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NEUROLOGICAL DISORDERS

Long-Term Cognitive Impairment in Kleine-Levin Syndrome

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Study Objectives: In Kleine-Levin syndrome (KLS), episodes of hypersomnia, cognitive, and behavioral disturbances alternate with asymptomatic periods. Because 50% of patients report decreased academic performances, we evaluated their cognitive status during asymptomatic periods, determinants of deficits, and changes during follow-up.

Methods: The cognitive assessment during asymptomatic periods in all consecutive patients with typical KLS and healthy controls included the non-verbal intelligence quotient (Raven Progressive Matrices), the Trail Making Test, the Stroop Color-Word Test, the Wechsler Memory Test, verbal fluencies, the Free and Cued Learning Memory Test, and the Rey-Osterreith Complex Figure. Cognitive status was reevaluated after 0.5 to 2 y in 44 patients.

Results: At baseline, compared with the 42 controls, the 122 patients with KLS exhibited lower non-verbal intelligence quotient, speed of processing, attention, and reduced retrieval strategies in episodic memory. Higher episode frequency, shorter episode duration, shorter time since last episode, deeper sleep, and megaphagia during episodes predicted impaired memory. The visuoconstructional abilities and non-verbal memory were intact. After a mean follow-up of 1.7 ± 1.0 y, the episode frequency decreased from 4.6 ± 4.8 to 1.7 ± 1.9/y. The logical reasoning and attention improved, the processing speed remained low, and the retrieval strategies in verbal memory further worsened.

Conclusions: In this field study, one-third of patients with KLS have long-term cognitive deficits affecting retrieval and processing speed. Cognitive function should be systematically tested in patients with KLS, which appears important to help patients in their academic studies.

Keywords: episodic verbal memory, Kleine-Levin syndrome, processing speed, retrieval

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Significance

Kleine-Levin syndrome is a rare disorder in adolescents, with relapsing-remitting episodes including hypersomnia, mental confusion, derealization and apathy. It has been considered benign because patients exhibit apparently normal sleep, cognition and behavior during asymptomatic periods and episodes become less frequent with older age. For the first time, we systematically assessed the cognitive abilities in a large, controlled cohort of patients and followed their performance 2 years later. One third of the patients had reduced short-term verbal memory, slow processing speed and reduced attention. Most defects improved at follow-up; however, the verbal memory became worse and processing speed remained reduced. These results suggest to systematically investigate cognitive performance in patients, to provide support for their academic studies, and to actively treat patients.

INTRODUCTION

Kleine-Levin syndrome (KLS) is a rare (approximately two cases per million individuals) neuropsychiatric disorder of unknown origin, which primarily affects adolescents.[1] It is characterized by recurrent episodes of hypersomnia, confusion, derealization, apathy, and decreased mood. In addition, one-third to two-thirds of patients exhibit disinhibited behavior with megaphagia and hypersexuality, hallucinations, and delusions during some episodes. Episodes typically last 1 to 4 w and are separated by long periods (that last several months) with apparently normal sleep, cognition, mood, and behavior. The disease tends to disappear after a median 14 y in adolescents; however, it persists in most patients when the onset is in adulthood and childhood.[2,3]

Cognition is severely impaired during episodes: 91% of patients have difficulties concentrating, and 87% of patients are lost in time and, in some cases, space.[2–4] They are bedridden and unable to read, answer the phone, or perform homework. During a formal neurological examination, the primary sensory and motor functions are unaffected; however, psychomotor slowness is obvious, with patients slow to speak and answer. Most patients have partial or complete retrograde amnesia of events during episodes.[2–4] Formal cognitive tests have rarely been used, and their validity has been questionable in uncooperative, sleepy, and inattentive patients.[5] The clinical and cognitive status changes at the end of an episode either abruptly (within hours) or with a progressive return to their basic levels that may last up to 1 w. Most patients have partial or complete retrograde amnesia of events during episodes.[1,3] During asymptomatic periods, cognition is supposedly unaffected.[6] Teenagers return to school and complete the missed lessons. Although cognitive tests have rarely been performed in the 168 cases published between 1925 and 2004, the case reports described persistent cognitive impairment and academic decline since disease onset in eight patients.[7–12] In addition to these eight cases, four Swedish patients exhibited residual short-term memory impairment on formal tests in the absence of spontaneous complaints, which persisted 6 y after the previous episode in one case.[12] The authors made a parallel between these abnormal cognitive tests and residual hypoperfusions in the temporal lobe between episodes. Several functional brain imaging studies highlight abnormal perfusion in patients with KLS, even during asymptomatic periods.[13–17] These results suggest that cognitive impairment and abnormal brain functioning during asymptomatic periods may be more frequent than expected by simple patient interviews and may

