Kleine–Levin Syndrome: A Systematic Study of 108 Patients

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Objective: Kleine–Levin syndrome is a rare disorder characterized by relapsing-remitting episodes of hypersomnia, cognitive disturbances, and behavioral disturbances, such as hyperphagia and hypersexuality.

Methods: We collected detailed clinical data and blood samples on 108 patients, 79 parent pairs, and 108 matched control subjects. We measured biological markers and typed human leukocyte antigen genes DR and DQ.

Results: Novel predisposing factors were identified including increased birth and developmental problems (odds ratio, 6.5). Jewish heritage was overrepresented, and five multiplex families were identified. Human leukocyte antigen typing was unremarkable. Patients were 78% male (mean age at onset, 15.7 $\pm$ 6.0 years), averaged 19 episodes of 13 days, and were incapacitated 8 months over 14 years. The disease course was longer in men, in patients with hypersexuality, and when onset was after age 20. During episodes, all patients had hypersomnia, cognitive impairment, and derealization; 66% had megaphagia; 53% reported hypersexuality (principally men); and 53% reported a depressed mood (predominantly women). Patients were remarkably similar to control subjects between episodes regarding sleep, mood, and eating attitude, but had increased body mass index. We found marginal efficacy for amantadine and mood stabilizers, but found no increased family history for neuropsychiatric disorders.

Interpretation: The similarity of the clinical and demographic features across studies strongly suggests that Kleine–Levin syndrome is a genuine disease entity. Familial clustering and increased prevalence in the Jewish population support a role for a major genetic susceptibility factor. Considering the inefficacy of available treatments, we propose that disease management should primarily be supportive and educational.

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Kleine–Levin syndrome (KLS) was first described more than 80 years ago.[1–3] The disorder is characterized by recurrent episodes of hypersomnia associated with cognitive and behavioral abnormalities, such as megaphagia (eating increased amounts of food) and hypersexuality. Episodes are separated by weeks or months of normal sleep and behavior.[4] KLS primarily affects adolescent boys and has an unpredictable course of recurrence and remission that lasts for years and most often mysteriously disappears in young adults.[5]

An underlying hypothalamic pathology is suggested by the critical role of this structure in regulating sleep, appetite, and sexual behaviors; however, no consistent hypothalamic abnormalities have been identified. Structural brain imaging and evaluation of the cerebrospinal fluid and serological inflammatory markers are unremarkable. Electroencephalographic (EEG) slowing is notable in most cases during episodes, without epileptic activity. Diffuse brain hypoperfusion, mostly focused on the thalamic and frontotemporal areas, has been reported.[6] Viral and autoimmune causative factors have been suggested, based on the frequent report of flu-like symptoms at onset and a significant association with DQB1*02.[7]

KLS poses diagnostic and therapeutic challenges. The identity of KLS as a disorder is often questioned, and cases are frequently misdiagnosed. Therapies are marginally helpful and have not been systematically evaluated. Stimulants are partially effective on sleepiness but not on cognitive and behavioral abnormalities. Lithium showed positive effects on preventing or delaying recurrences in a few reported cases.[8]

Published work on KLS primarily consists of single-case reports and retrospective, uncontrolled series that

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contain few patients.[5,7] In a recent review of these studies,[9] we found the disorder to be less benign than generally recognized, with a median disease duration of 8 years. We also observed that megaphagia was overemphasized. In this study, we sought to obtain a representative picture of the disorder through a cross-sectional, systematic evaluation of more than 100 new cases and comparison with matched control subjects.

Subjects and Methods

Recruitment of Patients

One hundred twenty-one potential subjects were aggressively identified using four different routes of ascertainment. First and foremost, we took advantage of a list of contacts available through the Kleine–Levin Syndrome Foundation (n = 81). Second, we personally contacted clinicians who have published or have reported one or several KLS cases in the literature, or large centers that are likely to treat such specialized and difficult patients. These include sleep centers from Barcelona, Madrid, Milano, Innsbruck, Munich, Montréal, Toronto, all French and Israeli sleep centers (via national sleep associations), Turkey, India, and Iran. Third, we attempted to identify patients with KLS worldwide by addressing letters to all members of the American Academy of Sleep Medicine, including the international members (3,534 diplomats). These 2 methods led to recruiting 31 additional patients. Finally, we created a Stanford University KLS Web site and responded to patients and family members who contacted us through this site (nine patients were identified using this source).

Confirmation of the Diagnosis in Identified Subjects

A semistandardized medical telephone interview focusing on medical history, symptoms, and evolution of KLS and concomitant disease was conducted in all families. These interviews were all conducted by a medical professional (MD or DO, with involvement of a psychiatrist and a neurologist) from February 2005 to June 2005. Of 121 patients contacted, 108 met three inclusion criteria. The first criterion was International Classification of Sleep Disorders II revised criteria for KLS both by phone interview and by questionnaire: (1) episodes of excessive sleepiness lasting more than 2 days and less than 4 weeks, occurring at least once a year; (2) intermixed with long intervals of normal alertness, mood, cognition, and behavior lasting usually months to years; (c) recurring at least every year interspersed with long periods normal sleep; (4) not better explained by a sleep disorder, a neurological disorder (eg, idiopathic recurrent stupor, epilepsy), a mental disorder (eg, bipolar disorder, psychiatric hypersomnia, depression), or the use of drugs (eg, benzodiazepines, alcohol). In addition to these recurrent episodes of hypersomnia, KLS patients should experience at least one of these symptoms: hyperphagia, hypersexuality, odd behavior, or cognitive disturbances (eg, confusion, feeling of derealization, or hallucinations). The second criterion is that the patient had also been diagnosed with KLS by his or her own pediatrician, neurologist, or sleep medicine expert. The third criterion is that the patient had returned a completed KLS questionnaire and a blood sample. Twenty-six of these patients had been under the care of one of us, and 51 provided medical records. We did not find face-to-face interview of patients more accurate than phone interview because the description of KLS was always retrospective. No patient was self-diagnosed.

