients. Importantly, however, it was noted they did not improve the more troublesome behavioural and cognitive disturbances (Gallinek, 1962). Other less potent stimulants were rarely beneficial or increased their hypersexuality. In two patients, flumazenil, a benzodiazepine receptor antagonist failed to elicit wakefulness. Neuroleptics (chlorpromazine, levomepromazine, trifluoperazine, haloperidol, thioridazine, clozapine and risperidone) were notably ineffective against derealization, psychotic and behavioural symptoms.

Numerous antidepressants including tricyclics (imipramine, clomipramine, amineptine) and serotonin-acting drugs (fluoxetine, fluvoxamine, sertraline, methylsergide, trazodone) had no effect on preventing relapses, except for one isolated reported case of recovery with the use of the monoamine oxidase inhibitor moclobemide (Chaudhry, 1992). Electroconvulsive therapy, ranging from 7 to 47 shocks (Gallinek, 1962; Vlach, 1962; Duffy and Davison, 1968; Chiles and Wilkus, 1976; Yassa and Nair, 1978), and insulin coma therapy (Savet *et al.*, 1986) had no effect on KLS symptoms (and even worsened confusion in the case of electroconvulsive therapy).

Table 4 Treatments used in patients with Kleine–Levin syndrome and reported effects

Treatment	No. patients	No effect	Moderate benefit	Clear benefit	Response rate (%)	One relapse then ended	No more relapses
Treatments of symptoms during an episode							
Stimulants (reduction of hypersomnia)	40	19	5	16	40		
Modafinil	2	2	0	0	0		
Methylphenidate	15	5	2	3	20		
Pemoline-piracetam-meclofenoxate	4	3	0	1	25		
Amphetamines	17	2	3	12	71*		
Flumazepil	2	2	0	0	0		
Neuroleptics (derealization, behavioural disorders)	28	25	0	3	11		
Treatments aimed at preventing relapses							
No drug treatment	32	16			16	11	5
Phototherapy	3	3			0	0	0
Antidepressants	23	21			9	0	2
Mood stabilizers							
Lithium	29	9			41*	8	12
Carbamazepine	19	14			21	1	4
Valproate, phenobarbital, phenytoin	10	7			20	1	2
Various							
Antiviral (i.v. acyclovir)	2	2			0	0	0
Melatonin	1	0			0	1	0
Benzodiazepines	4	4			0	0	0
Levodopa + benserazide	1	1			0	0	0
Electroconvulsive therapy	5	5			0	0	0

* $P < 0.05$ for a difference with no treatment, chi-square.

Various mood stabilizers, such as lithium and antiepileptic drugs were tried (Table 4). Only lithium had a reported response rate significantly higher than medical abstention (odds-ratio = 3.8, $P = 0.02$). Lithium was not a last chance treatment, given after other trials and thereby potentially tried closer to the natural end of the disease, as the option rank (i.e. if lithium was tried as first, second, third or fourth therapeutic option) and the number of episodes that preceded the lithium trial did not influence the reported response rate ($P = 0.22$ for option rank, $P = 0.95$ for pre-lithium number of episodes). In addition, recovery was imputable to lithium in three cases, with KLS episodes stopping when the drug was introduced, KLS relapsing soon after stopping the drug, and recovering again when lithium was re-introduced (Kellet, 1977; Smolik and Roth, 1988; Poppe *et al.*, 2003). Such a pattern was observed with carbamazepine in a single case (Mukaddes *et al.*, 1999b).

Risk factors for longer KLS course

Women had a longer disease course than men (9 ± 8.7 years versus 5.4 ± 5.6 years, $P = 0.01$), despite a comparable age at KLS onset (17.6 ± 8.9 years versus 16.6 ± 8.3 years) and an absence of differences in the duration of episodes and symptoms-free intervals. Women had the same frequency of megaphagia and psychotic symptoms, but a lower frequency of hypersexuality (24 versus 51%, $P = 0.002$) and cognitive impairment (80 versus 98%, $P = 0.004$).

