Narcolepsy and Other Central Hypersomnias

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ABSTRACT

Purpose of Review: This article focuses on the clinical presentation, pathophysiology, diagnosis, differential diagnosis, and management of narcolepsy type 1 and narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, and other central disorders of hypersomnolence, as defined in the *International Classification of Sleep Disorders, Third Edition* (*ICSD-3*).

Recent Findings: In *ICSD-3*, the names of some central disorders of hypersomnolence have been changed: narcolepsy with cataplexy and narcolepsy without cataplexy have been renamed narcolepsy type 1 and narcolepsy type 2, respectively. A low level of hypocretin-1/orexin-A in the CSF is now theoretically sufficient to diagnose narcolepsy type 1, as it is a highly specific and sensitive biomarker. Conversely, other central hypersomnias are less well-defined disorders with variability in the phenotype, and few reliable biomarkers have been discovered so far. The epidemiologic observation that influenza A (H1N1) infection and vaccination are potential triggering factors of narcolepsy type 1 (discovered during the 2009 H1N1 pandemic) has increased interest in this rare disease, and progress is being made to better understand the process (highly suspected to be autoimmune) responsible for the destruction of hypocretin neurons. Treatment of narcolepsy remains largely symptomatic, usually initially with modafinil or armodafinil or with higher-potency stimulants such as methylphenidate or amphetamines. Several newer wake-promoting agents and psychostimulants have also been developed, including sodium oxybate, which has a role in the treatment of cataplexy and as an adjunctive wake-promoting agent, and pitolisant, a selective histamine H_3 receptor inverse agonist that is currently only available in Europe.

Summary: Although far less common than many other sleep disorders, central hypersomnias are among the most severe and disabling diseases in the field of sleep medicine, and their early recognition is of major importance for patients, especially children, to maximize their quality of life and functioning in activities of daily living.

Continuum (Minneap Minn) 2017;23(4):989–1004.

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Relationship Disclosure:
Dr Dauvilliers has received personal compensation for speaking engagements and travel expenses, served as consultant for, and received research/grant support from Bioprojet Pharma, Flamel Technologies, Jazz Pharmaceuticals, Theranexus, and UCB SA. Dr Dauvilliers serves as specialty chief editor of the Sleep and Chronobiology section of *Frontiers in Neurology*. Dr Barateau has received reimbursement for travel expenses from Laidet Médical and has received personal compensation as a speaker for UCB SA.

Unlabeled Use of Products/Investigational Use Disclosure:
Drs Dauvilliers and Barateau report no disclosures.

INTRODUCTION

Excessive daytime sleepiness is the most common presenting symptom of rare sleep diseases, the hypersomnia disorders of central origin. These include narcolepsy type 1 and narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, and other hypersomnias (eg, due to a medical disorder or substance or associated with psychiatric disorders). Our understanding of the pathophysiology of central hypersomnias has improved considerably over the past 2 decades because of the integration of data from human and animal models. The diagnostic workup includes medical history, sleep logs, and polysomnography, followed by the multiple sleep latency test in most patients and, in some, additional evaluation with actigraphy, human leukocyte antigen (HLA) genotyping, and CSF examination for hypocretin. The current management of hypersomnias of

KEY POINT

- Narcolepsy type 1 is a well-defined entity characterized by excessive daytime sleepiness and cataplexy, whereas narcolepsy type 2 is a syndrome of sleepiness without cataplexy and is a considerably less specific and more heterogeneous syndrome.

central origin remains symptomatic, and good evidence for treatment (Level A) currently exists only for narcolepsy. This article reviews the clinical features, pathophysiology, diagnostic criteria, and treatment options for narcolepsy and other primary hypersomnias.

