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CASE REPORT

Kleine–Levin syndrome in two subjects with diagnosis of autistic disorder

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Abstract
Kleine–Levin syndrome (KLS) is a rare disease characterized by recurrent episodes of hypersomnia, cognitive and behavioural disturbances, compulsive eating and hypersexuality. The disease is predominantly described in typically developed adolescents. Here, we present two cases with the diagnosis of KLS and autistic disorder. The aim of this presentation is to illustrate the clinical expression and differential diagnosis of KLS in this group.

Key words: *Autistic disorder, Kleine–Levin syndrome*

Introduction

Kleine–Levin syndrome (KLS) is a rare disease characterized by recurrent episodes of hypersomnia, compulsive eating, hypersexuality and cognitive or behavioural disturbances (American Academy of Sleep Medicine 2005). The exact prevalence of KLS is unknown. The study reviewing and collecting data from all case reports between 1962 and 2004 revealed 186 reported cases with diagnosis of KLS (Arnulf et al. 2005). The same investigators at Stanford University have conducted a prospective research program including 108 new patients with diagnosis of KLS (Schenck et al. 2007). The disease is more commonly reported in males with onset during the second decade. Although the cause of KLS is unknown, some studies address an underlying diencephalic-hypothalamic dysfunction (Masi et al. 2000) or an autoimmune process for KLS (Dauvilliers et al. 2002). A possible association with HLA DQB1-201 suggests that it could be an autoimmune encephalitis restricted to the hypothalamus and adjunct areas (Dauvilliers et al. 2002). Besides, a recent report from Saudi Arabia described a multiplex KLS family in which six out of 12 family members had been affected. HLA typing in this family showed that four members out of six affected were homozygous at DQB1 02 loci. This study indicates that genes in the MHC locating on the short arm of chromosome 6 and other environmental factors might possibly be involved in the development of the disease (BaHammam et al. 2007).

Most of the reported cases in the literature have no other co-existing disorders and are described as entirely normal between attacks. There is a few cases described in association with brain damage or genetic and developmental diseases (Arnulf et al. 2005). Berthier and his colleagues (1992) are the only researchers who reported patients with KLS together with autistic spectrum disorders (ASD). They reported two patients with Asperger's disorder, one with cortical dysplasia and retinitis pigmentosa.

Here, we present two cases with the diagnosis of KLS comorbid with autistic disorder (AD). The aim of this presentation is to illustrate the clinical expression and differential diagnosis of KLS in this group.

Case 1

A 15-year-old girl was referred to our clinic due to episodes of hypersomnia, social withdrawal, irritability, eating unusual things and increase in stereotyped behaviours. A total of five episodes with similar behavioural features, all starting after a flu-like condition, lasting for 3–15 days in the last 3 years were described. During these episodes, her

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usual sleep duration increased to 12–18 h/day, she was very slow in her daily activities and always ready to go to sleep and irritable when awakened. She compulsively ate in larger amounts, and started eating unusual food like uncooked rice and pasta. She avoided spontaneous speech or used short sentences with limited vocabulary. She lost her interest in doing things she formerly liked, like listening to the music or being with her parents.

Her psychiatric evaluation showed excessive irritability, lack of eye contact, lack of emotional reciprocity and inability to respond to questions. She also displayed stereotypical behaviours such as rocking, smelling and curling her mothers' hair constantly.

She was born at term after an uneventful pregnancy. She was described to be at the the 90th percentile for weight and height at birth. Her early development revealed some delay; she sat at 9 months, walked at 20 months and gained speech with two-word sentences at the age of 3. She was reported as a mute and aloof child, who showed no interest in others and never developed imitative scenarioed plays and reciprocal interactions with others. She had repetitive stereotypical behaviours such as toe-walking and body rocking, curling and smelling her mothers' hair, writing the same things repetitively. Because of learning problems, she had to attend to a special needs programme at school. She achieved reading and writing at the age of 11.

Her medical history revealed the presence of grand mal seizures between the age of 2 and 9. Beside this, she was diagnosed with Sotos syndrome due to dysmorphic features such as broad forehead, hypertelorism, long pointed chin, acromegalic features, large ears and high arched palate. However, the diagnosis of Sotos syndrome has not been confirmed with laboratory findings.

Laboratory examinations including metabolic testing, MRI and sleep and wake EEG, thyroid function tests and complete blood cell count revealed no abnormality.