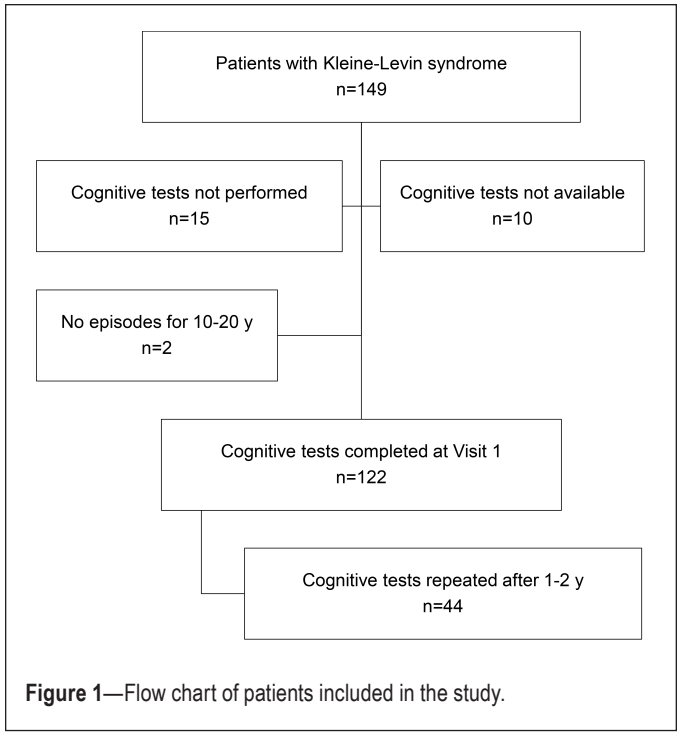

Figure 1—Flow chart of patients included in the study.

primarily translate in formal testing. We therefore systematically studied the cognitive status of patients with KLS during asymptomatic periods and compared their results with healthy controls to identify the determinants of deficits; we also compared their changes with time of follow-up and disease severity.

METHODS

Participants

Between 2007 and 2014, KLS was diagnosed in 149 patients in the Pitié-Salpêtrière Hospital, according to international criteria[6]: (1) episodes of hypersomnia lasting from 2 d to 4 w and occurring at least once per year; (2) during these hypersomnia episodes, patients exhibited cognitive abnormalities (e.g., confusion, slow speaking/thinking, derealization), abnormal behavior, hyperphagia, or hypersexuality; (3) the episodes were intermixed with intervals of normal alertness, mood, cognition, and behavior typically lasting several months; and (4) the symptoms were not better explained. Neurologists and psychiatrists interviewed and examined the patients, and reviewed the available tests (brain magnetic resonance imaging, brain scintigraphy, and biological tests focused on autoimmunity, amino acid metabolism, ammonemia, and toxic and drug uses). Patients with differential diagnoses were carefully excluded as previously described[3] (Figure 1). Cognitive tests were not available (n = 9), performed only during an episode (n = 1), or not performed prior to 2008 (n = 11), because of a lack of time (n = 2) or language issues (n = 2). Two patients were excluded from the analysis because their last episode was 10 and 20 y before Visit 1. Eventually, 122 patients with KLS (116 untreated, 6 treated), who were native French speaking, completed the full cognitive tests at Visit 1. Forty-four patients had a second cognitive assessment, because they were followed up in the center. Age- and sex-matched healthy controls were recruited by advertisement. They had no signs of sleep, neurological, psychiatric, or cognitive disorders, as assessed by a clinical interview and examination. They were recruited to match for age, sex, and education with the 42 patients having undergone a brain scintigraphy.[17] The controls but not the patients were paid for their participation. All subjects (plus their parents if minors) signed an informed consent prior to participation in the study, which was approved by the local ethics committee (CPP-IdF-06).

Investigations

At Visit 1, after the diagnosis was performed, the patients and their families completed the Stanford KLS questionnaire,[2] the Starkstein Apathy score,[18] and the Derealization/Depersonalization Inventory.[19] The controls completed the same questionnaires, with the exclusion of the questions relative to the syndrome. At Visit 2 (performed in only the patients), the time, number and duration of episodes since Visit 1, as well as the presence of a preventive KLS treatment were assessed. The cognitive tests were part of the standard clinical routine at the center since 2008. Patients coming from a long distance either slept in the center (without any polysomnography) or in Paris to avoid fatigue. A functional brain imaging, including single photon emission computed tomography scanning with technetium-99m exametazime or with technetium-99m ethyl cysteinate dimer, or positon emission tomography with 18F fluorodeoxyglucose (depending on available radiomarker) was performed for clinical purpose, unless it had been done elsewhere before. The cognitive tests (which lasted around 90 min) were administered at the same morning time and scored according to standard procedures by neuropsychologists in both visits.[20] The patients were interviewed regarding their educational levels and cognitive problems since the disease onset. The logical reasoning was assessed by the Progressive Matrices of Raven-38, which assigns a non-verbal intelligence quotient (nvIQ).[21] Seven cognitive domains were defined: speed of processing, attention, working memory, executive functions, visuoconstructional abilities, and episodic non-verbal and verbal memory. Executive functions, working memory, and attention were evaluated using the forward and backward Digit Span Test of the Wechsler Memory Test,[22] Trail Making Test-B,[23] a modified version of the Stroop Color Word Test (Part IV: naming the color and not the word itself, and Part IV-III, as an interference score calculated from Part III: naming the printed color) for the numbers of correct answers and errors,[24] the semantic verbal fluencies (number of animal names produced within 1 min) and the phonemic verbal fluencies (number of words starting with M and P produced within 1 min). The speed of processing was evaluated with the time of Trail Making Test-A, the number of correct answers in Stroop subtest I-III. The visuoconstructional abilities were evaluated with a copy of the Rey-Osterreith Complex Figure, whereas the figure delayed recall evaluated the episodic non-verbal memory.[25] The episodic verbal memory was evaluated with the Free and Cued Selective Reminding Test.[26] The results are shown as the raw results and standard deviations (z score) or centiles from the French norms for age, sex, and education.[27–33] Z scores were considered as pathological when lower than −1.5,

Table 1—Demographic and clinical characteristics of 122 patients with Kleine-Levin syndrome at time of the first cognitive evaluation (asymptomatic period, Visit 1) and 42 healthy controls.

