NEUROLOGICAL RARITY

Pract Neurol 2009; 9: 42–45

Kleine–Levin syndrome

D Radcliffe Lisk

Kleine–Levin syndrome, sometimes referred to as Rip van Winkle disease, is a rare sleep disorder mainly affecting teenage boys in which the main features are intermittent hypersomnolence, behavioural and cognitive disturbances, hyperphagia and in some cases hypersexuality. Each episode lasts for one or two weeks, and affected people are entirely asymptomatic between episodes. No definite cause has been identified but hypothalamic dysfunction seems likely. Relapses may occur every few weeks or months, and the condition may last for a decade or more before spontaneous resolution. There is no effective treatment but stimulants such as methylphenidate and modafinil as well as the mood stabiliser lithium carbonate have been tried with varying success.

A 19-year-old woman presented to the paediatric ward in June 2002 at the age of 16, with what was described in her notes as a "funny sleep disorder". Between February and May 2002 she had experienced three episodes of prolonged hypersomnia each lasting 6–8 days during which she was irritable, depressed, lethargic and ill-tempered. She would suddenly snap out of the symptoms at the end of the episodes and was perfectly normal between attacks. She also displayed abnormal behaviour with a feeling of "being alienated" and "under the control of some supernatural powers". She was promptly referred to a child and adolescent psychiatrist and ultimately to an adult psychiatrist. She had a normal CT brain scan, EEG and routine blood tests. It was thought that some of her episodes were suggestive of depersonalisation and derealisation associated with a depressive illness.

She continued to see the psychiatrists until 2005 when she was referred to me after the seventh attack of what was by then diagnosed as a dissociative syndrome. When I saw her she was perfectly normal with no abnormal physical, mental or neurological signs. She had been born by Caesarian section at 32 weeks due to placenta praevia, had weighed 4 lbs 3 oz, and had developed normally achieving all developmental milestones. She had a normal education attaining 11 exam passes at the age of 16 after which she went on to study ballet. There was no family history of psychiatric disorder and no history of recreational drug abuse. There was a history of possible viral meningitis when she was 10 years old and also of a head injury at the age of 13 when she fell in a park hitting her head against a metal bar, without loss of consciousness. The possibility of Kleine–Levin syndrome was suspected after her eighth

D Radcliffe Lisk
Consultant Neurologist, Basildon University Hospital, Nethermayne, Basildon, Essex SS16 5NL, UK; radcliffe.lisk@btuh.nhs.uk

10.1136/jnnp.2008.161950

attack. I was able to persuade her to document her daily experiences during the course of an attack, which she did with the greatest of difficulty due to the way she felt during these episodes. This was the attack starting on 11 July 2006 which lasted until 25 July, with just one day of normality during this period.

On the day of onset she woke up well, but when getting ready for work the "feelings" started. She tried to go to work but felt tearful and eventually lay down on the settee and fell asleep. She woke up an hour later, felt better and decided to go to work. As soon as she got there she felt bad again, was weepy, and had to be taken home. She felt very tired and went to bed. The following day she woke up at 10 am, felt bad and slept again. It was her boyfriend's birthday and she was offered a doughnut. After eating one she "had a craving for another, and another and soon there was none left for anyone else!" She continued in this state for the next two weeks apart from one day when she thought she was normal. The main features during this time were extreme drowsiness, a dreamlike state, and a feeling of derealisation. She found it difficult "to differentiate what is real and what is not". She described coping with this difficulty by "remembering what I usually do when I am normal" and putting on her make up "like doing it blindfolded". She spent most of the day in bed and developed a craving for milkshakes and also ate a lot of ice-cream and sweets. She was conscious of being short-tempered and at times abrupt with people which was completely out of character. She was able to recall most of the parts of the attack when she was awake; although she was drowsy, she was fully conscious but non-functional. In this state she was aware of her surroundings but saw them in an unrealistic way.

On day 15 of the attack she attended my clinic and on returning home she sat down for a while "and then suddenly I felt fine again and everything was back to normal except I had a headache". At this stage it was clear that she had all the cardinal features of Kleine–Levin syndrome, so confirming the diagnosis (hypersomnia, behavioural and cognitive disturbances and hyperphagia). The table shows the number and duration of attacks since 2002.