NARCOLEPSY TYPE 1 AND TYPE 2

Narcolepsy is classified into two distinct disorders according to the *International Classification of Sleep Disorders, Third Edition* (*ICSD-3*): narcolepsy type 1, formerly called *narcolepsy with cataplexy*, and narcolepsy type 2.[1] Narcolepsy type 1 affects about 1 in 2000 people in the world, with a bimodal age at onset, usually between 15 and 35 years of age.[2] The prevalence of narcolepsy type 2 remains unclear, as this disorder is more heterogeneous, with an unknown pathophysiologic mechanism.[3,4]

Clinical Features

Excessive daytime sleepiness is the major and most frequent initial symptom of narcolepsy. Excessive daytime sleepiness arises preferentially in monotonous situations or during periods of relative inactivity. Typically, naps are short and considered to be refreshing by patients, who may also recall the experience of dream activity just after falling asleep. Similarly, nocturnal sleep is usually considered refreshing, and morning waking is usually not difficult. In children, the phenotype can be slightly different: naps are inconsistently refreshing, patients sometimes fight against sleepiness and do not fall sleep, and they may present with hyperactive behavioral symptoms that can mimic attention deficit hyperactivity disorder. During episodes of sleepiness, automatic activities (ie, saying something inappropriate or out of context in a conversation, writing something inappropriate or illegible, or doing an activity such as driving to an inappropriate location with no memory of the event) can be seen.

Cataplexy is the pathognomonic symptom of narcolepsy type 1, defined by a loss of muscle tone in full consciousness triggered by emotions, particularly positive ones such as laughter or surprise (**Case 3-1**).[5] Cataplexy can either be generalized and lead to falls or partial, with lower limb collapse, head dropping, or dysarthria. Muscle stretch reflexes are abolished during generalized cataplexy, since the pathophysiology of cataplexy seems mediated by an intrusion of physiologic rapid eye movement (REM) sleep atonia into wakefulness, thereby interrupting conscious voluntary motor activity and waking muscle tone. Cataplectic attacks can be different in children. Sometimes they appear without a specific triggering factor; they can also arise in anticipation of a strong emotion to come and sometimes even during movement. Children can also present with cataplectic facial expressions, such as generalized face hypotonia, abnormal movements, and tongue protrusion.[6] Clinical signs and biological markers that should make the physician reconsider the diagnosis of supposed cataplectic attacks are listed in **Table 3-1**.

Other symptoms are often associated with narcolepsy, but they are not specific to the condition. Sleep paralysis is a transient paralysis lasting a few seconds or minutes while falling asleep or upon awakening. Hypnagogic (ie, while falling asleep) and hypnopompic (ie, upon awakening) hallucinations can occur at the same time as the paralysis and can be very frightening. These symptoms are also reported in the general population but are more frequent and severe in

Case 3-1

An 18-year-old man presented with a 2-year history of severe excessive daytime sleepiness that began a few months after a vaccination for influenza A (H1N1). He had to repeat a school year because of the excessive daytime sleepiness. He was overweight and had frequent sleep paralysis and nightmares. Six months after the onset of excessive daytime sleepiness, he developed episodes of weakness in his limbs and neck triggered by various emotional stimuli, especially when he laughed with his brother. The frequency was variable, from several episodes per day to several per week, depending on exposure to the stimuli. His brother had made a cell phone video that the neurologist was able to view, which led to the diagnosis of typical cataplectic attacks.

After reviewing the patient's sleep diary to ensure he was getting adequate nocturnal sleep, polysomnography was performed, followed by a multiple sleep latency test that showed fragmented sleep with no apnea, short sleep latency (2 minutes), and four sleep-onset rapid eye movement (REM) periods, confirming a clear-cut diagnosis of narcolepsy type 1.

Human leukocyte antigen genotyping was positive for the DQB1*0602 allele, and CSF hypocretin-1 levels in the CSF were undetectable (less than 10 pg/mL).

A modafinil treatment trial was started, with the dosage gradually increased to 200 mg in the morning and 200 mg at noon. Anticataplectic treatment (venlafaxine 37.5 mg/d) was introduced a few weeks later, with excellent efficacy.