Patients with a high number of episodes during the first year of KLS had a somewhat shorter KLS disease duration ($r = -0.23$, $P = 0.005$, $n = 65$ patients). In contrast, the age at

KLS onset, the presence of megaphagia, cognitive disturbances, psychotic signs and hypersexuality did not influence the course of the disease. Most notably, 39 patients with 'full-blown' KLS (suffering from hypersomnia, cognitive disturbances, eating disorders and hypersexuality) did not have a different disease duration (6.4 ± 6.6 years) when compared to 63 patients with 'incomplete' KLS (6.3 ± 6.9 years, $P = 0.97$).

Cases with secondary KLS

Causes

In 18 patients, KLS-like symptoms were observed in association with stroke or post-traumatic brain haematoma ($n = 5$), genetic or developmental diseases ($n = 6$), multiple sclerosis (Testa *et al.*, 1987), hydrocephalus (Lobzin *et al.*, 1973), paraneoplasia in the context of a carcinoma of the cervix utero (Takrani and Cronin, 1976), an autoimmune encephalitis (Fenzi *et al.*, 1993) or a severe infectious encephalitis ($n = 3$). The types of stroke reported were a multi-infarct dementia (Drake, 1987), a thalamic ischaemic stroke (McGilchrist *et al.*, 1993) and traumatic haemorrhages of the right hemisphere (Chiu *et al.*, 1989; Kostic *et al.*, 1998; Pelin *et al.*, 2004). The genetic diseases were heterogeneous and included a case of mosaicism with Robert's syndrome, phocomelia, mild mental retardation, optic atrophy, bilateral facial palsy (Hasegawa *et al.*, 1998), a case with Prader–Willi syndrome (Gau *et al.*, 1996), an unidentified disease with mental retardation and bilateral pyramidal syndrome (Livrea *et al.*, 1977), another complex case of consanguinity, mental retardation, an ectodermal disorder (incontinentia pigmenti), acanthosis

nigricans, and hereditary exostosis (Reimao and Shimizu, 1998) and developmental Asperger's disease in two patients, one with cortical dysplasia and retinitis pigmentosa (Berthier *et al.*, 1992). As for the three patients with infectious encephalitis of unknown origin, one had an acute viral meningo-encephalitis and high CSF lymphocyte counts (Merriam, 1986) while another had a meningo-encephalitis with neurological sequels, including left hypo-sensitivity, central facial palsy, concentric loss of visual fields and bilateral facial spasms (Persson *et al.*, 1969). KLS also occurred in a context of gastrointestinal symptoms in the 1930's in a woman with recurrent episodes of variable hypersomnia, sometimes severe insomnia, and diarrhoea lasting over a 30-year period (Wilder, 1972). The author discussed a possible encephalitis lethargica, while we would also suspect Whipple's disease.

Symptoms in secondary KLS

Compared to patients with primary KLS, the symptoms occurred significantly later in patients with secondary KLS (Table 5). They also experienced three times the number of episodes, which lasted three times longer and thus the time they were incapacitated was dramatically increased. The disease did not, however, last longer, and the cardinal signs (hypersomnia, megaphagia, cognitive disturbances, hallucinations and behaviour disorders) occurred with a similar frequency. Symptoms were often described in similar terms, for example, 'eating compulsively, without complaints of hunger or expression of satiety' (Drake, 1987) and the greedy consumption of '0.5 kg of biscuits, six tarts and several ice-creams' (Chiu *et al.*, 1989). A teenager saw ghosts and famous TV actors and believed he was being pursued by armed attackers (Merriam, 1986). Compulsions were also observed, such as nail-biting, hair pulling, scratching skin, laughing and crying, walking along straight lines (Wilder, 1972) and writing on clothes and extremities (Gau *et al.*, 1996).