Based on the criteria above, differential diagnosis that could mimic KLS, mostly of psychiatric (eg, bipolar disorder, drugs, medications), metabolic (recurrent metabolic encephalopathies), or neurological nature (eg, a Klüver–Bucy or partial complex seizures of neurological origin) were always considered and excluded. Because KLS is a rare diagnosis, these subjects always had been explored intensively for other potential causes, including often multiple EEGs and magnetic resonance images, and blood, endocrine, and metabolic workup; this information was available to us.

Thirteen patients were excluded based on death (1), incomplete data (6), or incorrect diagnosis (menstrual recurrent hypersomnia [1], sleep-related eating disorder [1], delayed phase sleep syndrome [2], acute disseminated encephalomyelitis [1], and narcolepsy [1]). Completed questionnaires and blood samples were provided by 79 parent couples of 81 patients. We also recruited 108 control subjects matched for age, sex, ethnicity, demographics, and country of origin (local friends for non-US patients). A series of 377 US subjects with unexplained central nervous system–mediated excessive daytime sleepiness (sleep apnea excluded before referral) enrolled at Stanford between 2002 and 2006 was also used for comparison. The Stanford Human Subjects Committee review board approved the study. All participants gave informed consent.

Questionnaire

Because there was no existing questionnaire on KLS, we developed a specific questionnaire, using the International Classification of Sleep Disorders criteria for KLS, our personal experience with KLS patients, and all the symptoms found in our previous review of 186 KLS published cases.[4] The prefinal version was submitted to external sleep experts (Yves Dauvilliers, Nathan Gadoth, Richard P. Allen), to the KLS Foundation, and to a panel of KLS patients, leading to minor corrections. The final questionnaire included 280 questions on onset, course, sleep, cognition, psychiatric symptoms, eating attitude, sexual behavior, response to therapies, personal and family history (see supplementary data; data also available at: http://med.stanford.edu/school/Psychiatry/narcolepsy/KLS.html). English and French versions are available. It also included the Stanford Sleep Inventory, the Hospital Anxiety and Depression Scale,[10] and the Eating Attitude Test.[11]

Biological Markers

Serum and DNA were collected, most often outside of an episode. Serum leptin, C-reactive protein levels, and high-resolution human leukocyte antigen (HLA)-DRB1 and DQB1 typing were performed as described elsewhere.[12,13]

Data Analysis

All variables are reported as mean ± standard deviation or percentage whenever appropriate. Dichotomous traits were compared between groups using χ^2 or Fisher's exact tests.

Table 1. **Ethnic Distribution of Kleine–Levin Syndrome Patients Recruited from the United States as Compared with Stanford Central Nervous System Hypersomniac Referrals and General US Census**

Ethnicity Groups	US KLS (n = 72)	Expected Based on US Census (n = 72)	Significance (OR)	Stanford Referrals (n = 377)	Expected Based on US Census (n = 377)	Significance (OR)
All whites	71 (98.6%)	54 (75.1%)	$p < 0.00003$ (24)	321 (85%)	283 (75.1%)	$p < 0.0001$ (1.9)
Jewish Americans	10 (13.9%)	2 (2.2%)	$p < 0.033$ (5.1)	5 (1.3%)	8 (2.2%)	NS
Hispanic Americans	1 (1.4%)	9 (12.5%)	$p < 0.017$ (0.1)	14 (3.7%)	47 (12.5%)	$p < 0.00001$ (0.27)
Native Americans	0 (0%)	1 (0.9%)	NS	6 (1.6%)	3 (.9%)	NS
Blacks	0 (0%)	9 (12.3%)	$p < 0.003$ (0)	15 (4.2%)	46 (12.3%)	$p < 0.00004$ (0.30)
Asian Americans	0 (0%)	3 (3.6%)	NS	19 (5.0%)	14 (3.6%)	NS
Pacific Islanders	0 (0%)	0 (0.1%)	NS	2 (0.53%)	0 (0.1%)	NS

Ethnicity was self-declared. Samples include Kleine–Levin syndrome (KLS) and patients recruited at Stanford from across the United States (US). Of note, hypersomnia referrals were not necessarily subsequently confirmed with a hypersomnia diagnosis. These were compared with the frequency expected from US census data (http://censtats.census.gov/data/US/01000.pdf). Note that Hispanic and black subjects were systematically underrepresented in all Stanford referrals. In contrast, increased Jewish heritage was observed only in KLS patients. OR = odds ratio; NS = nonsignificant difference.

Continuous variables were analyzed by t test and analysis of variance. HLA association was examined using the transmission disequilibrium test,[14] (trio study) or χ^2 and Fisher's exact tests (case–control). Median disease course was calculated using a Kaplan–Meier survival curve analysis using both "noncensured data" (in "cured" patients with terminated KLS) and "censured data" (others). A patient was considered "cured" when he/she had not had episodes for at least twice the longest interepisode duration before disease termination. To verify the adequacy of this criterion, we analyzed a subset of patients who had not had episodes for 5 years or more and are thus definitively cured (n = 26). We found that the use of this criterion would have been appropriate in all these cases. Comparison of disease course between groups was performed by the log-rank test.