Comment. In this case, the patient's cataplectic attacks were typical, but sometimes the recognition of this pathognomonic symptom can be more difficult. Identification of cataplexy during consultation or hospitalization or video recorded by relatives helps determine if the phenotype is typical or atypical. The first-line option for excessive daytime sleepiness should be modafinil (doses from 100 mg/d to 400 mg/d). Once adequate improvement of excessive daytime sleepiness is obtained, the cataplexy severity is evaluated and treatment started, if needed. The management of excessive daytime sleepiness alone sometimes improves cataplexy. This case also illustrates the burden of narcolepsy and the impact of a delayed diagnosis on scholastic performance.

patients with narcolepsy. Nighttime sleep is altered and fragmented, with multiple nocturnal arousals and sometimes significant sleep maintenance insomnia. REM sleep behavior disorder, a parasomnia characterized by a loss of normal skeletal muscle atonia during REM sleep, has an increased frequency in narcolepsy type 1, leading to abnormal behaviors and dream enactment. An increase in weight is frequent at disease onset, especially in children (30% of all patients with narcolepsy are obese, and up to 50% of children with narcolepsy are obese). Children may also experience precocious puberty.

Narcolepsy type 1 is a chronic disease with an often stable clinical course. The severity of cataplexy and sleepiness may improve with age, whereas nighttime sleep may worsen. In contrast, the clinical course of narcolepsy type 2 remains unclear. Some patients may later develop cataplexy and be reclassified as having narcolepsy type 1; other patients with narcolepsy type 2 may have a chronic

KEY POINT

- Pathophysiologic studies have shown that narcolepsy type 1 is caused by the early loss of neurons in the hypothalamus that produce hypocretin/orexin.

TABLE 3-1 Clinical Signs and Biological Markers of Typical Cataplexy and Atypical Attacks Suggesting an Alternative Diagnosis

▶ **Typical Cataplexy**
Clinical signs
Clear positive emotional trigger (eg, laughter, telling a joke, surprise)
Frequent attacks (multiple times per day or week)
Brief duration (seconds to 1–2 minutes)
Consciousness preserved
Generalized or segmental (face, head/neck, knee dropping/buckling with or without falling)
Biological markers
Presence of HLA DQB1*0602 allele
Low hypocretin-1 levels in the CSF (<110 ng/L)
▶ **Atypical Attacks**[a]
Clinical signs
Rarity of attacks (<1/year)
Nonrecurrence despite the absence of treatment
Long lasting (>2 minutes)
Alteration of consciousness
Unilateral or asymmetric localization
Affecting only the upper limbs (not the face, neck, or lower limbs)
No association with emotional triggers (except in children)
Relatives and people nearby do not notice the episodes
Only triggered by negative stimuli and emotion (eg, anger, fear, stress)
Prodromal symptoms or occurrence of symptoms after the episode of any kind (eg, warm feeling, sweat, dizziness, tinnitus, visual and auditory impairment, nausea, tingling sensation in the extremities)
Biological markers
Absence of HLA DQB1*0602 allele
Normal hypocretin-1 levels in the CSF (>200 ng/L)

CSF = cerebrospinal fluid; HLA = human leukocyte antigen.
[a] These clinical signs and biomarkers suggest an alternative diagnosis.

stable condition. In approximately one-half of patients with narcolepsy type 2, excessive daytime sleepiness may improve spontaneously, without the persistent neurophysiologic hallmarks of narcolepsy.[7]

Pathophysiology

Narcolepsy type 1 is caused by a selective loss of a small population of neurons in the lateral hypothalamus that synthesize hypocretin neuropeptides.[8] Hypocretin-1/orexin-A and hypocretin-2/orexin-B are neurotransmitters that were discovered 20 years ago.[9,10] Several genetic animal models of the disease exist, as across species (in both mice and dogs), disrupted hypocretin signaling leads to a narcoleptic phenotype with excessive daytime sleepiness and cataplexy.[11] Recently, hypocretin neurons were shown to be particularly susceptible to influenza A (H1N1) viral infection in

mice lacking B and T cells, and hypocretin neurons were destroyed after injection of autoreactive cytotoxic $CD8^+$ T cells in transgenic mice expressing influenza virus protein hemagglutinin in the hypocretin cells.[12,13] In some cases, narcolepsy type 2 may be caused by a less extensive loss of these neurons, but this disorder is probably heterogeneous, and knowledge about its pathophysiology is still limited.