The neurological signs that were observed between the episodes were various, with very few commonalities between patients. They included objective sensory disturbances of the

extremities (Wilder, 1972); impaired verbal abilities (Takrani and Cronin, 1976); bilateral pyramidal signs and mental retardation (Livrea *et al.*, 1977); frontal, pseudo-bulbar and pyramidal syndromes (Drake, 1987); left hemiplegia (Chiu *et al.*, 1989); parkinsonism (Berthier *et al.*, 1992); central facial palsy (McGilchrist *et al.*, 1993); upward-gaze palsy with mild ptosis (Fenzi *et al.*, 1993); and mental retardation (Gau *et al.*, 1996; Hasegawa *et al.*, 1998). Sleep recordings were performed in half of these patients and yielded the same abnormalities as in primary cases, including short REM sleep latency in two cases (Drake, 1987; Berthier *et al.*, 1992), hypersomnia of the harmonious type, with proportional increase of all sleep stages (Merriam, 1986) or with excess of REM sleep (Hasegawa *et al.*, 1998) and decreased sleep efficiency (Berthier *et al.*, 1992).

Pharmacological therapy (18 trials) was initiated in 8 of 18 patients. As in primary cases, antidepressants (3 trials), neuroleptics (2 trials) and a sedative (1 trial) had no effect, while carbamazepine and lithium were associated with a reduction (but not an ending) in the number of attacks in 1 of 3 patients and 3 of 4 patients, respectively.

Discussion

This systematic review reports on the largest number of KLS patients ever presented, with inclusion of all non-English language articles. The striking commonality of symptoms across patients is again demonstrated, suggesting a unique disease entity. Episodic hypersomnia and cognitive disturbances may constitute the core abnormality, while behavioural, eating and sexual disturbances are more variable and may occur only in a subset of episodes even within single patients. Age of onset, sex-ratio, triggering factors and frequency of symptoms are similar to two recent small case series reported in Europe by Dauvilliers *et al.* (2002) and Israel by Gadot *et al.* (2001). The analysis shows, for the first time, a worldwide distribution for KLS. Of note, one-sixth of the patients reported were Israeli, suggesting either a publication bias or a higher vulnerability in subjects with Jewish heritage. Follow-up prospective studies will be needed to shed light on potential ethnic differences.

Table 5 Differences between patients with primary and secondary Kleine–Levin syndrome

	Primary KLS	Secondary KLS	P
No. of patients	168	18	
Sex-ratio (% men)	69%	67%	0.83
Age of onset, years	18.9 ± 72.3	26.1 ± 17.5*	0.0002
Disease course, years median ± SE	8 ± 2	10 ± 2	0.24
Episode duration, days	11.7 ± 8.9	31.4 ± 56.5*	0.0001
Interval duration, months	5.9 ± 9.6	6.8 ± 9.3	0.73
Number of episodes	11.9 ± 14.5	38.3 ± 72.6*	0.0005
Time incapacitated, days	135.5 ± 168.5	673.5 ± 1245*	<0.0001
Megaphagia, % patients	80%	83%	0.95
Hallucinations, delusions, %	26%	44%	0.10
Hypersexuality, %	43%	28%	0.2

Data are mean ± SD, unless specified. *Significant difference with primary KLS, Student's t-test, except for disease course (Log rank test in Kaplan–Meier analysis), and for % of symptoms (chi-square test).

Triggering factors

The occurrence of an infection at the disease onset in more than two-thirds of the patients, already stressed by some authors, seems too frequent and too closely associated for KLS to be due to chance. Unfortunately, however, in rare cases where an infectious agent was identified, it differed from one patient to another. These agents may thus compensate a previously existing disease, or a coexisting infection with another yet undetected infectious agent may be responsible. Additional work in this area is needed as the studies of some notable infectious agents known to cause confusion, hypersomnia and various neuro-psychiatric symptoms such as Whipple's disease, malaria, California encephalitis or encephalitis lethargica-like agents (Dale *et al.*, 2004), have not been explored as possible aetiological agents. Infection, head trauma and alcohol are all known to increase the blood–brain barrier permeability (Rapoport *et al.*, 1971; Lo *et al.*, 2001; Nassif *et al.*, 2002) and could therefore facilitate the passage of a circulating pathogenic agent or immunoglobulin to the brain.

