L-Carnitine use as a trigger for the onset of Kleine-Levin syndrome: A case presentation

Kleıne- Levin sendromu'nda bir tetikleyici olarak L-Karnitin: Bir olgu sunumu

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SUMMARY

Kleine- Levin Syndrome (KLS) is a rare phenomenon characterized by repeating episodes of hypersomnia, cognitive and behavioral impairments, compulsive eating behavior, and hypersexuality. Postinfectious processes, alcohol consumption, sleep deprivation, psychological stress, getting vaccinated, head injury and genetic factors have been identified possible etiological factors. Abnormal metabolism of serotonin and dopamine have also been reported. Alcohol and cannabis have been listed among triggering factors. With its role as a mediator required to transport long-chain fatty acids to mitochondrial matrix and its contributions in increasing oxidation of fatty acids, L-carnitine helps to produce more energy from burning fat while maintaining economic use of muscle glycogen stocks. Animal studies have shown a continous increase in dopamine discharge within nucleus accumbens via acetyl L-carnitine application. Carnitine supplementation is known to cause increased dopamine levels within cortical, hippocampal and striatal regions of the rat brain. One case report reported severe psychotic symptoms in a patient with bipolar disorder, following acetyl L-carnitine use. In this case presentation, we have aimed to present clinical course of an adolescent using L-carnitine for ergogenic support, as a possible trigger for the onset of a KLS episode.

Keywords: Kleine- Levin Syndrome, l-carnitine, triggering factor, child, adolescent, ergogenic supplement

ÖZET

Kleine-Levin Sendromu (KLS) tekrarlayan hipersomnia ve çeşitli derecelerde bilişsel ve davranışsal bozulmalar, kompulsif yeme davranışı ve hiperseksüalite ile karakterize nadir bir hastalıktır. Postenfeksiyöz düzenekler, alkol kullanımı, uykusuz kalma, psikolojik stres, aşılanma, kafa travması ile genetik etkenler altta yatan olası nedenler olarak sunulmuştur. Etiyoloji için serotonin ve dopamin metabolizmasında anormallikler bildirilirken alkol ile esrar da olası tetikleyiciler arasında tanımlanmıştır. L-karnitin, uzun zincirli yağ astilerinin mitokondri matriksine taşınmasında gerekli bir aracı olarak görev yapma ve yağ asitlerinin oksidasyonunun artırılmasında rol almaktadır. Bu özelliğinden dolayı, hem yağlardan daha fazla enerji üretilmesine hem de kas glikojen depolarının ekonomik kullanımına yardımcı olmaktadır. Hayvan çalışmalarında asetil L-karnitin uygulaması ile nucleus accumbens bölgesinde süreğen biçimde dopamin deşarjında artışın elde edildiği gösterilmiştir. Sıçan çalışmaları ile karnitin takviyesi sonucu beynin korteks, hipokampus ve striatumunda dopamin seviyelerinin arttığı saptanmıştır. Bir olgu sunumunda bipolar bozukluğu olan bir bireyde asetil L-karnitin kullanımı sonrasında şiddetli psikotik belirtilerin ortaya çıktığı bildirilmiştir. Bu olgu sunumunda, olası bir tetikleyici olarak, ergojenik amaçlı L-karnitin kullanımı ardından KLS epizodu başlayan bir erkek ergenin klinik gidişinin paylaşılması ve tartışılması hedeflenmiştir.

Anahtar Kelimeler: Kleine- Levin Sendromu, L- karnitin, tetikleyici faktör, çocuk, ergen, ergojenik madde

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INTRODUCTION

Kleine-Levin Syndrome (KLS) is a rare disorder of episodic nature that is characterized by hypersomnia, and alterations in cognition, eating and behavior (1). Although exact prevalance is unknown, the disorder is estimated to have affected 1-5/1000000 individuals worldwide (2). Generally encountered in adolescents and young adults, KLS has been reported to show a male predominance. In a review of 239 cases, mean age of onset for the disorder was 15 years old, regardless of gender (3).