Results

Demographics and Ethnicity

Our sample was worldwide (Americas, Europe, Asia, Australia) and mostly composed of adolescent boys (75.9%; sex ratio, 3:1). Mean age of onset was 15.7 ± 6.0 years (range, 6–59 years) with 81.7% onset during their second decade. Girls were older (18.5 ± 9.5 years) at onset than boys (15.0 ± 4.2 years; $p < 0.01$), although they were pubescent earlier (11.8 ± 1.0 vs 13.2 ± 1.5 years; $p < 0.0001$). At KLS onset, 89% of US patients were located in eastern states, reflecting local regions of high population density (see Supplementary Fig A). Of 108 cases, only 7 (6.5%) had been described in previous case reports.

Of 108 international cases, 88 were non-Jewish whites, 18 Jewish, 1 Latino, and 1 Asian. In the United States, KLS presented in whites three times more frequently than expected, based on the US population census (Table 1).[15] Strikingly, six times more Jewish patients than expected were identified ($p < 0.033$), all Ashkenazi (not different in age, sex ratio, or age of onset). In US patients referred to our center for hypersomnia or narcolepsy, Hispanic and black patients were also underrepresented versus US census, but the frequency of Jewish subjects was as expected (see Table 1).

Events Surrounding Kleine–Levin Syndrome Onset

The first episode of KLS occurred most often in autumn (31.1%) or winter (31.1%), peaking in December (14.8%). Eighty-nine percent of patients remembered an event closely associated with onset, most often infections (72%; 25% with a coldlike syndrome with fever), alcohol use (23%), sleep deprivation (22%), unusual stress (20%), physical exertion (19%), traveling (10%), head trauma (9%), marijuana use (6%).

Symptoms Experienced during Episodes

Although "positive" symptoms such as irritability, aggressiveness, abnormal perception, increased eating, and sexuality were common, the overall impression was that of apathy, exhaustion, and dramatically increased sleep (Table 2). Only hypersexuality and depression differed by sex. There was no evidence for disease heterogeneity, as patients with full-blown KLS (hypersomnia, cognitive impairment, megaphagia, and hypersexuality) had similar demographic and clinical characteristics as those with "incomplete" disease (eg,

Table 2. **Nature and Frequency of Symptoms Reported during at Least One Episode of Kleine–Levin Syndrome in 108 Patients**

Hypersomnia	*100%*	*Cognitive impairment*	*100%*	*Altered perception*	100%
Sleep drunkenness	83%	Impaired speech[g]	94%	Dreamy state	81%
Postepisode transient insomnia	72%	Impaired concentration	91%	Erroneous perception	72%
Intense dreaming	59%	Incomplete recollection of episode	87%	Derealization	63%
Hypnagogic hallucinations	42%	Temporal disorientation	87%	Mind-body disconnect	52%
Sleep paralysis	14%	Impaired reading	75%	Altered taste	50%
		Unable to perform two tasks simultaneously	67%	Voices sound distant	36%
Eating behavior disorders	*95%*	Unable to make a decision	66%	Altered smell	35%
Hyperphagia[a]	66%	Impairment of memory	66%	Blurred vision	23%
Increased food intake[b]	56%	Eye–hand coordination impairment	66%		
Automatic eating	37%	Apathy	54%	*Psychological change*	87%
Decreased appetite[c]	34%	Spatial disorientation	43%	Irritability	65%
Eat whatever is presented	31%			Frustration	55%
Increased drinking	16%	*Meningeal and autonomic symptoms*	*89%*	Depressed mood[h,i]	53%
		Fever	68%	Agitation	47%
Sexual drive	*59%*	Photophobia	59%	Less polite	47%
Disinhibition, hypersexuality[d]	53%	Headache	48%	Anxiety	45%
Increased masturbation[d,e]	29%	Sweating	46%	Compulsions[j]	36%
Unwanted sexual advances[f]	17%	Hot flashes	24%	Delusions	35%
Decreased sexuality	6%	Nausea	18%	Hallucinations	27%

[a]Eating large amounts of food at once; mean weight gain per episode: 4.6 ± 3.1kg (range, 0.25-13.6kg).
[b]Food choices: sweet food, 45%; salty, 18%; sour, 6%. Choice of foods usually disliked: 20%. Increased appetite: 43%.
[c]Mean weight loss per episode 4.0 ± 2.7kg (0.7-11.3kg).
[d]58.5% of men, 34.6% of women; $p < 0.03$.
[e]35.4% of men, 7.7% of women; $p < 0.01$.
[f]Higher in men.
[g]Slow speaking/answering; mute, monosyllabic, repetitive; childish language with limited vocabulary (40%).
[h]80.7% of women, 43.9% of men; $p < 0.01$.
[i]Higher in women.
[j]Singing jingles, pacing, writing, drawing, painting, tapping, and watching the same video in a continuous loop.

without megaphagia or hypersexuality) (data not shown). Disease presentation and demographics in 18 Jewish patients also did not differ from other subjects.

Sleep was enormously increased during episodes, averaging 17.9 ± 3.6 hours per 24 hours (range, 14.7 ± 4.8 to 21.35 ± 2.5). Most patients were difficult to awaken and reported intense dreaming and hypnagogic hallucinations, whereas sleep paralysis was uncommon. A brief overshoot of insomnia was often seen at episode termination, sometimes associated with euphoria: "All I want to do is stay awake and get things done that I was unable to while in the episode. Plus, it is as if I have been reenergized."

