The sleep architecture of Saudi Arabian patients with Kleine-Levin syndrome

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ABSTRACT

الأهداف: صممت هذه الدراسة لوضع خط الأساس لهيكل النوم أثناء النوبة الحادة لمتلازمة كلاين–ليفن لمجموعة من المرضى السعوديين المصابين بمتلازمة كلاين–ليفن ومقارنة هذه السمات مع ما تم نشره للمجموعات الأخرى.

الطريقة: هذه دراسة بأثر رجعي لمجموعة من دراسات النوم لعدد 10 مرضى سعوديين مصابين بأعراض نمطية من متلازمة كلاين–ليفن حضروا لمركز اضطرابات النوم بجامعة الملك سعود خلال الفترة 2002م وحتى 2015م. تم جمع البيانات من دراسات النوم الليلية خلال النوبات الحادة من فرط النوم ومقارنتها مع ما تم نشره من دراسات أجريت لمجموعات تم تحديدها من خلال بحث منهجي لما سبق نشره من أبحاث في نطاق موضوع البحث.

النتائج: كان وقت النوم المسجل ذاتياً خلال النوبات (11.1 ± 6.7 ساعة) و إجمالي النوم المسجل (322.5 ± 108.7 دقيقة) واللذين كانا بشكل عام أقل مما تم نشره في المجموعات الأخرى. كما كانت كفاءة النوم ضعيفة عند 75 ± 25.1%، مع انخفاض نسبي لكمية النوم خلال حركة العين السريعة (16.5± 5.9%) والنوم العميق (خلال المرحلة الثالثة10.5 ± 6%) مع زيادة نسبية في كمية النوم خلال مرحلة النوم الأولى (7 ± 4.3%). كان هيكل النوم للمرضى السعوديين المصابين بمتلازمة كلاين–ليفن متشابهةً مع سبق نشره من أبحاث.

الخاتمة: هيكل النوم لمجموعتنا كان طبيعياً بشكل نسبي ومتشابه بشكلٍ عام مع ما سبق نشره من أبحاث، وكانت السمات الرئيسية انخفاضٌ في كفاءة النوم وانخفاض نسبي في كمية النوم خلال حركة العين السريعة والمرحلة الثالثة من النوم. قد يكون من المجدي إجراء دراسات نوم متزامنة مع التصوير الوظيفي لمزيد من التوثيق للفسيولوجيا المرضية لهذا المرض.

Objectives: To establish baseline sleep architecture during an acute attack of Kleine-Levin syndrome (KLS) in a cohort of Saudi Arabian KLS patients and compare these characteristics with other published cohorts.

Methods: This was a retrospective cohort study of the polysomnographic characteristics of 10 typical symptomatic Saudi Arabian KLS patients attending the University Sleep Disorders Center, King Saud University, Riyadh, Saudi Arabia between 2002 and 2015. Data were captured by nocturnal polysomnography during an acute attack of hypersomnia and compared with other published cohorts identified via a systematic literature search.

Results: Self-reported time asleep during episodes (11.1±6.7 hours) and recorded total sleep time (TST) (322.5±108.7 minutes) were generally shorter than other published cohorts. Sleep efficiency was poor at 75.0%±25.1%, with low relative amounts of rapid eye movement (REM) sleep (16.5±5.9% of TST) and deep non-REM sleep (stage N3; 10.5±6.0% of TST) and high relative amounts of non-REM sleep (stage N1; 7.0±4.3% of TST). The sleep architecture of Saudi Arabian KLS patients was similar to other published cohorts.

Conclusions: Sleep architecture of our cohort was relatively normal and broadly similar to other published studies, the main features being low sleep efficiency and low relative amounts of REM and stage N3 sleep. Time-course polysomnography studies with functional imaging may be useful to further establish the exact pathophysiology of this disease.

