Primary Hypersomnias of Central Origin

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ABSTRACT

Purpose of Review: This review discusses the various causes of primary hypersomnias with emphasis on clinical recognition, diagnosis, and treatment options.

Recent Findings: Narcolepsy is probably the most fascinating syndrome causing excessive daytime sleepiness. With increasing understanding of the hypocretin/orexin pathways and the neurotransmitters that subserve the role of wakefulness and sleep, newer therapeutic modalities with promising results are being investigated and opening new frontiers in the treatment of this rare but devastating disease.

Summary: This article reviews the primary hypersomnias of central origin. Where possible, clinical cases that highlight and explain the clinical syndromes are included. Treatment modalities and future directions are also discussed to help the clinician identify and treat the underlying disorder.

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Dr Kushida discusses the unlabeled use of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants for the treatment of narcolepsy with cataplexy; melatonin for the treatment of idiopathic hypersomnia; and amantadine, lithium, lamotrigine, valproic acid, and modafinil for the treatment of Kleine-Levin syndrome. Dr Malhotra reports no disclosure.

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INTRODUCTION

The symptom of hypersomnia is commonly encountered in clinical practice and can occur as a result of a sleep-related breathing disorder, or it may also occur secondary to a circadian rhythm disorder or other causes of disturbed nocturnal sleep. When hypersomnia does not result from the aforementioned conditions, it is termed hypersomnia of central origin. It is defined as an inability to maintain an alert state during the major waking episodes of the day.

Excessive daytime sleepiness (EDS) is the cardinal manifestation common to all types of hypersomnia. In comparison to hypersomnia due to various pathologies, such as sleep-disordered breathing, hypersomnia of central origin is a rare cause of EDS. It is important for the treating clinician to be cognizant of disease entities that constitute the umbrella term ''hypersomnia of central origin,'' to be able to diagnose them, and, most importantly, to manage them appropriately. The *International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual* (*ICSD-2*) lists a number of conditions that are grouped under this category of sleep disorders (**Table 4-1**).[2]

It may be normal for a preschooler to sleep 12 hours a night, but the same amount of nocturnal sleep with symptoms of EDS in an adult may raise suspicion for a sleep disorder. Sleep needs are individual, and the National Sleep Foundation provides an outline of normal sleep time based on the age of the person (**Table 4-2**).[1]

NARCOLEPSY

Introduction

A disorder of REM sleep, narcolepsy is the classic hypersomnia of central origin. EDS and episodic loss of muscle tone were identified in 1877 by Westphal,[3] and 3 years later, Gelineau coined the term narcolepsy. Subsequently, Adie recognized the loss of muscle tone as part of the constellation of the disease and named it cataplexy. Investigation

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KEY POINT

- Most whites and African Americans who have narcolepsy with cataplexy are positive for HLA-DQB1*0602, showing a strong association with this human leukocyte antigen type.

TABLE 4-1 ***International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*** **Diagnostic Criteria for Hypersomnia[a]**

- **Narcolepsy With Cataplexy**
- **Narcolepsy Without Cataplexy**
  Narcolepsy due to medical condition
  Narcolepsy, unspecified
- **Recurrent Hypersomnia**
  Kleine-Levin syndrome
  Menstrual-related hypersomnia
- **Idiopathic Hypersomnia With Long Sleep Time**
- **Idiopathic Hypersomnia Without Long Sleep Time**
  Behaviorally induced insufficient sleep syndrome
  Hypersomnia due to medical condition
  Hypersomnia due to drug or substance
  Hypersomnia not due to substance or known physiologic condition (nonorganic hypersomnia)
  Physiologic (organic) hypersomnia, unspecified

[a] Modified from American Academy of Sleep Medicine.[2] Used with permission of the American Academy of Sleep Medicine, Darien, IL, 2012.

into the etiology of this disorder established an association with HLA-DR2 in the Japanese population with narcolepsy.[4] Most whites and African Americans who have narcolepsy with cataplexy were also positive for HLA-DQB1*0602, showing a strong association with this human leukocyte antigen (HLA) type.[5] Additional research identified the hypocretin/orexin pathway and its ability to regulate sleep and wakefulness.[6] The finding of undetectable CSF levels of hypocretin-1[7] and hypothalamic hypocretinergic cell dropout in patients with narcolepsy and cataplexy further confirmed this association.

TABLE 4-2 **Age-Specific Sleep Needs as Recommended by the National Sleep Foundation[a]**

Age	Sleep
Newborns (0–2 months)	12–18 hours
Infants (3–12 months)	14–15 hours
Toddlers (1–3 years)	12–14 hours
Preschoolers (3–5 years)	11–13 hours
School-aged children (5–10 years)	10–11 hours
Preteenaged and teenaged children (10–17 years)	8.5–9.25 hours
Adults	7–9 hours

[a] Reprinted with permission from National Sleep Foundation.[1] *www.sleepfoundation.org/article/how-sleep-works/how-much-sleep-do-we-really-need*.

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TABLE 4-3 ***International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*** **Diagnostic Criteria for Narcolepsy With Cataplexy[a]**

A. Excessive daytime sleepiness present for at least 3 months.

B. Definite history of cataplexy, ie, loss of muscle tone triggered by laughter or strong emotions.

C. Should be confirmed by multiple sleep latency test preceded by an overnight polysomnogram consisting of at least 6 hours of sleep. A sleep latency of 8 minutes or less plus two or more sleep-onset REM periods are considered abnormal. Alternatively, a decreased CSF hypocretin level (<110 pg/mL) can be used.

D. The hypersomnia is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

[a] Modified from American Academy of Sleep Medicine.[2] Used with permission of the American Academy of Sleep Medicine, Darien, IL, 2012.

Epidemiology

The prevalence of this disease is between 0.03% and 0.05% of the population.[8] Both sexes are equally affected, with mean age at onset in the mid-twenties. A peak occurs around 15 years and another near 35 years, suggesting a bimodal distribution. Narcolepsy without cataplexy is comparatively less common than narcolepsy with cataplexy. It is prudent to exclude secondary hypersomnia resulting from systemic disease, drugs or medications, or CNS trauma or disease before making a diagnosis of narcolepsy without cataplexy. First-degree relatives of patients with narcolepsy have a 1% to 2% risk of developing this disorder. The *ICSD-2* diagnostic criteria for narcolepsy with and without cataplexy are outlined in Table 4-3 and Table 4-4.

