

Obstructive Sleep Apnea and Kleine Levin Syndrome a: Rare Comorbidity

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Abstract

While Kleine-Levin syndrome (KLS) is a very rare condition, OSA is a common disorder. In both conditions patients suffer from excessive daytime sleepiness which is episodic in KLA but may be also episodic in OSA when such patients gain or loose weight. Several reports of patients with comorbidities of OSA and KLS were reported raising the possibility that breathing disorder during sleep may be a rare symptom of KLS. In this review this possibility is critically explored and discussed.

Keywords: *Hypersomnolence; Kleine Levin Syndrome; OSA; Breathing*

Introduction

Kleine-Levin Syndrome (KLS) is a rare and peculiar sleep disorder manifesting with a unique form of periodic hypersomnia affecting mainly adolescent boys and to a lesser extent adolescent girls and young women [1]. The estimated prevalence of the syndrome worldwide is 1 - 5/10⁶ once the diagnostic criteria of the International Classification of Sleepiness Disorders, 3rd version (ICSD-3, revised in 2014), are applied [2]. Those criteria include the presence of recurrent episodes (≥ 2) of severe hypersomnia ($> 18/24h$) lasting days to weeks, associated with cognitive disturbances (confusion, amnesia, derealization), and behavioral abnormalities (overeating, hypersexuality). These episodes had to be interspersed by long periods of normal sleep, cognition, behavior, and mood. Although spontaneous typical hypersomnic attacks are the rule, "triggers" such as respiratory infection, stress, minor trauma, extreme climatic condition and menstruation were observed [3].

KLS affects negatively the life quality of young adults during their prime years since drug treatment to prevent, shorten or decrease sleepiness during attacks is yet to be found. Lithium carbonate was reported by some authors as helpful in few patients but failed in many others. Fortunately, the frequency, length and severity of the attacks is decreasing as the patients get older and usually disappear after 1 - 2 decades [4]. 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" [5], or "KLS like" [6] and therefore cannot be considered as KLS patients according to the ICSD3 criteria.

Another but common disorder characterized by daytime hypersomnolence is Obstructive Sleep Apnea (OSA).

Although breathing abnormalities during sleep are not considered a feature of an attack of KLS, there were very few observations of OSA and KLS comorbidity which raised the question if sleep berating disorder is an additional rare symptom of KLS or that the co-occurrence of both is just a coincidence [7].

Sleep disordered breathing in KLS

Breathing abnormalities during the hypersomnolent periods of KLS have only rarely been observed. Vardi, *et al.* [8] (patient 1), described a 33-year-old obese man (BMI, 46.5 kg/m²), with KLS who suffered from multiple diurnal narcoleptic attacks accompanied by bulimia. Polysomnography (PSG) during one of those attacks disclosed apneic spells and desaturations. Spirometry during one of the attacks was summarized as “mild restrictive impairment”. Unfortunately, the authors did not provide sufficiently detailed clinical description that would support a diagnosis of KLS, however, OSA cannot be completely ruled out. Lavie, *et al.* [9] (Patients 2 - 5), described 4 young lean male patients who suffered from the classical symptom triad (hypersomnia, bulimia, hypersexuality) of KLS. PSG in each patient, including both during and in-between hypersomnolent episodes disclosed the presence of OSA. In a more recent case report, de Araújo Lima, *et al.* [10] (patient 6), described a 19-year-old man with clinical history compatible with KLS starting at the age of 14 years who was first seen at the age of 15 years. His BMI was 32.1 Kg/m². PSG during one of his hypersomnolent episodes did not reveal significant degree of sleep disordered breathing. Five years later, a repeated PSG initiated by the presence of classical symptoms of OSA was performed during one of his hypersomnolent episodes. His BMI was 35.7 kg/m² and the apnea-hypopnea index (AHI) was 30.8, which indicated the presence of severe OSA. Treatment with CPAP was beneficial and reduced the frequency of the hypersomnolent episodes. Two very recent case reports described additional patients with comorbidity of OSA and KLS. Chawla, *et al.* [11] (patient 7), described a 36 year old healthy man with severe OSA (BMI 36.4; AHI 34.8) who was treated with CPAP for 6 month. On a follow-up visit he reported that with CPAP his excessive daytime sleepiness and hypersomnia became episodic and during some of those episodes he experienced excessive and compulsive eating with increased sex drive. Each episode lasted 3 - 4 days during which he slept for more than 12 hours and if woken up early he became irritated and went back to sleep. Following an attack, he was symptom free for 15 day. Brain MRI was normal and PSG did not contribute to the final diagnosis of OSA and KLS co-morbidity. Divya, *et al.* [12] (patients 8), have recently described a 56 years old female who suffered from episodic excessive sleepiness starting at the age of 47 years following emotional stress. She carried a diagnosis of atypical depressive disorder which did not respond to adequate doses of Escitalopram and Propranolol. An attack of hypersomnia started with an experience of dream-like feeling and evolved to excessive sleepiness and anorexia. After forced awakening she was irritable, sad and cried loudly. Total sleep time was 18 - 20 h/day and each episode lasted 8 days with an asymptomatic interval of 1 - 2 days which increased to one week, 3 - 4 months later. This pattern lasted for 5 years followed by complete remission for approximately a year. Hypersomnolent attacks reemerged and were preceded by minor head injury. The episodes were similar to her past episodes. Duration of the episodes was reduced to 2 - 3 days over the next 3 years while the symptom free periods gradually increased to 2 months. Hyperphagia, hypersexuality, hypnogogic or hypnopompic hallucinations or delusions were not experienced during the episodes and there was no menstrual trigger, history of drug abuse or sleep deprivation. Brain MRI disclosed Fazekas grade 1 leukoaraiosis affecting the periventricular and subcortical white matter. A diagnosis of KLS was entertained. Intolerance to lithium led to administration of oxcarbazepine resulting in improvement of mood and hypersomnia. The possibility of concomitant OSA was raised when the bedpartner observed and reported that she occasionally snored, mumbled during sleep and stopped breathing. Her BMI was 29.8 kg/m² and PSG disclosed severe OSA (AHI 33.3). CPAP was added to drug therapy resulting in improved sleep quality and complete resolution of symptoms.

Discussion

Do the above described 8 patients support the fact that breathing problems during sleep are part of KLS? In patient 1, data are not sufficient to establish a diagnosis of KLS although he probably suffered from OSA. Patient 6 suffered from KLS for 10 years and only then showed signs of classical OSA due to excessive weight, a dominant factor in severity of OSA as shown by Oksenberg, *et al* [13]. The onset of KLS symptoms in Patient 7 with severe OSA, was late in life, triggered by minor trauma. Patient 8 is an excellent example of atypical KLS with very late onset and features of depression rather than KLS. This patient is quite similar to the case reported by Edaki, *et al* [14].

It seems that the 4 patients reported by Lavie *et al.* are genuine examples of classical KLS concomitant with OSA, but since 1981, no other reports can be considered as non-coincidental OSA-KLS comorbidity.

Thus, as for now, it can be stated that the co-occurrence of KLS and OSA is most probably coincidental and not “a fact”. It is not surprising that a common condition like OSA with a worldwide mean prevalence of 22% in males and 17% in females [15], can coincidentally affect patients with KLS.

Conclusion

Although co-occurrence of KLS and OSA has been rarely described, most of those cases share similarities with KLS symptomatology but cannot be considered as genuine KLS patients according to present diagnostic criteria of this rare syndrome. Thus, at present there is no sound basis for the assumption that sleep disordered breathing in the form of OSA is a rare additional clinical symptom of KLS.

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