Etiology of the disorder still remains largely unknown and while there have been reported triggering factors for the disorder, no causal link has yet been determined. Commonly underlined triggering conditions for the onset and recurrence of the disorder have been listed as infection, fever, alcohol and marijuana consumption, sleep deprivation, psychological stress, head injury, menstruation and lactation, and situations involving heavy physical effort, general or local anesthesia (4). Along with these, abnormalities in serotonin and dopamine metabolism have also been reported, therefore, an imbalance of neurotransmitters within serotonergic or dopaminergic pathways has also been suggested as a possible mechanism (5).

A non-specific generalized slow-wave pattern in the baseline electroencephalography (EEG) has been reported in 70% of the cases during the episode, while normal brain waves are present in between the episodes, in general. Polysomnography (PSG) might reveal decreased sleep index along with increased number of arousals (6). Despite increasing number of imaging and laboratory tests in order to better understand the disorder, no specific diagnostic tool or results have yet been maintained. Therefore as for today, KLS diagnosis is mainly made by a thorough assessment and review of clinical symptoms.

According to International Classification of Sleep Disorders-IIIrd Edition criteria (ICSD3, 2014), that is commonly used to formally diagnose KLS, the individual needs to experience at least two episodes of recurrent hypersomnia or increased sleep-time that would continue for a period of 2 days to 5 weeks for each episode identified; episodes recurring at least once in every 18 months and generally, in a period of less than once a year; maintaining normal levels of consciousness, awareness, cognitive functioning, behavior pattern and mood in between the episodes; while presenting with at least one of the following during an episode; 1) cognitive deficits, 2) perceptual alterations, 3) eating problems (not eating or overating), 4) dysinhibitated behavior (i.e, hypersexuality), and hypersomnia and other related symptoms should not be caused by the clinical course of another sleep disorder, or other medical, neurological or psychiatric disorder (specifically bipolar disorder), or should not be present secondary to a substance or drug use of any kind (7).

For cases with mild- moderate episodes, supportive interventions such as reducing stress, avoiding dangerous situations and treatment of comorbid conditions have been recommended, in those with much more severe form of the disorder, pharmacological agents such as modafinil, risperidone, aripiprazole, lithium, sodium valproate and carbamazepine have been tried with favorable clinical outcome (1,8). In a study where 186 KLS cases were assessed, clinical response to amphetamine was 70%, while 20% for methylphenidate, especially when tested during the symptomatic phase. As for treatment options to prevent the emergence of episodes, clinical response was 41% for lithium, and 21% for carbamazepine (4).

Dietary supplements have been used by many individuals who are professionally involved in sports, in order to maintain better performance. L-carnitine has gained more popularity recently as a potential ergogenic aid due its role of converting fat into energy (9). L-carnitine exists naturally in all mammal species, and takes part in mitochondrial oxidation of fatty acids (10). Due to its charge in acting as a mediator required to transport long chain fatty acids to the mitochondrial matrix as well as being involved in the process of increasing the oxidation of fatty acids, L-carnitine facilitates energy production from fat and aids in economic use of muscle glycogen storage (11). L-carnitine has two esther forms called acetyl L-carnitine and propionyl L-carnitine, and both forms have high bioavailability (10).

Since L-carnitine supplementation was hypothesized to have a potential of increasing lipid oxidation, reserved muscle gycogen and exercise performance, a number of studies focusing on the given action mechanism of the compound have been conducted (11,12). Apart from recent studies that cover L-carnitine being used as an ergogenic supplement, different derivatives of the compound have also been evaluated, to be used for diverse purposes and conditions. Among these forementioned forms is acetyl L- carnitine; the short chained esther form of L-carnitine. Acetyl L-carnitine is produced from carnitine and acetyl-CoA, via carnitine acetyl transferase enzyme (13). This compound has vastly been studied in different neuropsychiatric conditions, specifically. Among such conditions are depression, fibromyalgia, fatigue, male infertility and sexual dysfunction, Alzheimer's Disease, alcohol abuse and Attention Deficit Hyperactivity Disorder (13). Aside from the psychiatric conditions mentioned above, manic episode and psychotic episode in two separate cases each diagnosed with bipolar disorder have been identified, following acetyl L-carnitine use (14,15).