Her psychiatric evaluation after recovery, showed that although she was more interested in her surroundings and more cooperative, she still suffered from a lack of appropriate gestures and mimics and a severe impairment in social interaction. She responded to the questions with one word answers. She still had stereotypical behaviours.

Her family history was unremarkable for psychiatric and developmental disorders. She received a premorbid diagnosis of autistic disorder according to DSM-IV criteria (American Psychiatric Association 1994) on the consensus of two clinicans (NMM, AK) who evaluated the patient independently. Due to the lack of structured diagnostic tools such as ADI-R and ADOS in Turkish, diagnostic confirmation and severity of the autistic symptoms were assessed using the Childhood Autism Rating Scale (CARS) (Shopler et al. 1980). The interrater correlation ($r = 0.84$) between two authors (NMM, AK) was examined for a previous study (Kilincaslan et al. 2006).

In addition, she received the diagnosis of KLS due to symptoms that included periodic hypersomnia, behavioural disturbance and changes in eating behaviour.

Case 2

A 15-year-old boy was referred by his parents to our clinic due to episodes of behavioural problems and excessive sleeping. Detailed psychiatric history revealed that his current problems started with excessive sleeping, at least 20 h/day. After a few days his hypersomnia increased to a whole day and decreased to 14 h/day and he showed excessive irritability, stereotypical behaviours, perseverative speech, loss of interest in the surroundings, repetitive laughing and crying, eating large amounts of food and sexual disinhibition. These attacks started a year ago and by the time of referral he had had eight of them. Although there were variations in behavioural problems between episodes, hypersomnia was the most prominent symptom and occurred in all. Hyperphagia and sexual disinhibition became apparent after the third episode. His inappropriate sexual behaviours included masturbating in front of his parents, touching his mother's genitals and attempting to look at girls' genitalia. A flu-like febrile illness and psychological stress due to school exams were described to be the triggering factors for the episodes.

His developmental history revealed that he was a premature child and had meningitis in his first week. His psychomotor development was within the normal range except for language. He used meaningful words at 20 months and two-word phrases at 3 years old. He had difficulty in initiating and sustaining verbal communication with others, used short sentences with limited vocabulary and had repetitive and perseverative speech. He was described as a mute and aloof child, who showed no interest in others and never developed imitative plays and reciprocal interactions with others. He had stereotypical behaviours such as toe walking and hand-flapping in preschool years. He later developed a special interest in music and spent most of his time listening to the music. Although he attended to a mainstream school, he had poor performance in school tasks. However, he was described as having a

relatively good memory for phone numbers and addresses.

After his first episode, he was referred to a paediatrician and a diagnosis of "acute encephalopathy" was considered. However, extensive laboratory examinations, including complete blood cell count, cerebrospinal fluid analysis, MRI, sleep and awake EEG, metabolic testing, and thyroid function tests showed no abnormality except for the presence of periventricular leucomalaise and thinning of the posterior body of the corpus callosum. Therefore, he was referred for psychiatric consultation. He was followed for some months with probable diagnoses of "psychotic disorder" and" depression" and was given haloperidol, risperidone, fluoxetine and fluvoxamine interchangeably. Due to the lack of response, his parents ceased administering the drugs. He was medication free for 4 months and had three more episodes before he was referred to our department.

During his first psychiatric evaluation, he was uncooperative, had no eye contact, and no response to questions and exhibited severe irritability and some stereotypical behaviours.

His psychiatric evaluation after episodes, when his parents described him as "normal", showed a marked impairment in the socio-emotional and communication areas. He was quiet, had no eye contact and exhibited a mild flexion posture. He answered the questions with a single word and could not sustain the conversation and describe his problems. He displayed some stereotypical behaviours such as smelling and forcing his mother to arrange her hair symmetrically. His full scale IQ in WISC-R was 54 (VIQ:50, PIQ:64). His total score in CARS was 33.

His family history was unremarkable except for the presence of obsessive-compulsive and schizoid traits in his mother.

After detailed psychiatric and physical examination, he received the diagnosis of autistic disorder according to DSM-IV criteria and KLS on the consensus of two independent clinician (NMM, AK).