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Kleine-Levin syndrome (KLS) is a rare, relapsing-remitting, debilitating sleep disorder that primarily affects adolescents and young adults.[1] Kleine first reported a series of 9 cases in 1925 in which both males and females experienced symptoms of recurrent hypersomnia, hyperphagia and cognitive disturbance.[2] Lewis[3] (1926) and Levin[4] (1929) described similar cases. Critchley and Hoffmann coined the eponymous name Kleine-Levin syndrome in 1942 when they described 2 naval personnel with periodic somnolence and "morbid hunger".[5] Patients with KLS experience periods of normality alternating with hypersomnia lasting one to a few weeks accompanied by cognitive, behavioral and psychiatric disturbances.[1] Its prevalence is approximately 2 cases per million in western populations.[6]

The distinct clinical features and use of established international diagnostic criteria for KLS according to the International Classification of Sleep Disorders[7] defines a relatively homogeneous population of patients with KLS. However, the diagnosis is often delayed or missed and many patients are sent to child or adult psychiatric services prior to a definitive diagnosis being made due to the differential diagnoses of psychotic disorders and depression.[1] Kleine-Levin syndrome has a putative genetic component to its etiology (first-degree relatives have an 800-4000-fold increased risk of developing KLS; multiplex families including affected monozygotic twins are described)[8,9] implicating organic pathology, but the exact etiology and pathophysiology remain uncertain. Brain imaging studies (MRI, CT scan) are largely normal,[10-12] although functional brain imaging (with single-photon emission computed tomography [SPECT] for instance) has revealed a spectrum of perfusion, pathway, and metabolic changes in the brains of KLS patients.[13-16] Several biochemical parameters have been measured in both the serum and cerebrospinal fluid (CSF) of affected individuals, with CSF hypocretin-1, a hypothalamic neuropeptide, the most commonly studied molecule, showing decreased (but not absent) levels in the CSF consistent with a hypothalamic disturbance.[17,18] Electroencephalography studies have revealed non-specific diffuse slowing of background activity in as many as 70% of patients and isolated or sequential low-frequency high-amplitude delta or theta waves in some patients.[19,20] In spite of these efforts, there are still no specific diagnostic biomarkers for KLS,[21] which would allow for rapid screening and diagnosis of the disease even by non-specialists.

Sleep studies are another modality that might be useful in the diagnosis of KLS, but data are limited due to the rarity of the disease, poor patient compliance, and loss to follow-up given the excellent prognosis of KLS.[14,22-24] It is unknown whether Arab populations have different KLS sleep architectures. We therefore sought to establish baseline sleep architecture during an acute attack in a relatively large cohort of Saudi Arabian KLS patients and compare these characteristics with other published cohorts.

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Methods.

Patients and diagnostic criteria. This was a retrospective cohort study. Ten patients (8 males and 2 females) diagnosed with KLS between 2002 and 2015 underwent polysomnography at the University Sleep Disorders Center, King Saud University, Riyadh, Saudi Arabia during an acute attack of hypersomnia. All patients (or their guardians) provided written informed consent to be included in the study. The Institutional Review Board of King Saud University approved the study protocol.

All patients met the diagnostic criteria for KLS according to the International Classification of Sleep Disorders.[7] These criteria state that: a) the patient experienced at least 2 recurrent episodes of excessive sleepiness and sleep duration, each persisting for 2 days to 5 weeks; b) episodes recurred usually more than once a year and at least once every 18 months; c) the patient had normal alertness, cognitive function, behavior, and mood between episodes; d) the patient demonstrated at least one of the following during episodes: 1) cognitive dysfunction, 2) altered perception, 3) eating disorder, 4) disinhibited behavior; e) the hypersomnolence and related symptoms were not better explained by another sleep disorder, other medical, neurologic, or psychiatric disorder (especially bipolar disorder), or use of drugs or medications.[7] All criteria must be met to diagnose KLS. Patients were not included if they had atypical associated symptoms, an uncertain diagnosis, or secondary KLS.