	Patients	Controls	P
Age, y	21.5 ± 9.0 (16–24)	22.5 ± 8.5 (18.2–24.5)	0.69
Sex ratio, % men	60.7	57.1	0.72
Body mass index, kg/m^2	22.2 ± 4.1 (19.7–23.4)	23.5 ± 4.1 (21.4–24.9)	0.17
Laterality, right handed %	85.0	91.0	0.41
Birth or development problems, %	30.4	3.0	0.001
Educational level, 3–7	4.6 ± 1.4 (4–6)	5.4 ± 1.3 (4–6)	0.002
Non-verbal intelligence quotient	107.7 ± 12.2 (100–115)	113.8 ± 10.5 (109–125)	0.040
Epworth Sleepiness Scale score, 0–24	6.0 ± 4.9 (3–8)	6.2 ± 3.3 (4–9)	0.82
Typical sleep time, min	510 ± 73 (480–540)	503 ± 95 (457–592)	0.63
Morning-Evening score, 0–86	49.7 ± 9.7 (44–56)	49.6 ± 9.8 (43–58)	0.98
Apathy score, 0–42	9.2 ± 4.2 (6.3–11)	9.1 ± 3.4 (7–10)	0.94
Hospital Anxiety and Depression scale			
Total score, 0–14	9.1 ± 5.7 (5–12)	8.6 ± 5.0 (6.3–9.5)	0.60
Anxiety score, 0–7	6.1 ± 3.6 (4–8)	6 ± 3.6 (6.3–9.5)	0.84
Depression score, 0–7	3.2 ± 3.3 (1–5)	2.7 ± 2.2 (1–2)	0.37

Data are mean ± standard deviation (first-third quartile).

except for the verbal memory test (−1.65). The 44 patients who had a second cognitive evaluation did not differ at study entry in sex, educational level, handedness, cognitive complaint, age at disease onset, or disease severity from the patients who had a single cognitive assessment (data not shown). The cognitive assessment at Visit 2 used the same tests in the same order with a version B when available (Taylor Complex Figure, beta version of the Free and Cued Selective Reminding Test).[34]

Statistical Analysis

Clinical measures were described as means ± standard deviation (SD) and first-third quartile (quantitative measures) and percentages (qualitative measures). They were compared between independent groups via Student *t*-tests (quantitative measures) and chi-square and Fisher exact tests (qualitative measures). Cognitive performances were described as means ± SD and z score (SD from normative French measures for age, sex, and education). The controls had a higher nvIQ and educational level than the patients; thus, the cognitive tests means were also compared between the groups by unbalanced analyses of variance after adjustment for nvIQ and educational level, and subsequently presented as the least-square means and standard errors. Correlations were tested using the Spearman rank correlation coefficient test and limited to changes between Visit 1 and Visit 2. The between-subjects differences were tested via paired Student *t*-tests. The comparisons between patients with and without cognitive deficiencies were assessed by two-sample Wilcoxon test, because one of the sample size was low. All tests were two-sided, with a significant $P < 0.05$. Computations were performed using the SAS-V9 statistical package (SAS Institute Inc, Cary, NC, USA).

RESULTS

The patients had more birth and developmental difficulties (Table 1) and a lower educational level than the controls (only 38% of the patients had the high-school A-level versus 62% of the controls, $P < 0.01$). The body mass index, handedness, daytime sleepiness, sleep time and quality, as well as the morning-evening, apathy, anxiety, and depression scale scores were similar in the patients during asymptomatic periods and the controls. At Visit 1, the patients had KLS for 5.6 ± 7.3 (1.3–6.4, Q1-Q3) y, with 15.4 ± 32.2 (5–14) episodes that lasted 15.9 ± 21.7 (7–15) d. Eleven patients had an adult onset (from age 20 to 45 y) disease. At time of Visit 1, 21 patients (17.2%) with KLS versus 5 controls (11.9%) were younger than 16 y old, and 7 patients (5.7%) with KLS versus 3 controls (7.1%) were younger than 15 y old, with no significant difference of percentage between groups. Thirty-five patients (29%) had prolonged (longer than 30 d) episodes. During at least one episode, the patients presented major hypersomnia (100%), cognitive problems (100%), including time (89%) and space (57%) disorientation, derealization (96%; derealization score: 64.3 ± 20.9), major apathy (93%; apathy score: 32 ± 7.5), logopenia (73%), depressive mood (72%), megaphagia (60%), hypophagia (39%), hypersexuality (38%), hallucinations (47%) and delusions (43%). The amnesia of the episode events was partial in 57% of the patients, and total in 10%.

Cognitive Evaluation at Visit 1

Since the disease onset, 53 of 107 patients (49.5%) reported a decreased performance at school or work, and had missed school or work during 18.7 ± 31.1 (4–20) w. During the asymptomatic periods, 35 of 96 patients (36.5%) had cognitive complaints, including problems regarding attention (25%), memory (19%), processing multiple information (4%), and finding ordinary words (4%). The cognitive evaluation was performed after 67 ± 80 (14–90) d from the end of the previous episode. All participants were cooperative and exhibited normal behavior during the tests. As indicated in Table 2, the speed of processing was slower in patients than in controls, with abnormal scores at

Table 2—Evaluation of cognitive functions (speed of processing, attention, working memory, and executive functions) in patients with Kleine-Levin syndrome and healthy controls at Visit 1.

