Clinical Reasoning: A teenage girl with excessive daytime sleepiness, "fainting spells," and dream mentations

Muruvet Elkay, MD
Ann Marie Bergin, MD
Sanjeev V. Kothare, MD

Address correspondence and reprint requests to Dr. Muruvet Elkay, Department of Neurology, Harvard Medical School, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115
Muruvet.Elkay@childrens.harvard.edu

SECTION 1

A 17-year-old girl presented with a history of difficulty falling asleep and maintaining sleep for the past 7–8 years. Sleep was disturbed by vivid dreams of people attacking her. She thrashed about in bed during sleep. She snored but did not twitch in her sleep. She had a history of sleepwalking, and sleep paralysis on awakening. On weekdays, she went to bed by 10:30 PM but took between 1 to 3 hours to fall asleep. She awoke at 6:00 AM. On weekends, she slept between midnight and 8:00 AM. Daytime somnolence was present with frequent naps (in the car, in front of the television, and in class), which were also interrupted by vivid dreams. She reported episodes of dizziness and feeling faint, during which she felt weak and sleepy. At times, she had "fainting spells" triggered by emotions. A cardiology evaluation was negative.

Perinatal history and development were normal. Attention deficit hyperactivity disorder (ADHD) was diagnosed at age 6. She had absence seizures from age 2–8 years, treated with valproic acid. At presentation she had been seizure-free and medication-free for 9 years.

Family history revealed sleepwalking and sleeptalking in her mother, younger brother, and maternal uncle. A maternal uncle had restless legs syndrome. There was no family history of seizures or excessive sleepiness.

Medications at presentation included clonidine 0.1 mg at bedtime for sleep initiation and amphetamine/dextroamphetamine 60 mg in the morning for maintaining alertness as well as for ADHD.

She was in the 12th grade with an individualized education plan for mathematics.

On examination she weighed 76 kilograms. Height was 167 cm. Body mass index was 27.3 (85th–95th percentile). The rest of the general, systemic, and neurologic examination was unremarkable. Oral examination showed enlarged tonsils.

Questions for consideration:

1. What is the differential diagnosis?
2. What initial investigations would you recommend?

GO TO SECTION 2

From the Department of Neurology, Harvard Medical School, Children's Hospital Boston, Boston, MA.
Disclosure: The authors report no disclosures.

SECTION 2

The differential diagnosis includes narcolepsy with cataplexy and excessive daytime sleepiness, obesity, sleep deprivation, obstructive sleep apnea (OSA), and REM sleep behavior disorder (RBD), given the vivid dream-enacting behaviors, and delayed sleep phase syndrome (DSPS).

Complete blood count, ferritin, total iron binding capacity, and thyroid-stimulating hormone were normal. The human leukocyte antigen (HLA) subtype HLA DRB1*1501, DQB1*0602, and other subtypes DRB1*0801&*1201,6,10; DQB1*0301,9,19&*0402, DRB3*02 for narcolepsy were normal. HLA testing for narcolepsy subtype is nonspecific and is positive in more than 25% of the normal population. However, a negative HLA rules out narcolepsy with cataplexy in 95% of cases. Hence, the test may be ordered, knowing the false negative and false positive rates of the test.[1] MRI of the brain was unremarkable.

Clonidine and amphetamine/dextroamphetamine were discontinued 2 weeks prior to a standard polysomnogram (PSG) and a multiple sleep latency test (MSLT). PSG showed mild OSA with significant upper airway resistance syndrome (UARS), mild periodic limb movements of sleep (PLMS) at 7/hour, and generalized spike-wave discharges in non-REM sleep and in wakefulness. MSLT showed sleep onset REM (SOREM) in 2 of the 5 naps and a normal sleep latency of 18 minutes. The other PSG findings are in the table. She underwent tonsillectomy, lost weight, and improved her sleep schedules. Follow-up PSG showed resolution of the OSA, improved sleep efficiency, and reduced snoring and arousal index.

Table Polysomnogram findings

Sleep efficiency	Total sleep time, min	Sleep stages N1/N2/N3/REM, %	AHI in REM and NREM	EMG activity in REM
91%	418	6/44/26/24	2/6	Atonia

Abbreviation: AHI = apnea-hypopnea index.

Questions for consideration:

1. How has your differential diagnosis changed?
2. What additional test would you consider?

GO TO SECTION 3

SECTION 3

Narcolepsy with cataplexy is unlikely in the presence of normal mean sleep latency and HLA testing. The unrefreshing and fragmented sleep, with REM intrusion at sleep onset and offset, is likely secondary to the sleep-disordered breathing, PLMS, and DSPS. This could also explain the 2 SOREM periods observed on her MSLT.