Investigations. All participants underwent full history and examination to confirm the diagnosis of KLS and to rule out concurrent disease. Eligible participants completed the Stanford KLS questionnaire

in English. The Stanford questionnaire includes 280 questions about personal and family history; KLS onset and course; triggers; symptoms during episodes including sleep, cognition, derealization, eating and sexual behavior, psychiatric symptoms, and meningeal symptoms; responses to therapy; and symptoms during asymptomatic periods including sleep, eating attitudes, depression, and anxiety.[25] Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale,[26] which measures anxiety and depression on a scale of 0-21 for each (0-1 normal, 8-10 borderline abnormal, 11-21 abnormal). Eating attitudes assessment was based on the EAT-26 eating attitudes test,[27] a screening test for eating disorders where a score of 20 or higher does not necessarily indicate pathology but would warrant further investigation by a health professional. The Epworth Sleepiness Scale (ESS) was used to assess daytime sleepiness. The ESS is a validated questionnaire consisting of 8 items that assess the likelihood of falling asleep during a variety of daily living situations.[28]

Polysomnography. Level 1 attended nocturnal sleep studies were performed at the University Sleep Disorders Center, King Saud University as previously described.[29] Briefly, sleep studies were performed at onset of the disease and at the peak of an episode. Alice 5 and 6 Lab Diagnostic Equipment (Respironics, Inc., Murrysville, PA) acquired standard polysomnography data with 4 leads for electroencephalography (EEG: C1-A4, C2-A3, O1-A4, O2-A3), electrooculography (EOG), chin electromyography (EMG), electrocardiography (EKG), oxygen saturation, chest and abdominal wall movements, airflow (thermistor and nasal pressure), and sleep position.

A trained polysomnography technologist scored the data manually in a blinded fashion. The following sleep parameters were assessed: lights off (10:20 ±81 min), lights on (5:46 ±19 min), time in bed (TIB), total sleep time (TST), sleep period time and sleep onset latency. Scoring included sleep stages and TST percentage, sleep onset latency, slow wave sleep onset latency and duration, rapid eye movement (REM) onset latency and duration, number of sleep cycles, stage shifts (total number of changes in sleep state from lights out to lights on), and arousals according to established criteria.[30,31] Since some patients slept beyond lights on time but polysomnography was only recorded overnight, TST represents self-reported data.

Search strategy and inclusion criteria. The PubMed database was searched on May 2017 for all articles on polysomnography in Kleine-Levin Syndrome using the search terms: ("kleine-levin syndrome"[MeSH Terms] OR ("kleine-levin"[All Fields] AND "syndrome"[All Fields]) OR "kleine-levin syndrome"[All Fields] OR ("kleine"[All Fields] AND "levin"[All Fields] AND "syndrome"[All Fields]) OR "kleine levin syndrome"[All Fields]) AND ("polysomnography"[MeSH Terms] OR "polysomnography"[All Fields]). To compare current data with other cohorts of patients, specifically to compare polysomnographic features, we applied the following inclusion criteria: a definite KLS diagnosis; study population was more than 2 subjects and polysomnography data available with sufficient details for comparison. Thirty-two articles were identified in total. After application of the inclusion criteria, 5 studies were available for comparison.[14,22-24,32]

Data analysis. Measures are reported as mean ± standard deviation (SD) and median (range) where available or percentages as appropriate. Distributions were assumed to be normal and differences between means were compared using the Student's t-test in GraphPad Prism (GraphPad Softare Inc., La Jolla, CA) where appropriate with a p-value of 0.05 considered statistically significant.

Results.

Demography and clinical features. The demographic and clinical features of the study population are shown in **Table 1**. The study population had similar demographic and clinical features to other major published cohorts[6,14,18,25,33] with predominantly male gender (75%; range 57.1-76.5%), onset in adolescence (age 15.9 ± 3.8 years) and a notable precipitating factor in 7/10 patients (2 menarche, 3 infection or flu-like symptoms, 2 unusual recognizable stress). The average length of a KLS episode was similar to other populations (18.5 ± 21.1 days). Kleine-Levin syndrome patients reported spending an average of 11.1 ± 6.7 hours asleep per 24 hours, which was shorter than in 2 other studies reporting the same data (17.2 [n=6]) (p<0.0001) and 17.9 ± 3.6 hours (n=25) (p<0.0001). However, overall symptomatology was as expected: all patients experienced cognitive impairment with impaired speech, confusion, altered perception, and apathy; megaphagia and decreased appetite occurred in half of patients; hypersexuality or disinhibited sexual behavior occurred in 30% of patients; hyperacusis occurred in all patients; and depression (40%) and anxiety (40%) were not uncommon during an episode, in line with previous studies.[6,14,18,25,33]

