

Sleep Medicine for the Neurologist

Rachel E. Salas, MD, and Charlene Edie Gamaldo

QUESTIONS

- 1. A multiple sleep latency test (MSLT) would be most useful in evaluating a patient for which of the following conditions?**
 - (A) Delayed sleep phase syndrome
 - (B) Insomnia
 - (C) Narcolepsy
 - (D) Obstructive sleep apnea (OSA)
 - (E) Restless legs syndrome (RLS)
- 2. A 20-year-old college student presents with complaints of excessive daytime sleepiness (EDS) for the last 2 years that has progressively worsened and has resulted in her missing several morning classes because she sleeps through her alarm clock. She denies experiencing episodes of loss of muscle tone in the context of strong emotion such as laughter and denies seeing things as she falls to sleep. She reports no problem with sleep once she goes to bed, although she reports 2 episodes in the last 2 years that are consistent with sleep paralysis. She reports a variable bedtime, and after further discussion describes herself as being a “night-owl.” She denies snoring or difficulty breathing while she sleeps. What would be the most appropriate next step in her evaluation?**
 - (A) Counseling on better sleep hygiene techniques
 - (B) MSLT
 - (C) PSG
 - (D) Set a back-up alarm clock
 - (E) Sleep diary and follow-up to review in the next few weeks
- 3. Which of the following neurotransmitters contribute to alertness and wakefulness?**
 - (A) Adenosine and GABA
 - (B) Dopamine and histamine
 - (C) Hypocretin (orexin) and galanin
 - (D) All of the above
- 4. OSA has been associated with which of the following conditions?**
 - (A) Depression and insomnia
 - (B) Erectile dysfunction and gastroesophageal reflux disease (GERD)
 - (C) Hypertension and daytime sleepiness
 - (D) All of the above
- 5. What is the role of PSG in the evaluation of a patient suspected of having RLS?**
 - (A) Evaluate for the presence of concurrent PLMD
 - (B) Evaluate for the presence of concurrent sleep apnea if history suggests sleep-disordered breathing risk factors
 - (C) Make the definitive diagnosis of RLS
 - (D) All of the above
- 6. RLS augmentation has been reported in association with which of the following medications?**
 - (A) Carbidopa/levodopa
 - (B) Methadone
 - (C) Tramadol
 - (D) A and C
 - (E) All of the above

ANSWERS

- 1. The correct answer is (C) narcolepsy.** The MSLT is an objective test of physiologic sleepiness. The MSLT is indicated if narcolepsy or idiopathic hypersomnia of central origin is suspected.¹ It is not routinely used to evaluate the daytime sleepiness associated with suspected OSA, other medical or neurologic disorders,

Dr. Salas is an assistant professor, Departments of Neurology and Medicine, Johns Hopkins University School of Medicine, Baltimore, MD. Dr. Gamaldo is an assistant professor, Departments of Neurology and Medicine, Johns Hopkins University School of Medicine, and assistant director, The Johns Hopkins Hospital Sleep Disorder Center.

insomnia, or circadian rhythm sleep disorders. The American Academy of Sleep Medicine (AASM) considers the MSLT to be the standard for the objective measurement of sleepiness.

The MSLT involves a series of 4 or 5 controlled nap sessions using a standardized protocol to optimize interpretability of the results.² Persons with narcolepsy fall asleep more quickly and have a propensity for rapid eye movement (REM) sleep during naps. A mean sleep latency of 8.5 minutes or less across the 4 or 5 naps and the presence of 2 REM-onset naps on the MSLT along with the appropriate clinical presentation are highly suggestive of narcolepsy. A polysomnogram (PSG) should be performed the night before the MSLT to assess nighttime sleep quality and quantity. A minimum of 6 hours of nocturnal sleep should be achieved before proceeding with the MSLT when evaluating for narcolepsy; however, one should be cautious in patients with a circadian rhythm disorder, which may affect the MSLT results. An extended sleep study may be useful in this case to ensure adequate sleep quantity and quality before beginning the MSLT. Untreated sleep-disordered breathing (eg, sleep apnea) or other causes of disrupted sleep should be ruled out and/or treated before proceeding with the MSLT so that these conditions do not confound MSLT results. Periodic limb movements with arousals demonstrated on overnight observation may also affect MSLT results.² It is important to remember that the MSLT is not validated as a diagnostic test in children younger than 8 years and that it is sensitive to sleep deprivation. Therefore, patients who have not been encouraged to obtain as much sleep as possible for 1 week prior to undergoing the MSLT may exhibit shorter sleep latencies.

