Case Report

Successful Use of Valproate in Kleine-Levin Syndrome: A Case Report and Review of Cases Reported from India

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ABSTRACT

Kleine-Levin syndrome (KLS) is characterized by recurrent episodes of hypersomnia and other symptoms and it is a really challenging for the physician, since its causes are not yet clear, and available treatment options are not having adequate support. Here, we are reporting a case with successful use of valproate in KLS and also reviewing the cases reported from India.

Key words: *India, Kleine-Levin syndrome, valproate*

INTRODUCTION

Kleine-Levin syndrome (KLS) is a rare disorder which mainly affects adolescent boys and characterized by recurrent episodes of hypersomnia, and sometime along with hyperphagia, behavioral and cognitive disturbances, and hypersexuality.[1] Several medications (stimulants, lithium, valproate, antipsychotics, and antidepressants) have been reported to provide variable benefit in different symptoms, with lithium being the most widely used drug.[2,3] We are presenting a case of KLS, who had complete remission with valproate and also reviewing the cases reported from India.

Access this article online	
Website: www.ijpm.info	Quick Response Code
DOI: 10.4103/0253-7176.162931	

CASE REPORT

A 17-year-old single male student of 12th standard, presented to our psychiatric outpatient clinic in September 2004 with hypersomnolence, low mood, decreased appetite and interest in studies, social and sexual disinhibition (such as singing obscene songs loudly at home, and touching unconsenting females' including mother's body parts-limbs, face and genitalia). Onset was acute, without any elicitable precipitating factor and course was episodic with average 7-10 days episode in every month for last 4 months and he maintained completely well in inter episodic period.

Provisional diagnosis of recurrent depressive disorder (brief episodes) was kept and he was started on sertraline (50 mg), on which he responded well. He remained asymptomatic for nearly 9 months, but started having similar episodes again from mid-2005, due to which sertraline were gradually hiked up to 150 mg/day, but of no use. Hence, he was admitted in our inpatient setting in March, 2006 for diagnostic evaluation and further management. After detailed evaluation, it was found that his sadness was not

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pervasive and depressive cognitions and associated disturbances were not present and hypersomnia remained predominant complaint as initially, he was sleeping 16-20 h/day. He was also not responding with these medications, hence differential diagnosis of KLS versus depression was kept and later finalized to KLS. His hemogram, renal functions, liver functions, blood sugar, routine urine, thyroid functions were within normal limits and chest X-ray, electrocardiography, electroencephalography (EEG), and magnetic resonance imaging brain were normal. In view of good literature support lithium was started from 600 mg/day and hiked to 900 mg/day (serum level 0.8 mEq/L). On which he has shown significant improvement initially for 6 months, but later again started experiencing similar symptoms. He also had three episodes of fall, unresponsiveness and epileptiform discharge in EEG twice. Hence, in view of seizure disorder and lack of response, neurologist's consultation was sought, who opined to start antiepileptic medication. Hence, lithium was switched to valproate (750 mg/day) in December 2006, on which he maintained completely well for 4 years, except brief re-emergence of symptoms on discontinuing valproate, which improved completely on resuming the medication. Valproate was gradually tapered and stopped in January 2011 on insistence of patient and family with discussing its pros and cons. Now index case has been maintaining well-off valproate for last 3 years without any episode of hypersomnolence, sexual disinhibition, sadness, or epileptic seizure.

DISCUSSION

Based on historical reports by Kliene and Levin, KLS was essentially described and termed by Critchley.[4] Thereafter, many researchers have reported their cases and reviewed cases with KLS.[2,3] Here, we are reporting a case with KLS, who responded well with valproate, after diagnostic dilemma and different psychotropic medications and also reviewing the other cases reported from India.