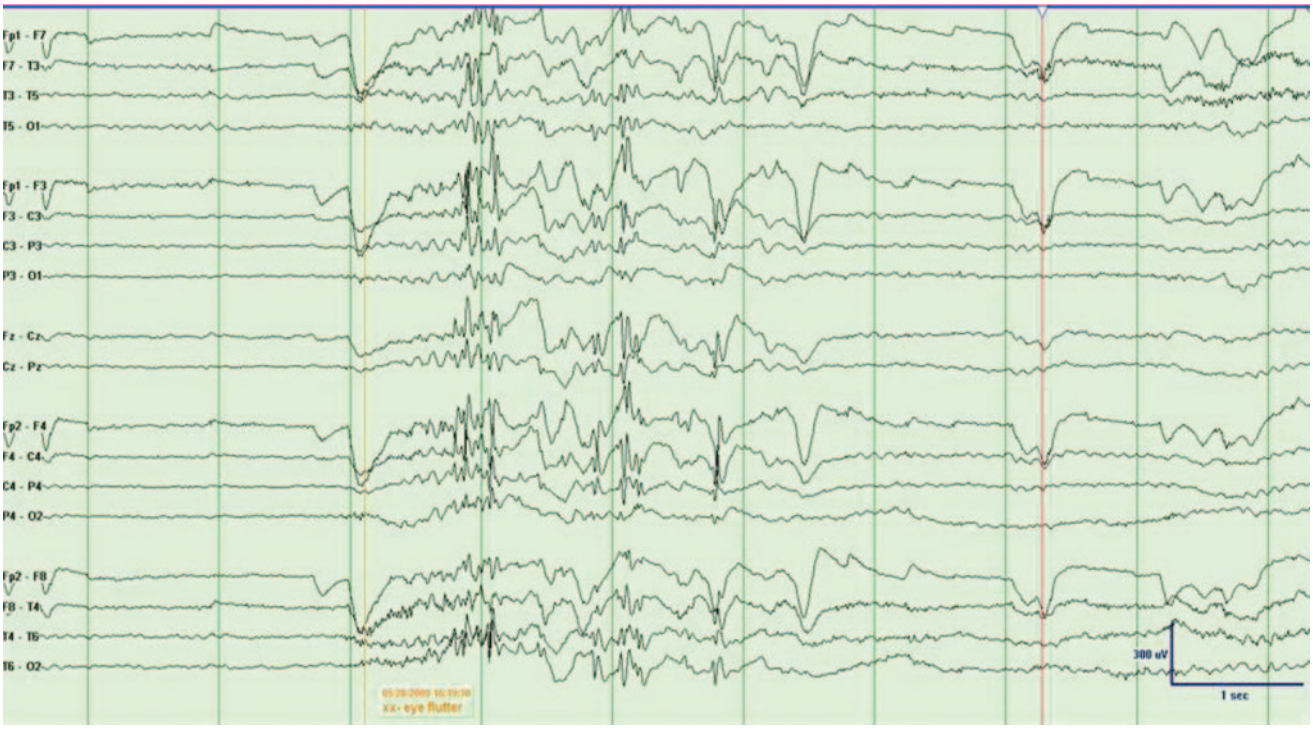
The presence of generalized spike-wave discharges during the sleep study and MSLT raised the possibility of a seizure disorder, particularly given her history of epilepsy. A 24-hour ambulatory EEG showed frequent 1- to 4-second bursts of 4 Hz, irregular generalized spike/polyspike and slow wave complexes potentiated by hyperventilation and associated with subtle clinical seizures (eyelid flutters, staring, and eye rolling) (figure). There was a photoparoxysmal response at 16–21 Hz stimulation frequencies.

On further inquiry, a history of ongoing staring spells was elicited, along with myoclonic jerks, and rare brief generalized tonic-clonic seizures witnessed most prominently in the early morning. The described fainting spells consisted of sudden jerking and loss of muscle control, usually not associated with emotion or stress, further suggesting epilepsy rather than cataplexy.

Questions for consideration:

1. What are your diagnoses now?
2. What treatment would you recommend?

Figure Ictal electroencephalography showing brief (2–3 s) generalized spike-wave discharges with subtle unresponsiveness and eyelid flutter



GO TO SECTION 4

SECTION 4

The patient has a primary generalized epilepsy with an overlap syndrome between phantom absences and juvenile myoclonic epilepsy (JME). Treatment with levetiracetam did not control her myoclonic jerks or staring spells, and caused mood changes. Levetiracetam was discontinued and she was started on valproate after counseling regarding possible side effects. She had a good clinical response and her EEG improved remarkably. We believe that treatment of OSA as well as effective use of appropriate antiepileptic drugs was responsible for the significant improvement in her sleep and daytime alertness, and disappearance of dream mentations and fainting spells.