All patients reported cognitive impairment, and almost all had difficulty reading and speaking: "I have trouble forming thoughts into words. I respond mostly with grunts and groans." Memory disturbances were common; only 13% had complete recollection of episodes: "It seems like a movie that is cut up so scenes are missing." Eye–hand coordination and simple gestures (such as finding one's key in a pocket) were difficult, and perceived abnormally (astereognosia); clumsiness led to broken limbs in three patients. Temporal disorientation was twice as frequent as spatial disorientation. Altered perception was always present and could affect all senses, with feelings that things were unreal, dreamlike: "Things seemed hazy, foggy"; "I would break a cup to see if it would break to reassure me things were normal."

Nearly all patients reported eating abnormalities during at least one episode. Patients ate large amounts of food with a preference for sweets and atypical food choices. Patients tended to eat any and all food that was presented, reminiscent of frontal lobe syndrome. Hyperphagia was observed in 66% of patients leading to striking weight gain (4.6 ± 3.1kg/episode): "I would not eat for 10 to 14 hours then would eat 4 or 5 peanut butter and jellies–without even chewing–very fast, then would start to fall sleep again with food still in my mouth." Notably, however, one third of the patients reported decreased appetite.

Half of the patients reported increased sexual drive

during at least one episode, but decreased sexuality was also experienced. One third of the patients had increased masturbation "to the point of bleeding" in one, sometimes with overt masturbation. A 17-year-old girl stated: "I have sporadic hyper-libido. I think of wanting to have sex with an old neighbor or being extra sexual and horny." Hypersexuality was significantly more frequent in men than in women.

When disturbed from sleep or other activities, apathy was common, but patients also expressed irritability or frustration, sometimes with aggression (36%): "I express inappropriate opinions, the things people think but don't say." Depressed mood was possible, particularly in women; 4 of 108 (3.7%) had suicidal thoughts "to get an episode to end." Patients were often anxious, "scared of being left alone," or afraid of novelty in their environment. Compulsive or childish behaviors were also frequent. Paranoid delusions or hallucinations occasionally occurred: "I feel like I can alter things with my mind." All these abnormalities were transient and reversed after episodes.

Restoration of Normal Function between Episodes

Patients and control subjects were remarkably similar between episodes (Table 3). Despite having similar eating habits and a low frequency of bulimia, patients had a higher body mass index (BMI) versus control subjects regardless of time spent in bed. Patients also had increased leptin, C-reactive protein (Fig 1), and greater frequency of snoring and witnessed apnea, but these disappeared after adjusting for BMI. Of interest, BMI did not differ between patients with and without megaphagia. Habitual sleep and wake time was similar in cases and control subjects between episodes (data not shown). Patients were slightly more anxious than control subjects. There was no difference in mean depression scores between groups.

Analysis of Disease Course Suggests Long-Term Impairment

At time of the study, 52 patients had active KLS, 25 considered themselves cured, and status could not be determined in 31 (intermediary) (Fig 2). Median episode duration (10 days) and interval between episodes (4 months) did not differ between men and women or in Jewish subjects (data not shown). Episodes recurred more quickly in patients with childhood onset (see Fig 2). Patients with active KLS had suffered more episodes than those who were cured or of undetermined status at time of the study. The disease lasted a median of 13.6 $\pm$ 4.3 years but was shorter for patients with cured KLS. Male sex and presence of hypersexuality predicted longer disease duration, as did onset in adulthood (age, >20 years; 14 patients) (Table 4). Because men were more often hypersexual than women, these two factors were dependent. The disease course was not affected by age of onset, presence of megaphagia, or depressive mood. Because only 25% of adult-onset KLS patients were cured after 12 years, the median disease course was estimated to exceed 22.7 years in this group.

Personal and Family Medical History

Surprisingly, 25% of patients reported problems at birth (long labor: n = 12; hypoxia: n = 6; premature or postmature birth: n = 9) versus 7.4% in control subjects (Table 5) and 8% in parents of KLS patients (data not shown). In addition, 16 patients (15%) had delayed speech, walking, or reading, whereas these were not observed in control subjects. Overall, one third of KLS patients suffered from birth and development issues, a percentage 6.5 times greater than in control subjects. Five KLS patients had genetic diseases, but those were diverse and unlikely to be relevant. Six patients and no control subjects had been treated for attention-deficit hyperactivity disorder before KLS ($p < 0.04$). The frequency of seizures, depression, anxiety, migraine, allergy, and autoimmune diseases in KLS patients was not different from control subjects (see Table 5 and data not shown). Interestingly, Jewish patients reported fewer birth or developmental problems (11.1%, similar to control subjects) than the rest of the group (37.8%; $p < 0.05$). There was no increased frequency of psychiatric, neurodegenerative, genetic, or autoimmune diseases in the first-degree relatives of KLS patients compared with control subjects (see Table 5 and data not shown).

Five multiplex families (5/104; 4.8% of the sample) were identified; two of these previously published.[16,17] Family relationships included father–son (n = 2), affected siblings (n = 2), and first cousins (n = 1). None of the control subjects had a family history of KLS ($p < 0.04$).

Human Leukocyte Antigen Class II Association

HLA-DR and -DQ alleles did not differ between cases and control subjects after Bonferroni correction and were not preferentially transmitted in 81 trios (see Supplementary Tables A and B). DRB1*0301-DQB1*0201 and DRB1*0701-DQB1*0202, associated with KLS in a smaller trio study,[7] had frequencies of 12.7 and 10.8% in transmitted versus 12.0 and 11.4% in nontransmitted haplotypes.