Cognitive Domains	Patients	Controls	P
No. of subjects	122	42	
Speed of processing			
TMT-A, sec	29.3 ± 13.2	28.3 ± 10	0.60
TMT-A, centiles	67.2 ± 25	62.3 ± 22.8	0.28
Subjects with deficient score (centile < 12), %	6.4%	5.6%	0.81
Stroop I, correct words	108.5 ± 17.8	121.1 ± 19.2	0.0002
Stroop I, correct words, z score	−0.2 ± 1.2	0.6 ± 1.3	0.0003
Subjects with deficient score (z ≤ 1.5), %	13.7%	2.4%	0.09
Stroop II, correct color-words n	97.8 ± 22.3	110.4 ± 21.9	0.002
Stroop II, correct color-words, z score	−0.59 ± 1.4	0.33 ± 1.36	0.0004
Subjects with deficient score (z ≤ 1.5), %	21.7%	2.5%	0.01
Stroop III, correct colors	72.1 ± 13.3	76.3 ± 17.8	0.11
Stroop III, correct colors, Z score	0.05 ± 1.17	0.41 ± 1.56	0.12
Subjects with deficient score (z ≤ 1.5), %	8.5%	7.3%	0.91
Attention			
WMS digit span forward (0–9), n	6.3 ± 1.1	7.1 ± 1.6	0.001
Subjects with deficient score (< 5), %	4.3%	0.0%	0.41
Stroop I, word errors	0.3 ± 0.7	0.1 ± 0.6	0.13
Stroop II, color-word errors	0.6 ± 1.2	0.2 ± 0.4	0.02
Stroop III, color errors	1.4 ± 1.8	0.4 ± 0.6	0.001
Stroop IV (interference), errors	1.7 ± 1.9	0.9 ± 1.2	0.01
Working memory			
WMS digit span backward (0–8), n	4.5 ± 1.1	4.6 ± 1.7	0.66
Subjects with deficient score (< 3), %	3.4%	9.7%	0.23
WMS total digit span (0–17), n	10.8 ± 1.8	11.7 ± 2.5	0.02
WMS total digit span (0–17), z score	0.1 ± 0.8	0.5 ± 1.2	0.01
Subjects with deficient score (z ≤ 1.5), %	1.6%	0.0%	0.99
Executive functions			
TMT-B, sec	64.4 ± 29.6	55.8 ± 20.7	0.08
TMT-B, centiles	64.7 ± 25.4	71.1 ± 21.4	0.19
Subjects with deficient score (centile < 12), %	4.5%	2.8%	0.97
TMT B minus A, seconds	35.1 ± 23.6	27.4 ± 15.3	0.06
Subjects with deficient score (> 70 sec), %	10.2%	2.4%	0.22
Stroop Interference, correct words	45.9 ± 10.3	50.7 ± 14.8	0.02
Stroop Interference, correct words, z score	0.24 ± 1.35	0.84 ± 1.98	0.03
Subjects with deficient score (z ≤ 1.5), %	7.8%	9.8%	0.92
Stroop Interference score	25.9 ± 9.1	25.6 ± 8.8	0.84
Stroop Interference score, z score	0.06 ± 1.05	−0.22 ± 1.02	0.14
Subjects with deficient score (z ≤ 1.5), %	4.9%	7.1%	0.86
Verbal fluency (categories), words n	21.1 ± 5.3	22.8 ± 5	0.08
Verbal fluency (categories), z score	−0.56 ± 0.9	−0.44 ± 0.81	0.45
Subjects with deficient score (z ≤ 1.5), %	13%	2.4%	0.10
Verbal fluency (letter M), n	11.7 ± 4.2	12.4 +4.8	0.41
Verbal fluency (letter M), z score	−0.89 ± 0.96	−0.99 ± 1.29	0.59
Subjects with deficient score (z ≤ 1.5)	22.6%	23.8%	0.83
Verbal fluency (letter P), n	13.1 ± 4.6	14.1 ± 5	0.23
Verbal fluency (Letter P), z score	−1.0 ± 1.49	−0.93 ± 1.56	0.79
Subjects with deficient score (z ≤ 1.5), %	27.0%	31.0%	0.58

Stroop, Stroop Color Word Test; TMT-A, Trail Making Test, part A; TMT-B, Trail Making Test, part B; WMS, Wechsler Memory Scale. Z scores, standard deviations from age, sex, and education French normative values. Data are mean ± standard deviation or %.

Table 3—Evaluation of cognitive functions (visuoconstructional abilities, non-verbal and verbal memory, non-verbal intelligence quotient) in patients with Kleine-Levin syndrome and healthy controls at Visit 1.