DISCUSSION Our patient presented with excessive daytime sleepiness, cataplexy (REM intrusion in wakefulness), and sleep paralysis. These symptoms, along with hypnagogic/hypnopompic hallucinations, characterize narcolepsy. Fragmented sleep at night is a newly recognized feature of narcolepsy. However, narcolepsy was unlikely given her normal sleep latency and HLA testing. Nocturnal sleep disturbances, such as vivid nightmares, may be part of RBD, which may be the initial manifestation of narcolepsy.[1] RBD, a parasomnia characterized by lack of electromyographic REM sleep atonia and emergence of purposeful complex motor activity associated with vivid dreams, was excluded by the sleep study.[2]

The sleep study confirmed UARS. This is characterized by incomplete obstruction of the airway during sleep, leading to increased respiratory effort and frequent arousals despite normal oxygen saturation, without significant apneas or hypopneas.[3] The resultant sleep fragmentation contributed to our patient's daytime sleepiness.

Based on her sleep habits, and the sleep study findings, she also has DSPS, the most common type of circadian rhythm sleep disorder seen in adolescents. This is characterized by sleep and wake times that are later than desired, often resulting in daytime sleepiness when conventional waking times are enforced.[4]

Most teenagers wake up after 8 AM, as observed in our patient. Generalized spike-wave discharges on EEG were diagnostic for idiopathic generalized epilepsy (IGE). Common IGEs in adolescents include juvenile absence epilepsy (JAE), JME, and IGE with generalized tonic-clonic seizures on awakening (GTCSA).[5]

IGE with phantom absences is a newly described IGE, which is not as yet accepted as a separate entity by the International League Against Epilepsy. It is characterized by phantom absences, infrequent GTCS, and absence status epilepticus.[6] The phantom absences are so called because they are so mild and short-lasting (2–4 seconds) as to be barely perceptible. Ictal EEGs display 3–4 Hz generalized spike/polyspike and slow wave discharges. Absence status epilepticus occurs in up to 50% of patients. It can last for hours, often with preserved, though waxing and waning, responsiveness.[7] In contrast, absences in JAE are characterized by severe impairment of consciousness, longer duration, and frequent automatisms which are unlikely to escape detection and recognition.[8]

The absence seizures were the main concern in our patient. She and her relatives were largely unaware of them. It is possible that she had frequent absence seizures and/or episodes of absence status epilepticus triggered by sleep deprivation due to UARS and PLMS. The patient also had myoclonic seizures which clinically suggested cataplexy at presentation.

Myoclonic seizures and the photoparoxysmal response seen in our patient are not usually described in IGE with phantom absences. However, the hallmark of JME is frequent early-morning myoclonic seizures and GTCS. Absence seizures in JME are present in 20% of patients, while photosensitivity is seen in 30%–90% of patients.[9]

In conclusion, our patient presented with symptoms suggestive of narcolepsy. HLA typing was normal. A standard polysomnogram with MSLT did not support the diagnosis of narcolepsy, but showed generalized spike-wave discharges. Later, she was found to have predominantly phantom absences, myoclonic seizures, and infrequent GTCS. This combination of seizure types can be explained by IGE with overlap between phantom absences and JME.[10] IGE with overlap between groups should be considered not only in the differential diagnosis of narcolepsy, but also in the evaluation of IGE in the spectrum of JME.

REFERENCES

1. Nevsimalova S. Clinical review: narcolepsy in childhood. Sleep Med Rev 2009;13:169–180.
2. Paparrigopoulos TJ. REM sleep behavior disorder: clinical profiles and pathophysiology. Int Rev Psychiatry 2005;17:293–300.
3. Montserrat JM, Badia JR. Upper airway resistance syndrome. Sleep Med Rev 1999;3:5–21.
4. Panossian LA, Avidan AY. Review of sleep disorders. Med Clin North Am 2009;93:407–425.
5. Beghi M, Beghi E, Cornaggia CM, Gobbi G. Idiopathic generalized epilepsies of adolescence. Epilepsia 2006;47:107–110.
6. Panayiotopoulos C. Syndromes of idiopathic generalized epilepsies not recognized by the international league against epilepsy. Epilepsia 2005;46:57–66.

7. Rubboli G, Gardella E, Capovilla G. Idiopathic generalized epilepsy (IGE) syndromes in development: IGE with absences of early childhood, IGE with phantom absences, and perioral myoclonia with absences. Epilepsia 2009;50:24–28.
8. Panayiotopoulos CP, Koutroumanidis M, Giannakodimos S, Agathonikou A. Idiopathic generalized epilepsy in adults manifested by phantom absences, generalized tonic-clonic seizures, and frequent absence status. J Neurol Neurosurg Psychiatry 1997;63:622–627.
9. Welty TE. Juvenile myoclonic epilepsy, epidemiology, pathophysiology, and management. Pediatr Drugs 2006;8:303–310.
10. Janz D. Progress in epilepsy research: the idiopathic generalized epilepsies of adolescence with childhood and juvenile age of onset. Epilepsia 1997;38:4–11.

Clinical Reasoning: A teenage girl with excessive daytime sleepiness, ''fainting spells,'' and dream mentations

Muruvet Elkay, Ann Marie Bergin and Sanjeev V. Kothare

Neurology 2010;74;e88-e92
DOI 10.1212/WNL.0b013e3181e04376