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Kleine-Levin Syndorme: aetiology and pathogenesis, symptoms, diagnosis and treatment

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STRESZCZENIE

CEL: Celem prezentowanej pracy jest przybliżenie etiologii, patomechanizmu, symptomatologii, postępowania diagnostycznego, a zarazem terapeutycznego w Zespole Kleine-Levine'a *(ang. Kleine-Levin Syndorme, KLS)*

POGLĄD: Zespół Kleine-Levine'a jest niezmiernie rzadką jednostką chorobową, na którą składają się napady hipersomnii, zaburzeń kognitywno-behawioralnych, hiperfagii i hiperseksualności, przeplatane asymptomatycznymi interwałami. Częstość ów schorzenia, o nieustalonej jak dotąd etiopatogenezie, na całym świecie oscyluje wokół 1-5 osób/ 1 000 000

mieszkańców, z predylekcją do płci męskiej, głównie w okresie dojrzewania. Brak obiektywnych metod diagnostycznych implikuje częste błędy rozpoznawcze w zespole *KLS*. Ponadto, do chwili obecnej nie ma jednoznacznego stanowiska ekspertów co do jego farmakoterapii. Niemniej jednak rokowanie wydaje się być korzystne, jako że kolejne epizody stają się rzadsze, o mniejszym nasileniu, aż do ich całkowitej remisji u większości pacjentów.
WNIOSKI: Dalsze badania naukowe dotyczące etiopatogenezy i terapii *KLS* są niezbędne.

ABSTRACT
AIM: The aim of the study is to present the aetiology, pathogenesis, symptoms, diagnosis and treatment of Kleine-Levin syndrome *(KLS)*.
VIEW: Kleine-Levin syndrome is an extremely rare disease entity that consists of attacks of hypersomnia, cognitive and behavioural disorders, hyperphagia and hypersexuality, which are alternated with asymptomatic intervals. The prevalence of this disease, whose etiopathogenesis has not been known yet, all over the world oscillates around 1-5 cases/1,000,000 inhabitants, with predilection for male gender, mainly during the puberty period. Lack of objective diagnostic methods implicates frequent diagnostic errors in *KLS*. What is more, up to now, an unequivocal position of experts concerning pharmacotherapy of this disease has not been established yet. However, prognosis seems to be favourable as the following episodes become rarer, of weaker intensity up to their complete remission in the majority of patients.
CONCLUSION: Further research of aetiology and pharmacological treatment of *KLS* is needed.
Słowa kluczowe: zespół Kleine-Levine'a, zaburzenia snu, hipersomnia, hiperfagia, hiperseksualność
Key words: Kleine-Levin syndrome, sleep disoreder, hypersomnia, hyperphagia, hypersexuality

INTRODUCTION

Kleine-Levin syndrome (*KLS*, also known as "Sleeping-Beauty syndrome", "recurrent hypersomnia and pathological hunger syndrome" or "periodic sleep disease syndrome") is a recurrent-remittent disease that was described for the first time in 1925 by Willi Kleine. The essence of the disease is sudden occurrence of hypersomnia episodes with concomitant cognitive or behavioural disorders alternated with asymptomatic periods [1]. Analogically to the onset of the disease, its end is equally unpredictable. Outstandingly non-specific semiotics of the disease, at the border of neurology and psychiatry, delays the time to the proper diagnosis by approximately 2.5 years [2]. Kleine-Levin syndrome cases occurring with the prevalence of 1-5 cases/1,000,000 inhabitants concern all the continents and each nationality, with the majority of Israeli people and Ashkenazi Jews living in the United States. It is a condition with predilection for male gender (male to female rate ratio amounts to 3:1), whose initial symptoms are noticed during the puberty period, usually around 15 years of age [3,4]. However, several casuistic cases with onset of the disease before 9 years of age and the youngest patient at the age of 4 are known [5], but also with onset after 35 years of age, with the oldest patient at the age of 82 [6]. Within the spectrum of Kleine-Levin syndrome, two subtypes were distinguished: the more frequent one – sporadic and definitely more rare – familial subtype [7].

AETIOLOGY AND PATHOMECHANISM OF *KLS*

Aetiology of *KLS* remains unknown and pathomechanism of the disease is not fully explained. Lack of seizure activity in *EEG* and ineffectiveness of antiepileptic drugs during the episodes exclude the epileptic nature of the condition. Due to the above, several other mechanisms responsible for the development of the disease are taken into consideration [3].