Discussion

Here, we present two subjects with recurrent hypersomnia, hyperphagia and associated behavioural problems. Besides a diagnosis of KLS, both received the diagnosis of autistic disorder. The diagnosis of AD and KLS in both subjects was made after detailed clinical examinations by authors. The important points that need to be discussed are the differential diagnosis of the episodes, comparison of the clinical presentation of KLS in subjects with ASD and typically developing individuals and the probable nature of this comorbidity.

The first point that needs to be clarified is whether the mood-related and behavioural symptoms in these subjects could be diagnosed as a mood disorder. Although irritability, increase in social withdrawal and ritualistic-compulsive behaviours are among the most common features of depression in individuals with autistic disorder (Ghaziuddin 2005), the presence of excessive and episodic hypersomnia, hyperphagia, eating unusual things and disinhibited sexual behaviours (case 2) are important factors suggesting the diagnosis of KLS. Besides this, the lack of previous history of depression in these subjects and their families, lack of response to antidepressant medication (case 2), spontaneous recovery from episodes are other features that support the diagnosis of KLS. In addition, since mood-related symptoms in both subjects resolved at the end of each episode, these symptoms could be considered as a part of KLS episode rather than a mood disorder. A review of the literature on characteristics of KLS (Arnulf et al. 2005) mentions the frequent presence of depressive mood and irritability in this group (48 and 92%, respectively). Therefore, due to this high overlap in symptoms of these two disorders, it seems necessary to distinguish KLS in subjects with mood-related symptoms. Since subjects with AD and other developmental delays have lifelong limitations in social-cognitive functions and behavioural problems, differential diagnosis could be possible with a detailed clinical examination and long-term follow-up.

The second important point is the comparison between clinical features of these subjects with KLS in normally developing individuals**.** Case 1 displays all cardinal symptoms of KLS, except hypersexuality, and it supports the view that "females with the diagnosis of KLS show a lower frequency of hypersexuality" (Arnulf et al. 2005). In case 2, all cardinal symptoms of KLS had been developed after two incomplete episodes. Therefore, in terms of symptom presentation, there is no difference between these subject and normally developing individuals.

The third point is whether the same underlying pathology contributed to these two separate clinical entities. Medical examination of these subjects revealed that case 1 suffered from mental retardation, overgrowth syndrome and epilepsy. Case 2 had a history of prematurity, low birth weight and meningitis in the neonatal period and his MRI revealed periventricular leucomalaise and thinning of the posterior body of the corpus callosum. Both of the subjects displayed conditions associated with autism. Therefore, the question is whether the

same brain pathologies could increase the vulnerability to KLS. Although some factors such as head trauma, viral infections or seizure disorder have been considered responsible for KLS in earlier reports (Orlosky 1982), current evidence suggests that most cases of KLS are idiopathic and unconnected with brain pathology. Arnulf et al. (2005) reviewed reported cases between 1962 and 2004, and stated that only 18 of 186 subjects with KLS were associated with medical disorders such as stroke, posttraumatic brain haematoma, genetic and developmental disorders, or infectious encephalitis. In addition, the connection between immune system and nervous system, and the likely role of autoimmune dysfunction were reported either in autism spectrum disorders (Ashwood 2006) or KLS (Ba-Hammam 2007). Therefore, it may be suggested that in these subjects, a triggering flu-like febrile illness suggesting of an autoimmune dysfunction along with the brain pathology might have made a contribution to this co-existence.

The last point is the probable influence of Sotos syndrome in symptom presentations of first case. A limited number of researches mentioned the presence of ADHD, irritability, stereotypic behaviour (Finegan et al. 1994), social contacts problems (Sarimski et al. 2003) in some subjects with Sotos Syndrome, but these were not higher than those observed for children with intellectual disabilities. However, the present subject displays life-long problems in socio-emotional, communication areas, and stereotypical behaviours; therefore meeting the diagnostic criteria for autistic disorder.

Given the complexity of neurological and psychiatric symptoms that may be encountered in patients with KLS, unrecognised diagnosis or misdiagnosis appears to be common (Gillberg 1987). Unrecognised diagnosis may be particularly true in subjects with interepisodic personality and cognitive maladjustment (Sagar et al. 1990). Therefore, it should be noted that KLS must be added to the spectrum of psychiatric disturbances that can induce recurrent episodes of daytime sleepiness and behavioural changes in patients with developmental disorders. Since the present understanding of KLS and its relationship with pervasive developmental disorders is limited, it should be the focus of future research in child and adolescent psychiatry.

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Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

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