World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Review Article

Kleine-Levin Syndrome: A review

P. Joshua Arun Stanley, S. Venkatesh

Department of Pharmacy Practice, K.K College of Pharmacy, Chennai-6000128, Tamil Nadu, India

Received: 05-04-2017 / Revised: 06-05-2017 / Accepted: 24-05-2017 / Published: 27-05-2017

ABSTRACT

Kleine-Levin syndrome (KLS) is a rare disorder characterized by (PERIODIC hypersomnia) associated with behavioural disturbances such as binge eating (hyperphagia), irritability, and increased sexual interest (hyper sexuality). Episodes are separated by weeks or months of normal sleep and behaviour. Between episodes, patients have normal sleep, mood and behaviour. Previous finding of reduced working memory capacity in Kleine Levin Syndrome. This deficit correlates to lower activation of the anterior cingulate cortex and adjacent dorsomedial prefrontal cortex and stronger activation in the medial and anterior thalamus and possibly the inferior frontal gyrus. Thalamic activation is also amplified in sleep deprivation, especially when participants remain alert. Thus, increased thalamic reactivity could also represent a compensatory response: through recruitment of thalamic networks, the brain is trying to compensate for increasing processing demands invoked by disturbed sleep or attenuated wakefulness.

Keywords: Kleine-Levin syndrome, *Hypersomnia, hyper sexuality, megaphagia, periodic recurrent*

INTRODUCTION

Kleine-Levin Disorder [KLS] is an uncommon issue portrayed by intermittent scenes of hypersomnia, behavioral or psychological aggravations, impulsive eating conduct and hyper sexuality [1].KLS was first depicted by Kleine in 1925 and it was explained by Levin in 1936. KLS were characterized as disorder by Critchely and Hoffman in 1942 [2].

The creators proposed that a potential instrument could include a type of gentle encephalitis influencing the hypothalamus and the frontal flaps. What's more, further reviews revealed the fiery penetrates in the hypothalamus [3, 4] and in the thalamus [3, 5]. A few patients with head injury has additionally been accounted for [6-8].Apart from this a few discoveries recommend that birth challenges may cause an procured cerebrum wounds in the hypothalamic district amid the planning and procedure of birth [9].

Epidemiology: Kleine-Levin disorder is uncommon, influencing an expected 1–5 for each million individuals [10]there are just around 200 revealed cases to date in the writing. It is a malady transcendently of adolescents, and young men are four circumstances more prone to be influenced than young ladies. It is uncommon for patients beyond 30 years old years to give their first scene, and, in spite of the fact that cases have been accounted for; a few creators address the presence of a grown-up onset type of the infection. In a gathering of 239 patients, the middle period of onset was 15 years in both guys and females, with an age scope of 4–80 years in guys and 4–69 years in females [11] Prevalence is marginally higher in the Ashkenazi Jewish population [10].In general, 5% of cases have been accounted for inside family members [12]proposing some level of expanded hereditary helplessness; in any case, no hereditary variation from the norm has been yet recognized.

Two instances of monozygotic twins with Kleine-Levin disorder have been described [13, 14] In these cases, both arrangements of twins were sure for the DQB1*0302/*0601 allele. In an extensive companion of 108 patients determined to have Kleine-Levin disorder, 25% had a confused birth history and 15% had some level of formative delay[12]The essentialness of this is misty, and, while a few creators have speculated that such perinatal abuse may incline certain people to build up the sickness sometime down the road, there is no evident proof to bolster this.

