Research Article ISSN 2693-2490

Journal of Psychology and Neuroscience

Atypical Kleine Levin Syndrome: Atypical or "Something Else"

Natan Gadoth MD*, Avi Gadoth MD

[1]*Maynei Hayeshua Medical Center and the Sackler Faculty of Medicine, Tel -Aviv University, Israel.*

[2]*Sourasky Medical Center, and the Sackler Faculty of Medicine, Tel-Aviv University, Israel.*

***Correspondence author**
N. Gadoth MD,
Dept. Neurology, Maynei Hayeshua Med. Ctr,
17 Povarsky, Bnei Barak,
Israel.

Submitted : 26 Oct 2023 ; Published : 11 Jan 2024

Citation: Gadoth (2024). Atypical Kleine Levin Syndrome: Atypical or "Something Else". J Psychol Neurosci; 6(1):1-9.
DOI : https://doi.org/10.47485/2693-2490.1083

Abstract

Objective: *To describe in some detail published cases who were diagnosed as atypical Kleine-Levin syndrome (KLS), and discuss the validity and usefulness of this diagnostic term.*

Methods: *The English written literature was reviewed using the search terms Atypical KLS, KLS mimic, KLS like and KLS variant. Only reports which provided complete clinical features were reviewed. The present diagnostic criteria of KLS were applied in each case and the reasons why each case was considered as atypical were outlined in a table form. The cases were grouped according to the primary etiologies which could explain the symptoms into infectious, autoimmune, cerebrovascular, head trauma, brain tumor and genetic metabolic disorders. Cases in whom we could not establish a definite diagnosis were coined "atypical "and a few which could not be assigned to a specific group were coined "miscellaneous".*

Results: *Fifty seven reports describing 60 "atypical" cases were found. Out of those, 14 suffered from a variety of medical conditions which could explain the symptomology while in 19 cases a definite diagnosis could not reached. Five cases were coined as "miscellaneous" since we could not assign them to a specific group.*

Conclusion: *The eponym "atypical" KLS, refers to patients in whom a variety of medical disorders were associated with sleep-wake disorder, however, it seems appropriate that in such cases the diagnosis should express the primary cause of the symptoms rather than suggesting that those cases are a variant of KLS.*

Keywords: Periodic hypersomnia, hyperphagia, hypersexuality, bipolar disorder, sleep, Kleine Levin

Introduction

Kleine Levin Syndrome (KLS), is a peculiar and rare type of periodic hypersomnia. The diagnostic criteria as defined in the 2014 revised version of the International Classification of Sleepiness Disorders, 3rd (ICSD-3), consist of the presence of recurrent episodes of unexplained sleepiness lasting from a few days to four weeks, which occur at least annually and may or may not be accompanied by impulsive and rapid consumption of large amounts of food (hyperphagia, "binge eating"), and hypersexuality (Darien, 2014). KLS affects mainly adolescent boys and to a lesser extent adolescent girls and young women (Gadoth & Oksenberg, 2017). In 1970, Miller was probably the first to suggest the possibility of Atypical KLS (AKLS), in a patient with clinical features of KLS in whom "a long history of serious pre-morbid psychopathology" was recorded. He noted that REM sleep deprivation and psychiatric disorders can mimic KLS (Miller, 1970). Since then, a significant number of reports describing patients with a variety of medical disorders showing some similarities to KLS, mainly recurrent hypersomnia episodes, were published. It was suggested and seems likely that patients with AKLS suffer from damage to brain circuits involved in sleep - wake regulation. Thus, in order to be able to precisely diagnose youngsters with KLS it is essential to be familiar with the clinical features of AKLS.

Methods

The PUBMED, Medline, Google scholar and Cochrane database were searched for English written publications using the search terms Kleine Levin Syndrome, Atypical Kliene Levin Syndrome, Kleine Levin variant, and Kliene Levin mimic. Only publications in the form of case reports, letters or meeting abstracts which provided detailed clinical descriptions of patients were reviewed. We have used the latest diagnostic criteria for ascertainment of the diagnosis of KLS in each case (Darien, 2014). Those criteria are the following:

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:

- Cognitive dysfunction
- Altered perception

- Eating disorder (anorexia or hyperphagia)
- 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.

Results

We have found 57 publications reporting 60 cases (43 males) who did not fulfill the above-mentioned diagnostic criteria. Twenty-six of those were reported between the years 1972-2005 during which 2 earlier versions of the diagnostic criteria were available (American Academy of Sleep medicine, 2005; Throphy, 1990). Twenty of the patients were previously considered as AKLS by Arnulf, Billiard or both (Arnulf et al., 2005; Billiard et al., 2011). An additional AKLS patients was previously mentioned by Gadoth (Gadoth, 2018). We did not include in this review 3 case reports (McGilchrist et al., 1993; Hasegawa et al., 1998; Reimão & Diamant, 1989), considered as AKLS by Arnulf and Billiard (Arnulf et al., 2005; Billiard et al., 2011), since the authors of those reports, stated clearly and correctly that their cases did not suffer from KLS or AKLS. We have also omitted the patient reported by Miller in 1970 as "atypical". (Miller, 1970). This case would have been diagnosed at present as KLS according to the 2014 diagnostic criteria mentioned above. We have summarized the epidemiological and relevant clinical "atypical" features of each case in Table 1 and 2. The 60 cases were divided into subgroups according to the primary cause of the symptoms i.e., infection, trauma, stroke etc. (Table 1). Similarly, we have included in Table 2, cases under the headings "Atypical" in whom a variety of clinical features did not meet the present KLS diagnostic criteria and "miscellaneous" for cases which could not be assigned to a specific group. The largest subgroup (Atypical) consisted of 19 patients in whom the characteristics of hypersomnia episodes, late onset of symptoms, presence of behavioral impairment in-between episodes, or progressive intellectual decline noticed since onset of symptoms, did not meet the KLS diagnostic criteria. Brain tumors, stroke and genetic - metabolic disorders were the cause of symptoms in 7 cases. In 5 cases the cause was significant brain trauma. There were 14 cases in whom the etiology of symptoms was caused directly by various infections or autoimmune disease processes. Autism could explain the symptoms in 5 patients and severe obstructive sleep apnea (OSA) was the cause of symptoms in 5 cases. The 5 patients in the "miscellaneous" group suffered from unspecified brain disease, Parkinson, epilepsy and migraine. In 4 cases a significant psychiatric morbidity could explain the symptomatology. In regards to the age of onset, the youngest case was one year old and the oldest was 80 years old. Eight cases were older than 50 at onset (mean age 65.25 years). It should be noted that in a recent study of 637 patients in whom the diagnosis of KLS was confirmed by the authors, the mean age of onset was 15.47± 0.39 years (Ambati et al., 2021).

