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A 52-year-old man with excessive daytime sleepiness

A 52-YEAR-OLD MAN presents because he is excessively sleepy in the daytime, specifically while driving his car, during telephone conversations, and while sitting in his physician's waiting room. The problem began about 3 years ago.

The patient regularly goes to bed at approximately 10 PM and awakens at 6 AM. During the night he wakes up frequently because of transient episodes of dyspnea, a choking sensation, xerostomia, and dry cough. He has morning headaches, but says he has no nocturnal enuresis, nasal congestion, rhinorrhea, epistaxis, chest pain, or fever. He also says he has no cataplexy or hallucinations while falling asleep or waking up, and has not gained weight.

The patient's wife says he often wakes himself up snoring, and she cannot sleep in the same room with him because he snores so loudly.

History and physical examination

The patient has a history of hypertension and coronary artery disease, for which he takes atenolol and wears a nitroglycerin skin patch. For the past 30 years he has smoked 2 packs of cigarettes per day and has drunk about 2 cups of coffee per day and 4 cans of beer every night before bedtime.

On physical examination, the patient is 5 feet 9 inches tall and weighs 258 lb (body mass index 38.1). His vital signs are normal. Examination of the pharynx reveals a low soft palate, narrow oropharynx, and enlarged tongue base. His neck veins are not distended, his lungs are clear on auscultation, and his heart examination is normal. He has no pedal edema, cyanosis, or pallor.

Initial tests

The patient's blood tests are normal, including a complete blood cell count and serum concentrations of electrolytes, blood urea nitrogen, creatinine, and glucose.

Chest radiography reveals mild cardiomegaly.

An electrocardiogram shows left ventricular hypertrophy but is otherwise normal.

Spirometry reveals a mild restrictive defect; peak expiratory flow is normal.

DIFFERENTIAL DIAGNOSIS OF SLEEPINESS

1 What is the most likely cause of this patient's excessive daytime sleepiness?

- Narcolepsy
- Delayed sleep phase syndrome
- Insufficient sleep syndrome
- Obstructive sleep apnea
- Periodic limb movement disorder

All of the above can cause excessive daytime sleepiness (TABLE 1).^{1,2} However, the clinical features of this patient are typical of obstructive sleep apnea.³

Obstructive sleep apnea is common, with a prevalence of 4% in middle-aged men and 2% in middle-aged women.⁴

Excessive daytime sleepiness is one of the most common presenting complaints with this disorder. Patients may also complain of frequent awakenings associated with xerostomia, a choking sensation, morning headaches, and heavy snoring (often noticed by the bed partner). Like our patient, many patients with obstructive sleep apnea drink alcohol just before bedtime, are hypertensive, have coro-

His wife cannot sleep in the same room because of his snoring



nary artery disease, are obese, and have a narrow upper airway.

Although patients with obstructive sleep apnea may have fleeting nocturnal episodes of dyspnea that resolve within seconds after awakening, nocturnal respiratory distress is not a common manifestation. When it does occur, it raises suspicion of an associated cardiopulmonary disorder.

Chest radiography and electrocardiography may reveal the consequences of hypertension, such as left ventricular hypertrophy. Spirometry may show a restrictive defect due to obesity.

Narcolepsy is a syndrome of unknown origin characterized by excessive daytime sleepiness to the point of irresistible sleep attacks, pathologic manifestations of rapid eye movement (REM) sleep, and disturbed nocturnal sleep.⁵ The syndrome was described as early as 1862, and the term “narcolepsy” was coined by a French neuropsychiatrist, Gélinau, in 1880.⁶

Narcolepsy is fairly common, with an estimated prevalence of 4 to 10 per 10,000 in the United States.⁷ Patients are usually young at presentation (20 to 30 years), but the diagnosis is typically delayed for many years owing to misdiagnosis or disregard of symptoms.⁸ The symptoms often emerge in the second decade of life and increase in severity through the third or fourth decades.

The REM sleep abnormality in narcolepsy has four main characteristics:

- Sleep attacks
- Cataplexy (sudden reversible loss of muscle tone, usually after an emotional stimulus)
- Sleep paralysis (a frightening inability to move one's limbs, speak, or open one's eyes when falling asleep or awakening)
- Hallucinations, which occur when falling asleep (hypnagogic hallucinations) or, less often, when waking up (hypnopompic hallucinations). Of note, the hallucinations associated with narcolepsy are most often visual—any report of auditory hallucinations should alert the physician to entertain a diagnosis of seizures or a psychiatric disorder.