An autoimmune process probably mediates the selective destruction of hypothalamic hypocretin neurons in narcolepsy type 1. This hypothesis is supported by many epidemiologic and clinical findings: rare family cases, frequent discordance in monozygotic twins, young and bimodal age at onset, and a strong association with the 2009 H1N1 influenza pandemic and its vaccine (**Case 3-1**) and with streptococcal infections. However, no specific antibodies against hypocretin neurons have yet been discovered, possibly because of very small amounts of antibodies or due to a specific T-cell activation. Genetic background is of major importance, as more than 98% of patients with narcolepsy type 1 carry the HLA class II HLA-DQB1*0602 allele,[14] compared to only 12% to 30% of the general population. More recently, the role of HLA class I[15] and other immune gene variants, such as the purinergic receptor *P2RY11* and T-cell receptor alpha locus *TRA*, was revealed.

Hypocretin neurons are normally active during wakefulness and function to stimulate other neurons in the cerebral cortex, basal forebrain, brainstem, and hypothalamus, producing norepinephrine, dopamine, serotonin, and histamine, which allow the maintenance of wakefulness through the day.[16] Hypocretin neurons also increase activity in the lateral pontine tegmentum that suppresses REM sleep and project to brain regions that regulate metabolism, motivated behaviors such as reward seeking, and the autonomic system. In narcolepsy, the loss of hypocretin signaling results in excessive daytime sleepiness, dysregulation of REM sleep, and obesity in many patients, but with a large intervariability in symptom frequency and intensity. During cataplexy, positive emotions relayed through the amygdala and medial prefrontal cortex probably activate circuits in the dorsal pons responsible for muscle weakness in the absence of hypocretin, including the sublateral dorsal nucleus.

Diagnosis

In *ICSD-3*,[1] narcolepsy type 1 is defined as the presence of excessive daytime sleepiness for more than 3 months, associated with either (1) the presence of cataplexy, a mean sleep latency of 8 minutes or fewer on the multiple sleep latency test, and at least two sleep-onset REM periods during the multiple sleep latency test or polysomnography or (2) a hypocretin-1 level of 110 pg/mL or less in the CSF, which is a highly specific biological measure.

Narcolepsy type 2 is defined by the presence of excessive daytime sleepiness without cataplexy for longer than 3 months, with a mean sleep latency of 8 minutes or fewer on the multiple sleep latency test, at least 2 sleep-onset REM periods on the multiple sleep latency test or polysomnography, and a hypocretin-1 level of higher than 110 pg/mL, if measured. Excessive daytime sleepiness must not be better explained by another cause, such as sleep deprivation, obstructive sleep apnea syndrome, circadian rhythm disorders, or the effect of a medication or substance abuse. If cataplexy appears over time, or if a hypocretin-1 measurement of 110 pg/mL or less is found, the condition is reclassified as narcolepsy type 1.

KEY POINTS

- The etiology of narcolepsy type 1 is not yet completely understood, but an autoimmune process is highly suspected, with a role of genetic (human leukocyte antigen DQB1*0602 allele) and environmental (influenza A vaccination) factors.
- Narcolepsy type 1 is associated with a wide range of sleep abnormalities and metabolic, cardiovascular, autonomic, and psychiatric consequences, in which the direct role of the hypocretin system remains to be defined.

KEY POINT

- Treatment of narcolepsy is symptomatic and focuses on improving sleepiness and cataplexy.

Narcolepsy type 1 is a chronic disease requiring lifelong treatment, as the destruction of hypocretin neurons is irreversible. On the other hand, narcolepsy type 2 has a variable phenotype and evolution, with improvement or even disappearance of the symptoms, the development of cataplexy, or a change in the phenotype to idiopathic hypersomnia (refer to the section on clinical features of idiopathic hypersomnia).