Author / (year of publication)	age at onset (y) / sex	KLS like symptoms	atypical features	Previously mentioned (ref.)
Tumors				
Argenta G/1981	18 / M	H	Lipoma of 3rd ventricle	(7)
Jungheim K/1999	22 / F	H, HP, S	Acromegaly, Munchausen syndrome, brain radiation necrosis	
Nishikuni K/2014	61 / M	H, HP, S	Colloid cyst 3rd ventricle, severe OSA worsened after removal of tumor	
Stroke				
Drake ME / 1987	60 / F	H, HP	Multi infarct state. late onset	(6,7)
Maskara S / 2009	79 / F	H, HP, S	Late onset, prolonged episodes (4 months), MCA stroke, ischemic angiopathy	
Genetic/Metabolic				
Gau SF / 1996	9.5 / M	H, HP	Prader Willi syndrome, small hypothalamus,	(6,7)
Bozinov N / 2018	23 / M	H	Citrullinemia, hyperammonemia stupor	
Trauma				
Chiu HF / 1989	16 / M	H, HP	Thalamic syndrome, multifocal traumatic brain damage	(6,7)
Kosti´c VS / 1998	19 / M	H, HP	epidural hematoma, prolonged coma, residual traumatic brain damage	(6,7)
Pelin Z / 2004	22 / M	H, HP	Abnormal in-between episodes, traumatic brain damage	(6,7)
Cheung G / 2006	62 / M	H, HP, S	Late onset, rapid cycling episodes, depression, traumatic brain damage	(7)
Javadpour A / 2020	25 / M	H	traumatic brain damage, prolonged coma, abnormal in-between episodes	

Infectious & autoimmune				
Persson T / 1969	29 / M	H, HP	Encephalitis, neuro-impairment, headache, persistent behavioral impairment	(6)
Takrani LB / 1976	48 / F	H	Paraneoplastic (uterine carcinoma)	(6)
Merriam AE / 1986	25 / M	H	Meningoencephalitis, altered periodic behavior	(6)
Testa S / 1987	20 / M	H	Multiple sclerosis, Schizophrenia, orthostatic hypotension	(6)
Fenzi F / 1993	8 / F	H, HP	Encephalitis, neuro-impairment	(6,7)
Thacker AK / 2007	15 / M	H, HP	TB meningoencephalitis with brain damage, rapid cycling of episodes	
Afshar K / 2008	28 / M	H, HP	Neurosarcoidosis	
Das A / 2012	10 / F	H, HP	PANDAS, episodes responsive to penicillin, drowsy in-between episodes	
Rout UK / 2014	11 / M	H, S	Involuntary movements, perseveration, hallucinations, anti-GAD65 low titer in serum	
Kahanna A / 2015	18 / F	H, S	TB meningoencephalitis	
Geraradi DM / 2015	9 /M	H, HP	PANS/PANDAS, hemihypertrophy, OCD, gradual onset and rapid cycling episodes	
Feigal J/2016	21.5 / F	H	Low IQ, substance abuse, neurological impairment, midbrain damage, suspected narcolepsy, NMDA encephalitis?	
Takayanagi M / 2017	13 / F	H	Influenza encephalitis with transient splenial lesion, delta waves during wake EEG	(6,7)
Tani M / 2020	14.5 / M	H, HP	Encephalitis influenza B, anti-NMDAR in CSF	
Autism				
Berthier ML / 1992	16 / M 16 / M	H, HP H	Asperger, retinitis pigmentosa, cortical dysplasia, Asperger, mental retardation, abnormal behavior between 2 episodes	(6,7)
Mukkades NM / 2009	12 F 15 / M	H, HP H, HP, S	Stots syndrome, mental retardation, epilepsy, sparse details of episodes and neurological evaluation. Very early infantile meningitis , mental retardation, MRI-periventricular leucomalacia with thinning of posterior corpus callosum	
Hakim Shoushtari M / 2015	1 / F	H, HP	Early onset, epilepsy with dysautonomic features, early infantile meningitis, neurological impairment	
OSA				
Vardi J / 1978	33 / M	H, HP	Diurnal narcoleptic attacks, ictal EEG, OSA	(2)
Cuetter AC / 1985	17 / M	H, HP	Severe OSA, remission with weight reduction	(6)
de Araújo Lima TF / 2014	13 / M	H	Mild OSA evolving to severe, improvement with CPAP	
Chawla G / 2019	35 / M	H, HP, S	Rapid cycling short episodes, severe OSA	
Divya MP / 2020	47 / F	H	severe OSA responding to CPAP, rapid cycling of episodes, brain leucoareosis	

Table 1: Patients with periodic hypersomnia due to specific etiologies inster. (HS-hypersomnia ; HP-hyperphagia; S-hypersexuality)