The objective evidence of the abnormality in REM sleep is that narcoleptic patients enter REM sleep within 15 minutes of falling asleep, a finding called *sleep-onset REM periods*.

TABLE 1

Common causes of excessive daytime sleepiness

Sleep-disordered breathing

Obstructive sleep apnea
Upper airway resistance syndrome
Central sleep apnea
Central alveolar hypoventilation syndrome

Neurologic disorders

Narcolepsy
Periodic limb movement disorder
Dementia
Parkinsonism
Idiopathic hypersomnia syndrome

Circadian rhythm disorders

Shift work sleep disorder
Jet lag (time-zone change)
Delayed and advanced sleep phase syndrome

Behavioral and psychiatric disorders

Insufficient sleep syndrome
Alcoholism
Malingering
Mental depression
Anxiety disorder
Panic disorder

Drug-related or environmental sleep disorders

Hypnotic-dependent or stimulant-dependent sleep disorder
Temperature-related or noise-related sleep disorder

Associated with other medical disorders

Myocardial ischemia
Chronic obstructive pulmonary disease
Gastroesophageal reflux disorder
Peptic ulcer disease

Delayed sleep phase syndrome is a common disorder of circadian rhythm that usually occurs in puberty or adolescence. It is defined as a persistent disturbance of the sleep-wake cycle in which sleep onset is often delayed until early morning (2 to 6 AM) and awakening is delayed until 10 AM to 2 PM without difficulty staying asleep.⁹ Excessive daytime sleepiness develops when a patient with delayed sleep phase syndrome is forced to wake up early for social or occupational reasons.

Insufficient sleep syndrome, a common nuisance of modern life, is suggested by excessive daytime sleepiness associated with a

Recordings performed during polysomnography

Audio and video monitoring

Uses microphone to measure snoring sound levels; information can support the diagnosis and differential diagnosis of sleep-disordered breathing by temporally correlating the sound with abnormal air flow, respiratory movements, and decreased oxygen saturation; video cameras record nocturnal behavioral events, such as periodic limb movement disorder, seizures, parasomnias (eg, sleepwalking)

Nasal and oral air flow measurement

Diagnoses and differentiates obstructive sleep apnea, upper airway resistance syndrome, and other sleep-disordered breathing conditions; usually via the use of thermistors

Electro-oculography

Determines REM sleep stage by detecting characteristic eye movements

Electroencephalography

Determines awake stage and various stages of sleep (stages 1, 2, 3, and 4, and REM sleep) by recording two or four channels

Electromyography

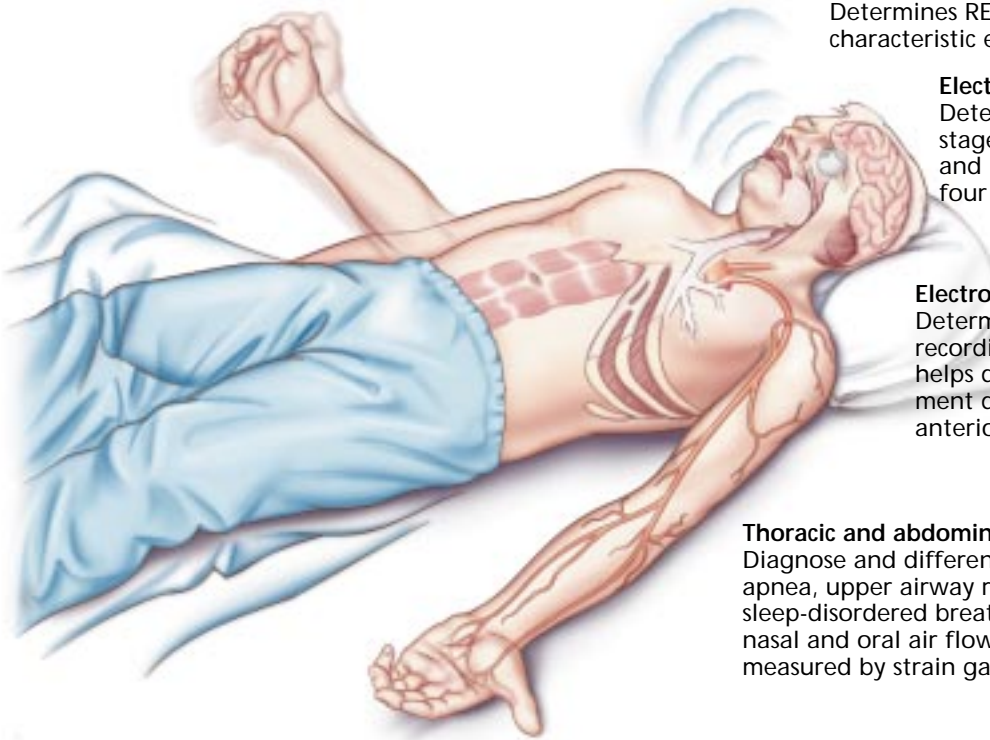
Determines REM sleep stage by recording activity over chin muscles; helps diagnose periodic limb movement disorder by activity over the anterior tibialis muscle