Treatment Options

Narcolepsy treatment is symptomatic and varies from a single drug targeting several symptoms to multiple drugs to address different symptoms.[17] Recent clinical trials and practice guidelines have confirmed that stimulants such as modafinil, armodafinil, or sodium oxybate (as first line); methylphenidate and pitolisant (as second line [pitolisant is currently only available in Europe]); and amphetamines (as third line) are appropriate medications for excessive daytime sleepiness.[17] Women of childbearing potential receiving modafinil or armodafinil should be forewarned about the potential for reduced efficacy of hormonal contraceptives while receiving these drugs, which induce hepatic cytochrome systems and reduce serum concentrations of estrogenic drugs, possibly leading to increased risk of contraceptive failure and unintended pregnancy. Use of barrier contraceptives, increased dose of hormonal contraceptives, or an alternative noninducing psychostimulant such as methylphenidate should be considered. Typical psychostimulant adverse effects include tremor, palpitations, and jitteriness. Patients receiving psychostimulants should also be instructed to carefully monitor their blood pressure to avoid the development of hypertension, and those receiving methylphenidate or amphetamines should have ECG monitoring to evaluate for QTc prolongation when target dosages are reached.

Sodium oxybate is the only medication approved for both sleepiness and cataplexy in adults. Specific anticataplectic treatment should depend on the severity of this symptom, as mild cataplexy frequently improves with increased alertness following the initiation of wake-promoting therapies. Antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs]) are commonly used for cataplexy based on expert consensus since no controlled trial evidence exists for this use. An algorithm for the management of the main symptoms of narcolepsy type 1 is presented in **Figure 3-1**. A list of common comorbidities and signs associated with narcolepsy type 1 and strategies for managing them are presented in **Table 3-2**.

Medications and guidelines for excessive daytime sleepiness in narcolepsy type 2 should be the same as for narcolepsy type 1. However, the treatment and phenotype should be regularly reassessed because of the variability of the narcolepsy type 2 phenotype and the possible evolution toward a normal condition.

Good sleep hygiene is also recommended, including avoiding sleep deprivation, maintaining a regular nighttime sleep schedule, and scheduling short naps. As most of the symptoms in narcolepsy type 1 are directly explained by hypocretin deficiency, hypocretin replacement could be an ideal specific therapy for narcolepsy type 1, but the development of a clinical formulation is limited by the impermeability of the blood-brain barrier to this large neuropeptide. Immune-based therapies, administered very close to disease onset, could modify the natural history and the clinical course of the disease, although

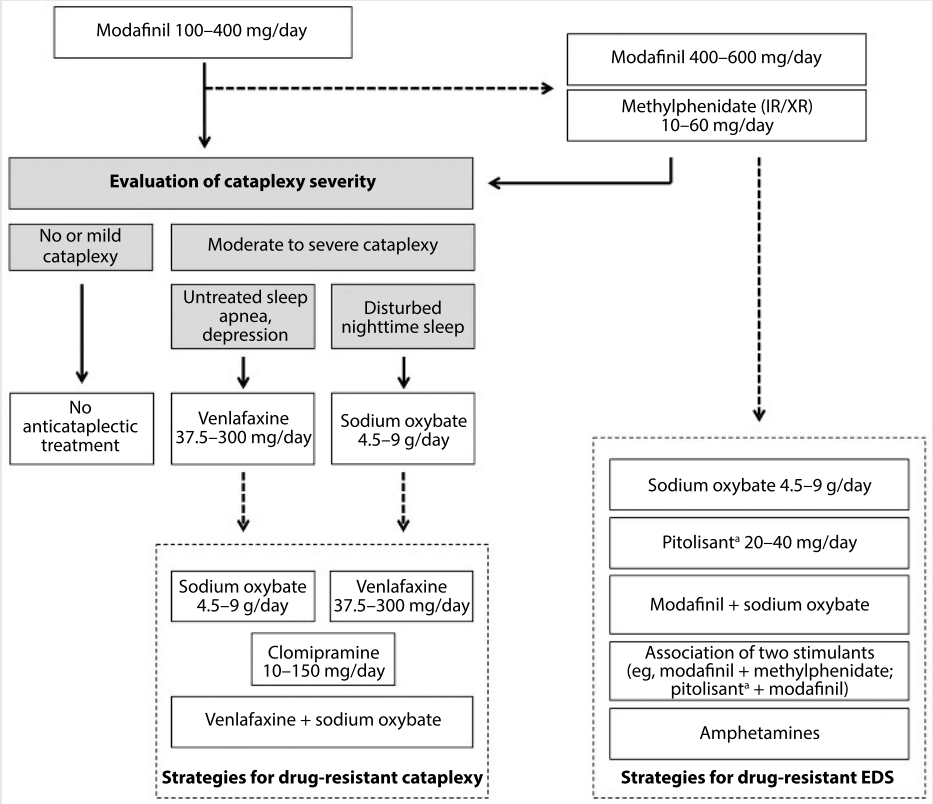

FIGURE 3-1 Decision tree for managing excessive daytime sleepiness and cataplexy in narcolepsy type 1.