Therapeutic Responses

Medication reports were tabulated based on reports and response per episode codified into the following: no change or worse, partial benefit, or important benefit. Benefit was subjectively defined by the patients as helping to terminate/shorten episodes, reducing episode intensity, or preventing episode recurrence. Of the various stimulants tried, amantadine, a drug with do-

Table 3. **Sleep, Eating, and Psychological Symptoms in 108 Control Subjects and 108 Kleine–Levin Syndrome Patients between Episodes**

Characteristics	KLS Patients	Control Subjects	*p*
n	108	108	
Age, yr	27 ± 11	26 ± 10	NS
Male sex	76%	76%	NS
Nighttime sleep			
Do not sleep well	17.1%	8.3%	NS
Sleep latency, min	23.6 ± 25.8	18.2 ± 14.7	NS
Time asleep, min	482 ± 90	465 ± 86	NS
Restless legs syndrome	9.5%	11.6%	NS
Sleepwalking (past or present)	18.5%	18.9%	NS
Night terrors (past or present)	15.5%	15.5%	NS
Snoring	22.9%	11.2%	0.04
Witnessed apnea	7%	1.4%	0.007
Daytime alertness			
Epworth Sleepiness Scale score	5.6 ± 3.9	6.1 ± 3.9	NS
Naps/week	1.3 ± 1.9	1.3 ± 1.8	NS
Refreshing naps	70.1%	70.1%	NS
Narcolepsy symptoms			
Cataplexy-like symptoms	2.7%	2.7%	NS
Hypnagogic hallucination	23.1%	26.8%	NS
Sleep paralysis	7.4%	7.4%	NS
Eating behavior			
EAT-26 score	5.2 ± 5.7	5.1 ± 4.7	NS
EAT score > 20	4.6%	0.9%	NS
Body mass index, kg/m^2	26.1 ± 5.7[a,b]	23.3 ± 3.6	<0.0001
Mood and anxiety (HADRS)			
Anxiety score	6.1 ± 3.8[b]	5.1 ± 3.3	0.04
Depression score	2.7 ± 3.3	2.1 ± 2.1	NS
Serum levels			
Leptin, ng/ml	8.3 ± 11.3[b,c]	5.1 ± 7.5	0.027
C-Reactive protein, ng/ml	2.6 ± 3.8[b,c]	1.2 ± 2.2	0.003

[a]Body mass index (BMI) with (26.2 ± 5.1kg/m^2) versus without megaphagia (25.9 ± 6.9kg/m^2) ($p < 0.80$).
[b]This significant difference disappears when controlled for BMI (analysis of variance with two factors).
KLS = Kleine–Levin syndrome; NS = not significant; EAT = Eating Attitude Test; HADRS = Hospital Anxiety and Depression Rating Scale.

pamine reuptake inhibitory stimulant and antiviral properties, had the most significant effect (Table 6). It helped terminate episodes or "gave clear moments" in 41% of patients. This effect was typically obtained only in the first trial, often lost in subsequent episodes. Modafinil, methylphenidate, and amphetamine occasionally improved alertness, but most patients remained "absent" or "awake but still in bed, eyes open, feeling bad." Stimulant use occasionally showed more positive, disabling symptomatology (eg, exacerbated aggression). Antidepressants were frequently used, with no effect on most KLS symptoms and a limited, occasional effect on depressive mood (bupropion and fluoxetine only). Among neuroleptics, only risperi-

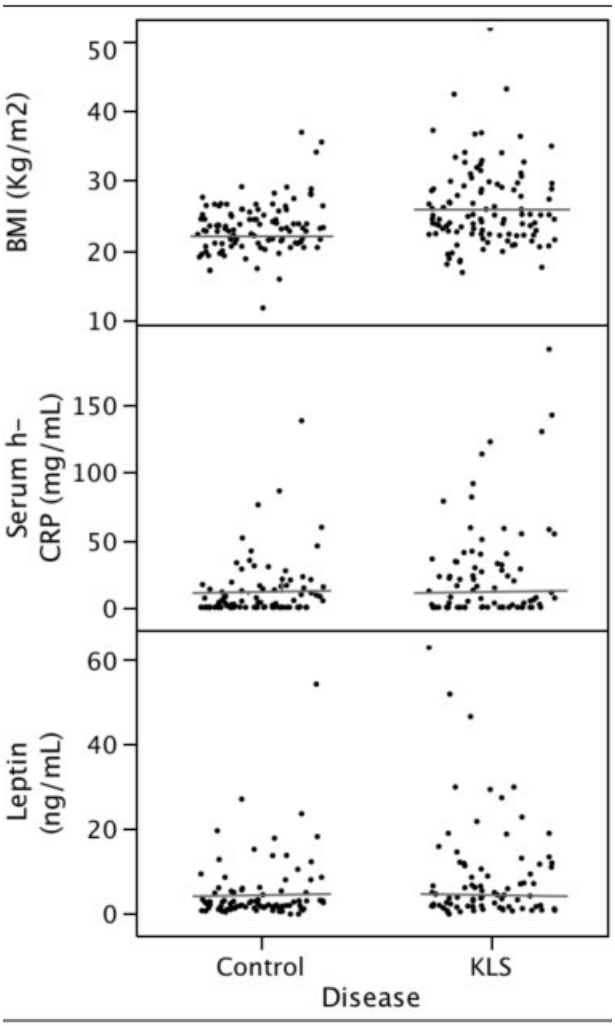

Fig 1. Body mass index (BMI), serum leptin, and serum C-reactive protein (CRP) in patients with Kleine–Levin syndrome (KLS) versus age-, sex-, and ethnicity-matched control subjects. Note greater BMI, leptin, and CRP levels ($p < 0.05$*). The significant difference in CRP and leptin disappeared after controlling for BMI (see Table 3). Samples were taken between episodes except for five subjects; no difference was observed in these subjects.*

done partially decreased delusional symptoms. Lithium and valproate showed equal benefit in preventing further episodes, with partial effects in one fourth of the patients (lengthening the interval between episodes).