Currently, opinions on the inflammatory pathomechanism are divided. Up to now, only 4 post-mortem brain examinations of patients with *KLS* were performed, in which an

insignificant, focal inflammation was observed. In three cases no lesions in brain cortex were showed, but in one patient perivascular infiltrations in amygdala and temporal lobe were observed. Intense inflammatory infiltration including thalamus and hypothalamus occurred in 2 patients, poorly intense infiltration was observed in 1 patient, whereas in the remaining 1 patient no inflammation features, but only depigmentation of locus coeruleus and substantia nigra were noted [8-11].

Autoimmune background of *KLS* is supported by its relapsing-remitting character and the onset in the puberty period, most often preceded by an upper respiratory tract infection, head injury, alcohol consumption that increases the permeability of blood-brain barrier promoting antibody flow to the brain. Three to five days before the occurrence of the first episode of hypersomnia dependent on *KLS*, some patients are treated for an acute upper respiratory tract infection, acute bronchitis or bronchiolitis, usually of viral aetiology. Several pathogens playing a potential role in development of *KLS* have been identified so far. Especially Epstein-Barr virus, herpes simplex virus, varicella-zoster virus, flu type A virus and adenoviruses are mentioned. Other triggering factors of *KLS* include: menstruation, lactation, anaesthesia, sleep deprivation, mental stress, non-specific physical exercise or some vaccines (against tuberculosis and typhoid fever) [2-4]. Two times more often occurrence of *KLS* in 30 European unrelated patients with a variant of human leukocyte antigens *(HLA)-DQB1*02* also suggests the immunopathomechanism of the disease [12]. However, the above correlation with the mentioned haplotype, as well as with the other haplotypes, was negated in the following studies involving 108 patients from the United States [13], 120 French patients [14] and 28 Taiwanese children [15]. An interesting observation also indicating the immune origin of the disease is a very good therapeutic response to intravenous administration of steroid and lithium carbonate that, apart from mood stabilisation, exhibits anti-inflammatory properties as well [16,17].

Accumulation of *KLS* cases in families and potentially higher risk of the disease in Jewish population suggests a genetic predisposition to this syndrome. Familial risk of developing the disease is low (amounts to 1% in first-degree relatives), but it was observed that in 4-5% of patients another person becomes ill, which suggests an 800-4000-fold increased tendency to the development of the disease in the first-line relatives. What is interesting, in the studies, sporadic and familial form of the disease did not differ in course, frequency and duration of episodes, accompanying neurological, psychiatric or autoimmune ailments, nationality of patients, their age, predilection for sex, haplotype or results of chromosomal analyses. Recurrence of episodes was slightly lower in the familial subtype. In turn, in 9 girls with hereditary *KLS* menstruation induced only the onset of the disease, but not its further episodes. Moreover, in case of familial form of the disease, speech disinhibition reaction and hypo-/hyperphagia were not as distinct and the end of episode was more sudden, with less intense post-episodic insomnia [13]. Whole-exome sequencing *(WES)* did not reveal any pathogenic lesions in the genome of patients with familial KLS. However, the results of genome-wide association study *(GWAS)* conducted among more than 400 patients suggested a slightly more frequent occurrence of *TRANK1* gene polymorphism compared to healthy control group, but it did not translate into a difference in clinical phenotype between the patients with one or more copies of the above-mentioned gene [3]. Chromosomal analysis conducted in 112 patients in France turned out to be normal in all the cases excluding one male patient with sporadic *KLS* and concomitant delay in development, paediatric anxiety disorders, concentration deficit and transitory autism spectrum symptoms. This patient inherited a 1.61-Mb duplication in Xp22.31 chromosomal region containing *HDH1*, *STS*, *VCX* and *PNPLA4* genes responsible for mild delay in development [18].

SYMPTOMATOLOGY AND COURSE OF *KLS*

In half of cases *KLS* episodes usually occur every three months, develop quite rapidly achieving maximum within 24 hours, whereas in other patients the episodes appear gradually within several days. Duration of the episodes is varied – it amounts to 2 days to many months, on average 1-3 weeks [2,3,5]. Thus, 1/3 of patients have at least one episode lasting for a minimum of 30 days [13,14]. Disease episodes are alternated with repeated asymptomatic intervals lasting for 15 days to 72 months, on average for 3.5 months [2]. Median disease duration oscillates around 15 years. The frequency of episodes decreases with age, the symptoms become less pronounced and in the majority of adult patients disappear after 30 years of life. However, disease onset before 12 or after 20 years of age prognoses further recurrence of episodes, regardless of age. Late recurrences, even after 10-15 years of asymptomatic period, were sporadically described [3].