Cognitive Domains	Patients	Controls	P
No. of subjects	122	42	
Non-verbal intelligence quotient	107.7 ± 12.2	113.8 ± 10.5	0.01
Subjects with deficient score (IQ < 80), %	0.8%	0.0%	0.56
Visuoconstructional abilities			
ROCFT, Score in copy, 0–36	34.5 ± 2.2	34.9 ± 1.7	0.25
ROCFT, Percentile in copy	84.5 ± 22.7	86.4 ± 23.1	0.66
Subjects with deficient score (centile < 12), %	1.9%	0.0%	0.99
Subjects with deficient score (copy type ≠ 1), %	59.0%	41.7%	0.09
Non-verbal memory			
ROCFT, Score in memory, 0–36	23.4 ± 6.2	24.8 ± 5.1	0.21
ROCFT, Percentile in memory	55.8 ± 30.3	62.4 ± 26	0.24
Subjects with deficient score (centile < 12), %	11.2%	5.4%	0.41
Subjects with deficient score (copy type ≠ 1), %	22.0%	25.7%	0.72
Verbal memory			
FCSRT, Immediate first recall, 0–16 words	9.4 ± 2	11.7 ± 2	< 0.00001
FCSRT, Immediate first recall, z score	−0.62 ± 0.96	0.35 ± 0.93	< 0.00001
Subjects with deficient score (z ≤ 1.65), %	19.2%	2.6%	0.02
FCSRT, Immediate second recall, 0–16 words	11.4 ± 1.9	12.9 ± 1.5	0.00003
FCSRT, Immediate second recall, z score	−0.57 ± 1.05	0.17 ± 0.82	0.0002
Subjects with deficient score (z ≤ 1.65), %	14.1%	0%	0.02
FCSRT, Immediate third recall, 0–16 words	12.5 ± 1.8	14.5 ± 1.3	< 0.00001
FCSRT, Immediate third recall, z score	−0.73 ± 0.97	0.20 ± 0.64	< 0.00001
Subjects with deficient score (z ≤ 1.65), %	15.2%	0%	0.02
FCSRT, Immediate free total recall, 0–48 words	33.6 ± 5.4	38.0 ± 3.8	< 0.00001
FCSRT, Immediate free total recall, z score	−1.31 ± 1.43	−0.25 ± 1.07	0.00003
Subjects with deficient score (z ≤ 1.65), %	36.8%	12.2%	0.003
FCSRT, Delayed free recall, 0–16 words	12.9 ± 2	14.1 ± 1.6	0.0004
FCSRT, Delayed free recall, z score	−0.73 ± 1.07	−0.62 ± 0.7	0.56
Subjects with deficient score (z ≤ 1.65), %	17.0%	7.7%	0.26
FCSRT, Delayed cued recall, 0–16 words	15.7 ± 1	15.7 ± 0.7	0.88
Subjects with deficient score (score < 14), %	1.9%	2.6%	0.69

FCSRT, Free and Cued Selective Reminding Test; ROCFT, Rey-Osterrieth complex Figure Test; Z scores, standard deviations from age, sex, and education French normative values. Data are mean ± standard deviation or %.

the reading Stroop Test II in 21.7% of the patients. The attention was also more reduced in patients than in controls, as indicated by a lower digit span forward and a progressively increasing number of errors with increasing task difficulty when reading the four sheets of the Stroop Color-Word Test (this increasing error rate was not observed in controls). Performances were as normal as in controls in the domains of working memory and executive functions. The logical reasoning was lower in patients than in controls, as indicated by a lower non-verbal intelligence quotient (Table 3). The copy and recall of the Rey-Osterrieth Complex Figure were normal. In contrast, verbal memory was altered, with abnormal immediate retrievals in 15% to 37% of the patients (versus 0 to 2.6% of the controls) at the Free and Cued Selective Reminding Test. After adjustment by educational level and nvIQ (Table S1, supplemental material), the patients had worse cognitive performances than the controls in short-term memory (lower forward digit span), verbal speed processing (slower at reading Stroop subtests I-II), attention (more errors in the Stroop subtest III and IV), and the capacity of self-initiated recovery of verbal episodic information (lower free total recall).

Similar results were identified following the exclusion of the 18 patients who had a recent (less than 7 d) episode, of the six treated patients at Visit 1, of the children younger than 16 y and younger than 15 y at time of Visit 1, and of patients who had KLS onset before age 16 y (data not shown).

Determinants of Cognitive Performances

When comparing the demographical and clinical characteristics of the patients with (n = 25) and without (n = 90) reduced speed of processing at the Stroop Test II, the patients with reduced speed processing had lower derealization scores during episodes (52 ± 27 versus 67 ± 19, P = 0.009) but had no other differences. The patients with (n = 50) versus those without

(n = 72) altered immediate free total recall spontaneously complained more frequently of difficulties in attention (40% versus 16%, P = 0.02) and memory (29% versus 12%, P = 0.04). They had a higher episodes frequency (4.6 ± 4.5 versus 3.2 ± 2.8 episodes per year, P = 0.048), and a shorter time since last episode (43 ± 46 versus 84 ± 94 days, P = 0.01), but no difference in age, sex ratio, prematurity or birth difficulties, education, disease course, and cumulated plus recent absence from school or job. During episodes, they had more frequently increased dreaming (80% versus 55%, P = 0.004), and megaphagia (59% versus 38%, P = 0.048). There were no differences of sleep time, sleepiness, anxiety, depression eating behavior, and apathy scores during asymptomatic periods between both groups. The patients with prolonged episodes or birth/developmental abnormalities did not perform worse on the cognitive tests than the other patients.