Author / (year of publication)	age at onset (y) / sex	KLS like symptoms	atypical features	Previously mentioned (ref.)
Atypical				
Wilder J / 1972	27 / M	None	Bouts of diarrhea, insomnia, Whipple?	(6)
Yassa R / 1978	44 / M	H, HP, S	Late onset, paranoid psychosis, gradual onset of hypersomnia	**P**
Striano S / 1986	17 / F	H	Single prolonged episode, (>3 months), atypical onset, sleep terrors, psychogenic polydipsia	
Ferguson BG / 1986	10 / M	H, S	Shallow sleep, confabulations, strange behavior	
Sagar SR/ 1990	10 / M 12 / M 18 / M	H, HP, S H, HP, S H	Cognitive and behavior decline. light sleep	(6,7)
Brown R / 1990	74 / F	H, HP	Late onset, kleptomania, manic attacks	**P**
Badino R / 1992	80 / M	H	Late onset, ptosis, gait impairment, post encephalitis, alcoholism	
Pike M / 1994	9 / M	H, HP	Onset immediately following 3 consecutive general anesthesia, short course, mainly behavioral, mild prolonged total sleep time	
Fontenelle L / 2000	14 / M	H, HP, S	Mental impairment in-between episodes	
Landtbolm AM / 2002	16 / M	H, HP, S	Brain hypoperfusion and short memory impairment long after clinical recovery (authors: solvent exposure?)	
Chakraborty R / 2007	17 / M	H	2 prolonged (9 &6 months) episodes, sleep fragmentation, absent REM sleep, OCD	
Bidaki R / 2011	2/ M	H	Prolong (3 months) episodes, seizure during episode, depressive state, suicidal attempts	**P**
Seo JG / 2014	55 / F	H, HP	Late onset, cognitive decline	
Lechman A / 2014	10 / M	H, HP, S	Recurrent bipolar attacks, oligoarthritic, short episodes with visual blurring and headaches, complex partial seizures	**P**
Neto FK / 2015	2.3 / M	H	Early onset, post viral encephalitis, rapid cycling episodes, reduced thalamic capitation	
Marčić M / 2018	14 / M	H, HP	Gradual onset of prolonged hypersomnia (6 months), visual hallucinations, normal MSLT	
Edaki O / 2019	28 / F	H, S	Short episodes, exposure to nerve gas, RLS, Depression	**P**
Miscellaneous				
Livrea P / 1977	12 / M	H, HP	EEG -occipital spikes and delta waves, mental retardation, pyramidal signs	(6)
Müller T / 1998	51 / M	H, HP	Dopa responsive Parkinson disease	(6)
Masi G / 2000	14 / M	H, S	Epilepsy with Rolandic spikes, self-mutilation, dreamlike state, depressive mood, suicidal ideation, impaired concentration in-between episodes	**P**

Sharma A / 2010	9 / M	H, HP	Complex partial seizures, Status epilepticus	
Nesbit AD/2016	41 / F	H	Sleep deprivation, brain stem neurological signs, brain stem migraine with aura, post episode insomnia	

Table 2: Patients with periodic hypersomnia due a veracity of etiologies HS-hypersomnia; HP-hyperphagia ; S- hypersexuality