EDS = excessive daytime sleepiness; IR = immediate release; XR = extended release.

[a] Pitolisant is currently only available in European Union countries.

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TABLE 3-2 Management of Symptoms and Comorbidities in Narcolepsy Type 1[a]

Symptoms and Comorbidities	Management Strategies
Disturbed nighttime sleep	Sodium oxybate; regular sleep-wake schedule; avoid long naps late in the day; avoid psychostimulant intake during the afternoon; hypnotic medications may be considered
Sleep paralysis/hypnagogic and hypnopompic hallucinations	Sodium oxybate, antidepressants (eg, venlafaxine, fluoxetine); provide information, education, and reassurance
Unpleasant dreams/ recurrent nightmares	Antidepressants; cognitive-behavioral therapy

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TABLE 3-2 **Management of Symptoms and Comorbidities in Narcolepsy Type 1**[a] *Continued from page 995*

Symptoms and Comorbidities	Management Strategies
Neuropsychiatric disorders	
Mood disorders/ anxiety disorders	Antidepressants; psychotherapy; avoid sodium oxybate if possible
Psychotic symptoms	Consider antipsychotic drugs such as aripiprazole; use psychostimulants with caution (except pitolisant[b], which is a new psychostimulant without dopaminergic activity, thus without any deleterious impact suspected on positive psychotic symptoms)
Attention deficit hyperactivity disorder	Methylphenidate; psychotherapy
Cardiovascular and metabolic disorders	
Overweight/obesity	Sodium oxybate, most psychostimulants; dietary measures and exercise; avoid tricyclic antidepressants; prescribe antidepressants at minimal doses
Type 2 diabetes mellitus	Sodium oxybate, most psychostimulants; dietary measures and exercise; avoid tricyclic antidepressants; prescribe antidepressants at minimal doses
Obstructive sleep apnea syndrome	Continuous positive airway pressure; loss of weight; use sodium oxybate with caution[c]
Cardiovascular diseases (eg, cardiac rhythm abnormalities, palpitations)	Use all psychostimulants with caution (except pitolisant[b], which is a good alternative in case of cardiovascular disorder)
Other sleep disorders	
Rapid eye movement (REM) sleep behavior disorder (RBD)	Melatonin, clonazepam, possibly sodium oxybate (if already indicated for cataplexy or excessive daytime sleepiness symptoms); antidepressants can worsen RBD and should be avoided or given at minimal doses if RBD is severe
Non-REM–related parasomnias (eg, sleepwalking, sleep terrors, enuresis)	Clonazepam; avoid sodium oxybate when possible
Restless legs syndrome (RLS), periodic leg movements	Sodium oxybate and antidepressants may worsen RLS and periodic leg movements and should be avoided or given at minimal doses if RLS is severe; check ferritin/transferrin saturation percentage to exclude iron deficiency; sometimes specific treatment of RLS is required

[a] Managing excessive daytime sleepiness and cataplexy should be a clinician's priority because they are often the most severe and disabling symptoms. This table provides management strategies for other symptoms and comorbidities usually associated with narcolepsy type 1. The medications used for excessive daytime sleepiness and cataplexy can improve some of those comorbidities, but the same medications can also worsen others. In these conditions, the drugs are not necessarily contraindicated, but should be used with caution, at minimal doses if required, and benefit-risk balance should be well assessed.

[b] Pitolisant is currently only available in European Union countries.

[c] Note that sodium oxybate has a sedative effect along with a theoretic risk of hypoventilation, but can also reduce weight and thus improve obstructive sleep apnea syndrome.

no current evidence exists to guide such an approach, and future controlled trials will be necessary to determine if immunomodulatory approaches could impact the natural history or clinical symptom burden in narcolepsy. Other new psychostimulants are expected to emerge within the next few years: JZP-110 (a phenylalanine derivative with dopaminergic and noradrenergic activity), longer-acting formulations of sodium oxybate, and a combination of modafinil with connexin inhibitors are currently in development.