Clinical Symptoms

The classic symptoms of narcolepsy include EDS, cataplexy, hypnagogic hallucinations, and sleep paralysis.

TABLE 4-4 ***International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*** **Diagnostic Criteria for Narcolepsy Without Cataplexy[a]**

A. Excessive daytime sleepiness present for at least 3 months.

B. Cataplexy is absent or very doubtful.

C. Must be confirmed by multiple sleep latency test preceded by an overnight polysomnogram consisting of at least 6 hours of sleep. A sleep latency of 8 minutes or less plus two or more sleep-onset REM periods are considered abnormal.

D. The hypersomnia is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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KEY POINTS

- Naps are usually refreshing and often recommended as part of the treatment plan for narcolepsy. Short daytime naps lasting about 30 minutes can result in the attenuation of the sleep drive for a few hours.
- Symptoms of subtle muscle weakness in cataplexy include slurring of speech, buckling of knees, jaw dropping, or even nodding of the head and should be specifically elicited during history taking.
- A rare sustained cataplectic episode, status cataplecticus, may occur following abrupt discontinuation of medications used to treat cataplexy. This is also referred to as rebound cataplexy.

Excessive daytime sleepiness. EDS is usually the heralding feature of narcolepsy, manifesting as episodes of an inadvertent and irresistible urge to sleep that appears without warning. These may last seconds to minutes and are known as sleep attacks. Sedentary and boring settings may predispose to and enhance the symptom of EDS. Naps are usually refreshing and often recommended as part of the treatment plan. Short daytime naps lasting about 30 minutes can result in the attenuation of the sleep drive for a few hours.[9]

Cataplexy. Cataplexy is defined as the sudden, involuntary loss or decrease of muscle tone. Episodes are most commonly precipitated by laughter; however, other intense positive emotions such as joy, elation, and even surprise can be potential triggers. These attacks may either be profound, with generalized atonia resulting in falls and injuries, or consist of localized loss of muscle tone that may be missed if this diagnosis is not considered (**Supplemental Digital Content 4-1**, *links.lww.com/CONT/A16*). Symptoms of subtle muscle weakness include slurring of speech, buckling of knees, jaw dropping, or even nodding of the head and should be specifically elicited during history taking. The diagnosis may be delayed by several years if these key symptoms are not elicited on initial evaluation. Most cataplectic attacks last a short duration, a few seconds to a few minutes.[10] However, a rare sustained cataplectic episode, status cataplecticus, may occur following abrupt discontinuation of medications used to treat cataplexy. This state is also referred to as rebound cataplexy.

Sleep paralysis. A terrifying experience when it occurs for the first time, sleep paralysis is characterized by an inability to move while being totally aware of one's surroundings. Typically occurring either at arousal or at sleep onset, these events rarely last more than a few minutes. Subsequent recurring attacks are deemed less stressful as patients readily recognize the phenomenon and its transient nature. Sleep paralysis, which occurs in two-thirds of patients with narcolepsy, is not pathognomonic of narcolepsy as it can be present even in the healthy population,[9] commonly in the setting of sleep deprivation.

Hallucinations. Simple or complex visual hallucinations are experienced by approximately two-thirds of patients with narcolepsy. These may either occur during the period of transition from wakefulness to sleep (hypnagogic) or from sleep to wakefulness (hypnopompic) with the former being typical of narcolepsy. Other forms, such as auditory and tactile hallucinations, may also be experienced. It is imperative to exclude an underlying psychiatric condition as a cause of the hallucinations that do not occur exclusively during sleep. Hallucinations during sleep stage transition are also reported in healthy people[9] and, therefore, are also not pathognomonic of narcolepsy.

Disturbed nighttime sleep. Although not a part of the classic tetrad, nighttime sleep disturbance is an essential symptom of narcolepsy, and for this reason several efforts at characterizing the nocturnal sleep of these patients have been made. A large number of patients with narcolepsy experience vivid dreams, sleep fragmentation due to multiple arousals, early morning awakenings, nocturnal eating, and unrefreshing nocturnal sleep.[11]

Automatic behavior. Nearly half of all patients with narcolepsy experience automatic behavior,[11] which is described as the act of pursuing a purposeful behavior with no reminiscence of it. Patients either seem awake and alert or may appear inattentive during an episode. Intrusion of microsleep into wakefulness is believed to account for this

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symptom. Sleep deprivation may precipitate automatic behavior in normal individuals and therefore this symptom is also not pathognomonic of narcolepsy.

Associated Conditions

Periodic limb movements of sleep. Very common in the narcoleptic patient, periodic limb movements of sleep (PLMS) may occur in 60% of these patients. These are characterized as a cluster of limb movements occurring during sleep that resemble a triple flexion response. This is a polysomnographic finding and it should be remembered that patients with PLMS may or may not have symptoms of restless legs during wakefulness. PLMS are more prevalent as the patient gets older, tend to be more prevalent in REM sleep, and are associated with more sleep disruption than in controls, most likely because of the PLMS-associated arousals.

REM sleep behavior disorder. REM sleep behavior disorder is an associated condition present in 7% to 36% of patients with narcolepsy (**Supplemental Digital Content 4-2**, *links.lww.com/CONT/A17*). The term *REM sleep behavior disorder* may be misleading, since patients with narcolepsy may demonstrate an increase in phasic and/or tonic muscle activity in nocturnal REM sleep without the associated behavioral component needed to make a diagnosis of REM sleep behavior disorder.

Presentation

Both EDS and cataplexy will be present in about half of the patients when the diagnosis of narcolepsy is made, and about 40% will progress and show symptoms of cataplexy later in the course of their disease. Occasionally, the onset of REM-related muscle atonia (cataplexy) precipitated by intense emotions occurs more than 40 years later, although most patients will experience their first episode of cataplexy within 10 years of the onset of symptoms of EDS.[11] **Case 4-1** demonstrates a typical presentation of narcolepsy.