Mood stabilizers had disappointing effects. Lithium, a compound suggested to be effective in a prior meta-analysis was reported as effective in only 24% of cases. Carbamazepine, benzodiazepines, and other antiepileptics similarly had little benefit, although it should be noted that mood stabilizers such as lithium, carbamazepine, and valproic acid were, together with amantadine, the only few drugs to rarely produce an "important benefit" (6–12% of cases). Intravenous immunoglobulins lengthened the between-episode interval in one of three patients. Nonmedical therapies were uniformly ineffective. The large majority of patients considered that most therapies were not worthwhile, and that the best course of action was to wait until the end of the episode in a home environment.

Discussion

Our sample of more than 100 new cases recruited sequentially within a single year is the largest ever reported. It is comparable in size with the bulk of all previously published cases. This suggests that KLS, although rare, is more prevalent than generally assumed. In such studies, there is a theoretical small risk for overdiagnosing KLS. We are, however, confident this was not the case here, as we selected participants after a consistent, long medical interview of patients (diagnosed by colleagues and never self-diagnosed) or their parents by phone, using the International Classification of Sleep Disorders criteria, and followed by a long

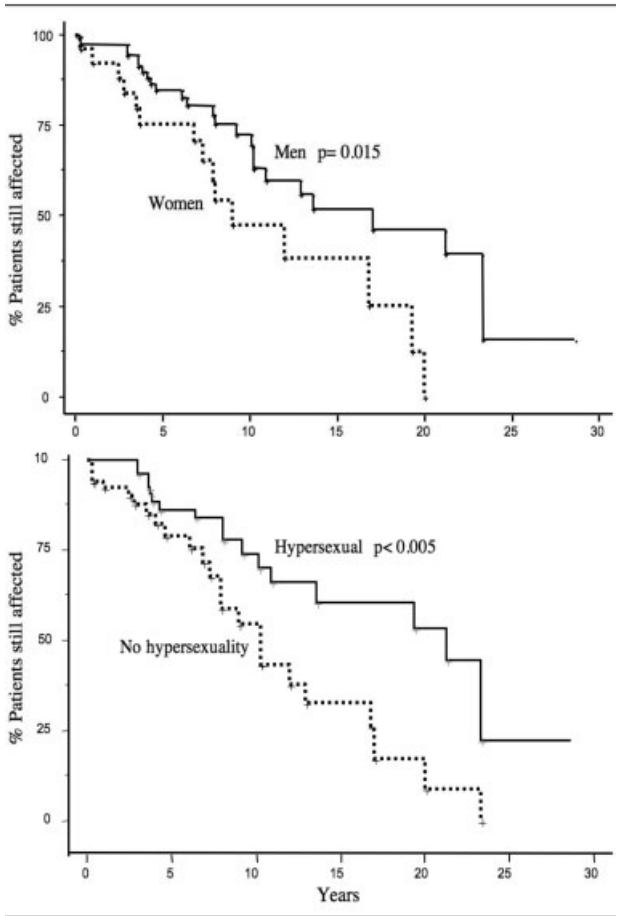

*Fig 2. (top) Disease course (percentage patients still affected), as calculated using the Kaplan–Meier estimate, was longer in men (*solid line; *median, 17 years) versus women (*dashed line; *median, 9 years). (bottom) The disease course was also longer in patients with (*solid line; *median, 21.2 years) versus without hypersexuality (*dashed line; *median, 10.2 years).*

Table 4. **Characteristics of Kleine–Levin Syndrome Episodes**

Characteristics	Mean ± SD (range)
Episode duration (days)	12.5 ± 7.5 (2–270)
Interval between episodes (mo)	5.7 ± 5.4 (0.5–66)
Onset < 12 years	3.2 ± 3.7[a]
Onset teen years	6.4 ± 5.6
Onset adulthood	5.5 ± 6.1
Total number of episodes	19 ± 19 (3–135)
Active KLS	25 ± 24
Cured KLS	15 ± 9
Intermediary KLS	13 ± 9
Disease duration (years)	13.6 ± 4.3 (1–27)
Cured KLS	8.9 ± 6.9
Men	17.0 ± 5.7[b]
Women	9.0 ± 2.8
Hypersexual	21.2 ± 1.5[c]
Not hypersexual	10.2 ± 1.9
Time incapacitated (days)[d]	237 ± 260 (17–1,568)

[a]Interepisode interval was shorter in patients with onset before age 12 versus later onset ($p < 0.03$). There was a mean of 19 episodes, but patients with active Kleine–Levin syndrome (KLS) suffered more episodes compared with "cured" or "intermediary" cases. Disease course lasted a mean of 13.6 years.
Duration was longer in male patients
([b]$p < 0.015$, log-rank test) and in patients with hypersexuality ([c]$p < 0.005$), both being interdependent.
[d]Median total time incapacitated (number of episodes × mean duration) was 237 days, with considerable variation.
SD = standard deviation.

written questionnaire. The diagnosis was retrospective (hence no need for face-to-face interview) and based on the patient history (generally obtained by parent interview, which we found more sensitive than patient interview because of the partial amnesia of episodes in KLS patients). We noted no difference between the patients we personally had in our charge versus those studied remotely. The medical records did not bring more information than the questionnaire (and often much less). Thus, we are confident that all participants were correctly diagnosed, and because all patients waited months, if not years, before being diagnosed with KLS, the risk for underdiagnosis appears to be greater than overdiagnosis.