***Corresponding Author Address:** P. Joshua Arun Stanley, Department of Pharmacy Practice, K.K College of Pharmacy, Chennai-6000128, Tamil Nadu, India. E-mail- joshuaarunstanley@gmail.com*

Etiology: It is not comprehended what causes KLS, but rather a few instruments have been proposed. One conceivable clarification is hypothalamic or circadian dysfunction[15] The thalamus likely assumes a part in the crazy sleeping[16] and patients with diencephalic–hypothalamic brokenness brought on by tumours encounter indications like those of KLS patients[15] Particularly, the average fleeting districts of the thalamus might be involved[17] in spite of the fact that examinations of KLS patients have not reliably discovered irregularities in this area[18] The worldly projection likewise seems to assume a part in the condition, perhaps bringing on subjective challenges. The lack of concern and disinhibit ion found in some KLS sufferers propose that the condition may include frontal projection brokenness too. The inclusion of the thalamus, fleeting projection, and frontal flap of the cerebrum proposes that there is a multifocal, localized encephalopathy. There are additionally relentless subclinical variations from the norm in KLS sufferers [16]another conceivable clarification concerns the digestion of serotonin and dopamine. Lop-sidednessin the neurotransmitter pathways of these chemicals could play a role [15] Viral diseases have additionally been recommended as a conceivable cause. Confirm for their part incorporates sores found in autopsies[15] CSF tests from KLS patients demonstrate that the condition has an alternate cause than flu related encephalopathy[19] Triggers of KLS may likewise influence the blood-mind hindrance, which could assume a part in the condition[16] There is constrained confirmation of what rolehypocretin may play, despite the fact that it regularly impacts hypersomnia[19]Androgen may (in a roundabout way) square melatonin receptors, conceivably by mean of vasodilation, and cause cholinergic variations from the norm at times of Kleine–Levin syndrome[20]Since KLS happens at a considerably higher rate in Jews and in a few families, it is likely that there is some hereditary segment notwithstanding natural factors[16]Genetic thinks about hold guarantee for understanding the illness, yet they have yielded conflicting results[21] and couple of patients are accessible for testing[16]Epilepsy and melancholy don't seem to bring about KLS. The condition's quick onset after diseases shows that the invulnerable framework is not to blame [16]. The etiology of Kleine-Levin disorder is obscure. Numerous patients report a prodromal influenza like disease or upper respiratory tract contamination (URI). In a current review in Taiwanese patients, a noteworthy connection was found between Kleine-Levin scenes and going before URI symptoms [22] the creators in this review revealed that 96.6% of first scenes of Kleine-Levin disorder happened after URI side effects, fever, or encephalitis. Intermittent occasions were activated by disease (65%), fever (20%), mental occasions/stretch (5%), and lack of sleep (5%). There was no relationship with inoculations. No regular variety was found. Similar to the case in narcolepsy with cataplexy, an immune system instrument has been recommended; be that as it may, the proof is a great deal less vigorous in Kleine-Levin disorder. The DQB1-0201 haplotype was observed to be twice as continuous in a controlled investigation of 30 European patients [23] Be that as it may; this has not been reproduced in bigger patient populations [24]

SYMPTOMS

Hypersomnia: Hypersomnia is one of the major clinical side effects of KLS in an investigation of 186 cases it was available in all announced cases. The standard rest length amid scenes went from 12 to 24h/day. The patients spent the vast majority of the night and the day asleep [25]. A few creators announced that their patients remained a rousable, awakening suddenly to void and eat. They got to be distinctly forceful when stirred or kept from rest, The need of rest for some announced male teenagers was intense to the point that 'he was discovered dozing under a neighbour's porch [26] another 'left his classroom amid a session, set down on the floor of the hallway and fell asleep [27]. A short enduring sleep deprivation was accounted for toward the finish of an episode [28]. Rest side effects changed from forthright hypersomnia amid the primary scene to an overwhelming weakness joined by an inclination 'as though in dusk amongst rest and waking' amid later scenes

Intellectual Aggravations –Cognitive Disturbances: In an Orderly investigation of 186 cases Psychological Aggravations were accounted for in all cases, for example, perplexity, fixation, consideration and memory surrenders. Once in a while unusual reactions to question were accounted for. Irregular discourse was accounted for in 66% of cases 1. A 16 year old kid did not know how to eat a steak with cutlery [29]. Numerous patients revealed amnesia of the occasions that happened amid an assault. A few patients revealed scholastic decay and a gentle durable memory brokenness between episodes[30, 31, 32]

Eating Conduct Issue–Eating Behaviour Disorder: In a Methodical investigation of 186 cases seventy five per cent of the patients had changes in eating practices amid scenes. In lion's share cases bigger measure of sustenance was taken [25]. Expanded sustenance admission went from three circumstances his standard diet [33], with 7-30lb [3.2-13.6] weight pick up. A few patients even

stole nourishment in shops or plates of different patients in the hospital [34, 35, and 36]. A few patients ate sustenance which they rejected before, for example, Turkish young ladies who ate watermelon rinds [37].