With this case report, we have aimed to discuss the possibility of L-carnitine supplement acting as a triggering factor for the onset of a KLS episode, in a male adolescent who had started to use the compound on his own for its ergogenic action, along with a review of relevant literature.

CASE HISTORY

The case was a 13 year old male adolescent who had applied to a child psychiatry outpatient unit in the company of his parents with primary complaints as irritability, increase in total sleep time, angry outbursts whenever family members would try to wake him, overeating, mood swings and dysinhibitated behavior that was mainly inappropriate and sexual in nature.

In the clinical interview, the family reported that the case had been sleeping excessively for the past couple of days prior to application, only to be woken up for meeting his basic daily needs. He was reported to eat excessive amounts of food during the time he would be awake, and had behavioral disruptions such as talking to himself about things that were unreal and engaging in meaningless monologues, inappropriate laughing, defiant behavior, inappropriate sexual talk and conduct. Reported symptoms had a sudden onset, and due to similar complaints and symptoms, they had actually applied to an emergency unit of a university hospital 4 months ago, followed by an admission to the intensive care unit for further diagnostic procedures. Data collected from the hospital records at that time revealed the case was followed up with preliminary diagnoses as psychotic episode, manic episode, possible drug intoxication and encephalopathy, following his initial evaluation in the emergency unit, from where he was transfered to the intensive care unit of the same hospital for differential diagnostic procedures and treatment. His EEG result was nonspecific, indicating a generalized slowing in the baseline wave. All other laboratory tests were normal. The case had been followed up for nearly 10 days with none other than supportive treatment, and following remarkable reduction in the symptoms, was discharged with nearly full remission. A review of his personal history revealed that he had been going to the gym for a few months before the onset of symptoms, and had started himself on L-carnitine for ergogenic purposes, and continued using for approximately 4 weeks.

No significant feature was identified regarding medical, developmental and family history of the case. Neither did he meet any criteria for the diagnoses of other sleep related disorders, mood disorder, substance use disorder or any other psychiatric and neurological disorders. Results of physical examination, laboratory tests including complete blood count, biochemical test panel, and thyroid function tests, along with magnetic resonance imaging (MRI) of the brain were normal. Although non-specific, only difference was observed in EEG results, where there was a generalized slowing of baseline brain activity during symptomatic phase, EEG activity was measured to be completely normal in between episodes. Sudden onset of symptoms, episodic nature of the clinical picture, almost full remission in between symptomatic phases, characteristics of reported and observed clinical symptoms along with test results were all suggestive of KLS as the primary diagnosis. The case was

started on 400 mg/day carbamazepine, and admitted to the inpatient unit where he was monitored for 2 weeks. Since none of the symptoms at application were observed and improved daily functioning was maintained, the case was discharged, to be followed up in the outpatient unit. 3 months into his last episode, the case is still on 400 mg/day carbamazepine and yet remains symptom-free.

DISCUSSION

An uncommon disorder frequently misdiagnosed as other certain psychiatric and medical conditions, KLS might pose severe negative impact on daily functioning and quality of life in the face of severe symptoms (1). The case we have presented had no problems prior to the emergence of KLS symptoms, only to have become unable to attend school, meet his basic everyday needs, resulting in significant functional impairment following the onset of frequent and severe episodes caused by the disorder. A thorough review of diagnostic criteria for other psychiatric conditions ruled out depressive disorder, bipolar disorder, schizophrenia and related disorders. Normal neurological examination results and negative results for infectious markers ruled out the possibility of encephalitis and/or menengitis; while other neurological conditions such as epileptic seizures and lesions of temporal lobe had also been excluded via neurological examination, brain MRI and EEG. Based on data from relevant literature that suggested the syndrome generally presented during adolescence and predominantly affected males, we might suggest that our case fit the typical case profile, as previously described in relevant literature. In a study where 108 KLS cases were evaluated, main symptoms of the condition have been identified as hypersomnia, cognitive disturbances, alterations in perception, odd behavior and emotional problems (8). A review of relevant literature indicated that most commonly identified behavior profiles in KLS were overeating and inappropriate sexual conduct (16) that were similarly among the most striking clinical symptoms our case had presented with.