Diagnostic criteria of *KLS*, established by consensus, include at least two separate episodes lasting for 2 to 42 days, occurring at least once a year, with undisturbed sleep, mood, cognitive and behavioural processes in remission period, when there is no better explanation of the above-mentioned symptoms [19]. What is more, in the episodic period a patient should exhibit hypersomnia with accompanying cognitive dysfunctions, impaired perception, eating disorders and/or disinhibited behaviour. In general, semiotics of the condition is based on a number of purely neurological and psychiatric symptoms or, definitely most often, on symptoms at the border of neuropsychiatry [3]. Up to now, the following forms of *KLS* were distinguished: mild *KLS* (1-week episodes occurring 2-3 times a year), moderate (a 7-10-day episode once a month or 3-6-month episodes 2-3 times a year) and severe (40-80 episodes per year with long-term impairment of cognitive functions and mood) [2].

A crucial and obligatory symptom of *KLS* is a spectacular hypersomnia, usually preceded by an overwhelming feeling of tiredness and irresistible need of sleep. During the episode, sleep time is remarkably prolonged (especially in teenagers), without any relation to biological rhythm and its median time is estimated to 18 hours per day, with short breaks for meals and physiological activities. A patient sleeps all night until the afternoon of the next day and then takes an afternoon nap. A brighter period and short insomnia usually take place around 6 p.m. What is important, a summary sleep duration does not correlate with its effectiveness. A patient wakes up himself spontaneously, whereas forced attempts of sleep interruption are very difficult and sometimes end with irritability and aggression of the patient [2,3]. Sporadically, patients report lucid dreams, hallucinations and a feeling of fatigue probably resulting from the accompanying derealization but sleep catalepsy has not been noted so far [13]. A short-term insomnia develops in the final stage of the episode and when it ends, a patient returns to his basic, pre-episodic rhythm of sleep and vigilance [2].

Cognitive disorders during a *KLS* episode include problems with speech, reading and memory in relation to which a secondary post-episodic amnesia usually occurs [20]. Recurrence of the disease also impairs concentration and logical thinking ability that overstrains a non-verbal intelligence quotient thus restricting multitasking and fulfilling duties that have been simple so far. All of these factors reduce patient activity, both at school and at work, thus prolonging the sick-leave absence [2].

During a multi-day episode of sleepiness, 9 in 10 patient experience derealization compared to a feeling of a complete detachment from reality and undeniable belief of being asleep or inside a bulb in which the daily routine is observed from a distant perspective, or a feeling of separation of mind from the body. The observed abnormalities included disturbed vision, hearing, smell, taste, a feeling of hot/cold and pain, which was unpleasant for the majority of patients and forced them to awkward, and sometimes even dangerous behaviours, such as e.g. skin burn after pouring it with hot water. Brain scintigraphy indicates a strong correlation between derealization accompanying *KLS* and hypoactivity of right temporoparietal junction – the area in the brain responsible for the integration of somatosensory, vision and hearing stimuli [3].

Frequently observed symptoms typical for *KLS* are eating disorders, usually in the form of hyperphagia. During the episodes patients eat compulsively, with predilection for

sweets and snacks. On the other hand, behaviour typical for bulimia i.e. self-induced vomiting or other methods of body mass control have not been described in the discussed disease entity yet. Interestingly, patients exhibit a tendency to amnesia in the form of memory loss with regard to episodic hyperphagia. On the contrary, 1/3 of patients do not show any interest in food and even lose weight during the episode, as they usually sleep in meal periods [2].

A principal symptom indicating disinhibited behaviour in patients with *KLS* is excessive sexual drive (hypersexuality) especially expressed in male gender. Patients show a tendency to more frequent masturbation, using obscene language among other people, making indecent sexual advances or exhibitionism [2].