State of mind Issue: In a Deliberate investigation of 186 cases for the most part 50% of the patients had a depressive state of mind amid episodes [25]. Almost 15% of the patients revealed self-destructive musings and two patients endeavoured suicide [38]. In the most cases the discouraged temperament finished at 4ach scene in some uncommon case it continued longer. A couple cases 8% answered to be hypomanic for two or three days toward the finish of KLS episode [39, 40]. Another 8% had a mellow impact and 7% were anxions with two of them freezing when taken off alone.

Hyper Sexuality and Other Enthusiastic Practices: In an efficient survey of 186 cases half of the patients had manifestations with hyper sexuality amid scenes. The hyper sexuality level was expanded in guys with increment masturbation, vulgar language [25]. Sexual ambushing of female guests was noted [30, 41, and 42]. Some other urgent practices like habitual singing, written work on dividers and stripping down backdrop in two other patients [43, 44] and enthusiastic to set fire in one patient [38]

Medicinal Examinations and Tests

Cerebrospinal Liquid Investigation: In an efficient review directed in 186 cases CSF protein levels and white cells include were typical all patients however an irresistible meningitis were found [25]. CSF levels of serotonin and a serotonin metabolite were expanded (five circumstances the typical qualities) in one patient [46]. The CSF levels of hypocretin-1 a hypothalamic peptide that has been appeared to be lacking in narcolepsy were found inside ordinary ranges in five KLS patients yet somewhat diminished (111 and 137 pmol.1-1 in two patients amid an episode [46]

Electroencephalograms and Mind Imaging: In a methodical survey of 186 patients Cerebrum automated tomography and attractive reverberation imaging were performed and it was typical in all cases. Utilitarian imaging measuring cerebral blood stream by single photograph outflow tomography was performed around 9 patients matured 13-27 years [25]. Cerebral blood streams were typical in four patients and were lessened in five patients. The lessening was observed to be happened in the worldly or fleeting frontal zone of either as both sides [42, 47, 48, 49, 50, 51, and 52] and in the basal ganglia [48]. Mind neuro obsessive examination was performed after the demise of two patients with KLS [46, 53]. There were exceptional indications of fiery encephalitis inside the hypothalamus in two patient's gentle aggravation in one patient.

Hormonal Test: In an orderly survey of 186 cases a portion of the patients had an adjustment in levels of pituitary hormones. Hormonal estimations were performed amid scenes in 45 patients. The plasma levels of thyroid-empowering hormone (TSH, 21 patients), cortisol at 8 a.m. what's more, 4 p.m. (20 patients) and adrenocorticotropic hormone (ACTH, 4 patients) were constantly typical, while those of development hormone (GH) were either ordinary (10 of 12 patients), expanded (1 of 12 patients)[36] or diminished (1 of 12 patients)[54].

Current Treatment: No pharmaceutical has been convincingly shown to be proficient in the treatment of KLS. Antipsychotics, for example, risperidone have been utilized for delayed maniacal symptoms [55, 56]. Benzodiazepines might be utilized for treatment of an anxiety [55]. Lithium has additionally been proposed as a safeguard agent [57] other state of mind stabilizers and antiepileptic considers have included valproic acid [58], carbamazepine [59], phenytoin, gabapentin [60] and lamotrigine. In any case, none demonstrated advantageous huge outcome. Antidepressants including tricyclics, specific serotonin reuptake inhibitors and serotonin-nor-epinephrine reuptake inhibitors have not been appeared to have any prophylactic impact either.