Thoracic and abdominal respiratory movements

Diagnose and differentiate obstructive sleep apnea, upper airway resistance syndrome, and other sleep-disordered breathing conditions, complementing nasal and oral air flow measurements; usually measured by strain gauges

Pulse oximetry

Measures oxygen saturation; indirectly diagnoses sleep-disordered breathing by detecting and temporally correlating the occurrence of hypoxia and sleep-disordered breathing



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FIGURE 1

chronic lack of time available for nocturnal sleep. The excessive daytime sleepiness goes away when sleep time is increased, such as on weekends, days off, and vacations.

Periodic limb movement disorder is characterized by repetitive, stereotyped movements, recorded on electromyography as

bursts of anterior tibialis muscle activity during sleep, each lasting 0.5 to 5 seconds and occurring at intervals of 5 to 120 seconds (average about 30 seconds). These bursts lead to a significant number of arousals.¹⁰

About one third of these patients have associated **restless leg syndrome**, which is



Normal sleep cycle

The five stages of sleep, including their repetition, occur cyclically. The first cycle ends after completion of the first REM stage and usually lasts for 100 minutes. Each subsequent cycle lasts longer, as its respective REM stage extends. So a person may complete five cycles in a typical night's sleep.

STAGE 1

Drowsiness. Polysomnographic activity is 50% lower than during wakefulness. The eyes are closed. This and the other three stages that occur before the rapid eye movement (REM) stage last 5 to 15 minutes.

STAGE 2

Light sleep. Polysomnography shows intermittent periods of muscle contraction and relaxation. The heart rate slows, body temperature decreases.

STAGES 3 AND 4

Deep sleep, characterized by slow, high-amplitude waves on electromyography.

Stages 2 and 3 repeat backward before REM is reached. The normal cycle is therefore stage 1, 2, 3, 4, 3, 2, REM.

STAGE 5, RAPID EYE MOVEMENT (REM)

REM sleep occurs approximately 90 minutes after sleep onset. REM sleep is distinguished by physiologic changes, heightened brain activity, and paralysis of major voluntary muscles. Changes include rapid eye movements, accelerated and erratic heart rate and respiration, twitching of the face, fingers, and legs, and paralysis of chin and neck muscles are typical. Dreaming occurs during the REM stage, possibly because of heightened brain activity.

often provoked by rest and relieved by movement and is associated with paresthesia of the lower extremity and an irresistible urge to move. Most patients with restless leg syndrome (70% to 80%) have polysomnographic evidence of periodic limb movement disorder.

Restless leg syndrome and periodic limb movement disorder can cause excessive daytime sleepiness or insomnia. Both of these disorders may be either idiopathic or associated with obstructive sleep apnea or narcolepsy. Although the exact prevalence in the general population is unknown, the incidence of restless leg syndrome varies from 5% to 15% depending on the study.¹¹

■ HOW TO DIAGNOSE OBSTRUCTIVE SLEEP APNEA

2 Which test is most diagnostic of obstructive sleep apnea in this patient?

- Sleep history and physical examination
- Overnight electroencephalography by itself
- Overnight pulse oximetry by itself
- Polysomnography
- Multiple sleep latency testing

The sleep history, ie, the symptoms and the exact times of sleep onset and frequency of nocturnal awakenings, can suggest or support the diagnosis of obstructive sleep apnea, but it is not diagnostic. It may, however, be sufficient for the diagnosis of circadian rhythm disorders, insufficient sleep syndrome, or narcolepsy, if the patient has accompanying symptoms of sleep attacks, cataplexy, sleep paralysis, and hypnagogic or hypnopompic hallucinations.

Our patient's sleep history certainly supports the diagnosis of obstructive sleep apnea.³

The physical examination may also give clues that suggest obstructive sleep apnea, eg, obesity, structural craniofacial abnormalities, an edematous or deviated nasal septum, an elongated soft palate and uvula, redundant pharyngeal mucosa, and enlarged tonsils or tongue.³ Neurologic, psychiatric, cardiac, pulmonary, or other medical diseases associated with obstructive sleep apnea may present with physical findings specific to those diseases. However, many of these patients may not have obstructive sleep apnea, and further confirmatory diagnostic testing is required.