Several other episodic neuropsychiatric diseases are potential mimics for KLS and were always considered. These include temporal lobe epilepsy (which was ruled out here by EEG), Klüver–Bucy syndrome secondary to bilateral temporal lesions of various causes (which was ruled out by magnetic resonance imaging), idiopathic recurrent stupor caused by benzodiazepine or endodiazepine (episodes are shorter and not associated with derealization), metabolic encephalopathies, for example, those with hyperammonemia such as mild cases of ornithine transcarbamylase deficiency (but patients present with protein intolerance, intense vomiting, and gastrointestinal symptoms not seen in KLS; further, the EEG is also abnormal), and bipolar disorders (with sadness and without typical precursor feelings suggesting KLS episode offset and onset or flu-like symptoms).

The use of matched control subjects and the systematic protocol of clinical evaluation allowed us to identify important new core abnormalities and risk factors. We also found no support for an association with HLA class II antigens, and thus no suggestion of an autoimmune cause. We found the disease to be less benign than currently perceived. The clinical course was longer than previously reported with a median of 8.9 to 13.6 years, and even longer in the adult-onset form. KLS is also exceptionally disabling with impact on daily function and an unpredictable pattern of recurrence. Our patients averaged 19 episodes of a mean of 12.5 days, totaling more than 8 months of incapacitation over 14 years.

Our review of symptoms and demographics was strikingly similar to that based on a recent review of the literature,[9] suggesting causative homogeneity and a distinct clinical entity. Perception and cognitive disturbances were consistently found in addition to hypersomnia and represent previously overlooked core elements of the syndrome. A continuously altered, dreamlike perception was a highly sensitive (100%) KLS symptom, whereas it is not observed in other sleep and mood disorders, and only transiently in rare temporal seizures. This symptom, possibly missed in numerous case reports,[9] could be used in further studies to increase specificity. In contrast, hyperphagia and hypersexuality were more variable across patients and across episodes, suggesting they are less sensitive symptoms than previously claimed.[2,3] BMI was increased regardless of the presence of megaphagia, regardless of whether patients were in an episode and regardless of total time spent in bed, suggesting a core metabolic abnormality. Hypersexuality was more prevalent in male patients and increased median disease duration from 10 to 21 years, suggesting association with disease severity. These differences with previous reports suggest that our detailed direct patient interview methodology yielded a more accurate but severe picture of the disease course. Indeed, using this methodology, late-onset relapses were more frequently reported as our patient population included more "cured" subjects than when analyzing published reports,[9] typically reporting patients closer to onset.

The pathophysiology underlying KLS remains enigmatic. Basic motor, cerebellar, and sensory functions

Table 5. **Family (First-Degree Relatives) and Personal Medical History in Kleine–Levin Syndrome Patients and Control Subjects**

Characteristics	KLS Patients	Control Subjects	Significance (OR)
Subjects, n	108	108	
Family history			
Kleine–Levin syndrome	4.8%	0.0%	$p < 0.04$
Major depression/bipolar	8.3%	6.5%	NS
Seizures	6.5%	1.8%	NS
Neurodegenerative diseases[a]	2.8%	2.8%	NS
Stroke	4.6%	2.8%	NS
Autoimmune diseases[b]	12.0%	6.5%	NS
Genetic diseases[c]	3.7%	1.8%	NS
Attention-deficit disorder	3.7%	3.7%	NS
Personal history			
Birth difficulties	25%[d]	7.4%	$p < 0.0005$ (4.2)
Developmental delay	14.8%	0,0%	NA
Birth or development problems	34.2 %[c]	7.4%	$p < 0.000001$ (6.5)
Genetic diseases[d]	5.5%[d]	0.0%	$p < 0.04$
Attention-deficit disorder	5.5%[d]	0.0%	$p < 0.04$
Depression	5.5%	3.7%	NS
Autoimmune diseases	5.5%	3.7%	NS
Right-handed	81.5%	87.0%	NS
Age at puberty, yr	12.9 ± 1.5	12.7 ± 1.2	NS
Irregular menstruations	30.1%	21.4%	NS

[a]Alzheimer's and Parkinson's diseases.
[b]Lupus, multiple sclerosis, arthritis, psoriasis, type I diabetes, thyroiditis.
[c]Gaucher's disease, neurofibromatosis, von Willebrand syndrome, optic atrophy with ataxia (Kleine–Levin syndrome [KLS]), muscular dystrophy, cystic fibrosis (control subjects).
[d]Klinefelter's syndrome, von Willebrand syndrome, polycystic kidney, mental retardation in combination with familial history of optic atrophy and ataxia, mental retardation combined with autism and developmental delay of unknown cause.
NS = not significant difference; OR = odd ratio; NA = not applicable statistics.

are intact, whereas sleep and higher associative brain functions are altered. Together with the diverse symptomatology reported, these results suggest that KLS is associated with widespread brain abnormalities involving primarily the thalamus, hypothalamus, and frontotemporal areas.[6,18] A striking fourfold increase in self-reported birth difficulties was found in KLS patients versus control subjects. This finding is reminiscent of autism,[19,20] epilepsy,[21] and schizophrenia.[22] Birth difficulties could cause perinatal brain injury and subsequent symptomatology, as established in developmental disorders and epilepsy.[21] Alternatively, increased prevalence of obstetric complications could reflect an underlying fetal KLS pathology. Birth difficulties are prevalent in children with hypothalamic defects, indicating a role for the fetal hypothalamus in the timing and process of birth.[23] In light of this, increased obstetric complications in KLS could signal an underlying brain dysfunction rather than an incidental factor conferring future liability.