In the treatment of *KLS* the main task for psychiatrists is to treat the concomitant mood lowering and flattened affect, especially in women [14]. Fortunately, suicidal thoughts and actions are extremely rare [21,22]. Seventy percent of patients present high level of anxiety resulting from a fear of going out alone, meeting other people, staying alone at home or hospital. Some patients demonstrate impolite behaviours and even verbal or psychical aggression, especially in attempts of preventing them from rest, that is ideally pictured by a situation in which two teenagers used a knife in order to intimidate their families [14]. What is more, 1/3 of patients experience transitory and temporary hallucinations (e.g. a snake near the bed) and delusions (e.g. a belief of having the ability to stop the clock hands with thoughts or of being a God) [3]. Behavioural disorders in the form of its regression (childish speech, repetitive compulsive behaviour) or antisocial activities, i.e. Setting fire or thefts were observed as well [23].

Hypersomnia, hyperphagia and hypersexuality show a tendency to reduce their intensity during the following relapses of the disease. On the contrary, apathy and neurocognitive disorders usually continue both during the episodes and the interepisodic period [2].

Neurological examination performed during the episodes is usually within normal range, without motor or sensory deficits or symptoms indicating the damage of cerebellum and cranial nerves, excluding vision ataxia described in several cases [13,14].

A classical triade of symptoms: hypersomnia, hypersexuality and hyperphagia occurs in less than 5% of cases [13]. A tetrade of symptoms. composed of hypersomnia, confusion, apathy and derealization, is present definitely more often [2].

DIAGNOSTICS OF *KLS*

Diagnostic imaging

Results of head computed tomography *(CT)* and magnetic resonance imaging *(MRI)* in patients with *KLS* are usually within normal limits, but functional brain imaging techniques reveal some striking inconsistencies [2]. Single-photon emission computed tomography *(SPECT)* conducted during the episodes revealed hypoperfusion of thalamus, hypothalamus, frontal, parietal, and rarely, temporal, occipital area and the area of basal ganglia. After hypersomnia had subsided, the majority of the described lesions underwent regression. Residual cortical hypoperfusion was observed sometimes, especially during persistent episodes and in patients with prolonged disease duration [24-29]. In turn, examination with the use of functional magnetic resonance imaging *(fMRI)* indicated the presence of abnormal feedbacks during the asymptomatic period within the cortical areas responsible for the control over specific neural networks, the so-called salience network and executive control network [30-32]. It is also worth mentioning that there are reports on very interesting studies that demonstrate a suppression of the interaction between thalamus and brainstem during an episode, with concurrent maintenance of the connection between thalamus and brain cortex [33]. Thus, it seems that an implication of the abnormal thalamopontine interaction is a disturbance in the functioning of ascending reticular arousal system *(ARAS)*, followed by hypersomnia [4].

Electroencephalography *(EEG)*

Electroencephalography without any abnormalities is observed only in 30% of patients with *KLS* [2]. In the remaining cases, a non-specific, general or focal inhibition of basic bioelectrical brain activity dominates during an episode. Single or sequential waves of high amplitude and low frequency may be registered, especially in the frontotemporal region [34].

Polysomnography *(PSG)*

Polysomnography results are often difficult for interpretation, because quality of the examination depends on the fact whether sleep is monitored only at night or during 24 hours, at the beginning or in the end of an episode, directly after the diagnosis of the disease or during its further course. In the metaanalysis of published single cases, the mean total sleep duration at night in 40 patients fluctuated around 445+/-122 min with the following distribution: *NREM* or *N1* sleep phase – 6%, *N2* – 56%, *N3* – 19%, *REM* – 19%. On the other hand, in 15 patients monitored for 24 hours total sleep duration amounted to 740 min. However, prolonged sleep duration was associated with its decreased effectiveness and frequent awakenings starting from the N2 phase [3,34]. Multiple sleep latency test *(MSLT)* did not reveal any statistically significant difference in the mean sleep latency and *REM* phase [35].

Biological markers

A marker for *KLS* that would be specific and sensitive enough has not been discovered yet. A statistically significant difference in the number of white blood cells, level of inflammatory markers, 51 various cytokines, C-reactive protein *(CRP)*, leptin or 6-hydroxymelatonin sulphate *(6-SM)* has not been demonstrated. In a small cohort of asymptomatic patients, elevated *sVCAM1* concentration compared to the control group was observed [2,4,36,37].