Cognitive Evolution at Follow-Up

Forty-four patients (35%) had a second cognitive assessment, which was performed 1.7 ± 1.0 y (20.6 ± 11.6 mo) after Visit 1. One patient was retested less than 6 mo (at 5.9 mo exactly) after Visit 1, 13 patients were tested between 6 mo and 1 y after, 18 patients were retested after 1 to 2 y and 12 patients were tested after 2 y. This subgroup did not differ at Visit 1 from the 80 patients with KLS who had no second cognitive assessment. Since Visit 1, the patients suffered 2.7 ± 2.8 (range: 0–12) episodes, including five patients without a new episode, and 34 ± 38 d spent in episodes. The frequency of the episodes was reduced from 4.6 ± 4.8 per year before Visit 1 to 1.7 ± 1.9 per year between Visits 1 and 2. Almost all patients (n = 36; 82%) were untreated at Visit 1, whereas 36 patients (lithium, n = 24, sodium valproate, n = 11, lamotrigine, n = 1) were treated at Visit 2 and 8 patients were not treated. At Visit 2 (Tables 4 and 5), the speed of processing did not change (except for an improved time at the Trail Making Test A), the attention improved (they performed less errors with increasing task demand in the Stroop Word-Color Test), the working memory did not change, the executive functions slightly improved, the non-verbal intelligence quotient improved at the point of normalizing (which became a mean not different from the controls quotient, data not shown; but P = 0.06), and the visuoconstructional abilities and non-verbal memory (which were not deficient before) did not change. In contrast to these stabilities or improvements in cognitive functioning, the patients further worsened their performances in the capacity to self-initiate the recovery of verbal information (lower free total recall).

No marker of the disease severity (frequency or duration of episodes, time since last episode, time incapacitated) predicted the improvement of time in the Trail Making Tests A and B, the reduction of errors in the Stroop Test and the decreased score in the free total recall.

DISCUSSION

Patients with KLS may have impaired cognitive abilities that persist during asymptomatic periods, regardless of the disease severity. In addition to a lower logical reasoning and nvIQ, they have slower speed of processing, reduced attention, and reduced retrieval strategies in episodic verbal memory, compared with healthy controls. Specifically, 37% of patients with KLS have altered immediate episodic verbal memory. Executive functions, visuo-constructional abilities, and non-verbal memory are intact. After 1.7 y of disease course, the speed of processing remains reduced, the retrieval strategies in episodic verbal memory further worsen, but the previously impaired logical reasoning and attention improve. Other cognitive performances are unchanged.

Whether KLS affects cognition during asymptomatic periods, and even when the disease has receded, is a recent matter of concern. Our findings confirm and extend several previous abnormalities identified in isolated cases and small series assessed during asymptomatic periods. Impaired verbal and non-verbal memory, a low average of intellectual functioning,[8,15,35,36] and reduced digit span[35] were identified in individual patients. The capacity of verbal and non-verbal short-term memory was reduced in four patients, and this reduction persisted 13 y after the previous episode in one patient.[16] Eight patients performed with lower accuracy and longer latency in a taxing verbal memory task than controls, whereas their general cognitive capacity and performance on repetition of digits and letters were intact.[14] In contrast, the repetition of digits (even in the simple forward order) is reduced in our group, likely because its larger size allows the identification of more subtle differences. Importantly, our patients exhibit a slower speed of processing as well as reduced attention. A lower nvIQ is also a surprising finding because many patients were high-level students prior to the disease. However, this test may be adversely influenced by the lower speed of processing. In contrast, tasks that involve mental flexibility and working memory are performed within normal ranges. Regarding episodic memory, the patients have robust deficits of immediate but not delayed recall, indicating a difficulty in the retrieval of information immediately after encoding (which translates to a problem in the frontal or subcorticofrontal cognitive network rather than a hippocampal defect). Nevertheless, once the information is acquired, the retention of verbal information and the "long-term" episodic memory are intact.

Brain functional imaging may provide substrates for understanding the mechanisms of the lower cognitive performance during KLS asymptomatic periods. In functional magnetic resonance imaging (fMRI), brain activations in areas related to working memory and effortful processing (left dorsolateral prefrontal cortex, bilateral posterior parietal cortex, and left thalamus) increased in patients with KLS with mounting effort in the verbal working memory task.[14] Patients with higher performing working memory had increased thalamic activation assessed in contrast to the higher performing controls who had decreased thalamic activation, which suggests increased effort at a lower load.[14–16] The thalamus is hypoperfused during rest in single photon emission computed tomography in patients with KLS[13,17]; thus, these results suggest a persistent thalamic dysfunction between episodes, which is compensated by overactivation of the same network in patients when they have to cope with cognitive tasks. However, this "thalamic" explanation may be oversimplistic because the executive functioning also requires several other intact areas when the cognitive effort increases, including the mesial prefrontal gyri[37] and

Table 4—Evolution of speed of processing, attention, working memory and executive functions after on average 1.7 y in 44 patients with Kleine-Levin syndrome.