Disscusion

As often happens with rare clinical syndromes lacking a biological marker such as KLS, the early described diagnostic clinical characteristics tend to expand with time as additional cases are published. The recurrent attacks of hypersomnia, hyperphagia and hypersexuality, the classical Critchley "tirade " (Critchley & Hoffman, 1942), affecting previously healthy youngsters who "grow out of it", reminded authors as well as public of legendary "sleepers" such as Kumbhakarna, a giant who was made by the Gods to fall asleep for 6 months, and upon waking up he ate everything ("Ramayana": ancient Indian mythological epic, 8th-4th century BC), (Chilakamarri & Kryger, 2019), "The sleeping beauty" by the Grimm brothers (Nebhinani & Suthar, 2017), Honi HaMeagel , a- 1st century BC Jewish scholar who fell asleep for 70 years (Klein, 1901) and Washington Irving's fictional Rip Van Winkle who fell asleep and woke up after 20 years (Lisk, 2009). By using the eponym "Kleine Levin" in publications of atypical cases, a "mysterious fragrance" was added and subsequently, a growing number of "atypical" cases were published i.e. 20 until 2011 (Arnulf et al., 2005; Billiard et al., 2011; Gadoth, 2018), and a total of 60 according to the present report. In contrast to KLS where brain CT and MRI are normal, the findings in "atypical" cases such as in those with multiple sclerosis, tuberculosis with meningeal involvement, sarcoidosis, multi-infarct state, PANDA & PANS, and autoimmune encephalitis, are localized to thalamic/hypothalamic and additional brain areas involved is sleep-wake control such as the floor of the 3rd ventricle, diencephalon and fronto-temporal cortex (Gomp & Anaclet, 2020). Interestingly, there is a striking similarity between the morbidities associated with AKLS and those found in a large group of patients diagnosed as "atypical or narcolepsy like" who suffered from traumatic brain injury, acute disseminated encephalomyelitis, hypothalamic sarcoidosis, multiple sclerosis and Parkinson disease (Guilleminault & Cao, 2011). Moderate-severe OSA can mimic the clinical features of KLS since recurrent daytime hypersomnia is common. We found 5 cases of OSA mimicking some features of KLS. As expected in OSA weight reduction (Vardi et al., 1978), or treatment with CPAP resolved the symptoms (Vardi et al., 1978; Cuetter, 1995; de Araújo Lima, 2014; Chawla et al., 2019; Divya et al., 2020). In the case of severe OSA reported by Nishikuni, hypersomnia, bulimia and hypersexuality appeared few days after the surgical removal of a colloid cyst blocking the foramen of Monroe and subsequent removal of postoperative hemoventricle (Nishikuni et al., 2014). The authors suggested that the damage to structures near the foramen of Monroe and the 3rd ventricle during the surgical procedure was responsible for worsening of OSA and the onset of transient "Atypical KLS". The patient with severe OSA reported by Divya had a past history of late onset of recurrent episodes of hypersomnia with quite atypical features as to the duration, frequency and cycling of episodes and abnormal brain imaging (Dyvia et al., 2020). Psychiatric morbidity is not rare in KLS, mainly during the hypersomnia episodes but also prior to the onset of KLS symptoms, between episodes or years after cessation of episodes, mainly in the form of mood disorders (Gadoth, 2020). Indeed, Groos reported that 16.5% of 115 patients had a history of psychiatric disorder prior to the appearance of KLS (Groos et al., 2018) while only 4 (6.6%) patients of the present case series suffered from significant psychiatric morbidity. We found 5 case reports of various autistic disorders with clinical features resembling those of KLS. Berthier reported 2 patients with Asperger syndrome. One of them suffered from retinitis pigmentosa and cortical dysplasia and the other from low IQ, clumsiness and features of OCD (Berthier et al., 1992). Two patients with "autism" were reported by Mukkades. One suffered from meningitis during the first week of life and later was diagnosed with mental retardation while the other had an early onset seizure disorder (Mukaddes et al., 2009). Hakim Shaushatri reported a patient with ataxia, tremor and active seizure disorder during which 3 episodes coined as KLS attacks were recorded (Hakim Shoushtari et al., 2015). Two patients were diagnosed with PANDAS and PANS/PANDAS. The patient with PANDAS was drowsy between episodes which did not return after treatment with Penicillin (Das & Radhakrishnan, 2012), while the patient with PANS had typical and rapidly cycling (every 2 weeks) bouts of clinical and behavioral features compatible with OCD (Gerardi et al., 2015). Although the majority of children with PANS suffer from disordered sleep mainly due to Periodic Limb Movement Disorder and REM sleep without atonia, it was postulated that neuroinflammation is the mechanism responsible for the clinical characteristics of PANS (cognitive, motor and sleep impairment in the form of sleep-wake cycle disturbances (Gagliano et al., 2021). Of special interest are 3 patients with AKLS and one with typical KLS in whom antibodies to GAD65 or NMDAR were detected. In regard to the 2 cases in whom anti- NMDAR antibodies were found; in the patient reported by Tani there were no clinical features suggestive of autoimmune encephalitis. Moreover, the possibility of Anti NMDAR encephalitis was ruled out since CSF and serum were negative for anti-NMDAR on cell-based assay (Tani et al., 2020). On the other hand, the case by Fiegel, with anti-NMDAR in the CSF, is intriguing. The clinical pictures and the lack of CSF pleocytosis are not typical for this form of encephalitis, however, the presence of 2 oligoclonal bands in the CSF cannot be ignored (Feigal et al., 2016). As for the cases with anti-GAD65; The patient reported by Tse (Tse et al., 2021), suffered from relatively late onset KLS, but there was no evidence of a neurological disorder associated with anti-GAD65, i.e., Stiff Person Spectrum Disorder, cerebellar

ataxia, epilepsy, limbic encephalitis, cognitive impairment, myelopathy or brain stem dysfunction (Budharm et al., 2021). The elevated titer of anti-GAD65 antibodies found may be related to concomitant latent autoimmune diabetes detected in this patient. In the case reported by Rout, with clinical features of AKLS, GAD65 antibody serum titer was only 9 times higher than in normal controls while titers over 1000-fold higher than the upper limit of normally indicate a high clinical specificity for GAD65 neurological autoimmunity (Rout et al., 2014). Low titers similar to those found in this patient may be found incidentally in a number of neurological disorders without autoimmunity to GAD65, isolated DM1, and even healthy controls Budharm et al., 2021).

Few conclusions can be drawn from the present review. 1. Lumping cases with some features of KLS may indicate that those cases have in common a malfunctioning sleep-wake neural-circuits, which in some of those patients is transient either due to successful treatment of the cause of the symptoms (epilepsy, OSA, neurometabolic, psychiatric, infectious and autoimmune disorders), or restoration of lost function as in cases with stroke or TBI. 2. Splitting classical KLS from AKLS is essential for further studies to elucidate the etiology of KLS and develop specific treatment. This approach may also help in solving the mystery why is KLS a disorder of youth which resolves spontaneously towards the end of the third decade of life, in the majority of the patients. Finally, it seems to us that using the term AKLS should be abandoned. Instead, such cases should be diagnosed according to their primary cause of symptoms which can cause also periodic hypersomnia.

This work was performed in Maynei Hayeshua Med. Ctr.
All authors have read and approved the manuscript

The Authors Declare

No financial support was received

Conflict of Interest

There was no conflict of interest

List of Abbreviations

KLS	: Kliene Levin Syndrome
AKLS	: Atypical Kline Levin Syndrome
ICSD	: International classification of Sleep Disorders
REM	: Rapid Eye Movements
OSA	: Obstructive Sleep Apnea
CT	: Computerized Tomography
MRI	: Magnetic Resonance Imaging
PANDAS	: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections
PANS	: Pediatric Acute -onset Neuropsychiatric Syndrome
CPAP	: Continues Positive Airway Pressure
BMI	: Body Mass Index
OCD	: Obsessive Compulsive Disorder
GAD	: Glutamic Acid Decarboxylase
NMDAR	: N-Methyl –D- Aspartate-Receptor
CSF	: Cerebro Spinal Fluid
TBI	: Traumatic Brain Injury
DM1	: Diabetes Mellitus type 1
P (table)	: significant psychiatric morbidity
MSLT	: Multiple Sleep Latency Test
RLS	: Restless Legs Syndrome