In some of the cases with KLS, it is possible to determine an underlying cause acting as a facilitator for the emergence of symptoms related to the syndrome (4,7). As we mentioned before, infection, fever, alcohol and/or marijuana use, sleep deprivation, psychological stress, head trauma, menstruation or lactation, physical effort and general/local anesthesia jave previously been reported as triggering factors for the onset or recurrence of a KLS episode (4). Even though forementioned factors have not been mentioned in our case's history, presence of a temporal relationship between onset of KLS symptoms and starting himself on L-carnitine for ergogenic purposes might indicate a causal link, in between.

Probable causal relationship between L-carnitine use and emergence of an index KLS episode might be explained through possibility of creating an imbalanced serotoninergic and/or dopaminergic system caused by L-carnitine use as suggested in literature, similar to what has so far been postulated as the hypothetical etiological base of the disorder. It has long been suggested that cases with KLS might reflect an imbalance in both dopaminergic and serotoninergic systems, though clinical importance was predominantly attributed to the imbalanced dopaminergic system. For instance, an imaging study on KLS reported reduced striatal dopamine binding potentials throughout symptomatic attack phase of the disorder (17). Again, 5-hydroxyindolacetic acid (5-HIAA, metabolite of serotonin) and homovanilic acid (HVA, dopamine metabolite) levels in cerebrospinal fluid (CSF) were measured in a sample of patients with periodic hypersomnolance. Results indicated increased or slightly increased HVA levels i CSF of patients with KLS, which was interpreted as a sign of increased dopamine cycle, by the researchers (18). Another study suggested a decline in dopaminergic hypothalamic tone, during symptomatic phase (5). Such findings support the need to better focus on dopaminergic and serotoninergic systems, specifically on the dopaminergic system. At this point, depicting the effects of L-carnitine and its derivatives on dopaminergic and serotoninergic system have mainly been limited to animal studies. While L-carnitine supplementation increased the status of carnitine located in various localizations of the study- animal's brain, no significant increase was observed among young rats. Again, L-carnitine supplementation was observed to cause significant increase in cortical, hippocampal and striatal

dopamine of the rat brain (19). Another study reported acetyl L-carnitine increased the level of 5-HIAA, as well as acetyl L-carnitine administration prior to 3,4-Methylenedioxymethamphetamine (MDMA, extacy) injection prevented serotonin (5-HT) loss in rats (20). Acetyl L-carnitine was shown to exert its potential agonistic effects on 5-HT1A receptors (20). Moreover, chronic acetyl L-carnitine supplementation was reported to increase 5-HT levels in the cerebral cortex, and caused a reduction in serotonin turnover through a decrease in 5-HIAA/5HT ratio. Long term acetyl L-carnitine use was shown to increase dopamine and serotonin output within mesocorticolimbic area of the brain and protected against exposure to acute stress (21).

As a conclusion, supplementation of L-carnitine and its derivatives were shown to create an effect on dopaminergic and serotoninergic systems, in animal studies conducted so far. We might only speculate that same or similar effects might develop in humans and some individuals might in particular be vulnerable to the effects caused by such compounds, due to their genetic profile or being exposed to early life environmental manipulation and damage.

Another probable explanation to consider L-carnitine use as a triggering factor is linked to catabolic processes. One common denominator in conditions that have been reported to trigger KLS episodes such as infection, fever, alcohol and head trauma, is increased levels of catabolism in all. Therefore, these nonspecific events might facilitate emergence of given clinical picture, by causing accumulation of toxic aminoacid or protein concentrations within metabolic pathways with partially erroneus enzymatic activity (16). Current biochemical data states L-carnitine plays a part specifically in catabolic processes of fatty acids. In that sense, we might only hypothesize that L-carnitine might be regarded as a candidate for the place of other yet-undetermined triggering factors of KLS, with its common feature of being linked to catabolic processes.

