

Review article

Kleine–Levin syndrome; An update and mini-review

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Abstract

Since 1962, when Critchley and Hoffman coined the term Kleine–Levin Syndrome (KLS) for the triad of hypersomnia, excessive eating and “often abnormal behavior” which they have observed in 11 adolescent boys, the number of patients recognized with this rare syndrome expanded, the spectrum of the clinical presentation, disease course, prognosis, gender specificity and the presence of familial cases were established. However, in spite of the progress made in neuroscience, the search for the cause, neuroanatomy, pathophysiology and drug treatment of KLS is still ongoing. In this mini-review we will describe in some detail the scientific efforts made to understand in depth the complex symptomatology of KLS and refer also to updated findings reached up till now.

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1. Introduction

Kleine–Levin syndrome (KLS) seems to be a very rare disorder manifesting recurrent attacks of unexplained sleepiness accompanied by aberrant behavior. Patients with KLS were reported world-wide, however, most of the patients according to publications in English and French were young Caucasians while Asians were rarely reported either due to decreased awareness, misdiagnosis and/or due to different ethnic–environmental factors. Indeed, in a literature survey 168 patients were detected until 2005, out of them only six were Japanese, one Chinese and one Thai [1]. However, this survey of papers published either in English or French did not include publications in Japanese. The truth of matter is that recurrent hypersomnia/KLS was, and still is, a

subject of interest in Japan. Examples of this interest is the case report by Tsueno Muramatsu published in 1936 (personal communication), a report of 28 personal cases with periodic hypersomnia in 1965 [2] and the 55 cases of KLS registered in “Ichushi” – the Japan Medical Abstract Society, between the years 1983–2005 (personal communication). Unfortunately significant scientific information which is published in languages other than English or French fails to reach the international scientific community.

However, either increased awareness or a greater tendency to publish in English may explain the fact that seven years after the mentioned above 2005 survey [1], the first case of KLS was reported from Thailand in 2010 [3], 30 patients were diagnosed in Taiwan [4], and 44 Chinese patients were reported in 2016 [5]. If we use the accepted worldwide occurrence of KLS (1–5 per million individuals) [6], then, the expected number of patients in Taiwan (population: 23×10^6) should be 23–115 (low and high estimate respectively), in Japan,

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125–629 (population: 125.9×10^6) and in China, 1320–6600 (Population: 1.32×10^9). It is quite possible that increased awareness of the syndrome may have played a major role in Taiwan and led to the detection of the expected number of KLS patients as mentioned above. As a matter of fact, increased awareness played a major role in our experience in Israel where following early publications of single case reports [7–9], clinical presentation at local scientific meetings and a wide exposure of the syndrome via printed and electronic media, resulted in either professional or self-referral of patients who have been either misdiagnosed or had experienced the first hypersomnolent episode of KLS. Indeed, we were able to diagnose more than 40 patients during a brief period of time and to report 34 of them in detail [10]. This number of Israeli Jewish patients exceeds the expected 6–30 patients among a Population of 6.3×10^6 in 2015. Interestingly, we have not encountered yet an Israeli-Arab patient.

We hope that by publishing this updated mini-review in the official journal of the Japanese society of child neurology, there will be an increase in the awareness of KLS which hopefully may provide not only an update of the syndrome but may also help to answer the question whether KLS is indeed less frequent in people of Asian origin.

2. Historical and cultural notes

Mythological and legendary descriptions of people who fell asleep for extended periods of time and woke up either by the miracle of love (the “sleeping beauty” by the Grimm brothers) or at different era either in the past or future (Rip Van Winkle who woke up after 20 years and Honi HaMea’gel (Hebrew); Honi the Circle-drawer, a Jewish scholar of the 1st-century BC, who fell asleep and woke up after 70 years; Kumbhakarna, in the Indian mythological epic Ramayana who was granted by the Gods to sleep for six months, and when he woke up, he ate everything in the vicinity, including humans), thrilled the imagination of so many in the past and present as can be concluded from Walt Disney’s movie “Sleeping Beauty” and the quiet recent paper entitled “Sleeping Beauty: Kleine–Levin Syndrome” [11].

As happened in other rare syndromes, there were descriptions of single patients with features compatible with KLS before the syndrome was recognized. Apparently, the first report of a youngster with episodic sleep attacks was published in 1705 [12]. Thereafter, 12 cases with similar features were published between 1786 and 1924 [13]. Three psychiatrists deserve credit for their contribution to the establishment of the syndrome. Willi Kleine who worked in Germany reported five cases with periodic hypersomnia, two of those suffered also from excessive eating and hypersexuality [14]; Nolan Lewis

who practiced in Washington, described in 1926 a young boy with attacks of sleepiness, cognitive and behavioral impairment, excessive eating and visual hallucinations [15], and finally, Max Levin who practiced in Baltimore described a 19 year old male with similar symptoms in 1929. Consequently, in 1936 he outlined a new syndrome characterized by periodic hypersomnia and “morbid hunger” which was based on seven previously published cases [16,17].

Subsequently, McDonald Critchley and Lovell Hoffman coined the eponym Kleine–Levin syndrome in 1942, omitting the names of others who have published similar cases including Nolan Lewis. In this particular paper and later in 1962, Critchley outlined the fundamental clinical basis of KLS as a triad of periodic hypersomnia, excessive eating and abnormal behavior. He also noted that young adolescent males are predominantly affected, that the syndrome will spontaneously disappear and that the excessive eating is compulsive [18,19].

In the following years the general layout of Critchley’s observations was fortified by additional cases, however, it became evident that not all patients suffer from the classical triad, that females are also affected and that conditions such as febrile illness, infection and stressful situations among several others, may trigger either the onset of the syndrome or herald one or all periods of hypersomnia.

As frequently happens with “strange” rare disorders, the increased awareness of KLS due to medical and media expanding exposure led to a progressive increase in the number of patients published which also permitted the establishment of more flexible diagnostic criteria.

3. Kleine Levin syndrome in brief

KLS is indeed a strange rare disorder with an estimated prevalence of $1\text{--}5/10^6$ population when the diagnostic criteria of the International classification of Sleepiness Disorders, 3rd version (ICSD-3, revised in 2014), are applied [6]. Those criteria consist of the presence of recurrent episodes of unexplained sleepiness lasting from a few day 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. It affects mainly adolescent boys and to a lesser extent adolescent girls and young women [20]. Reports of men and women with late onset symptoms consisting mainly of attacks of hypersomnia with mood disorders or accompanied by anorexia “resembling KLS”, were coined as “atypical” [21,22], or “KLS like” [23] and thus, cannot be considered as KLS patients.

Although reported worldwide, it seems to be more frequent in Israel [9,20] and in American Jews with a tendency towards Ashkenazi Jewish origin [24].

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