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REVIEW ARTICLE

Kleine Levin Syndrome: Is it just a sleep disorder?
A review of psychiatric features during symptomatic and asymptomatic periods

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ABSTRACT:
Kliene Levin syndrome (KLS) is a peculiar sleep disorder of youth, consisting of idiopathic periodic hypersomnia attacks associated with behavioral and sometimes psychiatric symptoms during an attack. With the growing awareness of the syndrome and a steep rise in published cases, it became evident that psychiatric abnormalities may be present before the onset of hypersomnic events, in between events and first appear following years after complete recovery. Those observations suggest that psychiatric morbidity may be part of the symptomatology of KLS. In the present paper the results of a systematic literature search of publications using the key words KLS with psychiatric features, Atypical KLS, KLS like, KLS mimic and sleeping beauty syndrome will be discussed, in attempt to support the view that KLS is indeed a neuropsychiatric disorder and not just a sleep disorder of youth. Moreover, the recognition that KLS might imitate psychosis and other psychiatric disorders in which periodic hypersomnia is present, may decrease the number of KLS patients in whom the correct diagnosis may be delayed or totally missed.

Introduction:

Kleine Levin Syndrome (KLS), is a rare neuropsychiatric disorder affecting mainly young males. The syndrome consists of periodic hypersomnia with or without hyperphagia and hypersexuality (1). Critchley and Hoffman (2) in their seminal paper coined the eponym Kleine – Levin Syndrome in honor of two psychiatrists, Willi Klein and Max Levin who published similar cases in 1925 and 1929 respectively. (3,4). Unfortunately, Nolan Lewis who published a similar case in 1926 was not included in the eponym (5). The peculiar features of the syndrome, in particular recurrent sleep attacks lasting several weeks aroused childhood memories of legendary " sleepers" such as Kumbhakarna (a giant who the gods made him fall asleep for 6 months and when he woke up he ate everything ["Ramayana" : ancient Indian mythological epic, 8th-4th century BC], The Grimm brothers "The sleeping beauty", Honi HaMeagel, a 1st century BC Jewish scholar who fell asleep for 70 years [Talmud Bavli, Taanit 23a] and Washington Irving's Rip Van Winkle who fell asleep and woke up after 20 years. Thus, titles of manuscripts such as "the sleeping beauty" (6 -9) and Rip Van Winkle disease (10, 11) attracted authors and the public, raising memories from their childhood and probably played a role in the increased awareness of the syndrome. Indeed, 239 cases were known in 2009 while 637 cases were reported in 2021. Similarly, a growing number of "Atypical" KLS patients were published (11 in 2011 and 60 in a 2022 literature review (Gadoth N, In preparation). The latest diagnostic criteria of KLS established in 2014 are (12):

1. Episodes recur usually more than once a year and at least once every 18 months
2. The patient has normal alertness, cognitive function, behavior and mood between episodes
3. The patient must demonstrate at least one of the following during an episode: A. Cognitive dysfunction, B. Altered perception, C. Eating disorder (anorexia or hyperphagia), D. Disinhibited behavior (such as hypersexuality)
4. Symptoms are not better explained by another sleep, medical, neurologic or psychiatric disorder (especially bipolar disorder), or use of drugs or medications.

In spite of the above-mentioned diagnostic requirement No. 4, patients with psychiatric disorders and KLS symptomatology were published under a variety of headings such as Kleine Levin Syndrome, Atypical Kliene Levin Syndrome, Kleine Levin like, Kliene Levin mimic, Kleine Levin and psychosis, Kliene Levin and Bipolar disorder. Those observations which become more obvious with the growing awareness of the syndrome, led to the hypothesis that KLS may be associated or linked to psychiatric morbidity. Although, a variety of psychiatric disorders were observed in patients with KLS prior to onset of typical KLS events and also after long remissions of hypersomnic attacks, the understanding that psychiatric morbidity has a strong association with KLS emerged quite lately. In this paper, the results of a systematic literature review of published clinical case reports as well as recently published molecular genetic data will be provided as support for the presence of a link between certain psychiatric disorders and KLS.

The evolvement of the concept

Levin in 1936 was the first to mention psychiatric symptoms in 7 patients with KLS (4). Critchley and Hoffman noted that symptoms of aggression and confusion during the attacks are common and suggested the possibility of the presence of "schizophrenic patterns" in some patients. They were also the first to mention depression and elation following an episode of hypersomnia (2). Several early reports mentioned the existence of psychiatric morbidity not only during an attack of hypersomnia but also following an attack. (13, 14). Jeffries, in a review of 40 patients including a single personal case with KLS, found that 19% suffered from depression, 24% from mania and 8% of both disorders. Conditions such as depression and anxiety and even mania were mentioned as initial symptoms of an attack (14). The growing number of reports describing cases in whom the diagnosis of KLS was masked by psychiatric disorders and *vice versa* implies that there is a strong association between certain psychiatric disorders and KLS. Indeed, all 3 cardinal features of KLS i.e. hypersomnia, eating disorder and hypersexuality, i.e. "the Critchley triad", are common features in psychiatric disorders and thus, not specific to KLS. In particular, impaired sleep in the form of either insomnia or hypersomnia and sometimes both, are extremely common is psychosis indicating the presence of circadian rhythm alterations (15,16). Hypersexuality is frequently encountered in patients with mania and those with bipolar schizoaffective disorder while eating disorder, either anorexia or bulimia,are common in psychosis with emphasis on mood disorders (17) .