Polysomnography is the gold standard diagnostic test for obstructive sleep apnea.³

Entering REM sleep within 15 minutes of sleep onset is abnormal

Full polysomnography usually includes electroencephalography, electro-oculography, electromyography, electrocardiography, and oronasal air flow monitoring, and measurement of chest wall effort, body position, snoring sound, and oxyhemoglobin saturation (FIGURE 1). End-tidal carbon dioxide monitoring may also be included; it provides information about alveolar hypoventilation, and it is especially useful in children.

The diagnosis is based on the number of events of apnea or hypopnea recorded. The American Sleep Disorders Association defines apnea as cessation of air flow for 10 seconds or more; hypopnea is a transient, partial cessation of air flow for 10 seconds or more associated with a decrease in air flow of 50% or more or a decrease in amplitude less than 50% accompanied by a decline in oxygen saturation of at least 3%. The average number of events per hour is called the *apnea-hypopnea index* (AHI). An AHI of 5 or higher, coupled with suggestive symptoms such as excessive daytime sleepiness, is diagnostic.

In obstructive sleep apnea, the electroencephalogram may show frequent periodic arousals or awakenings and reduced sleep efficiency (the amount of total sleep time during a sleep study) along with reduced stage 3, stage 4, and REM sleep. (See sidebar, “Normal sleep cycle” for a review of the stages of the sleep cycle.) These findings, however, are nonspecific and are not diagnostic by themselves.

The relevance of electroencephalography in this diagnosis is that it tells us what stage of sleep the patient is in when he or she has respiratory disturbances. REM sleep causes paralysis and hypotonia of all the skeletal muscles except the respiratory and extraocular muscles. Therefore, during REM sleep, low muscle tone predisposes the patient to obstructive respiratory events, including apnea and hypopnea.

Pulse oximetry by itself is not useful in diagnosing obstructive sleep apnea because significant oxygen desaturation may or may not occur. On the other hand, oxygen desaturation during episodes of abnormal breathing suggests sleep-disordered breathing such as in obstructive sleep apnea, central sleep apnea, central alveolar hypoventilation, or upper air-

way resistance syndrome.

The **multiple sleep latency test** is the gold standard for quantifying excessive daytime sleepiness.¹² It is performed during the daytime, usually following polysomnography. The patient is given four or five opportunities to fall asleep in a dark, quiet room at 2-hour intervals. Each time, the time needed to fall asleep (sleep latency) is measured by determining sleep onset with continuous electroencephalography.

A *mean sleep latency* (the average value of all four or five readings) of 5 minutes or less is considered severe or pathologic daytime sleepiness, 5 to 10 minutes is moderate daytime sleepiness, and 10 minutes or more is normal.

Many patients with obstructive sleep apnea have pathologically short sleep latency, but this is not specific because patients with any cause of excessive daytime sleepiness (TABLE 1) may exhibit short sleep latency on multiple sleep latency testing.

Another integral part of the multiple sleep latency test is the assessment of *sleep-onset REM periods*, ie, periods of REM sleep within the first 15 minutes of sleep onset. Two or more naps with sleep-onset REM periods during the test highly suggest narcolepsy, although this may occur in some patients with severe obstructive sleep apnea, periodic limb movement disorder, or other sleep disorders.

Case continued

The patient underwent a thorough sleep study.

On polysomnography, the patient's sleep was very fragmented owing to frequent arousals and awakenings, with a sleep efficiency of 63% (normal > 70%–75%). He did not go into stage 3 or 4 sleep at all (which together normally account for 15% to 20% of time asleep), and his REM sleep was markedly short.

Of note, the patient had 140 events of apnea or hypopnea in 300 minutes of recording, for an apnea-hypopnea index of 28 events per hour. Of these episodes, 94 were of obstructive apnea (during which the patient made an effort to breathe), 8 were of central apnea (during which the patient made no effort to breathe), and 38 were of hypopnea.

Falling asleep
in < 10 minutes
during daytime
is abnormal



The patient's mean oxygen saturation during sleep (while breathing room air) was 88%, and the lowest recorded was 68%. The oxygen saturation was below 90% for 32% of the total sleep time. There were 42 desaturation events, defined as a 4% drop in the oxygen saturation from baseline.