Pathophysiology

The connection between major histocompatibility complex and narcolepsy was initially reported in the Japanese population and led to the consideration of an autoimmune basis in the development of narcolepsy. An association of HLA-DR with narcolepsy was reported in the Japanese population, and subsequently other HLA types were also associated with narcolepsy, with the most closely linked being HLA-DQB1*0602. Twelve percent to 34% of the general population has this allele, and more than 90% of patients with narcolepsy and cataplexy test positive for this HLA type.[12] The HLA link is less certain in patients with narcolepsy without cataplexy, although more than 40% of these patients are positive for this HLA.[12] Additionally, up to 30% of patients positive for HLA-DQB1*0602 do not have narcolepsy.[5,12]

The discovery of the hypocretin/orexin neurons in the lateral hypothalamus furthered understanding of the pathophysiology of this disorder.[6] Hypocretin-1 and hypocretin-2 are the two peptides that result from the splitting of their precursor, preprohypocretin. Hypocretin-1 is implicated in human narcolepsy. These hypocretin peptides bind to their own specific receptors, which are found in the histaminergic tuberomamillary nucleus, the ventrolateral preoptic nucleus, the cholinergic pedunculopontine nucleus, the brainstem monoaminergic system, and also diffusely in the basal forebrain.[13] As previously mentioned, patients who have narcolepsy with cataplexy show low or undetectable CSF hypocretin levels, with most patients testing positive for HLA-DQB1*0602.[7] Additionally, histologic examination on brain

KEY POINTS

- The presence of a sleep-onset REM period on an overnight sleep study of a patient with a history of excessive daytime sleepiness and muscle atonia that occurs in the setting of an emotional outburst may be suggestive of a diagnosis of narcolepsy with cataplexy.
- Hypocretin-1 and hypocretin-2 are the two peptides that result from the splitting of their precursor, preprohypocretin. Hypocretin-1 is implicated in human narcolepsy.

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Case 4-1

An 8-year-old boy was brought to the office by his parents because of a 2-week history of abrupt onset of overwhelming sleepiness. He was inappropriately falling asleep in the day despite getting over 10 hours of uninterrupted nocturnal sleep. No history of sleep paralysis or visual hallucinations could be elucidated from the patient or his family. He described an episode of falling off his bicycle without any clear reason, and another episode when his knees buckled and he fell to the ground after hearing his brother tell a joke. (The accompanying video [**Supplemental Digital Content 4-3**, *links.lww.com/CONT/A18*] demonstrates a different patient with similar clinical history and presentation.) He had an unexplained weight gain of about 3 kg (6 lbs) over 2 months. He had nothing remarkable in his medical or psychiatric history and no history of recent trauma or medication use. His routine blood work and EEG were normal, as was the MRI of the brain with and without gadolinium. An overnight polysomnogram (PSG) was normal, with a subsequent multiple sleep latency test (MSLT) showing a mean sleep-onset latency of 2.3 minutes and a sleep-onset REM period (SOREMP) on each of the five naps. Human leukocyte antigen typing was positive for HLA-DQB1*0602, and CSF hypocretin level was undetectable.

Comment. The patient's history of a rather abrupt onset of excessive daytime sleepiness (EDS) and episodes of muscle atonia that occurred during an emotionally charged situation was highly suggestive of narcolepsy with cataplexy. This diagnosis was confirmed with a normal PSG and a MSLT positive for multiple SOREMPs and a sleep-onset latency shorter than 8 minutes. HLA typing for HLA-DQB1*0602 and abnormal CSF hypocretin levels may help confirm the diagnosis if the MSLT results are equivocal, unlike in this case. Additionally, the presence of a SOREMP on an overnight sleep study with a history of EDS and muscle atonia that occurs in the setting of an emotional outburst may also be suggestive of a diagnosis of narcolepsy with cataplexy. An MSLT is still necessary to confirm this diagnosis since the presence of a SOREMP on an overnight PSG is not included in the diagnostic criteria outlined in the *International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*. Treatment was initiated with sodium oxybate 3 g in two divided doses, resulting in improvement of the patient's symptoms of EDS and cataplexy. The sodium oxybate dose was increased to 4.5 g in three divided doses a few months later.

tissue in patients with narcolepsy showed evidence of hypocretin neuronal cell loss in the lateral hypothalamus (**Figure 4-1**).

The inhibition of the motor effector of the H reflex is the proposed mechanism for the development of the atonic process encountered in cataplexy. This mirrors the mechanism that explains the atonia normally seen in REM sleep.[14] However, this theory cannot explain the general loss of muscle tone and areflexia seen in muscles that are not clinically affected during a cataplectic episode. Since magnetic stimulation via the transcranial route is not impaired in cataplexy, presynaptic inhibition of the afferent sensory neuron has been proposed as an alternative mechanism for the development of cataplexy.[15]

Diagnostic Tools

Epworth Sleepiness Scale. The Epworth Sleepiness Scale (**Appendix A**) assesses subjective daytime sleepiness through a short and simple questionnaire. The

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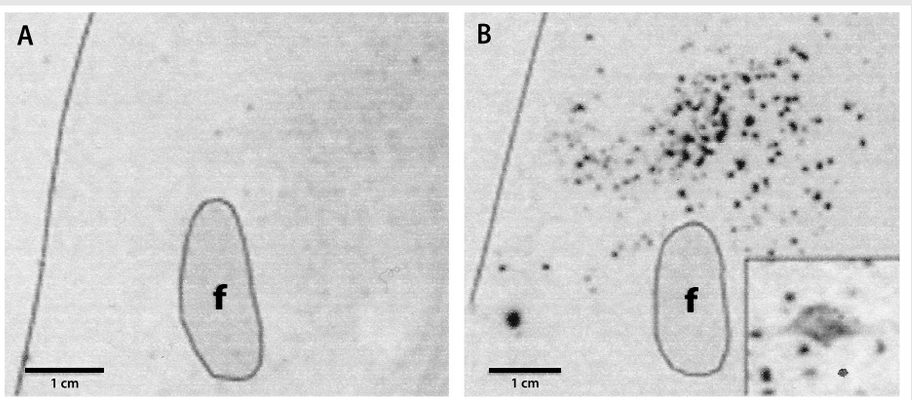

FIGURE 4-1 Prehypocretin messenger RNA in the lateral hypothalamus stains darkly in the control subject (*B*), but is undetectable in the patient with narcolepsy (*A*).

f = fornix.