References

1. American Sleep Disorders Association, Diagnostic Classification Steering Committee. International Classification of Sleep Disorders: Diagnostic and Coding Manual, ICSD-R. Westchester (IL): American Academy of Sleep Medicine; 2005.
2. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* 2005;28:113–21.

2. The correct answer is (E) sleep diary and follow-up to review in the next few weeks. This patient endorses 2 of the 4 classic narcolepsy symptoms: EDS and sleep paralysis. The other symptoms in the classic narcolepsy tetrad are cataplexy and hypnagogic/hypnopompic hallucinations. The symptoms in

the tetrad represent normal physiologic features of REM sleep that abnormally intrude during the wake state in patients with narcolepsy. Not all these symptoms are present in every patient diagnosed with narcolepsy. Moreover, patients without narcolepsy may also endorse experiencing 1 or more of these symptoms on occasion, particularly in severely sleep-deprived contexts (particularly EDS and sleep paralysis).¹ The patient has other key complaints that are more suggestive of a circadian rhythm disorder than of narcolepsy, specifically delayed sleep phase syndrome.² Therefore, the most appropriate next step in her evaluation would be for her to maintain daily sleep logs over the next month. Sleep hygiene tips as well as the importance of obtaining a minimum of 7.5 to 8.5 hours of sleep need to be emphasized and should be part of her management once her sleep logs are reviewed.

The patient currently has no symptoms consistent with sleep-disordered breathing or any other reason to warrant a PSG at this time.¹ An MSLT may be considered in the future as well if she is found not to have a circadian disorder or if other symptoms consistent with narcolepsy are present.¹ Setting up a back-up clock may be helpful while she is in the process of being evaluated but is by no means adequate in the management of her symptoms.

References

1. American Sleep Disorders Association, Diagnostic Classification Steering Committee. International Classification of Sleep Disorders: Diagnostic and Coding Manual, ICSD-R. Westchester (IL): American Academy of Sleep Medicine; 2005.
 2. Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine report. *Sleep* 2007;30:1445–9.
- 3. The correct answer is (B) dopamine and histamine.** Both histamine and dopamine have been associated with the regulation of alertness and wakefulness. Dopaminergic fibers within the reticular activating system, histamine neurotransmitters generated from the tuberomammillary nucleus in the posterior hypothalamus, and hypocretin (orexin) produced in the lateral hypothalamus contribute to the production of wakefulness. GABA and galanin are inhibitory neurotransmitters produced in the ventrolateral preoptic nucleus of the anterior hypothalamus. Adenosine is a ubiquitous metabolic byproduct of wakefulness. Extracellular adenosine increases with prolonged wakefulness, allowing it to

inhibit the wake promoting cells, particularly in the basal forebrain.¹

Reference

1. Espana RA, Scammell TE. Sleep neurobiology for the clinician. *Sleep* 2004;15:27:811–20.

4. **The correct answer is (D) all of the above.** OSA has been identified as an independent risk factor for cardiovascular disease, including hypertension, heart disease, and stroke. The sleep fragmentation that often occurs as a result of sleep apnea frequently leads to complaints of daytime sleepiness and fatigue. In addition, some individuals may also complain of problems with sleep maintenance insomnia due to the arousals and awakenings that can occur at the termination of an apneic event. The cardiovascular impact as well as the sleep fragmentation associated with OSA may cause some men to present with loss of libido as well as overt erectile dysfunction. GERD can manifest over the course of the night as intra-abdominal pressure increases as the individual attempts to breathe against a collapsed airway.¹

Reference

1. Al Lawati NM, Patel SR, Ayas NT. Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. *Prog Cardiovasc Dis* 2009;51:285–93.