Table 1: Reported cases with KLS from India

Author	Demography	Presentation (other than hypersomnolence)	Treatment and outcome
Mendhekar *et al*., 2001	11 years male 13 years male	Onset at 11 and 13 years; preceded with fever; symptoms — headache, confusion, odd behavior 2nd case-sexual disinhibition; EEG, CT head-normal	Complete remission with lithium
Malhotra *et al*., 1997	14 years female 16 years male 13 years male 17 years male	Onset at 12 years (Case 1), 15 years (Case 2), 11 years (Case 3), 16.5 years (Case 4) of age Symptoms - hyperphagia, social and sexual disinhibition Duration of episodes: 3-4 days (Case 1), 10 days (Case 2), 2-4 weeks (Case 3), 3-4 days (Case 4) Preceded by fever in Cases 2 and 3 EEG (Case 1): right temporoparieto-occipital sharp wave	Cases 1 and 2 remitted spontaneously after five and two episodes, respectively Case 3 was given lithium carbonate 450 mg/day and remained well at 18 months follow-up Case 4 lithium was tried but stopped due to side effects. Asymptomatic for 9 months follow-up
Sagar *et al*., 1990	16 years male 16 years male 18 years male	Onset at 10 years (Case 1), 12 years (Case 2), 17 years (Case 3) of age; Preceded by fever in Cases 1 and 3 Symptoms — hyperphagia, social and sexual disinhibition, academic decline Duration of episodes: 2-3 weeks (Case 1), 8-9 days (Case 2), 7-10 days (Case 3) Inter episodic IQ=90 (Case 1), 80 (Case 2), 71 (Case 3)	Carbamazepine tried in Case-2, but stopped due to lack of efficacy Rest cases improved without any medication
Prabhakaran *et al*., 1970	26 years male	Preceded by fever Hyperphagia, sexual disinhibition, poor memory Duration of episode: 3-4 days Inter episodic IQ=75	He maintained well-up to 6 months of follow-up without medications
Narayanan *et al*., 1972	21 years male	Onset 19 years; had hyperphagia Duration of episode: 3-4 days	Methylamphetamine 30 mg was given upon which he improved
Agrawal and Agrawal, 1979	16 years male	Onset at 16 years; preceded by fever Symptoms — hyperphagia, visual hallucination Duration of episode 6-10 weeks Inter episodic IQ=75	Earlier misdiagnosed with schizophrenia and tried on phenothiazine Complete remission on dextroamphetamine
Gupta *et al*., 2011	9 years male	Onset at 7 years. Duration of episode: 1 year Symptoms — hyperphagia, weight gain IQ=75 (composite score), MRI brain-normal	Treatment and follow-up not mentioned
Aggarwal *et al*., 2011	22 years female	Onset at 16 years; preceded by fever Symptoms — hyperphagia, confusion, irrelevant talk, sexual disinhibition. Duration of episode: 15-20 days	On methylamphetamine 25 mg-asymptomatic for 1 year and on modafinil 100 mg-asymptomatic for 2 years
Shukla *et al*., 1982	25 years male	Onset at 24 years; preceded by fever Symptoms — hyperphagia, oddities, irrelevant talk, sexual disinhibition. Duration of episode: 10 days	Had three episodes before prescribing dexedrine 5 mg. later maintained well up to 5 months of follow-up

KLS – Kleine-Levin syndrome; EEG – Electroencephalography; CT – Computed tomography; IQ – Intelligence quotient; MRI – Magnetic resonance imaging

In our electronic search for Indian studies on KLS, by using PubMed and Google Scholar, we could find 15 cases reported from India.[5-13] Of them 13 were males and 2 females, similar to male preponderance reported in the literature.[2,3] While presenting to psychiatric services their age was between 9 and 26 years and they had onset between 7 and 24 years of age. In two-third of patients (10 out of 15 patients), it was preceded with fever and their episodes of somnolence were lasted from 3 days to 10 weeks. Hypersomnia and hyperphagia were present in all, while two-third of patients also had social and sexual disinhibition (11 out of 15 patients). Other symptoms were cognitive disturbances (low intelligence quotient, impaired memory, confusion, and academic decline), irrelevant talk, and perceptual disturbances. Nearly one-third of patients improved spontaneously without any medication, while rest was given lithium, carbamazepine, methylamphetamine, dextroamphetamine, and modafinil. Longest asymptomatic follow-up period is reported for 2 years [Table 1].[5]

Though literature supported lithium for higher response rate,[2,3] but index patient had remarkable response with valproate, not with lithium, like earlier two reports. Like earlier report,[14,15] index patient also improved on lower dose of valproate (divalproate 750 mg vs. 500 mg valproate). Compared to other cases reported from India,[5,13] index patient had longest follow-up (7 years) and remained asymptomatic in this period, except small exacerbation on discontinuation of valproate treatment, which improved completely on resuming the drug. Similar to our patient, anticonvulsants (like valproate) are the preferred treatment for KLS patient, and may also offer benefits in case of comorbid epilepsy.[1] Valproate may be a good alternative to lithium in terms of efficacy as well as side-effect profile.

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How to cite this article: Nebhinani N, Avasthi A, Modi M. Successful use of valproate in Kleine-Levin syndrome: A case report and review of cases reported from India. Indian J Psychol Med 2015;37:352-4.

Source of Support: Nil, **Conflict of Interest:** None declared.