Modified from Nishino S, et al, Sleep Med Clin.[19] © 2012, with permission from Elsevier. *www.sciencedirect.com/science/article/pii/S1556407X12000434.*

chance of falling asleep in eight common situations is graded from 0 to 3. A total score greater than 10 is indicative of EDS.[16]

Multiple sleep latency test. The multiple sleep latency test (MSLT) was designed to record the physiologic tendency to fall asleep in the absence of external alerting factors.[17] To be considered valid, the MSLT has to be preceded by an overnight sleep study polysomnogram (PSG), essentially to ensure that the patient is not sleep deprived and has slept sufficiently. Sleep-disordered breathing that may account for the symptom of EDS and may give a false-positive MSLT is also ruled out with the PSG. Although a diagnosis of sleep-disordered breathing does not rule out narcolepsy, it makes it less likely to be the sole cause of the EDS. Avoidance of all medications influencing sleep from 2 weeks before the test is necessary, although sometimes impractical.

For the MSLT, five 20-minute naps at 2-hour intervals are scheduled during the day, and the patient, dressed in street clothes, is instructed to lie in bed and try to fall asleep during each of the five naps. Sleep onset as well as the presence of REM sleep during the nap is noted. REM sleep occurring within 15 minutes of sleep onset is deemed a SOREMP. A short sleep-onset latency of less than 8 minutes is considered abnormal. If this short sleep-onset latency is accompanied by at least two SOREMPs, a diagnosis of narcolepsy may be made in the right clinical setting.[18] If the patient does not sleep during a nap, the nap is interrupted after 20 minutes and the patient waits for the next nap time.[17]

Polysomnogram. Patients with narcolepsy often show abnormalities on the PSG that include a decrease in total sleep time, a short sleep-onset latency, sleep fragmentation, REM without atonia, and PLMS. Often, the presence of a SOREMP on the PSG may alert a physician to consider narcolepsy in the differential diagnosis in a patient with EDS.

HLA. Testing for serum HLA-DQB1* 0602 typing is available and more commonly seen in patients with narcolepsy and cataplexy. However, there is a higher chance for narcolepsy patients

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KEY POINT

- A finding of low (less than 110 pg/mL) or undetectable CSF hypocretin levels will nearly always be seen in patients with true narcolepsy with cataplexy.

without cataplexy to be HLA negative than positive, and upward of 30% of the general population may be positive for this HLA type without having symptoms of narcolepsy.[5,12]

Hypocretin. CSF measurement of hypocretin is commercially available, and the finding of low (less than 110 pg/mL) or undetectable CSF hypocretin levels will nearly always be seen in patients with true narcolepsy with cataplexy.[7]

Diagnostic Criteria

The *ICSD-2* has developed slightly different criteria for narcolepsy, depending on the presence or absence of cataplexy. These criteria take into consideration the duration of symptoms, the presence or absence of cataplectic events, and specific diagnostic modalities used to make the distinction between narcolepsy with cataplexy and narcolepsy without cataplexy (**Tables 4-3** and **4-4**).

Another issue that a clinician may face is whether to draw blood for HLA typing and/or CSF analysis for hypocretin levels. In the presence of cataplexy with a positive MSLT, these tests may not be necessary. However, they may help to confirm the diagnosis

TABLE 4-5 Pharmacologic Treatment of Excessive Daytime Sleepiness

Drug	Dosage	Common Side Effects
Stimulants		
d-Amphetamine	5–10 mg once or twice daily (morning and noon) Maximum daily dose 60 mg	Palpitations, tachycardia, elevated blood pressure, anorexia, weight loss, insomnia, psychosis (rare), potential for abuse
Methamphetamine[a]	5–10 mg once or twice daily (morning and noon) Maximum daily dose 60 mg	Same as *d*-amphetamine, more anorexigenic, very high abuse potential
Methylphenidate HCl	10–20 mg once or twice daily (morning and noon) Maximum daily dose 60 mg	Same as *d*-amphetamine, less anorexigenic, less abuse potential
Wake-Promoting Agents		
Modafinil	100–200 mg once or twice daily (morning and noon) Maximum daily dose 400 mg, although 600 mg has been used	Headache, nausea, insomnia
Armodafinil	150–250 mg once or twice daily	Similar to modafinil
Other		
Sodium oxybate[b]	Starting dose 1.5 g taken at bedtime and again 2–4 hours after sleep onset Usual effective dose 4.5–6 g per night Maximum daily dose 9 g	Headache, nausea, dizziness, enuresis, worsened sleep-disordered breathing

[a] Methamphetamine is not approved by the US Food and Drug Administration (FDA) for narcolepsy.
[b] Sodium oxybate is also FDA-approved for treatment of cataplexy.

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in the presence of equivocal MSLT results.

Treatment

Excessive daytime sleepiness. Stimulants have been the mainstay of treatment, but with the advent of wake-promoting agents and the availability of sodium oxybate, additional treatment options are now available for the treatment of EDS (**Table 4-5**).

Stimulants. Various amphetamines (eg, *d*-amphetamine, methamphetamine) and methylphenidate are included in this class of medications that have been used for the treatment of EDS. Pemoline was taken off the market by the US Food and Drug Administration (FDA) because of its association with idiosyncratic liver failure leading either to transplantation or death and therefore will not be discussed here.

The initial reports of amphetamine use for the treatment of EDS dates back to 1935, when nine patients with narcolepsy were treated with Benzedrine.[5] Amphetamines, therefore, were the principal agents used for the treatment of the symptom of EDS associated with narcolepsy. Amphetamines alleviate sleepiness by blocking dopamine reuptake at the nerve terminal and reversing its transporter action at the synaptic cleft. Amphetamines also facilitate the free cytosolic movement of dopamine contained in storage vesicles and its release in the synaptic region by interacting with the vesicular monoamine transporter 2. Additionally, at higher doses, these compounds prevent degradation of the catecholamines by acting as an inhibitor of monoamine oxidase.[10] Divided doses of up to 60 mg of *d*-amphetamine are given on waking up and at noon. Methamphetamine shares a mechanism of action similar to all amphetamines, as does methylphenidate, except that methylphenidate has a weak binding effect on the serotonin transporter.[20] The first accounts of methylphenidate usage at doses up to 300 mg in treating EDS in patients with narcolepsy date back to 1959.