A recent valid, reliable, and informative narcolepsy-specific instrument referred to as the Narcolepsy Severity Scale was developed to monitor symptom severity and changes after treatment.[18] Physicians can use this brief scale to assess narcolepsy type 1 symptom frequency, severity, and consequences; to detect changes in symptoms after treatment; and to provide guidance on whether treatment goals are met.

Clinical evidence shows that medications approved for adults are also effective in children,[19] but specific guidelines are still lacking. Several multicenter clinical trials are currently ongoing in the pediatric narcolepsy type 1 population.

All patients with narcolepsy and central hypersomnias with uncontrolled sleepiness should be warned about the possible risks of driving while impaired and instructed not to drive when drowsy. Sleepiness and vigilance under medication can be objectively measured with the maintenance of wakefulness test, which may be important in assessing the capacity to drive. In some cases, medical restriction of driving privileges may need to be considered, depending on the severity of excessive daytime sleepiness symptoms and previous reported history of near misses or motor vehicle collisions. For more information, refer to the article "Driving Safety and Fitness to Drive in Sleep Disorders" by Jon Tippin, MD, FAAN, FAASM, and Mark Eric Dyken, MD, FAHA, FAASM, FANA,[20] in this issue of *Continuum*.

IDIOPATHIC HYPERSOMNIA

Idiopathic hypersomnia is another rare central hypersomnia that has been identified more recently than narcolepsy type 1 and is probably even more rare, although no epidemiologic studies are available to date. The sex ratio seems to be in favor of women, and the age at onset of the disease is often after puberty but under 30 years old.[21]

Clinical Features

Two idiopathic hypersomnia phenotypes have been described, one with prolonged nighttime sleep and the other without long nighttime sleep.[22,23] A pervasive excessive daytime sleepiness characterizes the first form, with a prolonged nocturnal sleep duration of more than 10 or 11 hours and good-quality nighttime sleep with few arousals. It is associated with difficulties in waking up in the morning, a symptom known as sleep inertia and defined by reduced vigilance during the minutes or hours following arousal in the morning or from daytime naps. Patients describe an excessive time to be fully operational and sometimes describe mental confusion.[24] Daytime naps are typically long, lasting up to several hours, and unrefreshing in quality. In the form of idiopathic hypersomnia called *idiopathic hypersomnia without long sleep time*, the nighttime sleep is of normal quantity and quality (more than 6 hours and fewer than 10 hours), without sleep inertia, and sleep during the daytime is short and refreshing. These two phenotypes of idiopathic hypersomnia sometimes overlap and are pooled as one

KEY POINTS

- All patients with narcolepsy and central hypersomnias with uncontrolled sleepiness should be warned about the possible risks of driving while impaired and instructed not to drive when drowsy.
- Idiopathic hypersomnia is another rare central hypersomnia that has been identified more recently than narcolepsy type 1 and is probably even more rare.

KEY POINT

■ The etiology of idiopathic hypersomnia is still unknown, but homeostatic and circadian disturbances and a deficient arousal system have been suggested.

diagnosis in *ICSD-3*. Hypnagogic hallucinations and sleep paralysis are rare in idiopathic hypersomnia, and the workup must exclude the presence of cataplexy.

Idiopathic hypersomnia is a disorder with frequent phenotype variation, and a continuum may exist between the forms with and without long sleep time and narcolepsy type 2. Indeed, the presence of one sleep-onset REM period is the only different diagnostic criterion between narcolepsy type 2 and idiopathic hypersomnia, and this electrophysiologic biomarker is unstable and sometimes not reproducible. The symptoms of idiopathic hypersomnia can be severe and chronic, but it is also important to inform patients that idiopathic hypersomnia symptoms disappear over time in up to 50% of patients. Clinicians must regularly reevaluate the presence and severity of symptoms, the diagnosis, and management (**Case 3-2**).