Our most intriguing findings are the familial clustering and a potential increased risk in the Jewish population, supporting a role for genetic susceptibility factors. HLA-DQ2 has been suggested to be associated,[7] but we could not replicate this finding in our much larger independent sample. Although familial risk was low (1% per first-degree relative), we readily identified multiplex families and estimate an 800- to 4,000-fold increased risk in first-degree relatives (estimating KLS prevalence at 2–10 per million, and 5 first-degree relatives per proband). Increased familial clustering is consistent with multiple prior reports of multiplex families in the literature. Shared environmental effects cannot be excluded, but delayed onset among siblings[17] argues against the sole effect of an infectious agent. One sixth of KLS patients reported

Table 6. **Effects of Treatments in Kleine–Levin Syndrome Patients**

Treatment	n	No Change or Worse	Partial Benefit	Important Benefit
Stimulants				
Modafinil	43	79%	21%	0%
Methylphenidate	27	89%	11%	0%
Amantadine	24	58%	29%	12%
Amphetamine	14	87%	13%	0%
Bupropion	4	50%	50%	0%
Antidepressant drugs				
Sertraline	17	100%	0%	0%
Fluoxetine	16	81%	19%	0%
Others[a]	23	87%	13%	0%
Melatonin	15	87%	13%	0%
Phototherapy	6	94%	6%	0%
Neuroleptics				
Risperidone	8	63%	37%	0%
Others[b]	15	100%	0%	0%
Antiepileptic drugs				
Carbamazepine	22	91%	9%	0%
Valproate	17	75%	19%	6%
Benzodiazepines[c]	26	96%	4%	0%
Others[d]	13	100%	0%	0%
Lithium	30	77%	17%	7%
Others				
Immunoglobulins	3	66%	33%	0%
Acyclovir	2	100%	0%	0%
Corticosteroid	2	100%	0%	0%
Nonmedical therapies				
Vitamin supplements	24	100%	0%	0%
Phototherapy	6	83%	17%	0%
Others[e]	4	100%	0%	0%

Medication reports were tabulated based on reports and response per episode codified into no change or worse, partial benefit, or important benefit. Benefit was subjectively defined by the patients as helping to terminate/shorten episodes, reducing episode intensity, or preventing episode recurrence.
[a]Amitryptilin, clomipramine, fluvoxamine, trazodone, moclobemide, venlafaxine, nortryptilin, imipramine, phenelzine, amineptine, mirtazapine, citalopram.
[b]Amisulpride, levomepromazine, thioridazine, quietapine.
[c]Clonazepam, lorazepam, diazepam, alprazolam, temazepam, zolpidem.
[d]Gabapentine, phenytoine, lamotrigine, tiagabide.
[e]Acupuncture, hypnotherapy, psychotherapy.

between 1962 and 2004 were from Israel,[5] potentially a reflection of a long-standing interest in KLS. In our series, Jewish ancestry was also significantly overrepresented in patients from the United States but not in hypersomnia referrals. The predominance of Ashkenazi descent also suggests a role for Jewish-specific or enriched polymorphisms in this population. This finding is exciting in light of recent identification of strong genetic effects in infectious disease manifestations,[24,25] including the development of herpes simplex virus encephalitis.[26] The parallels with herpes simplex virus encephalitis and the interplay between pathogen and inherent genetic risk (in the later case a Toll-like receptor mutation affecting immune re-

sponse) are particularly interesting in light of the increased reports of infections or viral syndromes before the first and subsequent KLS episodes. These findings point to the potential of identifying such loci through modern genetic association techniques or potential viral triggers through study of samples taken near the onset of an episode. Alternative causative factors for KLS are nonetheless possible, including a mild recurrent metabolic encephalopathy of unknown origin.

A limitation of this study was its retrospective design, a design known to favor recall bias. In this case, however, we are encouraged by the fact that remarkably few differences were found between cases and control subjects, and the fact that birth is not temporally related to KLS onset (birth difficulties were one of the only significant differences). Furthermore, we did not examine all patients in person or interviewed all family members, thus potentially underestimating familial risk. Additional replication and more systematic studies are needed to confirm and extend on these observations.

The results of our survey of attempted therapies were disappointing. A novel utility of amantadine was found in the symptomatic treatment of episodes. Similarly, lithium and valproate had occasional preventive effects. Importantly, these effects were marginal, rare, and most cases patients elected to abandon further use. Furthermore, the overstated efficacy of these therapies has had the consequence of blurring differential diagnosis and causative boundary with psychiatric disorders. In contrast with bipolar disorder, depression, and schizophrenia, KLS patients did not report psychiatric symptoms between episodes and had no significant family history for these disorders, confirming the distinct nature of KLS. We believe this finding is important because it is common for patients with KLS to be misdiagnosed with a psychiatric entity and sometimes hospitalized, with negative consequences considering the exacerbation of the cognitive symptoms in novel environments.

In conclusion, this study supports the existence of KLS as a disease entity and suggests that disease management should be primarily supportive and educational. This typically involves instructing parents to let children sleep with adequate supervision (eg, avoidance of driving and surveillance if depressed mood). Occasional trials of valproate and amantadine may be proposed. We also suggest that the cause of KLS involves a strong genetic predisposition. KLS has parallels to symptoms of broad interest in neurology, psychiatry (episodic course, cognition, depression), and medicine (increased sleep, altered food intake, and hypersexuality); thus, further research on KLS is likely to benefit the greater neuropsychiatric and medical communities.

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