Wake-promoting agents. Modafinil is a nonamphetamine wake-promoting agent whose mechanism of action is not yet fully elucidated. However, it is thought to not only increase the release of monoamines, such as norepinephrine and dopamine, but also elevate hypothalamic histamine levels. Wake-promoting agents have become the favored medication and are the first-line agents for treating EDS in narcolepsy,[21] and modafinil may be used at up to 400 mg in divided doses. Armodafinil is an active enantiomer of the racemic drug modafinil and has the same indications for use as modafinil. However, it has a considerably longer half-life and a longer wake-promoting effect than modafinil.[22] It was approved by the FDA for treating EDS in narcolepsy in June 2007. The dose is either 150 mg or 250 mg given daily in the morning.

The use of γ-hydroxybutyrate, also known as sodium oxybate, for treatment of narcolepsy dates back to 1979. γ-Hydroxybutyrate became infamous as the ''date rape drug'' and subsequently went into medical oblivion. A renewed interest in sodium oxybate led to well-designed randomized double-blind studies comparing different doses of sodium oxybate to placebo in the treatment of EDS, cataplexy, and overall sleep efficiency.[23] Although its exact mechanism of action remains unclear, it is known that sodium oxybate is naturally occurring and has its own receptors as well as an affinity for activating γ-aminobutyric acid B receptors.[10] Its efficacy for daytime alertness in combination with modafinil is superior to either drug taken alone.[21] Sodium oxybate consolidates

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and counters sleep fragmentation seen in patients with narcolepsy by significantly increasing slow-wave sleep. It is available as a liquid formulation and prescribed to be taken at bedtime and about 2 to 4 hours later. The patients set an alarm and take the medication 2 to 4 hours after bedtime. Based on the dosing studies, the recommended starting dose is 3 g in divided doses to a maximum of 9 g a night.

Cataplexy. Treatment is directed toward prevention of the occurrence of muscle atonia and thereby preventing falls and injuries. Various medications were tried with this goal in mind, and the first observed improvement in treatment of cataplectic events dates back to 1960 with imipramine. This paved the way for other tricyclic antidepressants to become the drugs of choice for treating cataplexy. Subsequently, other agents that alter the metabolism of norepinephrine, namely the selective serotonin reuptake inhibitors (SSRIs) and the selective serotonin norepinephrine uptake inhibitors, were investigated. **Table 4-6** lists the medications that are prescribed for the treatment of cataplexy along with their doses and notable side effects. Currently, none of these medications is FDA-approved for the treatment of cataplexy.[10]

Tricyclic antidepressants. This was the first class of medications available for the treatment of cataplexy, and imipramine was the first drug used for this purpose. Protriptyline and clomipramine are probably the most widely used drugs from this class and share the common mechanism of action of blocking norepinephrine reuptake to improve cataplexy.[10] Although these medications belong to the class of antidepressants, the doses needed to treat cataplexy effectively are well below those used for the treatment of depression, with anticholinergic side effects remaining the same.

Selective serotonin reuptake inhibitors. The most commonly prescribed medication from this class is fluoxetine. It is inferior in efficacy to the

TABLE 4-6 Medications Used in the Treatment of Cataplexy

Drug	Dosage	Common Side Effects
Tricyclic		
Imipramine	Start with 10–25 mg given at bedtime Maximum effective dose 125–150 mg	Dry mouth, constipation, drowsiness
Protriptyline	Start with 5–10 mg given at bedtime Maximum effective dose 60 mg	Same as imipramine
Clomipramine	Start with 10–25 mg given at bedtime Maximum effective dose 10–150 mg	Same as imipramine
Selective serotonin reuptake inhibitor		
Fluoxetine	Start with 10–20 mg in the morning Maximum dose 60 mg	Nausea, insomnia, diarrhea
Fluvoxamine	Start with 25–50 mg in the morning Can be given in divided doses (morning/lunch) to a maximum of 300 mg	Nausea, diarrhea, headache
Serotonin-norepinephrine reuptake inhibitor		
Venlafaxine	Start with 75 mg in the morning Can be given in divided doses (morning/lunch) to a maximum of 375 mg	Nausea, constipation, somnolence, dry mouth, dizziness

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tricyclics in its anticataplectic effect largely because of the affinity of the SSRIs toward the serotonin pathway.[10] Therefore, higher doses of the SSRIs are usually required to see similar therapeutic effects.

Selective serotonin norepinephrine uptake inhibitors. The most frequently used medication in this class is venlafaxine, which is effective in doses lower than those used to treat depression. Venlafaxine along with modafinil and sodium oxybate are the most used and continued medications for treatment of narcolepsy and cataplexy when compared to stimulants and TCAs, as well as SSRIs, which are tried but rarely continued.

Management Considerations

Management is symptomatic rather than curative. Although various medications treat the individual symptoms, sodium oxybate is favored over the others because of its effectiveness in treating the primary symptoms, including EDS and REM-related atonia (cataplexy), simultaneously. If EDS persists, the addition of a wake-promoting agent or stimulant is advisable. In narcolepsy without cataplexy, either a wake-promoting agent or a stimulant, or even sodium oxybate, may be tried as first-line therapy. To help the treating physician make therapeutic choices, practice parameters have been published by the American Academy of Sleep Medicine.[24] Treatment directed specifically for associated disorders (such as REM sleep behavior disorder, sleep-disordered breathing, and PLMS) should be used.