Autopsy Report

In some reported autopsy cases inflammatory infiltrates were observed in the hypothalamus in two patients [61, 62] and in the thalamus in two patients [61, 53].

Conclusion

The underlying etiology of KLS remains elucidated. An autoimmune mechanism has been suggested. In some cases infection in the brain region and injuries is also detected. KLS are often misdiagnosed or unrecognized. More long-term follow-up studies are needed to understand the underlying pathological condition and the risk factor involved in these patients.

REFERENCES

1. American Academy of Sleep Medicine. International Classification of Sleep Disorders:Diagnostic and Coding Manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005
2. Critchley M, Hoffman H. The syndrome of periodic somnolence and morbid hunger (Kleine-Levin syndrome). Br Med J. 1942;1: 137–139
3. Fenzi F, Simonati A, Crosato F, Ghersini L, Rizzuto N. Clinical features of Kleine-Levin syndrome with localized encephalitis. Neuropediatrics. 1993;24(5):292–295.
4. Takrani LB, Cronin D. Kleine-Levin syndrome in a female patient. Can Psychiatr Assoc J. 1976;21(5):315–318
5. Carpenter S, Yassa R, Ochs R. A pathologic basis for Kleine-Levin syndrome. ArchNeurol. 1982;39(1):25–28.
6. Billiard M, Podesta C. Recurrent hypersomnia following traumatic brain injury. SleepMed. 2013;14(5):462–465.
7. Pike M, Stores G. Klein-Levin syndrome: A cause of diagnostic confusion. Arch DisChild. 1994;71:355–357
8. Ferguson BG. Kleine-Levin syndrome: a case report. J Child Psychol Psychiatry. 1986;27(2):275–278
9. Swaab D. The human hypothalamus in metabolic and episodicdisorders. Prog Brain Res 2006;153:3– 45
10. Frenette E, Kushida CA. Primary hypersomnias of central origin. Semin Neurol. 2009;29(4):354–367.
11. Billiard M, Jaussent I, Dauvilliers Y, Besset A. Recurrent hypersomnias: a review of 339 cases. Sleep Med Rev.2011;15:247–257.
12. Arnulf I, Rico TJ, Mignot E. Diagnosis, disease course, and management of patients with Kleine-Levin syndrome. Lancet Neurol. 2012;11(10):918–928.
13. Ueno T, Fukuhara A, Ikegami A, Ohishi F, Kume K. Monozygotic twins concordant for Kleine-Levin syndrome. BMC Neurol. 2012;12:31.
14. Peraita-Adrados R, Vicario JL, Tafti M, García de León M, Billiard M. Monozygotic twins affected with Kleine-Levin syndrome. Sleep. 2012;35(5):595–596.
15. Oliveira MM, Conti C, Saconato H, Fernandes do Prado G. Pharmacological treatment for Kleine-Levin syndrome. Cochrane Database Syst Rev. 2009;(2):CD006685.
16. Arnulf I, Rico TJ, Mignot E. Diagnosis, disease course, and management of patients with Kleine-Levin syndrome. Lancet Neurol. 2012;11(10):918–928.
17. Pearce, J. M. (2008). "Kleine–Levin Syndrome: History and Brief Review". European Neurology. **60** (4): 212–4.
18. Ramdurg, Santosh (2010). "Kleine–Levin Syndrome: Etiology, Diagnosis, and Treatment". Annals of Indian Academy of Neurology. 13 (4): 241–246.doi:10.4103/0972-2327.74185. PMID 21264130
19. Kodaira, Minori; Yamamoto, Kanji (2012). "First Attack of Kleine-Levin Syndrome Triggered by Influenza B Mimicking Influenza-associated Encephalopathy". Internal Medicine. 51 (12): 1605–1608.
20. Brown, DW (1993). "Abnormal fluctuations of acetylcholine and serotonin". Medical Hypotheses. 40 (5): 309–310. doi:10.1016/0306-9877(93)90011-e.PMID 8350780
21. Arnulf I, Rico TJ, Mignot E. Diagnosis, disease course, and management of patients with Kleine-Levin syndrome. Lancet Neurol. 2012;11(10):918–928.
22. Huang YS, Guilleminault C, Lin KL, Hwang FM, Liu FY, Kung YP. Relationship between Kleine-Levin syndrome and upper respiratory infection in Taiwan. Sleep. 2012;35(1):123–129.