Type 1 narcolepsy is characterised by hypersomnia and chronically low orexin-A level (hypocretin-1) in the cerebrospinal fluid *(CRF)*. In a group of patients with *KLS* analysed by Wang et al., during the episode orexin-A level in *CRF* was lower compared to the asymptomatic patients, but it did not exceed the level below which type 1 narcolepsy is diagnosed (110 pg/ml) [38].

Neuropsychological tests

Certain cognitive symptoms reported during an episode of *KLS* may be explained by abnormalities in working memory detected in neuropsychological tests. Thus, patients experience disturbances within higher nervous activities such as language, problem solving or visual and spatial coordination. They are additionally enhanced by thalamus that functions abnormally during the episodes and has control over working memory. What is more, results of scientific analyses suggest that in patients with persistent episodes or prolonged duration of the disease, residual disorders in working memory are noted for quite a long time after the episode has subsided [4].

Diagnostics of the first hypersomnia episode requires that a physician urgently excludes other life-threatening causes of excessive somnolence, i.e. metabolic disorders (hyperammonaemia in liver encephalopathy), endocrine disorders, increased intracranial pressure, epileptic state, neuroinfection or drug intoxication [1].

TREATMENT OF *KLS*

There are no randomized controlled clinical trials whose results would unambiguously confirm the effectiveness of certain pharmacotherapy in the treatment of *KLS*.

The only known medication preventing the development of *KLS* episode that has already started, is methylprednisolone administered intravenously at the dose of 3 g/day for 3 consecutive days that interrupted the episode within one week in 40% of patients and

quenched the episode in 60% of patients but only in case of administration within the first 10 days of hypersomnia [16]. In several further research studies amantadine was used for the same purpose, with effectiveness of 50% [13].

Stimulants such as modafinil, methylphenidate or amphetamine introduced to therapy during the symptomatic intervals shortened their duration without any effect on their frequency [2]. There are numerous reports confirming that one of the oldest normothymic drugs having neuroprotective and anti-inflammatory properties – lithium, shortens the duration of *KLS* episodes and lowers their frequency. In a large, prospective controlled study, 71 patients with *KLS* taking lithium at the mean dose of 1000 mg/day experienced less frequent episodes of definitely weaker intensity compared to the control group [17]. However, lithium pharmacotherapy requires not only strict monitoring of its level, but also creatinine and *TSH* levels, in order to detect the adverse reactions of this medication early enough. A beneficial effect of other mood stabilizers, anticonvulsant medications (i.e. valproic acid [39], carbamazepine [40], phenytoin [20], gabapentin [41], lamotrigine [42], tricyclic antidepressant drugs [20], selective serotonin reuptake inhibitors [20], serotonin-norepinephrine reuptake inhibitors [20]) and antipsychotic drugs (i.e. risperidone [43], aripiprazole [39]) on alleviating the course of hypersomnia episodes was described as well. In one patient with persistently recurrent symptoms of *KLS*, sodium hydroxybutyrate was applied with a good effect [44], whereas acetazolamide was used in the other patient [45].

Undoubtedly, both patients and their families benefit from observing the principal rules of preventive management. It is recommended that during the episode a patient sleeps at home, under the surveillance of the family, which would undoubtedly prevent him/her from unnecessary anxiety and irritation associated with the necessity of staying at unknown hospital environment. It is worth explaining to the family that any attempts of stimulation or waking up a patient are pointless and unpleasant and may even induce a burst of uncontrolled aggression. Driving is strictly prohibited due to excessive somnolence, automatic behaviour and impaired perception. It is advised to remember not only about a strict control of the amount of liquids and food taken, but also about the control over the amount of produced urine (at least once a day). A regular patient monitoring and early intervention in case of the presence of suicidal thoughts and actions is also crucial. The occurrence of the episode should be reported to school, because mental performance may worsen during the episode that may require the introduction of an individual schedule. During the intervals between the episodes it is important to preserve undisturbed sleep and vigilance pattern, because sleep deprivation, similar to alcohol consumption or a contact with the infected patient, may induce the following episode of the disease [3].

KLS IN FURTHER RESEARCH STUDIES

Kleine-Levin syndrome is an extremely rare disease entity. Thus, further research studies concerning etiopathogenesis and natural course of this disease are strongly desired. Conducting a valuable randomised control study on the non-established pharmacotherapy of the disease is incredibly complicated due to its interval course and self-limiting character. What is important, results of further studies on *KLS* may lead to a better understanding of the sleep and vigilance rhythm itself as well as of other hypersomnias [2].

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