In between episodes, 2 out of 10 patients reported restless legs, and snoring was common (50%). Sleepwalking, night terrors, nightmares, and sleep paralysis occurred in a minority of patients similar to previously described cohorts. Saudi Arabian KLS patients never went to bed before 11 pm, reflecting

Table 1 - Demographic and features of the KLS patients undergoing polysomnography.

Characteristics	n (%)	mean ± SD	Median	Range
Number of patients	10			
Age at interview (years)		29.1 ± 11.9	26.0	14-58
Gender: Male	(80.0)			
Body mass index		23.8 ± 4.6	23.7	17.7-32.9
Age at disease onset (years)		15.9 ± 3.8	14.0	12-23
Disease duration (years)		13.2 ± 8.9	12.5	0-35
First episode duration (days)		11.1 ± 6.7	10.5	3-25
Precipitating factors				
First menarche	20			
Infection/fever/flu	30			
Unusual stress	20			
Total number of episodes	>3			
Mean episode duration (days)		18.5 ± 21.1	9.0	4-60
Sleep symptoms during symptomatic periods				
Hypersomnia	(100)			
Intensive dreaming	(90)			
Paralysis	(50)			
Cognitive symptoms				
Cognitive impairment/impaired speech/confusion	(100)			
Eating behavior disturbance				
Megaphagia	(50)			
Decreased appetite	(50)			
Sexual disturbances				
Hypersexuality or disinhibition	(30)			
Other psychiatric symptoms				
Hallucinations/delusions	(30)			
Split body/mind, feeling of disembodiment	(100)			
Anxiety	(40)			
Depression	(40)			
Meningeal symptoms				
Photophobia	(10)			
Hyperacusia	(100)			
Headache	(10)			
Post-episode symptoms				
Incomplete recollection of episodes	(100)			
Night time sleep (between episodes)				
Do not sleep well	(80)			
Sleep latency, min		55.0 ± 51.8	30.0	20-180
Time asleep, min,		696 ± 126	720.0	84-162
Restless legs syndrome	(20)			
Sleepwalking	(10)			
Night terrors	(0)			
Snoring	(50)			
Nightmares	(10)			
Sleep paralysis	(0)			
Witnessed apnea	(0)			
Go to bed before 11 pm	(0)			
Daytime alertness				
Sleepiness during the day	(20)			
Epworth sleepiness score, 0-24				
Mood and anxiety		9.3 ± 3.2	9.5	2-14
Anxiety score		4.4 ± 5.3	2.0	1-16
Depression score		6.3 ± 2.6	6.0	2-11
Combined score		10.7 ± 7.3	7.5	3-24
Eating behavior				
Score		13.9 ± 8.6	15.5	1-27

Table 2 - Sleep architecture during episodes in KLS patients.