The patient also underwent multiple sleep latency testing. His mean sleep latency was 4.2 minutes (indicative of severe sleepiness). He did not, however, have any sleep-onset REM periods.

■ THERAPY

3 What is the initial therapy of choice in this patient, once the diagnosis of obstructive sleep apnea is confirmed?

- Medroxyprogesterone
- Nasal decongestant and steroid spray
- Nasal continuous positive airway pressure (CPAP)
- Uvulopalatopharyngoplasty
- Tracheostomy

Medroxyprogesterone and other progestational agents have been found to stimulate ventilation in small groups of patients, thereby providing evidence of benefit in the treatment of central sleep apnea and alveolar hypoventilation. However, these agents have not shown consistent benefit in obstructive sleep apnea and so are not recommended for routine treatment.³

Nasal decongestants and steroid sprays may reduce resistance to air flow by decreasing mucosal thickening and turbinate hypertrophy. Nasal congestion, often caused by seasonal allergies, may cause obstructive sleep apnea by increasing the upper airway resistance to air flow. However, nasal decongestants would not benefit our patient, as he has no symptoms or signs of chronic nasal congestion.

Nasal CPAP is highly effective in obstructive sleep apnea. It works by opening the upper airway, acting as a "pressure splint," thereby reducing obstruction to air flow.³ It has been used to treat obstructive sleep apnea for more than a decade and currently is the most commonly used specific treatment.

The single most important drawback of

nasal CPAP is that many patients cannot tolerate it or do not accept it long-term: about 50% stop using it within a few years.

More sophisticated CPAP machines may help with compliance. For example, some of them can automatically adjust the pressure with each breath, depending on the airway resistance.

Surgery. Numerous novel techniques and procedures have been developed to improve the efficacy of, and compliance with, obstructive sleep apnea therapy.¹³ These include surgery of the palate and tongue base and implanted electrical nerve stimulation.

Surgical procedures aim to relieve the anatomic obstruction at specific levels in the upper airway and include nasal reconstruction, uvulopalatopharyngoplasty, mandibular osteotomy with genioglossus advancement, hyoid myotomy with suspension, maxillo-mandibular advancement, tongue base resection, and tracheostomy (to bypass all upper airway obstructions).¹⁴ Tracheostomy was first used to treat obstructive sleep apnea in pickwickian syndrome (named for the somnolent "fat boy" in *The Pickwick Papers* by Charles Dickens) but is now rarely performed for sleep apnea.

Surgery has a limited role in the primary treatment of obstructive sleep apnea, although it is a useful secondary treatment in patients with a structural abnormality causing air flow obstruction, and in patients with documented moderate to severe obstructive sleep apnea for whom other medical therapies have failed, including nasal CPAP.

A number of procedures—eg, uvulopalatopharyngoplasty, laser-assisted uvulopalatoplasty, cautery-assisted palatal stiffening, radiofrequency ablation—are currently used to relieve snoring,¹⁵ but their success rates vary and long-term success is unknown. For example, uvulopalatopharyngoplasty relieves symptoms and reduces the apnea-hypopnea index in only 50% of carefully selected patients with obstructive sleep apnea, and other treatments have not been evaluated systematically in this condition. Surgery should only be performed along with preoperative and postoperative polysomnographic evaluation.

Other treatments have been used to

CPAP is usually very effective, but long-term compliance is poor



relieve obstructive sleep apnea, either alone or in combination with other treatments, with varying success.

Weight loss by dietary control and physical exercise is often effective, but patients often have difficulty keeping off the weight they lose.

Positional therapy (ie, sleeping on one's side rather than on one's back) may be as effective as nasal CPAP for some patients. A simple means of keeping the patient off his back is to tell him to wear a backpack with a ball in it during sleep. Patient preference and tolerability should be considered in selecting CPAP vs positional therapy in this patient population.¹⁶

Oxygen therapy is useful in patients with significant oxygen desaturation, but usually only as an adjunct to nasal CPAP.

Other measures include avoiding sedative-hypnotic medications, avoiding alcohol consumption just before going to bed, and using dental devices that adjust the position of the tongue and mandible.

CONCLUSIONS

Obstructive sleep apnea may be difficult to diagnose and may be misdiagnosed as asthma, emphysema, or congestive heart failure. The diagnosis in a patient such as ours is less difficult if a physician suspects it and confirms it with polysomnography. In middle-aged, elderly, or obese adults with snoring and excessive daytime sleepiness, a high suspicion for obstructive sleep apnea leads to earlier diagnosis, prevents morbidity, and reduces mortality secondary to complications.

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