5. **The correct answer is (B) evaluate for the presence of concurrent sleep apnea if history suggests sleep-disordered breathing risk factors.** In a patient with RLS symptoms, one must exclude other sleep disorders such as sleep apnea if the patient displays the risk factors. Because RLS is diagnosed based on clinical symptoms, a PSG is not required for a definitive diagnosis. Evaluating for concurrent PLMD is incorrect because PLMD is a diagnosis of exclusion and would be ruled out if a diagnosis of RLS is made.¹ PLMS occur in RLS and in PLMD. Approximately 80% of patients with RLS have a significant number of PLMS. Patients with PLMD have PLMS but do not have the wake time sensory symptoms to make the diagnosis of RLS. Other sleep disorders or other clinical conditions that may be associated with PLMS must also be excluded when diagnosing PLMD. The only way to make the diagnosis of PLMD is with a PSG.^{2,3}

There are 4 criteria which must be fulfilled to make a diagnosis of RLS: (1) an urge or compulsion to move the legs, usually accompanied by uncom-

fortable or unpleasant sensations, primarily in the legs; (2) the urge to move or uncomfortable sensations that begin or worsen during rest; (3) symptoms (the urge to move or uncomfortable sensations) are partially or totally relieved by movement (at least initially in presentation); and (4) the urge to move or the uncomfortable sensations are worse in the evening or early part of the night compared to during the day. If the diagnosis of RLS is complicated by coexisting chronic pain syndrome, a PSG may help validate the presence of PLMS and hence RLS. If there are concerns about the cause of actual sleep disruption in the setting of what appears to be minimal RLS symptoms, then a PSG may help to define the sleep disruption as related to PLMS (therefore RLS) or not PLMS (therefore not RLS). If the patient still has sleep disruption following adequate treatment of RLS sensory symptoms, a PSG should be performed.^{2,3}

References

1. American Sleep Disorders Association, Diagnostic Classification Steering Committee. *International Classification of Sleep Disorders: Diagnostic and Coding Manual, ICSD-R*. Westchester (IL): American Academy of Sleep Medicine; 2005.
 2. Earley CJ. Clinical practice. Restless legs syndrome. *N Engl J Med* 2003;348:2103–9.
 3. Gamaldo CE, Earley CJ. Restless legs syndrome: a clinical update. *Chest* 2006;130:1596–604.
6. **The correct answer is (D) A and C.** Carbidopa/levodopa remains the most effective drug for the treatment of RLS symptoms; however, chronic use leads to rapid worsening of RLS symptoms, which is referred to as RLS augmentation. Augmentation has only been found to be associated with dopaminergic drugs and tramadol and has not been reported with the use of any of the other opioids such as methadone.^{1,2} For this reason, carbidopa/levodopa should be used in limited situations, such as when patients are going to the movies or on long car or plane rides and should never be used more than 2 to 3 times per week. Since carbidopa/levodopa is effective in at least 98% of patients, it can be used as a diagnostic tool. If the supposed RLS symptoms do not improve with this medication, then the diagnosis is in doubt.³

There are 4 main features of augmentation.³ (1) The daily duration of symptoms (number of hours per day affected by symptoms) is the most clinically significant feature of augmentation. Initial symptoms may occur only at bedtime, but with chronic use of a dopamine agent, symptoms develop

in the early evening or late afternoon. (2) The frequency of symptoms (number of days affected by symptoms) increases as the process of augmentation progresses (eg, a patient who presents with symptoms occurring 4 or 5 nights per week complains of nightly symptoms after a year on a dopamine agent). (3) The parts of the body affected by RLS symptoms increase (eg, a patient who initially complains of RLS symptoms just below the knee later presents with symptoms involving the whole leg). More distinctively, the patient may develop symptoms involving the arms or the trunk. (4) The intensity of the symptoms is the most difficult to quantify but for patients is the most disturbing. The core feature of RLS is the intense urge to move the legs (akathisia). This intensity increases as part of augmentation and may lead to more intense or vigorous efforts by the patient to relieve the symptoms.

Distinguishing between augmentation and progres-

sive worsening based on disease progression is difficult; however, augmented symptoms will abate with removal of the dopaminergic medications, while disease progression will not change. One should always look for other causes of disease progression, such as new-onset iron deficiency, addition of offending medications (eg, selective serotonin reuptake inhibitors), or significant sleep loss (sleep apnea).

References

1. Earley CJ. Clinical practice. Restless legs syndrome. *N Engl J Med* 2003;348:2103–9.
2. Gamaldo CE, Earley CJ. Restless legs syndrome: a clinical update. *Chest* 2006;130:1596–604.
3. Garcia-Borreguero D, Allen RP, Kohnen R, et al. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine-International Restless Legs Syndrome Study Group consensus conference at the Max Planck Institute. *Sleep Med* 2007;8:520–30.