23. Dauvilliers Y, Mayer G, Lecendreux M, et al. Kleine-Levin syndrome: an autoimmune hypothesis based on clinical and genetic analyses. Neurology. 2002;59:1739–1745.
24. Arnulf I, Lin L, Gadoth N, et al. Kleine-Levin syndrome: a systematic study of 108 patients. Ann Neurol.2008;63:482–493.
25. Frank Y, Braham J, Cohen BE. The Kleine–Levin syndrome. Case report and review of the literature. Am J Dis Child 1974; 127: 412–3.
26. Gallinek A. The Kleine–Levin syndrome: hypersomnia, bulimia, and abnormal mental states. World Neurol 1962; 3: 235–43
27. Fro¨sher W, Maier V, Fritschni T. Periodic hypersomnia: case-report with biochemical and EEG findings. Sleep 1991; 14: 460–3
28. Russell J, Grunstein R. Kleine–Levin syndrome: a case report. Aust N Z J Psychiatry 1992; 26: 119–23.
29. Rosenow F, Kotagal P, Cohen BH, Green C, Wyllie E. Multiple sleep latency test and polysomnography in diagnosing Kleine–Levin syndrome and periodic hypersomnia. J Clin Neurophysiol 2000; 17: 519–22.
30. Fresco R, Giudicelli S, Poinso Y, Tatossian A, Mouren P. Kleine–Levin syndrome—recurrent hypersomnia of male adolescents. Ann Med Psychol (Paris) 1971; 1: 625–68.
31. Sagar RS, Khandelwal SK, Gupta S. Interepisodic morbidity in Kleine–Levin syndrome. Br J Psychiatry 1990; 157: 139–41
32. Masi G, Favilla L, Millepiedi S. The Kleine–Levin syndrome as a neuropsychiatric disorder: a case report. Psychiatry 2000; 63: 93–100
33. Shukla G, Bajpai H, Mishra D. Kleine–Levin syndrome: a case-report from India. Br J Psychiatry 1982; 141: 97–104.
34. George HR. A case of the Kleine–Levin syndrome of long duration. Br J Psychiatry 1970; 117: 521–3.
35. Prabhakaran N, Murthy GK, Mallya UL. A case of Kleine–Levin syndrome in India. Br J Psychiatry 1970; 117: 517–9.
36. Rosenow F, Kotagal P, Cohen BH, Green C, Wyllie E. Multiple sleep latency test and polysomnography in diagnosing Kleine–Levin syndrome and periodic hypersomnia. J Clin Neurophysiol 2000; 17: 519–22
37. Mukaddes NM, Alyanak B, Kora ME, Polvan O. The psychiatric symptomatology in Kleine–Levin syndrome. Child Psychiatry Hum Dev 1999a; 29: 253–8
38. Gallinek A. The Kleine–Levin syndrome. Dis Nerv Syst 1967; 28: 448–51.
39. Vlach V. Periodical somnolence, bulimia and mental changes (Kleine–Levin syndrome). Cesk Neurol 1962; 25: 401–5.
40. Reynolds CF 3rd, Black RS, Coble P, Holzer B, Kupfer DJ. Similarities in EEG sleep findings for Kleine–Levin syndrome and unipolar depression. Am J Psychiatry 1980; 137: 116–8.
41. Goldberg MA. The treatment of Kleine–Levin syndrome with lithium. Can J Psychiatry 1983; 28: 491–3.
42. Garland H, Sumner D, Fourman P. The Kleine–Levin syndrome. Some further observations. Neurology 1965; 15: 1161–7.
43. Yassa R, Nair NP. The Kleine–Levine syndrome—a variant? J Clin Psychiatry 1978; 39: 254–9.
44. Will RG, Young JP, Thomas DJ. Kleine–Levin syndrome: report of two cases with onset of symptoms precipitated by head trauma. Br J Psychiatry 1988; 152: 410–2.
45. Mukaddes NM, Kora ME, Bilge S. Carbamazepine for Kleine–Levin syndrome. J Am Acad Child Adolesc Psychiatry 1999b; 38: 791–2
46. Powers PS, Gunderman R. Kleine–Levin syndrome associated with fire setting. Am J Dis Child 1978; 132: 786–9
47. Koerber RK, Torkelson R, Haven G, Donaldson J, Cohen SM, Case M. Increased cerebrospinal fluid 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in Kleine–Levin syndrome. Neurology 1984; 34: 1597–600.
48. Argentino C, Sideri G. Kleine–Levin syndrome. Riv Neurol 1980; 50: 26–31.