Future Directions

Since antihistamine agents cause drowsiness, various manipulations of the histamine receptor have been attempted in order to develop therapeutic targets for the treatment of EDS. Stimulation of postsynaptic H1 receptors has been shown to increase wakefulness, and animal studies have demonstrated enhanced histaminergic neurotransmission as well as stimulation of the H1 receptors postsynaptically with H3 autoreceptor inverse agonists and antagonists.[25] With the current understanding of the hypocretin/orexin pathway in regulating wakefulness, and knowledge regarding the association of narcolepsy in patients with low or undetectable hypocretin levels and hypocretin cell destruction, it is intuitive that hypocretin replacement therapy would be the most rational approach for treatment of narcolepsy. This has been tried, with encouraging results, in animal studies with central administration of hypocretin-1.[26] An intranasal hypocretin delivery method has also been tried. Gene therapy and cell transplantation have been investigated as therapeutic options in animal models. Additionally, in their review of the orexin receptors, Scammell and Winrow[27] have suggested the possibility of developing orexin receptor agonists that may promote wakefulness in narcolepsy patients with EDS. Since more and more evidence indicates an immune-mediated death of the hypocretin-secreting neurons in the development of narcolepsy, focus has shifted to immunotherapy, although without much success. Plasma exchange, immunoglobulins, and steroids have been tried with no clear benefits.

IDIOPATHIC HYPERSOMNIA

Introduction

Idiopathic hypersomnia (IH) was first described in the 1950s by Roth to distinguish patients with EDS who were not narcoleptics.[28] It has an unknown etiology and is typified by symptoms of nonrefreshing sleep with difficulty waking up, which could either be in the morning or after a nap. IH continues to be a poorly understood entity, and a diagnosis of IH is made only after other causes of EDS have been excluded. It is

KEY POINTS

- Various medications treat the individual symptoms of narcolepsy with cataplexy, but sodium oxybate is favored over the others because of its effectiveness in treating the primary symptoms, including excessive daytime sleepiness and REM-related atonia (cataplexy), simultaneously.
- Idiopathic hypersomnia has an unknown etiology and is typified by symptoms of nonrefreshing sleep with difficulty waking up, which could either be in the morning or after a nap.

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therefore a diagnosis of exclusion and must be made with caution.

Epidemiology

Since IH is a poorly understood entity, the precise prevalence of this disorder remains unknown. Patients with narcolepsy outnumber patients with IH by a ratio of 10:1 based on a general survey of sleep clinics, with both sexes being equally affected.[29] A familial predisposition has been noted with symptoms typically starting in the teenage years or as a young adult. CSF hypocretin levels are normal, and an HLA association is inconclusive.[30]

Clinical Manifestations

The cardinal manifestation of IH is EDS despite a normal total sleep time and an absence of sleep-disordered breathing and normal sleep architecture in an overnight sleep study. Clinically, patients report difficulty waking up in the morning, feel sleepy during the day, and typically want to return to sleep. Naps are not refreshing, even if they last a few hours. Sleep inertia or a feeling of grogginess and an inability to perform mental or physical tasks immediately upon waking up is commonly encountered but is not pathognomonic of IH and therefore not considered as part of the diagnostic criteria. Inappropriate sleep intrusion is commonly seen. This can be disturbing and also dangerous. Patients also frequently show a depressed mood, but the diagnostic criteria for mood disorder as laid out in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* for mood disorder must not be met.[29] **Case 4-2** describes a typical presentation.

Pathophysiology

The cause of IH is speculative, as little is known of its pathophysiology. Abnormal melatonin secretion and a circadian dysfunction have been postulated. Aberrant homeostatic sleep drive has also been suggested based on the finding of a lesser quantity of slow-wave sleep in these patients. Additionally, an association with the hypocretin/orexin system and hypothalamic dysfunction has been proposed, but evidence in this regard is lacking.

Case 4-2

A 22-year-old woman presented to the sleep clinic with abrupt-onset sleepiness following a week of flulike symptoms. She had an unremarkable medical and psychiatric history and was employed as a cashier in a local bank. Three months before her presentation, her total sleep time was about 9 to 11 hours per night and she took no daytime naps. Meticulous history elucidated no cataplectic events. Routine laboratory and imaging studies were normal. An overnight polysomnogram showed a prolonged sleep time of more than 10 hours. The multiple sleep latency test showed a mean sleep-onset latency of 0.6 minutes and no sleep-onset REM period on any of the five naps. Human leukocyte antigen typing was negative for HLA-DQB1*0602; CSF hypocretin level was not checked. After ruling out medication or substance abuse, a diagnosis of idiopathic hypersomnia (IH) was made. Wake-promoting agents were started, and the patient responded well to therapy.

Comment. IH is one of the most baffling conditions encountered by the sleep physician. As the name suggests, the cause is unknown, and at this time IH tends to be a catch-all diagnosis after other causes of hypersomnia have been effectively ruled out. Treatment is symptomatic with stimulants and wake-promoting agents.

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TABLE 4-7 ***International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*** **Diagnostic Criteria for Idiopathic Hypersomnia With Long Sleep Time**[a]

A. Almost daily excessive daytime sleepiness occurring for at least 3 months.

B. Documented prolonged nocturnal sleep of at least 10 hours with laborious morning or end-of-nap arousals.

C. Nocturnal polysomnogram (PSG) excludes other causes of daytime sleepiness.

D. PSG documents a short sleep latency and a prolonged sleep period of greater than 10 hours.

E. A multiple sleep latency test performed after the overnight PSG will show a mean sleep latency of less than 8 minutes and fewer than two sleep-onset REM episodes.

F. The condition is not explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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Diagnosis

The diagnostic criteria as laid out by the *ICSD-2* are presented in **Table 4-7** and **Table 4-8**. Subjective sleepiness is estimated using the Epworth Sleepiness Scale and objectified with the MSLT. To help differentiate circadian rhythm disorder, actigraphy and sleep diaries are powerful tools to document the sleep-wake schedule.[31]

Differential Diagnosis

Other causes of hypersomnia (**Table 4-1**) need to be meticulously considered and excluded before a diagnosis of IH can be made.