	Visit 1	Visit 2	P
Age at the visit, y	21.1 ± 6.3	23.0 ± 11.3	
Speed of processing			
TMT-A, sec	31.6 ± 15.5	26.6 ± 9.3	0.02
TMT-A, centiles	61.8 ± 27.2	69.0 ± 24.9	0.08
Subjects with deficient score (centile < 12), %	9.1%	2.3%	0.36
Stroop I, words	103.4 ± 17.1	106.8 ± 14.8	0.11
Stroop I, z score	−0.52 ± 1.14	−0.3 ± 1	0.11
Subjects with deficient score (z ≤ 1.5), %	14%	11.4%	0.72
Stroop II, color-words	93.7 ± 23.8	94.1 ± 19.1	0.94
Stroop II, z score	−0.86 ± 1.51	−0.8 + 1.2	0.84
Subjects with deficient score (z ≤ 1.5), %	23.2%	20.5%	0.75
Stroop III, colors	70.5 ± 14.2	70.5 ± 13.6	0.96
Stroop III, z score	−0.1 ± 1.3	−0.2 ± 1.2	0.37
Subjects with deficient score (z ≤ 1.5), %	9.1%	6.8%	1.00
Attention			
Stroop I, word errors	0.2 ± 0.8	0.02 ± 0.2	0.08
Stroop II, color-word errors	0.6 ± 1.2	0.3 ± 0.5	0.09
Stroop III, color errors	1.2 ± 1.4	0.3 ± 0.7	0.00006
Stroop IV (interference), errors	1.7 ± 1.8	0.9 ± 1.3	0.0008
WMS digit span forward (0–9), n	6.3 ± 1.2	6.3 ± 1.3	0.90
Subjects with deficient score (< 5), %	6.8%	6.8%	1.00
Working Memory			
WMS Digit span backward (0–8), n	4.3 ± 1.0	4.6 ± 1.3	0.09
Subjects with deficient score (< 3), %	2.3%	4.5%	1.00
WMS total digit span (0–17), n	10.6 ± 1.7	10.9 ± 2.3	0.21
Executive function			
TMT-B, sec	68.0 ± 30.8	59.2 ± 22.4	0.03
TMT-B, centiles	58.9 ± 24.6	68.4 ± 24.8	0.08
Subjects with deficient score (centile < 12), %	4.5%	2.3%	1.00
TMT B minus A, sec	36.4 ± 20.8	32.4 ± 18.5	0.24
Subjects with deficient score (> 70 sec), %	4.5%	2.3%	1.00
Stroop interference, correct words	43.9 ± 10.6	45.9 ± 10.7	0.04
Stroop interference, correct words, z score	0.02 ± 1.5	0.2 ± 1.4	0.17
Subjects with deficient score (z ≤ 1.5), %	7%	6.8%	0.69
Stroop interference score	26.1 ± 8.5	24.8 ± 9.3	0.25
Stroop interference score, Z score	−0.09 ± 0.99	0.3 ± 1.1	0.07
Subjects with deficient score (z ≤ 1.5), %	6.8%	2.3%	0.61
Verbal fluency (letter M), n	12.0 ± 3.4	12.0 ± 4.3	0.86
Verbal fluency (letter M), z score	−0.8 ± 0.81	−0.9 ± 1.1	0.70
Subjects with deficient score (z ≤ 1.5)	14.3%	31.7%	0.06
Verbal fluency (letter P), n	13.1 ± 4.1	12.6 ± 4.4	0.70
Verbal fluency (letter P), z score	−1.1 ± 1.4	−1.4 ± 1.7	0.60
Subjects with deficient score (z ≤ 1.5), %	28.6 %	36.6%	0.44
Verbal fluency (categories), words n	20.5 ± 4.8	20.1 ± 4.9	0.86
Verbal fluency (categories), z score	0.6 ± 0.9	−0.75 ± 0.83	0.85
Subjects with deficient score (z ≤ 1.5), %	16.7%	12.2%	0.56

Stroop, Stroop Color Word Test; TMT-A, Trail Making Test, part A; TMT-B, Trail Making Test, part B; WMS, Wechsler Memory Scale. Data are mean ± standard deviation, or %.

the inferior parietal cortex,[38] which were hypoperfused in 41 patients with KLS.[17] Similarly, the anterior cingulate and anterior insular cortex were hypoactivated during a verbal working memory task, whereas the left dorsolateral prefrontal

Table 5—Evolution of non-verbal intelligence, visuoconstructional abilities, non-verbal and verbal memory after on average 1.7 y in 44 patients with Kleine-Levin syndrome.