References

1. Darien, I. L. (2014). *The diagnostic criteria of the American Academy of Sleep Medicine*. The international classification of sleep disorders. (3rd edition). American Academy of Sleep Medicine. Retrieved from https://learn.aasm.org/Listing/a1341000002XmRvAAK
2. Gadoth, N., & Oksenberg, A. (2017). *Kleine-Levin syndrome; an update and mini-review. Brain Dev, 39*(8), 665-671. DOI: 10.1016/j.braindev.2017.04.003
3. Miller, D. L. (1970). Kleine-Levin syndrome: an atypical case? *Psychiatr Q, 44*(1), 26-35. DOI: 10.1007/BF01562956
4. American Academy of Sleep Medicine. (2005). *The international classification of sleep disorders- Revised Diagnostic and Coding Manual*. (2nd edition). Chicago, IL. Retrieved from https://search.worldcat.org/title/international-classification-of-sleep-disorders-diagnostic-coding-manual/oclc/67281425
5. Thorpy, M. J. (1990). International Classification of Sleep Disorders: Diagnostic and Coding Manual. Diagnostic Classification Steering Committee. American Sleep Disorders Association.
6. Arnulf, I., Zeitzer, J. M., File, J., Farber, N., & Mignot, E. (2005). Kleine–Levin syndrome: a systematic review of 186 cases in the literature. *Brain, 128*(12), 2763–2776. DOI: 10.1093/brain/awh620
7. Billiard, M., Jaussent, I., Dauvilliers, Y., & Besset, A. (2011). Recurrent hypersomnia: a review of 339 cases. *Sleep Med Rev, 15*(4), 247-257. DOI: 10.1016/j.smrv.2010.08.001
8. Gadoth, N. (2018). Breathing abnormalities during sleep in Kleine-Levin Syndrome: fact of coincidence? *Curr Opinion Pulmonary Med, 24*(4), 403-405. DOI: 10.1097/MCP.0000000000000488
9. McGilchrist, I., Goldstein, L. H., Jadresic, D., & Fenwick, P. (1993). Thalamo-frontal psychosis. *Br J Psychiatry*, 163, 113-115. DOI: 10.1192/bjp.163.1.113
10. Hasegawa, Y., Morishita, M., & Suzumura, A. (1998). Novel chromosomal aberration in a patient with a unique sleep disorder. *J Neurol Neurosurg Psychiatry, 64*(1), 113-116. DOI: 10.1136/jnnp.64.1.113
11. Reimão, R., & Diamant, A. (1989). Periodic hypersomnia, congenital ectodermal disorders and multiple exostosis. *Arq Neuropsiquiatr, 47*(1), 76-79. DOI: 10.1590/s0004-282x1989000100010
12. Wilder, J. (1972). A case of atypical Kleine–Levin syndrome: 30 years' observation. *J Nerv Ment, 154*(1), 69–72. DOI: 10.1097/00005053-197201000-00009