FURTHER INVESTIGATIONS

- She had a normal MR brain scan.
- An interval EEG showed widespread theta components with posterior temporal slow waves bilaterally.
- With the greatest of difficulties we were able to do an EEG and SPECT scan and limited sleep studies during an attack; there were no epileptiform or focal features on the EEG although there was more theta activity with attenuation of alpha rhythm, and vertex sharp transients of sleep. The SPECT scan during an attack was normal but some workers believe it is best to compare with a scan between attacks to detect subtle differences.

TABLE Summary of Kleine–Levin episodes

Episodes	Date of onset of attacks	Duration of attacks (days)
1st	15 February 2002	8
2nd	26 May 2002	8
3rd	10 May 2002	6
4th	22 December 2003	7
5th	27 November 2004	9
6th	31 December 2004	8
7th	10 June 2005	9
8th	17 January 2006	9
9th	11 July 2006	15
10th	20 July 2006	6
11th	21 August 2006	8
12th	27 November 2006	9
13th	20 February 2007	14

The diagnosis of Kleine–Levin syndrome is entirely clinical

- She had a limited sleep study at home during an attack where she was restless and removed some of the sensors. Monitoring took place between 10.15pm and 3.30am. There were EEG and EMG features of wakefulness even when she appeared to be sleeping. There was also a substantial amount of stage 3 and 4 sleep with REM latency of 47 minutes. She had frequent awakenings in stage 2 sleep and only a small amount of REM sleep.
- A full sleep study under laboratory conditions was later done between attacks. She was not on any medication such as antidepressants during this study which did not in fact add much to the original study. She had a sleep efficiency of 75% with no REM sleep and frequent awakenings. There was no evidence of obstructive sleep apnoea or any motor sleep disorders such as periodic limb movements.

In spite of her many attacks, she continued in gainful employment. In March 2007 she was started on methylphenidate 10 mg twice a day which was reduced to daily after a few months because of adverse effects. She has not had a recurrence since then but in the past she has gone for as long as 19 months without an attack.

DISCUSSION

The first case of what was probably Kleine–Levin syndrome was reported by Brierre de Boismont in 1862, but it was not until 1925 that Willi Kleine published several cases of recurrent hypersomnia. Within the next decade Max Levin made the association between morbid hunger and periodic hypersomnolence and in 1962 Critchley introduced the eponymous name of the disorder. The key features of the syndrome are episodic hypersomnia, behavioural and cognitive disturbances, compulsive eating (hyperphagia) and in some cases hypersexuality.

The condition is extremely rare with only about 200 cases reported in the literature. It occurs mainly in teenage males but about a third of the cases are females. In a 2005 literature review of 186 published cases, only 12 were from the UK.[1] In about 60% of cases, a precipitating factor was suspected, most frequently a mild flu-like illness or fever but also head trauma, alcohol and stress. My patient had a history of possible viral meningitis and also of head injury but their relevance is very uncertain. In the same review,[1] the onset of the illness was in the second decade in 81% of cases and the median duration of episodes was 12 days. The median inter-episode duration was 3.5 months with a range from 2 weeks to 72 months.

Apart from the hypersomnia, my patient demonstrated typical higher level disorders including derealisation, altered perception, confusion, poor concentration and inattention. She also exhibited abnormal eating behaviour including hyperphagia, binge eating and a peculiar craving for sweets which has been described in 12% of patients. Irritability was also evident and this is present in 92% of patients, and depression in almost half of reported cases. There were no reported incidents of hypersexuality in my case but this is present in about 40% of patients and tends to be more common in males.

The diagnosis of Kleine–Levin syndrome is entirely clinical, notwithstanding the fact that many patients have been exhaustively investigated with neuroimaging, electoencephalography and sleep studies.[2] Brain CT and MRI were normal in all cases, as here, but SPECT studies have shown some reduction of blood flow in the thalamus, basal ganglia and frontotemporal areas in some patients, but not in mine.[3] The EEG both during and between attacks showed slow wave background in my patient, which is described in most patients but is non-specific. There are no diagnostic features on polysomnography but reduced REM sleep latency, increased as well as decreased amounts of REM sleep, decreased sleep efficiency and frequent awakenings from stage 2 sleep have all been described.[4]

Differential diagnoses include sleep disorders such as narcolepsy, non-convulsive status epilepticus, encephalitis, psychotic affective or dissociative disorders, and hypothalamic tumours. In practice, with the exception of non-convulsive status, very few of these conditions cause intermittent hypersomnolence with intervening periods of normality. Familial hemiplegic migraine may be complicated by coma or encephalopathy which is episodic and should therefore also be considered in the differential diagnosis.