	Visit 1	Visit 2	P
Non-verbal Intelligence			
PMR-38 Score (0–60)	46.1 ± 6.4	49.0 ± 6.9	0.09
PMR-38 Non-verbal intelligence quotient	104.9 ± 9.9	111.2 ± 10.7	0.003
Visuoconstructional abilities			
ROCFT, Score in copy, 0–36	34.4 ± 2.1	35.0 ± 1.9	0.024
ROCFT, centile in copy	82.4 ± 23.4	89.8 ± 20.9	0.035
Subjects with deficient score (centile < 12), %	2.8%	2.5%	0.52
Subjects with deficient score (copy type ≠ 1), %	55.6 %	20.0%	< 0.0001
Non-verbal memory			
ROCFT, Score in memory, 0–36	22.0 ± 6.9	25.9 ± 6.5	< 0.0001
ROCFT, Centile in memory	48.0 ± 33.6	68.3 ± 31.4	< 0.0001
Subjects with deficient score (centile < 12), %	19.4%	5.0%	0.11
Subjects with deficient score (copy type ≠ 1), %	20.0%	5.0%	0.12
Verbal memory			
FCSRT, Immediate first recall, 0–16 words	9.6 ± 2.1	9.4 ± 1.7	0.67
FCSRT, Immediate first recall, z score	−0.5 ± 0.99	−0.5 ± 0.7	0.95
Subjects with deficient score (z ≤ 1.65), %	14.7%	5.1%	0.32
FCSRT, Immediate second recall, 0–16 words	11.5 ± 2.2	11.5 ± 1.9	0.98
FCSRT, Immediate second recall, z score	−0.5 ± 1.1	−0.4 ± 0.8	0.48
Subjects with deficient score (z ≤ 1.65), %	11.8%	10.3%	0.86
FCSRT, Immediate third recall, 0–16 words	12.6 ± 2	12.2 + 1.9	0.09
FCSRT, Immediate third recall, z score	−0.67 ± 0.98	−0.8 ± 0.8	0.43
Subjects with deficient score (z ≤ 1.65), %	14.7%	12.8%	0.81
FCSRT, Immediate free total recall, 0–48 words	35.0 ± 4.9	32.9 ± 4.4	0.007
FCSRT, Immediate free total recall, z score	−0.98 ± 1.2	−1.4 ± 1.2	0.02
Subjects with deficient score (z ≤ 1.65), %	32.6%	40%	0.48
FCSRT, Delayed free recall, 0–16 words	13.0 ± 1.7	12.5 ± 1.9	0.15
FCSRT, Delayed free recall, z score	−0.51 ± 1.0	−0.8 ± 0.9	0.14
Subjects with deficient score (z ≤ 1.65), %	12.2%	22.5%	0.22
FCSRT, Delayed cued recall, 0–16 words	15.6 ± 1.0	15.9 ± 0.4	0.17
Subjects with deficient score (< 14), %	2.7%	0%	0.98

FCSRT, Free and Cued Selective Reminding Test; PMR-38, Progressive Matrices of Raven-38 items; ROCFT, Rey-Osterrieth Complex Figure Test.

cortex was hyperactivated in fMRI in patients compared with controls.[14] These results suggest that patients operate with a deficient executive and associative network (as evidenced by hypoperfusion during resting state), but are able to compensate for many cognitive tasks (as evidenced by hyperactivity when stimulated in the previously hypoperfused area), with the price of decreased processing speed and attention abilities.

The altered episodic memory and slower speed of processing may represent an after-effect of the major confusion and mental slowness present during episodes. Indeed, the patients with altered episodic memory have a KLS form including more frequent and more recent episodes, as well as episodes containing increased dreaming and more frequent megaphagia. Notably, the cognitive defects are not a consequence of missed school days, because cumulated absence from school, as well as the proportion of patients having completed the 10th y of schooling at time of KLS onset are similar between patients with and without cognitive deficiencies.

In this sample, we cannot determine whether cognition was previously altered prior to the onset of KLS because it was not measured. Notably, the patients with and without birth/developmental abnormalities have similar cognitive performances, which rules out a deleterious effect of perinatal problems on adolescent cognition. Furthermore, more than one- third of patients complain of daily cognitive problems that did not previously exist, and half of the patients notice that their academic or work performance had decreased since disease onset. These findings suggest that the cognitive problems are by-products of the episodes rather than a predisposing condition.

The cognitive disturbances that persist (and, for immediate verbal retrieval, worsen over time) challenge the concept of KLS as a benign disorder. The abnormalities in tests may translate in real life as decreased academic and work performances (in addition to the deleterious effect of missed days), as noted by half of the patients. Because attention, episodic memory, and speed of processing are affected, we now advise patients to reduce the

work load at school (suppressing, for example, minor subjects), to make recurrent pauses during homework, as well as to be allowed extra time to complete an examination. This negative message should be balanced by the observation that many abnormalities improve with time. Nonetheless, some measures of speed processing remain altered, and the episodic memory further worsens despite a reduced episode frequency. In this case, cognitive remediation may be advised on an individual basis, even if its benefit is not yet formally proven.

The limitations of our study include the higher educational levels and smaller size in the control than in the patient groups (although the inclusion of 42 controls allows reliable comparisons). This bias was circumscribed by two means: (1) adjusting the statistics for the educational levels and nvIQ (which is a valid method since the first and third quartiles of educational levels completely overlap); (2) displaying z scores adjusted for age, sex, and educational level from French normative in the KLS group, and showing percentages of patients with abnormal scores. Eventually, the patient group was sufficiently large to provide reliable measures, and the close follow-up of 44 patients allowed the investigation of the deficit trajectories over time. A follow-up of the controls in the same conditions would be useful in further studies to overcome the test-retest effect (tests training despite beta versions, cognitive maturation in teenagers), which could explain the improvement of several tests over time in patients with KLS. The potential benefits of medical care on this improvement cannot be analyzed here because we treated nearly all patients after Visit 1. Notably, lithium therapy provided a major reduction of episode frequency and duration in our cohort, whereas valproate was rarely used.[39] In patients with bipolar disorder (who also suffer from long-term cognitive impairment), the effects of lithium on cognition are controversial. Some authors argued for a small but negative effect on speed of processing and verbal memory,[40] but there was no specific deleterious effect of lithium on cognition, when it was compared to other mood stabilizers in a longitudinal controlled study in adults with bipolar disorder.[41] Others suggest that lithium could have a therapeutic effect on cognitive dysfunction, because it may stimulate neuronal plasticity, resilience pathways, and neuroprotective processes.[42]

In conclusion, in this field study, patients with KLS may have long-term cognitive deficits, which mainly affect their verbal retrieval and speed of processing. These results suggest that cognitive functions should be systematically tested in patients with KLS, which appears important to help patients in their academic studies.

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