Clinical psychiatric features in KLS

Groos et. al (18), have to be credited for the first extensive long term psychiatric evaluation of a large cohort of KLS patients in France. Those authors have evaluated 115 patients with verified diagnosis of KLS. The participants underwent an

initial extensive psychiatric evaluation during an asymptomatic period and a yearly follow up evaluation during the following 1-10 years (mean number of psychiatric evaluation: 2 ± 1.4, range 1–11). The authors found that 19 out of the 115 patients (16.5%) had a history of psychiatric disorder prior to the appearance of KLS. Out of those, 10 continued to suffer from their psychiatric morbidity after remission of attacks of KLS. Moreover, in 25 patients (21%), a new psychiatric disorder appeared 1-6 years after KLS onset. The various psychiatric disorders reported prior to KLS onset, during symptomatic events and those which were present during remission are summarized in table 1.

Table 1: Psychiatric characteristics of Kleine Levin Syndrome [Modified after Groos E. et al. [18].

Before KLS onset	During symptomatic period	During remission
Anxiety disorder & Separation and social anxiety disorder	Hallucinations: visual, auditory, tactile, olfactory, gustatory	Single & recurrent major depression, Adjustment and anxiety disorder
Bipolar disorder & suicide	Self-mutilation	Bipolar disorder, Dysthymia
Short duration psychosis	Delusions	Nonspecific psychotic episodes, schizoaffective disorder,
Disruptive behavior	Eating disorder (Hyperphagia /Anorexia	Eating disorder,
ADHD	Hypersexuality/ Sexual inhibition / Decreased sexuality	Cannabis dependency

Is Kleine – Levin syndrome just a sleep wake disorder?

The mentioned about data indicate that significant psychiatric morbidity is part of KLS symptomatology and not just a coincidence of a rare disorder with common and frequent psychiatric ailment. It was claimed in the past that the impaired mood of many patients after complete remission of KLS is secondary to the events experienced during the symptomatic period. Indeed, those patients who suffered from a "mysteries" disease which was correctly diagnosed in many cases after years of doubt as to the "organicity" of their complains, will be subdued, feel unworthy and live in the state of anxiety anticipating the next event. In our experience, some patients experience dramatic events related to attacks of hypersomnia. One of our patients was diagnosed with KLS at the age of 7 years and thereafter lost for follow-up. Being of good general health he was enlisted to the Israeli Defense Forces but did not reveal that he suffers from KLS. Soon after his assignment to an infantry combat unit, he was found asleep during a field exercise. On forced arousal by his fellow soldiers, he acted "strange", confused and combative. Suspected of drug abuse he was put in stockade and the next morning brought before a military court. Meanwhile, his mother was notified and immediately reported to the military court that her son was suffering from KLS diagnosed 11 years earlier. A late-night call to me from military police and my confirmation that what happened was indeed an attack of KLS and not drug abuse, which was fortified by negative toxicology screen resulted in his release and reassignment to a non-combat unit. Another female patient suffered from attacks of KLS until the age of 25 years. At the age of 32 years, she traveled to New-Zealand with a friend and both took a wilderness trek during which they split and took different routes. Lonely in wilderness she fell asleep and woke up several days later. Even after many years of full recovery, patients carry along traumatic memories of their past experience. In an attempt to find out what happened to our patients years after complete recovery, we were able to reach by phone 25 of our 40 patients. Of those only 14 showed for a follow-up interview while the others were reluctant claiming that going back to their past is very painful (19).

In addition to emotional residuals which are normal considering the nature of KLS, the psychiatric morbidity outlined above cannot be ignored. Among the 23 patients in whom psychiatric morbidity appeared after the onset of KLS, 14 (60.86%) suffered from mood disorder (19). Out of those, six were classified as recurrent major depression and the rest with other forms of depression including a patient with bipolar type 1 disorder. In the light of those findings, one could expect similarities in neuroimaging findings for mood disorders and KLS. However, neuroimaging findings in depression (20), and other mood disorders (21), differ significantly from those

reported in KLS (22). However, some clinical features of KLS are similar to those of bipolar disorder and to a lesser extent, schizophrenia. Young age of onset, episodic attacks of hypersomnia, depression and hallucinations followed by complete recovery in -between episodes are experienced by patients with bipolar disorder. The good response to Lithium carbonate can explain reports of KLS misdiagnosed as bipolar disorder and vice versa (23-26). Finally, a quite recent large -scale study of 637 patients with confirmed KLS found a strong association of KLS with circadian regulation neurocircuits genes as well as with bipolar disorder and schizophrenia (27).

Conclusion:
There is no doubt that KLS is not just a periodic hypersomnia disorder and thus should be classified as a neuropsychiatric disorder of youth with good prognosis. Clinicians should be aware of this association, include in the work-up of patients with KLS a psychiatric evaluation and be aware of misdiagnosing KLS as depression or other forms of psychosis.

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