TABLE 4-8 ***International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*** **Diagnostic Criteria for Idiopathic Hypersomnia Without Long Sleep Time**[a]

A. Almost daily excessive daytime sleepiness occurring for at least 3 months.

B. Normal nocturnal sleep of at least 6 hours and less than 10 hours with laborious morning or end-of-nap arousals.

C. Nocturnal polysomnogram (PSG) excludes other causes of daytime sleepiness.

D. PSG documents a normal sleep period of greater than 6 hours but less than 10 hours.

E. A multiple sleep latency test performed after the overnight PSG will show a mean sleep latency of less than 8 minutes and fewer than two sleep-onset REM episodes.

F. The condition is not explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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KEY POINTS

- Naps are usually not refreshing in patients with idiopathic hypersomnia, in contrast to patients with narcolepsy, who find scheduled naps very rewarding.
- Kleine-Levin syndrome consists of symptoms of hyperphagia, hypersomnia, and hypersexuality.
- Kleine-Levin syndrome is a clinical diagnosis, and the investigations are done merely to rule out other causes of hypersomnia.

Treatment

It is advisable to try behavioral interventions even if they are of unclear value in treatment of IH. Issues pertaining to sleep hygiene need to be emphasized, including planning or taking naps if possible. Naps, however, are usually not refreshing in patients with IH, in contrast to patients with narcolepsy, who find scheduled naps very rewarding. Increasing the total time spent in bed is also not useful and should not be recommended. Approach to pharmacologic treatment is similar to that of narcolepsy. Stimulants and wake-promoting agents are the mainstay of treatment. Treatment with melatonin as well as levothyroxine has also been tried with some success.[32] Antidepressants have no role in the treatment of IH.

RECURRENT HYPERSOMNIA

Kleine-Levin Syndrome

Introduction. Kleine-Levin syndrome (KLS) is a classic, but rare, cause of recurrent hypersomnia. The eponym was coined by Critchley and Hoffman in 1942, recognizing the work of Kleine and Levin, who reported the first patients in Germany and New York, respectively.[33] The syndrome consists of symptoms of hyperphagia, hypersomnia, and hypersexuality. **Case 4-3** outlines the typical presentation of this condition.

Epidemiology. KLS is a rare cause of hypersomnia, with an estimated prevalence of 1 in 1 million. Although the peak age at initial presentation is usually in the second decade of life, patients 4 years old and 80 years old have been reported in the literature. KLS is more common in men, who outnumber women by a ratio of 2:1. A disproportionately large number of cases are found in the Ashkenazi Jewish population compared to patients of other ethnicities. No clear association has been demonstrated to suggest an inheritable trait or genetic susceptibility for the development of KLS, although one-third of patients with KLS report associated birth or developmental issues.[34,35] Familial cases have also been reported, but these are rare.

Clinical presentation. The initial episode in KLS is frequently preceded by a precipitating factor in 9 of 10

Case 4-3

A 23-year-old man experienced multiple episodes, each lasting a few days, of hypersomnolence, binge eating, and excessive and inappropriate sexual arousal occurring intermittently during the past 2 years. During these episodes he was sleeping 18 to 20 hours a day. When awake, he would go on an eating binge or report inappropriate sexual arousals. These episodes would last days to weeks and be followed by spontaneous and complete resolution of symptoms. He did not report any prodromal symptoms and often had partial amnesia for his behavior during these episodes. During one of these episodes he had an overnight polysomnogram which showed increased sleep time but was otherwise normal. Other laboratory and imaging studies were also normal.

Comment. Kleine-Levin syndrome is a clinical diagnosis, and the investigations are done merely to rule out other causes of hypersomnia. As in this case, a history of recurrent episodes of excessive daytime sleepiness with binge eating and hypersexuality are key features of Kleine-Levin syndrome. Various medications have been tried to treat this condition, but none has been consistently effective.

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patients. Infection or high fever is the most common complaint. Stress, alcohol use, travel, and sleep deprivation have also been reported to precipitate symptoms of this syndrome. Less than 15% of patients can identify a prodromal event to account for recurrent episodes. Clinically, patients report periods of excessive sleepiness that may last 2 days to 4 weeks with recurrence of symptoms at least once per year. Patients typically have normal cognitive functioning with normal alertness between episodes. EDS is explained by no other medical, neurologic, sleep, or psychiatric disorder, nor by substance abuse or medication use. Few symptoms differ between the sexes, although men present with significantly more symptoms of hypersexuality than women. During an active episode, the sleep needs increase drastically, with patients sleeping in excess of 12 hours over a 24-hour period. Most episodes resolve spontaneously within a 30-day period, and the interepisode hiatus almost never surpasses 15 months. The recurrence of episodes becomes less frequent, less severe, and shorter in duration as time passes. Persistent remissions have been reported in patients when the disease started before adulthood and when hypersexuality was not present.[34,35]

Diagnosis. The diagnostic criteria are outlined in the *ICSD-2* with an emphasis on the recurrence of the disorder (**Table 4-9**).

Polysomnogram. Studies evaluating PSGs done during and between episodes of hypersomnia show a tremendous amount of discrepancy when the results are compared. Therefore, no clear and beneficial conclusions can be drawn. Sleep study evaluation done by Huang and colleagues showed no differences between PSG done during and between episodes. However, when the results were divided into the start and end of episodes and analyzed separately, slow-wave sleep increased and REM sleep decreased significantly during the later half.[36] MSLT performed in patients with KLS has also shown inconsistent results and is therefore not used as a diagnostic criterion, emphasizing the point that KLS is a clinical diagnosis.

Imaging studies. CT and MRI scans have always been normal in patients with idiopathic KLS.[33] SPECT, however, has demonstrated a reduced perfusion of the thalamus during an active KLS episode that eventually reversed to normal as the symptoms resolved. This was the most reliable finding, present in all subjects investigated.[37]

KEY POINTS

- Most episodes of Kleine-Levin syndrome resolve spontaneously within a 30-day period, and the interepisode hiatus almost never surpasses 15 months.
- SPECT has demonstrated a reduced perfusion of the thalamus during an active Kleine-Levin syndrome episode that eventually reversed to normal as the symptoms resolved.