13. Yassa, R., & Nair, N. P. (1978). The Kleine-Levine syndrome—a variant? *J Clin Psychiatry, 39*(3), 254-259. Retrieved from https://pubmed.ncbi.nlm.nih.gov/273020/
14. Striano, S., Bilo, L., & Meo, R. (1986). An unusual case of Kleine-Levin syndrome associated with sleep terrors. *Electroencephalogr Clin Neurophysiol, 64*(6), 517-520. DOI: 10.1016/0013-4694(86)90188-4
15. Ferguson, B. G. (1986). Kleine-Levin syndrome: A case report. *J Child Psychol Psychiatry, 27*(2), 275-278. DOI: 10.1111/j.1469-7610.1986.tb02336.x
16. Sagar, R. S., Khandelwal, S. K., & Gupta, S. (1990). Interepisodic morbidity in Kleine-Levin syndrome. *Br J Psychiatry*, 157, 139-141. DOI: 10.1192/bjp.157.1.139
17. Brown, R., & Malcolm, M. T. (1990). Kleine-Levin syndrome in a 74-year-old female. *Int Journal Geriatric Psychiatry, 5*(2), 133–135. DOI: https://psycnet.apa.org/doi/10.1002/gps.930050211
18. Badino, R., Caja, A., Del Conte, I., Guida, C., & Ivaldi, M. (1992). Kleine-Levin syndrome in an 82-year-old man. Ital *J Neurol Sci, 13*(4), 355-356. DOI: 10.1007/BF02223102
19. Pike, M., & Stores, G. (1994). Kleine-Levin syndrome: a cause of diagnostic confusion. *Arch Dis Child, 71*(4), 355-357. DOI: 10.1136/adc.71.4.355
20. Fontenelle, L., Mendlowicz, M. V., Gillin, J. C., Mattos, P., & Versiani, M. (2000). Neuropsychological sequelae in Kleine-Levin syndrome: case report. *Arq Neuropsiquiatr, 58*(2B), 531-534. DOI: 10.1590/s0004-282x2000000300021
21. Landtblom, A. M., Dige, N., Schwerdt, K., Säfström, P., & Granérus, G. (2002). A case of Kleine-Levin syndrome examined with SPECT and neuropsychological testing. *Acta Neurol Scand, 105*(4), 318-321. DOI: 10.1034/j.1600-0404.2002.1c162.x
22. Chakraborty, R., & Chatterjee, A. (2007). Comorbid obsessive-compulsive disorder in a patient with Kleine-Levin syndrome. *German J Psychiatry, 10*(3), 1–2. Retrieved from https://web.archive.org/web/20180409224618id_/http://www.gjpsy.uni-goettingen.de/gjp-article-chakraborty2-OCD.pdf
23. Bidaki, R., Sedaghati, M., Hakim-Shooshtari. M., & Ghalebandi, M. F. (2011). Kleine-Levin syndrome: A Case Report from Iran. *Iranian J Psychiat Behavior Sci, 5*(1), 74-76. Retrieved from https://brieflands.com/articles/ijpbs-2950.pdf
24. Seo, J. G., Kang, K., Park, S. P., & Lee, H.W. (2014). Kleine-Levin syndrome-like symptoms in a middle-age female with cognitive dysfunction. *Sleep Biol Rhythms, 12*(3), 224–226. DOI:10.1111/sbr.12060
25. Lachman, A. (2014). Kleine-Levin syndrome as a neuropsychiatric presentation: A case report and review. *South African J Psychiatry, 20*(2), 60-62. Retrieved from DOI: http://dx.doi.org/10.7196/SAJP.494
26. Neto, F. K., Noschang, R., Fussiger, H., Guzman, T.A., & Nunes, M. L. (2015). Refractory Kleine-Levin Syndrome at Age 3 Years: Response to lithium therapy. *J Sleep Med Disord, 2*(5), 1033-1034. Retrieved from https://repositorio.pucrs.br/dspace/bitstream/10923/12786/2/Refractory_Kleine_Levin_syndrome_at_age_3_years_response_to_lithium_therapy.pdf
27. Marčić, M., Marčić, L., & Titlić, M. (2018). A Case of Kleine-Levin Syndrome: Diagnostic and Therapeutic Challenge. *Acta Med Iran, 56*(1), 62-66. https://acta.tums.ac.ir/index.php/acta/article/view/5227
28. Edaki, O., Khawaja, I. S., & Schneck, C. H. (2019). An atypical case of Kleine-Levin syndrome. *Prim Care Companion CNS Disord, 21*(1), 18l02319. DOI: 10.4088/PCC.18l02319
29. Argenta, G., Bozzao, L., & Petruzzellis, M. C. (1981). First CT findings in the Kleine-Levin Critchley syndrome. *Ital J Neurol Sci, 2*(1), 77-9. DOI: 10.1007/BF02351691
30. Jungheim, K., Badenhoop, K., Ottmann, O. G., & Usadelet, K. H. (1999). Kleine-Levin and Munchausen syndromes in a patient with recurrent acromegaly. *Eur J Endocrinol, 140*(2), 140-2. DOI: 10.1530/eje.0.1400140
31. Nishikuni, K., Oliveira, M. F., Takahashi, L. R., & Rotta, J. M. (2014). Transient Kleine-Levin syndrome following a neuroendoscopic procedure. *J Neuropsychiatry Clin Neurosci, 26*(3), E53-5. DOI: 10.1176/appi.neuropsych.13080192
32. Drake, M. E. Jr. (1987). Kleine-Levin syndrome after multiple cerebral infarctions. *Psychosomatics, 28*(6), 329-30. DOI: 10.1016/s0033-3182(87)72524-9
33. Maskara, S., Govindarajan, R., Medcalf, P., & Ansell, M. (2009). Kleine-Levin syndrome presenting in later life. Midlife and beyond, *Neurology*: 059-066.
34. Gau, S. F., Soong, W. T., Liu, H. M., Hou, J. W., Tsai, W.Y., Chiu, Y. N., Yeh, Y. C., Wang, P. J., & Wang, T. R. (1996). Kleine-Levin syndrome in a boy with Prader-Willi syndrome. *Sleep. 19*(1), 13-7. https://pubmed.ncbi.nlm.nih.gov/8650457/
35. Bozinov, N., Han, M., Lau, W., & Santini, V. (2018). Late diagnosis of a rare urea cycle disorder mimicking Kleine-Levin syndrome. *Neurol Clin Pract, 8*(6), e43-e45. DOI: https://doi.org/10.1212/CPJ.0000000000000547
36. Chiu, H. F., Li, S. W., & Lee, S. Kleine-Levin syndrome 15 years later. (1989). *Aust N Z J Psychiatry, 23*(3), 425-7. DOI: 10.3109/00048678909068302
37. Kosti´c, V. S., Stefanova, E., Svetel, M., & Kozi´c, D. (1998). A variant of the Kleine–Levin syndrome following head trauma. *Behav Neurol, 11*(2), 105-108. DOI: 10.1155/1998/413989
38. Pelin, Z., Ozturk, L., & Bozluolcay, M. (2004). Posttraumatic Kleine–Levin syndrome: a case report. *Eur Psychiatry, 19*(8), 521-522. DOI: 10.1016/j.eurpsy.2004.06.005
39. Cheung, G. (2006). Posttraumatic Kleine-Levin syndrome. *Gen Hosp Psychiatry, 28*(5), 443-445. DOI: 10.1016/j.genhosppsych.2006.03.011
40. Javadpour, A., Yaghmaei, S., Mostafeenezhad, N., & Schofield, P. (2020). Delayed appearance of Klein-Levin Syndrome caused by traumatic brain injury: A case report. *Mathews J Case Rep, 5*(1), 63. DOI: https://doi.org/10.30654/MJCR.10063
41. Persson, T., Olsson, L., & Ortman, E. (1969). The Kleine–Levin syndrome: report of a case and discussion. *Behav Neuro Psychiatry, 1*(6), 4-6. https://pubmed.ncbi.nlm.nih.gov/5377814/