Variables	Current study	Luo et al[24] 2016	Erdem et al[22] 2013	Huang et al[23] 2008	Dauvilliers et al[32] 2002	Gadoth et al[14] 2001
Number of subjects	10	7	6	10	18	14
Predominant country/region of origin	Saudi Arabia	China	Turkey	Taiwan	Europe	Israel
Type of study	Nocturnal	Nocturnal	24-hour	Nocturnal	24-hour	Nocturnal
Total sleep time (min)	322.5 (108.7)	453.6 (57.6)	1805.7 (746.5)	289 (74.8)	701 (270)	567.7 (204.5)
Sleep efficiency (%)	75.0 (25.1)	89.7 (8.9)	85.4 (5.3)	78.0 (16.0)	80 (12)	75.5 (13.8)
Sleep-onset latency (min)	31.2 (42.7)	6.6 (7.7)	14.9 (25.5)	NA	28 (18)	22.5 (23.5)
REM sleep latency (min; n=9)	109.5 (83.6)	76.4 (45.5)	65.8 (15.0)	NA	133 (110)	85.1 (46.7)
Sleep stage 1 (%)	7.0 (4.3)	9.3 (5.1)	2.2 (1.7)	18.0 (10.2)	9 (8)	0.7 (0.78)
Sleep stage 2 (%)	56.5 (17.6)	50.5 (8.2)	72.7 (5.9)	47.0 (11.9)	52.7 (10)	51.9 (8.8)
Sleep stage 3 (%)	10.5 (6.0)	18.4 (9.1)	12.7 (4.9)	19.1 (10.2)	16 (8)	13.1 (8.8)
REM sleep (%)	16.5 (5.9)	21.8 (3.9)	12.4 (2.8)	16.9 (4.5)	17 (6)	18.5 (6.8)

NA - not available, REM - rapid eye movement

cultural differences and endemic sleep habits of Saudi Arabians, in particular adolescents.[34] Eight out of 10 patients reported sleeping badly between episodes (7.6-12.1% in other series), reflected in their Epworth sleepiness scores,[28] which were borderline high (9.3 ± 3.2). Our KLS patients reported high levels of baseline depression (6.3 ± 2.6) and high EAT-26 eating attitude scores, with 66.7% of patients scoring 20 or higher. Overall, this population was a fairly typical KLS population exhibiting the clinical homogeneity observed in other studies when rigorous diagnostic criteria are applied, notwithstanding some likely culturally-driven sleep habits in Saudi Arabia.

Sleep architecture. The sleep architecture measured by polysomnography of our study population (during episodes) and compared to other published cohorts (during episodes, both nocturnal and 24-hour polysomnography studies) is shown in **Table 2**. Overall, the sleep architecture of Saudi Arabian KLS patients was relatively normal and broadly similar to other published studies (**Table 2**) and especially the largest previous study from Dauvilliers et al,[32] recognizing the caveat that all polysomnography studies performed to date in KLS patients only contain very small numbers of patients.

Total sleep time (TST) was among the lowest of the published studies (322.5 ± 108.7 min), and significantly shorter than 2 out of the 3 comparable nocturnal polysomnography studies (322.5 ± 108.7 minutes versus 453.6 ± 57.6 min;[24] and 567.7 ± 204.5 minutes[14]). Sleep efficiency was poor at 75.0 % ± 25.1%, with low relative amounts of REM sleep (16.5 ± 5.9% of TST) and deep non-REM sleep (stage N3; 10.5 ± 6.0% of TST) and high relative amounts of non-REM sleep (stage N1) (7.0 ± 4.3% of TST). This was consistent with the poor sleep efficiency seen across all studies (range 75.0-89.7) and the similar distributions of sleep stages. Rapid eye movement (REM) sleep latency was normal (109.5 ± 83.6 minutes), similar to the largest study from Dauvilliers et al[32] and although 2/10 patients had short REM sleep latency <50 minutes as observed by others.[14,22,24] this was not related to any other clinical feature or disease severity. Sleep onset latency (31.2 ± 42.7 min) was not dissimilar to self-reported sleep latency (51.8 ± 48.0 min; t-test, p=0.32).

Although only 3 patients had repeat polysomnography during non-symptomatic periods, there were no significant differences in sleep architecture during symptomatic and asymptomatic periods (data not shown), consistent with other studies that included these data and showed only marginal differences with persistent poor efficiency sleep during asymptomatic periods.[14,23,32] Only Erdem et al,[22] in their small study of 6 Turkish KLS patients, reported lower REM latency and stage N3 sleep in symptomatic individuals.