49. Lu ML, Liu HC, Chen CH, Sung SM. Kleine–Levin syndrome and psychosis: observation from an unusual case. Neuropsychiatry Neuropsychol Behav Neurol 2000; 13: 140–2.
50. Arias M, Crespo Iglesias JM, Perez J, Requena-Caballero I, Sesar-Ignacio A, Peleteiro-Fernandez M. Kleine–Levin syndrome: contribution of brain SPECT in diagnosis. Rev Neurol 2002; 35: 531–3.
51. Landtblom AM, Dige N, Schwerdt K, Safstrom P, Granerus G. A case of Kleine–Levin syndrome examined with SPECT and neuropsychological testing. Acta Neurol Scand 2002; 105: 318–21.
52. Landtblom AM, Dige N, Schwerdt K, Safstrom P, Granerus G. Short-term memory dysfunction in Kleine–Levin syndrome. Acta Neurol Scand 2003; 108: 363–7.
53. Portilla P, Durand E, Chalvon A, Habert M, Navelet Y, Prigent A, et al. SPECT-identified hypoperfusion of the left temporomesial structures in a Kleine–Levin syndrome. Rev Neurol (Paris) 2002; 158: 593–5.
54. Carpenter S, Yassa R, Ochs R. A pathologic basis for Kleine–Levin syndrome. Arch Neurol 1982; 39: 25–8.
55. Chesson AL Jr, Levine SN, Kong LS, Lee SC. Neuroendocrine evaluation in Kleine–Levin syndrome: evidence of reduced dopaminergic tone during periods of hypersomnolence. Sleep 1991; 14: 226–32.
56. Arnulf I, Lin L, Gadoth N, et al. Kleine-Levin syndrome: a systematic study of 108 patients. Ann Neurol. 2008;63:482–493.
57. Arnulf I, Zeitzer JM, File J, Farber N, Mignot E. Kleine-Levin syndrome: a systematic review of 186 cases in the literature. Brain. 2005;128:2763–2776.
58. Muratori F, Bertini N, Masi G. Efficacy of lithium treatment in Kleine-Levin syndrome. Eur Psychiatry. 2002;17(4):232–233.
59. Crumley FE. Valproic acid for Kleine-Levin syndrome. J Am Acad Child Adolesc Psychiatry. 1997;36(7):868–869.
60. Mukaddes NM, Kora ME, Bilge S. Carbamazepine for Kleine-Levin syndrome. J Am Acad Child Adolesc Psychiatry. 1999;38(7): 791–792.
61. Itokawa K, Fukui M, Ninomiya M, et al. Gabapentin for Kleine-Levin Syndrome. Intern Med. 2009;48(13):1183–1185.
62. Fenzi F, Simonati A, Crosato F, Ghersini L, Rizzuto N. Clinical features of Kleine-Levin syndrome with localized encephalitis. Neuropediatrics. 1993;24(5):292–295.
63. Takrani LB, Cronin D. Kleine-Levin syndrome in a female patient. Can Psychiatr Assoc J. 1976;21(5):315–318