42. Takrani, L.B., Cronin D. (1976). Kleine–Levin syndrome in a female patient. *Can Psychiatr Assoc J, 21*(5), 315-318. DOI: 10.1177/070674377602100508
43. Merriam, A. E. (1986). Kleine–Levin syndrome following acute viral encephalitis. *Biol Psychiatry, 21*(13), 1301-1304. DOI: 10.1016/0006-3223(86)90313-6
44. Testa, S., Opportuno, A., Gallo, P., & Tavolato B. (1987). A case of multiple sclerosis with an onset mimicking the Kleine-Levin syndrome. *Ital J Neurol Sci, 8*(2), 151-155. DOI: 10.1007/BF02337589
45. Fenzi, F., Simonati, A., Crosato, F., Ghersini, L., & Rizzuto, N. (1993). Clinical features of Kleine-Levin syndrome with localized encephalitis. *Neuropediatrics, 24*(5), 292-295. DOI: 10.1055/s-2008-1071559
46. Thacker, A. K., Aeron, A., Haider. J., & Rao, K. M. (2007). Kleine-Levin syndrome in tubercular meningitis. *Ann Indian Acad Neurol, 10*(4), 270-271. DOI: 10.4103/0972-2327.37823
47. Afshar, K., Engelfried, K., & Sharma, O. P. (2008). Sarcoidosis: a rare cause of Kleine-Levine-Critchley syndrome. *Sarcoidosis Vasc Diffuse Lung Dis, 25*(1), 60-63. Retrieved from https://www.mattioli1885journals.com/index.php/sarcoidosis/article/view/2645/2046
48. Das, A., & Radhakrishnan, A. (2012). A case of PANDAS with Kleine-Levin type periodic hypersomnia. *Sleep Med, 13*(3), 319-320. DOI: 10.1016/j.sleep.2011.11.003
49. Rout, U. K., Michener, M. S., & Dhossche, D. M. (2014). GAD65 autoantibodies in Kleine-Levin syndrome. *J Neuropsychiatry Clin Neurosci, 26*(2), E49-E51. DOI: 10.1176/appi.neuropsych.13050110
50. Khanna, A., Sinha, A. K., Periwal, P., & Talwar, D. (2015). Hyper somnolence in Kleine-Levin syndrome secondary to tuberculous meningitis. *Astrocyte, 2*(1), 52-53. DOI:10.4103/2349-0977.168240
51. Gerardi, D. M., Casadonte, J., Patel, P., & Murphy, T. K. (2015). PANDAS and comorbid Kleine-Levin syndrome. *J Child Adolesc Psychopharmacol, 25*(1), 93-98. DOI: 10.1089/cap.2014.0064
52. Feigal, J., Lin, C., Barrio, G., Kranz, P. G., & Preud'Homme, X. (2016). Anti-N-Methyl-d-Aspartate Receptor Encephalitis Presenting with Features of Kleine-Levin Syndrome and Demyelination. *Psychosomatics, 57*(3), 310-314. DOI: 10.1016/j.psym.2015.11.005
53. Takayanagi, M., Okabe, S., Yamamoto, K., Komatsu, J., Suzuki, R., Kitamura, T., & Ohura, T. (2017). Kleine-Levin syndrome elicited by encephalopathy with reversible splenial lesion. *Pediatr Int, 59*(8), 929-931. DOI: 10.1111/ped.13326
54. Tani, M., Konishi, Y., Nishida, T., Takahashi, Y., & Kusaka, Y. (2020). A case of Kleine-Levin syndrome with positive anti-NMDA-type glutamate receptor antibodies. *Pediatr Int, 62*(3), 409-410. DOI: 10.1111/ped.14088
55. Berthier, M. L., Santamaria, J., Encabo, H., & Tolosa, E. S. (1992). Recurrent hypersomnia in two adolescent males with Asperger's syndrome. *J Am Acad Child Adolesc Psychiatry, 31*(4), 735-738. DOI: 10.1097/00004583-199207000-00023
56. Mukaddes, N. M., Fateh, R., & Kilincaslan, A. (2009). Kleine-Levin syndrome in two subjects with diagnosis of autistic disorder. *World J Biol Psychiatry, 10*(4 Pt 3), 969-972. DOI: 10.1080/15622970801901810
57. Hakim Shoushtari, M., Ghalebandi, M. F., Tavasoli, A., & Pourshams, M. (2015). Kleine-Levin Syndrome in an 8 Year Old Girl with Autistic Disorder: Does Autism Account a Primary or Secondary Cause? *Iran J Child Neurol, 9*(4), 61-64.
58. Vardi, J., Flechter, S., Tupilsky, M., Rabey, J. M., Carasso, R., & Streifler, M (1978). Kleine–Levin syndrome with periodic apnea during hypersomnic stages—E.E.G. study. *J Neural Transm, 43*(2), 121-132. DOI: 10.1007/BF01579071
59. Cuetter, A. C. (1985). Sleep Apnea and the Kleine-Levin Syndrome. *Mil Med, 150*(5), 286-288.
60. de Araújo Lima, T. F., da Silva Behrens, N. S., Lopes, E., Pereira, D., de Almeida onseca, H., Cavalcanti, P. O., Pradella-Hallinan, M., Castro J., Tufik, S., & Coelho. F. M. (2014). Kleine-Levin Syndrome: A case report. *Sleep Sci, 7*(2), 122-125.
61. Chawla, G., Niwas, R., Dutt, N., & Swamy, M. K. (2019). Obstructive sleep apnoea with co existent Kleine-Levine syndrome in a middle-aged man. *Monaldi Arch Chest Dis, 89*(3), 49-51. DOI: 10.4081/monaldi.2019.1163
62. Divya, M. P., Kumar, A., Gupta, S., Tale, S., Saini, L. K., & Gupta, R. (2020). Obstructive Sleep Apnea Comorbid with Late-Onset Kleine–Levin Syndrome: A Rare Condition. *Sleep Vigilance, 4*(2), 247-249. DOI: 10.1007/s41782-020-00096-3
63. Livrea, P., Puca, F., Barnaba, A., & Di Reda, L. (1977). Abnormal central monoamine metabolism in humans with 'true hypersomnia' and 'subawkefulness'. *Eur Neurol, 15*(2), 71-76. DOI: 10.1159/000114792
64. Müller, T., Kuhn, W., Börnke, C., Büttner, T., & Przuntek, H. (1998). Kleine-Levin syndrome and Parkinsonian symptoms-a case report. *J Neurol Sci, 157*(2), 214-216. DOI: 10.1016/s0022-510x(98)00087-2
65. Masi, G., Favella, L., & Millepiedi, S. (2000). The Kleine–Levin syndrome as a neuropsychiatric disorder: a case report. *Psychiatry, 63*(1), 93–100. DOI: 10.1080/00332747.2000.11024898
66. Sharma, A., Singh, S. M., Grover, S., & Malhotra, S. (2010). Non-Convulsive Status Epilepticus Presenting as recurrent hypersomnia. *J Neuropsychiatry Clin Neurosci, 22*(2), E5-E6. DOI: 10.1176/jnp.2010.22.2.247.e5
67. Nesbitt, A. D., Leschziner, G. D. (2016). Migraine with brainstem aura presenting as recurrent hypersomnia (Kleine-Levin syndrome). *Prac Neurol, 16*(5), 402-405. DOI: 10.1136/practneurol-2016-001418
68. Ambati, A., Hillary, R., Leu-Semenescu, S., Ollila, H. M., Lin, L., During, E. H., Farber, N., Rico, T. J., Faraco, J., Leary, E., Goldstein-Piekarski, A. N., Huang, Y. S., Han, F., Sivan, Y., Lecendreux, M., Dodet, P., Honda, M., Gadoth, N., Nevsimalova, S., Pizza, F., Kanbayashi, T., Peraita-Adrados, R., Leschziner, G. D., Hasan, R., Canellas, F., Kume, K., Daniilidou, M., Bourgin, P., Rye, D., Vicario, J. L., Hogl, B., Hong, S. C., Plazzi, G., Mayer, G., Landtblom, A. M., Dauvilliers, Y., Arnulf, I., & Mignot, E. J. (2021). Kleine-Levin syndrome is associated