Although we have conceptualized L-carnitine supplementation as a triggering factor for our case, we also believe that our report needs to be cautiously addressed, in the sense that it consists of findings from only one case with nearly no replicated findings from other studies, making it even harder to confirm an actual causal relationship existed between L-carnitine use and KLS. We believe future studies including case reports, case series and hopefully researches designed to be conducted in larger samples, employing rigorous methodology shall provide more insightinto this mysterious clinical entity we have identified as Kleine- Levin Syndrome.

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REFERENCES

1. Miglis MG, Guilleminault C. Kleine- Levin Syndrome. Current Neurology and Neuroscience Report 2016; 16(6): 60.

2. Frenette E, Kushida CA. Primary hypersomnias of central origin. Seminars Neurology 2009;29(4):354–367

3. Billiard M, Jaussent I, Dauvilliers Y, Besset A. Recurrent hypersomnias: a review of 339 cases. Sleep Medication Review 2011;15:247–257.

4. 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(Pt 12):2763-76.

5. Chesson AL, Levine Sn, Kong LS, Lee SC. Neuroendocrine evaluation in Kleine-Levin Syndrome: Evidence of reduced dopaminergic tone during periods of hypersomnolence. Sleep 1991; 14(3):226-232

6. Huang YS, Lakkis C, Guilleminault C. Kleine-Levin syndrome: current status. Medical Clinics of North America 2010; 94(3):557-562.

7. American Academy of Sleep Medicine: International Classification of Sleep Disorders: Diagnostic and Coding Manual, Third ed., Westchester: American Academy of Sleep Medicine, 2014

8. Arnulf I, Lin L, Gadoth N, File J, Lecendreux M, Franco P et al. Kleine-Levin syndrome: a systematic study of 108 patients. Annals of Neurology 2008; 63(4):482-493.

9. Cerretelli P, Marconi C. L-carnitine supplementation in humans. The effects on physical performance. International Journal of Sports Medicine 1990;11:1.

10. Gülçin İ. Antioxidant and antiradical activities of L-carni-

tine. Life sciences 2006;78(8):803-11.

11. Williams MH. Nutritional ergogenics in athletics. Journal of Sports Sciences 1995;13(S1):S63-74.

12. Heinonen OJ. Carnitine and physical exercise. Sports Medicine 1996;22(2):109-32..

13. Patra BN. Current Status of use of Acetyl-L-Carnitine in Neuropsychiatry. Delhi Psychiatry Journal 2012; 15:208-212.

14. Evcimen H, Mania I, Mathews M, Basil B. Psychosis precipitated by acetyl-L-carnitine in a patient with bipolar disorder. Primary care companion to the Journal of clinical psychiatry. 2007;9(1):71.

15. Goodison G, Overeem K, de Monte V, Siskind D. Mania associated with self-prescribed acetyl-l-carnitine in a man with bipolar I disorder. Australasian Psychiatry 2017;25(1):13-4.

16. Arnulf I. Kleine-Levin Syndrome. Sleep Medicine Clinic 2015; 10(2):151-161.

17. Hoexter MQ, Shih MC, Felício AC, Tufik S, Bressan RA. Greater reduction of striatal dopamine transporter availability during the symptomatic than asymptomatic phase of Kleine-Levin syndrome. Sleep Medicine 2010;11(9):959.

18. Livrea P, Puca FM, Barnaba A, DiReda L. Abnormal central monoamine metabolism in humans with 'true hypersomnia' and 'sub-wakefulness'. European Neurology 1977;15:71-6.

19. Juliet PA, Balasubramaniam D, Balasubramaniam N, Panneerselvam C. Carnitine: a neuromodulator in aged rats. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2003;58(11):B970-4.

20. Alves E, Binienda Z, Carvalho F, Alves CJ, Fernandes E et al. Acetyl-L-carnitine provides effective in vivo neuroprotection over 3, 4-methylenedioximethamphetamine-induced mitochondrial neurotoxicity in the adolescent rat brain. Neuroscience 2009;158(2):514-23.

21. Tolu P, Masi F, Leggio B, Scheggi S, Tagliamonte A et al. Effects of long-term acetyl-L-carnitine administration in rats: I. increased dopamine output in mesocorticolimbic areas and protection toward acute stress exposure. Neuropsychopharmacology. 2002;27(3):410-20.