TABLE 4-9 ***International Classification of Sleep Disorders, Second Edition: Diagnostic and Coding Manual*** **Diagnostic Criteria for Recurrent Hypersomnia (Kleine-Levin Syndrome and Menstrual-Related)[a]**

A. Recurrent episodes of excessive sleepiness last 2 days to 4 weeks.

B. The episodes recur at least once a year.

C. The patient has normal alertness, cognitive functioning, and mental status between attacks.

D. The hypersomnia is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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KEY POINT

- Women with menstrual-related hypersomnia experience episodes of recurrent sleepiness coinciding with their menstrual cycles.

CSF analysis. One study demonstrated a decrease in the CSF hypocretin level during a KLS episode when compared with the baseline during an asymptomatic period and suggested a hypothalamic dysfunction that is intermittent.[38] It is not clear whether this decline in CSF hypocretin occurs as a cause or an effect of a KLS episode, or even whether it occurs consistently.

Pathology. Because KLS is a rare disorder, brain tissue analysis is uncommon. No specific abnormalities of the hypothalamus have been demonstrated, however.[39]

Treatment. Various treatments have been tried in patients with KLS. Only a limited number of patients have demonstrated a major response to treatment with valproic acid, lithium, amantadine, or lamotrigine.[35,40–42] Modafinil has been tried and showed a decrease in the duration of the episodes but had no effect on recurrence. Since the condition is intermittent, the clinician has to be careful before reporting a certain treatment option successful, as it may in reality only coincide with the end of an episode.

MENSTRUAL-RELATED HYPERSOMNIA

Menstrual-related hypersomnia is a very rare condition. Women with this disorder experience episodes of recurrent sleepiness coinciding with their menstrual cycles. A diagnostic criterion, similar to one recommended for KLS, has been put forth in the *ICSD-2* (**Table 4-9**). A review by Billiard and colleagues[43] compared occurrence of this disorder with other forms of recurrent hypersomnias, such as KLS, in women and found that the onset of hypersomnia may occur at menarche, during menstruation alone, or during menstruation in conjunction with other factors such as alcohol use or a bout of influenza. This review also noted the association of depression in up to one-third of women with menstrual-related hypersomnia. No familial cases of this disorder have been identified. Some case reports indicate that treatment with oral contraceptives may be effective. It is suggested that the episodes of hypersomnia are triggered by progesterone, and the instigation of anovulatory cycles with oral contraceptive treatment causes an inhibitory effect on progesterone secretion, resulting in resolution of symptoms. However, this concept is purely hypothetic with no conclusive evidence supporting or refuting it.

In addition to the primary hypersomnias described above, other causes of hypersomnia as classified by the *ICSD-2* are briefly discussed below.

BEHAVIORALLY INDUCED INSUFFICIENT SLEEP SYNDROME

Classified under the category of hypersomnia of central origin, this cause of hypersomnia occurs as a result of sleep deprivation and is most commonly seen among adolescents. It usually does not need intense investigation because the history of sleep deprivation and of patients catching up on their sleep on weekends makes the diagnosis obvious. If a sleep study is done, it will show a short sleep-onset latency and high sleep efficiency and may occasionally also reveal a SOREMP. Sleep deprivation may be a result of social or work-related factors, and patients may report neurocognitive impairment as a result of insufficient sleep time. Stimulant medications are not recommended, since behavioral modifications are sufficient to treat this condition.

HYPERSOMNIA DUE TO OTHER CAUSES

Metabolic syndromes, toxic or infectious disease processes, and drugs may cause hypersomnia by depressing CNS alerting centers. Traumatic brain injury

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(TBI) and neurodegenerative processes that directly affect the CNS are also known to cause hypersomnia. When evaluating a patient with hypersomnia, the history of medical conditions, such as Niemann-Pick type C disease, Prader-Willi syndrome, myotonic dystrophy, Parkinson disease, cervical spine or whiplash injury, and TBI, should either be specifically asked for or investigated, as deemed necessary. Posttraumatic hypersomnia is prevalent and often missed as a cause of unexplained hypersomnia. Other causes include multiple sclerosis, vascular disorders, and encephalitis. Patients with EDS and symptoms of neuromyelitis optica who are positive for anti–aquaporin 4 antibody (AQP4) have also been reported, suggesting an immunologic attack to AQP4 resulting in damage to hypocretin-secreting neurons and the development of secondary narcolepsy. Reports of moderately decreased hypocretin levels in patients with secondary narcolepsy exist in the literature. There are also reports of improvement in symptoms of hypersomnia in secondary narcolepsy with improvement in the causative neurologic disorder and concomitant improvement in hypocretin levels. In addition to medical causes, a complete list of all current medications should be reviewed, since a simple measure of discontinuing a medication known to cause hypersomnia may be sufficient to treat the patient effectively. The use of over-the-counter medication and illicit drug use must be elicited. When the cause of hypersomnia cannot be explained on the basis of an underlying medical condition, medication, or drug use, the possibility of a psychiatric disorder should be considered and investigated.

VIDEO LEGENDS

Supplemental Digital Content 4-1

Adult cataplexy. Video demonstrates cataplexy elicited by the strong emotional stimulus of conducting an orchestra. The patient becomes excited, has loss of muscle tone with unbuckling of the knees, and falls to the ground. Consciousness is preserved completely, and he never loses awareness. He recovers quickly, regaining his muscle strength and standing up as if he never experienced the episode.

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Supplemental Digital Content 4-2

REM sleep behavior disorder in a child. Video demonstrates REM sleep behavior disorder (RBD) in a child. RBD in children is narcolepsy unless proven otherwise. Although the electrographic recordings are blurry, the video shows the patient exhibiting dream enactment behavior with loss of muscle tone during REM sleep. Patients with RBD require in-depth review and assessment for CNS hypersomnia, which is also a manifestation of anomalous REM sleep control.

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Supplemental Digital Content 4-3

Child cataplexy. Video demonstrates laughter-induced cataplexy in a child. This child has the hypocretin gene defect leading to narcolepsy with cataplexy. He is dancing and playing, and children are laughing in the background, which leads him to become excited and lose muscle tone in the legs. While the condition is exclusively genetically based in animals, it is not the case in humans, and was not the case in this patient.

links.lww.com/CONT/A18

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KEY POINT

- Posttraumatic hypersomnia is prevalent and often missed as a cause of unexplained hypersomnia.

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