10.1136/jnnp.2008.161950

The cause of Kleine–Levin syndrome is unknown. Intermittent hypothalamic dysfunction seems likely but there is no objective evidence for this. Postmortem studies are rare because the condition is not fatal. Microglial infiltration in the thalamus and midbrian as well as decreased pigmentation in the substantia nigra have been described. Increased urinary melatonin has been found in one case only and two further cases were associated with reduced CSF hypocretin-1 during attacks.[5] Histocompartibility antigens HLA-DR1 and 2 and HLA-DQ2 have been found in some patients and a Jewish heritage and familial clustering in a few cases would suggest some genetic susceptibility.[6] Occasional isolated cases may have been symptomatic to strokes and traumatic brain injury, as well as to developmental disorders such as learning disability, cortical dysplasia and acanthosis nigricans.

Several medications have been tried, either mood stablisers such as lithium and sodium valproate, or stimulants like methylphenidate and modafinil.[7–9] Lithium is the most frequently tried medication, usually given as prophylaxis, but has only a modest effect; it reduces the risk of recurrence and shortens the duration of episodes.[7] Methylphenidate has also been used both as prophylaxis and during episodes as a wake-promoting agent. Due to the rarity of the syndrome, none of these treatments has been subjected to randomised controlled trials and their use remains anecdotal. Most patients go into spontaneous remission, with a median duration of the disorder of eight years.

PRACTICE POINTS

- Kleine–Levin syndrome is rare but relatively easy to diagnose clinically.
- Patient demographics are wider than originally described; cases are not confined to intermittently hypersomnolent and hypersexual teenage boys.
- Investigations are often non-specifically abnormal during symptomatic episodes but not pathognomonic.
- Various drug treatments have been suggested with variable success; the long-term prognosis is generally good.

Most patients go into spontaneous remission, with a median duration of the disorder of eight years

ACKNOWLEDGEMENTS

I am indebted to Dr A K Simonds, Consultant in Respiratory Medicine at the Royal Brompton and Hartfield NHS Trust who organised and reported on the sleep studies at home and in hospital. My appreciation also goes to the mother of the patient who was extremely resourceful and cooperative in the clinical management of her daughter. This article was reviewed by Paul Reading, Middlesbrough, UK.

REFERENCES

1. Arnulf I, Zeitzer JM, File J, *et al.* Kleine-Levin Syndrome: a systematic review of 186 cases in the literature. *Brain* 2005;**128**:2763–76.
2. Gadoth N, Anat K, Vainstein G, *et al.* Clinical and polysomnographic characteristics in 34 patients with Kleine-Levin Syndrome. *J Sleep Res* 2001;**10**:337–41.
3. Huang YS, Guilleminault C. SPECT findings in the Kleine-Levin Syndrome. *Sleep* 2005;**28**:955–60.
4. Rosenow F, Kotagal P, Cohen BH, *et al.* Multiple sleep latency test and polysomnography in diagnosing Kleine-Levin syndrome and periodic hypersomnia. *J Clin Neurophysiol* 2000;**17**:519–22.
5. Bauvilliers Y, Baumann DR, Carlander B, *et al.* CSF hypocretin-1 levels in narcolepsy, Kleine-Levin syndrome and other hypersomnias and neurological conditions. *J Neurol Neurosurg Psychiatry* 2003;**74**:1667–73.
6. Arnulf I, Lecendreux M, Franco P, *et al.* Kleine-Levin syndrome:State of the art. *Rev Neurol* 2008 Jul 22 (Epub ahead of print).
7. Poppe M, Friebel D, Reuner U, *et al.* The Kleine-Levin Syndrome: effects of treatment with lithium. *Neuropediatrics* 2003;**34**:113–19.
8. Muratori F, Bertini N, Masi G. Efficacy of lithium treatment in Kleine-Levin syndrome. *Eur Psychiatry* 2002;**17**:232–3.
9. Papacostas SS, Hadjivasilis V. The Kleine-Levin Syndrome: report of a case and review of the literature. *Eur Psychiatry* 2000;**15**:231–5.

PN

Kleine–Levin syndrome

D Radcliffe Lisk

Pract Neurol 2009 9: 42-45
doi: 10.1136/jnnp.2008.161950