with birth difficulties and genetic variants in the TRANK1 gene loci. *Proc Natl Acad Sci USA, 118*(12), e2005753118. DOI: 10.1073/pnas.2005753118
69. Critchley, M., & Hoffman, H. L. (1942). The syndrome of periodic somnolence and morbid hunger (Kleine–Levin syndrome). *Brit Med J, 1*(4230), 137-139. DOI: 10.1136/bmj.1.4230.137
70. Chilakamarri, P., & Kryger M. H. (2019). When sleep can be a curse. *Sleep health, 5*(5), 431-432. DOI: 10.1016/j.sleh.2019.07.002
71. Nebhinani, N., & Suthar, N. (2017). Sleeping beauty syndrome: A case report and review of female cases reported from India. *Indian J Psychol Med, 39*(3), 357-360. DOI: 10.4103/0253-7176.207319
72. Klein, S. (1901). Some Mistakes in the Interpretation of Names and Places in Zion. Yedioth Society of Eretz Israel History and Ethnography. Lisk, D. R. (2009). Kleine-Levin syndrome. *Pract Neurol, 9*(1), 42-45. DOI: 10.1016/j.slsci.2014.09.001
73. Gomp, H. S., Anaclet, C. (2020). The neuroanatomy and neurochemistry of sleep-wake control. *Curr Opin Physiol,* 143-151. DOI: 10.1016/j.cophys.2019.12.012
74. Guilleminault, C., & Cao, M. T. (2011). Narcolepsy diagnosis and management. In: M. H. Kryger., H. Roth., & W. C. Dement (Eds,) Principles and practice of sleep medicine, (Fifth edition), Chapter 84, pp 957-968, Elsevier.
75. McArdle, N., Ward, S. V., Bucks, R. S., Maddison, K., Smith, A., Huang, R. C., Pennell, C. R., Hillman, D. R., & Eastwood, P. R. (2020). The prevalence of common sleep disorders in young adults: a descriptive population-based study. *Sleep, 43*(10), 1-11. DOI: 10.1093/sleep/zsaa072
76. Gadoth, N. (2020). Obstructive sleep apnea and Kleine Levin Syndrome: a rare comorbidity. *EC Pulmonol Res Med*, 132-134.
77. Groos, E., Chaumereuil, C., Flamand, M., Brion, A., Bourdin, H., Slimani, V., Lecendreux, M., & Arnulf, I. (2018). Emerging psychiatric disorders in Kleine-Levin syndrome. *J Sleep Res, 27*(5), e12690. DOI: 10.1111/jsr.12690
78. Gadoth, N. (2023). Kleine Levin Syndrome: Is it just a sleep disorder? A review of psychiatric features during symptomatic and asymptomatic periods. *Med Res Arch, 11*(7.1), DOI: https://doi.org/10.18103/mra.v11i7.1.3983
79. Gagliano, A., Puligheddu, M., Ronzano, N., Congiu, P., Tanca, M.C., Cursio, I., Carucci, S., Sotgiu, S., Grossi, E., & Zuddas, A. (2021). Artificial Neural Networks Analysis of polysomnographic and clinical features in Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): from sleep alteration to "Brain Fog". *Nat Sci Sleep*, 13, 1209-1224. DOI: 10.2147/NSS.S300818
80. Tse, C., Mignot, E., & Lim, M. (2021). An unusual case of post -traumatic brain injury Kleine -Levin syndrome with anti-GAD-65 antibodies. Sleep, 44, Supplement, A320 (Abstract).
81. Budharm, A., Sechi, E., Flanagan, E. P., Dubey, D., Zekeridou, A., Shah, S.S., Gadoth, A., Naddaf, E., McKeon, A., Pittock, S. J., & Zalewski, N. L. (2021). Clinical spectrum of high-titre GAD65 antibodies. *J Neurol Neurosurg Psychiatry, 92*(6), 645-654. DOI: 10.1136/jnnp-2020-325275.