Duration of the disease

This study is also the first to report on the median duration of the disease, a relatively longer than expected 4–8 years, which is an important variable to report to patients first presenting with the disease. Four years was a lower estimate based on patients with disease terminated at time of publication (other subjects with longer course duration are more likely not to be published), while 8 years may be slightly overestimated if patients lost in follow-up are generally cured. One long-term follow-up study via phone or in-person interviews reported that 25 patients were in good health several years after the cessation of their KLS episodes, suggesting that complete recovery and a good prognosis is the rule for KLS (Gadoth *et al.*, 2001). They did not, however, report on the final duration of the disease. In <4% of cases, a permanent cognitive decline was observed, though it was difficult to causally associate it to KLS, missed school days, or the sedative side-effects of treatments. If confirmed in a series with long-term follow-up, it would raise the idea that some rare patients may present permanent lesions, which would support early aggressive medical intervention (Landtblom *et al.*, 2003).

Secondary KLS cases

The older age in secondary KLS is probably due to the presence of stroke as a cause in five patients, a disease that affects preferentially older subjects. Since symptoms are similar in nature and frequency to those with primary KLS, as are responses to treatment and disease duration, one can hypothesize that secondary cases are not actually 'secondary', but rather primary cases incidentally coexisting with genetic, vascular or inflammatory neural lesions. These lesions would only facilitate KLS, causing longer and more frequent episodes.

Treatment

The evaluation of treatment, based on case-reports, was hard to assess because of the unpredictable spontaneous course of the disease and of the absence of placebo-controlled studies. It was evaluated in a large population of patients, and, as generally predicted, results were extremely disappointing. Amphetamine-stimulants significantly improved sleepiness (Table 4) but not the other more serious symptoms, suggesting a very imperfect therapeutic relief. The potential benefit of lithium at preventing relapses (Table 4), only administered in 29 cases, if confirmed, should be balanced against its known difficulty of use and unfavourable side-effect profile. We also noted that antiepileptic mood stabilizers (especially carbamazepine) were commonly prescribed, probably based on the possible efficacy of lithium, but results were similar to no drug treatment, strongly suggesting that this practice has no justification. Antidepressant therapies were similarly ineffective. We believe that additional therapeutic trials using other medications, such as immunosuppressive or novel antiviral agents, with double-blind placebo-controlled multicentre design, are warranted.

Limitations of the study

There are several limitations to our study that are inherent to any systematic review. Only published case-reports are considered, and, even if KLS cases are more likely to be published when compared to other diseases because of the rarity of the syndrome and its striking symptoms, the published cases may not be representative of the general KLS population. A likely bias may be a trend towards publishing details of patients with a more complete series of symptoms (hypersomnia, cognitive changes, megaphagia and sexual disinhibition) and to report more severe and/or unusual cases, rather than subjects with just recurrent isolated hypersomnia. This could lead to a seemingly apparent homogeneity of the published disease. Importantly, however, it is an accepted fact that even recurrent hypersomnia without ancillary symptoms is a rare occurrence in clinical practice. The second limitation pertains to data available in published studies. The rate of information we found in articles was unusually high for symptom occurrence and disease course, but was as low as 27% for selected data such as hormonal levels or sleep studies, reducing the validity of these last findings. For the same reason, it is possible that the apparent success of any treatment will be more often published than a failure to respond.

Potential pathophysiological mechanisms

This study also highlights possible pathophysiological mechanisms for the disorder. Partial complex epilepsy, a condition that can produce episodes of recurrent abnormal behaviour, can be ruled out. The poor response of the condition to antiepileptic therapy also substantiates this hypothesis. A local brain lesion is also unlikely, considering the polymorphism of the symptomatology. Finally, EEG, brain flow SPECT,

or neuropathological data showed that frontal, temporal and sometimes occipital and parietal lobes can be involved, not to mention the thalamus (Huang *et al.*, 2005).

The finding of a possible Jewish predisposition, occasional familial clustering, and the association with infectious triggering factors suggest that KLS is due to environmental factors acting on a vulnerable genetic background. This general picture and the fluctuating symptomatology in KLS are consistent with the recent report of an HLA association in KLS and the possibility of an autoimmune mediation of the disorder.

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