Discussion. Here we present the first comprehensive comparison of the sleep architecture of KLS in Arabs and other KLS patients. In terms of clinical features, our study population represented a fairly typical KLS population compared to existing datasets. However, Saudi Arabian KLS patients self-reported spending less time asleep (approximately 5 hours per 24 hours) during an episode than in other published series,[6,25] a finding mirroring the shorter TST in 2 out of 3 comparable nocturnal polysomnography studies.[14,24] However, sleep architecture was otherwise relatively normal and broadly similar to other published studies, the main features being low sleep efficiency and low relative amounts of REM sleep and stage N3 and high relative amounts of non-REM sleep. Our findings support previous suggestions that sleep monitoring has

only limited use in the diagnosis of KLS.[1] The shorter self-reported and detected TST values than in most other studies may have arisen for a number of reasons. First, these data may reflect an artifact of the artificial sleep study environment or an unknown sleep pressure in our experimental set-up. Second, the reported data may include reporting bias, since patients self-reported the questionnaire data and were only directly monitored overnight, by polysomnography. Third, there may have been additional napping or unrecorded sleep outside the study period that was unaccounted for. Finally, since the cohort had been followed up for 13 years, they may have entered the later stages of the natural history of KLS, namely more derealization and apathy and less hypersomnia.

The sleep architecture of Arab KLS patients was similar to KLS patients of other ethnicities, in line with the hypothesis that KLS, when properly diagnosed, is a very clinically (and presumably biologically) homogeneous disease. This is no doubt in part due to the striking KLS phenotype (namely, the long duration of episodes and the associated cognitive, behavioral, and psychiatric disturbances), the application of robust diagnostic guidelines (ICSD-2 and 3) that have now been available for many years to ensure uniformity of diagnosis,[35] the presence of international databases, and the availability of a standardized and comprehensive questionnaire to enable inter-group comparisons.[25] In this regard, KLS serves as a model of how to effectively study orphan diseases and, as here, include or exclude variables of diagnostic or pathophysiological importance. In that regard, the value of polysomnography appears to be mainly limited to the research setting.

Our study did not capture any potential temporal dynamics in sleep architecture during the course of KLS episodes, which may shed light on the pathobiology of the disease. In their study of Taiwanese patients, Huang et al[23] examined their polysomnography data according to when it was performed with respect to the onset of clinical symptoms and established that slow wave sleep was reduced in the early part of episodes (before the end of the first half) but returned to normal during the second half, even though clinical symptoms persisted. Conversely, REM sleep was normal during the first half and increased during the second. This was an important study from both the biological and clinical perspectives, since it highlighted that sleep structure evolves over time and that the timing of diagnostic modalities is important for capturing relevant information. A longitudinal polysomnography time course study, perhaps coupled with functional imaging studies such as functional MRI, might be useful for better coupling of functional changes, the sleep phenotype, and disease dynamics. However, as with all polysomnography studies, such a study would be difficult to perform since sleep duration and structure depend on the time when the test is performed and most patients struggle with sleep studies, especially multiple sleep latency testing.

Our clinical analysis revealed that Saudi Arabian KLS patients are late sleepers (after 11 pm), the majority slept badly between episodes, and they had relatively high Epworth sleepiness scores,[28] high levels of baseline depression, and poor eating attitudes. Arab societies including that in Saudi Arabia have cultures that disfavor sufficient sleep and the population is generally poorly educated on sleep hygiene.[36] Indeed, in one study of over a thousand adolescents, sleep disturbances were present in 65% of individuals and a third experienced excessive daytime sleepiness,[34] similar to the data presented here. These baseline cultural and habitual factors may have also contributed to the short TST seen here.

Study limitations. This study has a number of limitations. This was a retrospective study of relatively few patients. Although 3 patients had second polysomnography studies performed during the asymptomatic period, the majority only had one test making comparisons over time and between symptomatic and asymptomatic periods difficult.

In conclusions, Saudi Arabian patients with KLS appear to have poor efficiency sleep with low relative amounts of REM sleep and stage N3 sleep and high relative amounts of non-REM sleep. These findings are in line with other studied groups of KLS patients and the homogeneous KLS phenotype. Although polysomnography has only limited clinical benefit, time-course studies with functional imaging may be useful in further establishing the exact pathophysiology of this disease.

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