Pathophysiology

Idiopathic hypersomnia is probably a heterogeneous disease, and this could explain why its physiopathology remains largely unknown. No biomarker specific to idiopathic hypersomnia has yet been identified. A circadian or homeostatic dysregulation or a disturbance in brain arousal systems is suspected. A dysfunction of the γ-aminobutyric acid–mediated (GABAergic) signaling pathway was reported in 2012,[25] but no active component in the CSF has been found and no difference with other central hypersomnias has been shown. Moreover, these results were not replicated in a 2016 study.[26] No genetic factor has yet been identified in idiopathic hypersomnia.

Case 3-2

A 25-year-old woman presented with a 1-year history of hypersomnolence, without mood disorders or any comorbid conditions. She slept an average of 11 hours at night and needed a 2-hour nap every afternoon. She lost her job because she was always late, as awakening in the morning and after the nap was extremely difficult, and she had major sleep inertia. Brain MRI was normal. Polysomnography followed by a multiple sleep latency test showed normal sleep at night, with high efficiency (95%) and a mean sleep latency of 7 minutes, without any sleep-onset rapid eye movement (REM) periods.

She was diagnosed with idiopathic hypersomnia. Modafinil was started but was not effective for her hypersomnolence and sleep inertia at a maximal dose of 600 mg/d. A second-line therapy, methylphenidate, was introduced; however, it was not well tolerated, with resultant irritability and palpitations. She was lost to follow-up but returned to the clinic 3 years later. She had stopped the medication during her pregnancy and felt no rebound of excessive daytime sleepiness. Polysomnography was again performed and showed normal mean sleep latency on the multiple sleep latency test (15 minutes). The psychostimulant did not need to be renewed.

Comment. This case illustrates the difficulty in managing hypersomnolence and sleep inertia symptoms in idiopathic hypersomnia and the variability of the idiopathic hypersomnia phenotype with possible evolution toward a normal condition, which is a relatively common phenomenon in clinical practice. Women of childbearing age must be informed that modafinil could decrease the efficiency of contraceptive agents, so another contraceptive method should be employed.

Diagnosis

The diagnosis of idiopathic hypersomnia must be established according to *ICSD-3*,[1] with the presence of all of the following criteria: (1) excessive daytime sleepiness, irrepressible need to sleep, or daytime lapses into sleep for the past 3 months without cataplexy; (2) a mean sleep latency on the multiple sleep latency test of 8 or fewer minutes and/or a total sleep time on a continued 24-hour polysomnography recording of more than 11 hours, after correction of chronic sleep deprivation; (3) no more than one sleep-onset REM period on polysomnography and the multiple sleep latency test. In *ICSD-3*, wrist actigraphy and a sleep diary over 1 week preceding polysomnography can be used to demonstrate the prolonged sleep time and exclude insufficient nighttime sleep duration. It is important to confirm the persistence of excessive daytime sleepiness after a period of sleep extension, and excessive daytime sleepiness must not be explained more clearly by another sleep disorder (such as circadian rhythm disturbances), endocrine or neurologic disorders (in particular, vascular, tumor-associated, infectious, or neurodegenerative lesions affecting the arousal circuits), psychiatric disorders, or use of drugs or sedating medications.

The most challenging differential diagnosis is probably major depressive disorder, as hypersomnolence and fatigue can be among the first or main symptoms in mood disorders. Furthermore, patients with idiopathic hypersomnia can present with depressive symptoms, probably because of disease-related impairment in function and quality of life. When a patient presents with depressive symptoms and a suspicion of idiopathic hypersomnia, the physician should carefully evaluate the date of onset of every symptom, the evolution of excessive daytime sleepiness depending on mood, and the effect of the treatment of depressive symptoms on excessive daytime sleepiness. An evaluation by a psychiatrist or a therapeutic trial with antidepressants is sometimes needed before further investigations are carried out.

Treatment Options

Modafinil is effective in the treatment of excessive daytime sleepiness in idiopathic hypersomnia and should be the first-line therapeutic option.[27,28] Methylphenidate is the second-line treatment,[29] and amphetamines or pitolisant (currently available only in European Union countries) can be proposed when idiopathic hypersomnia is resistant to modafinil and methylphenidate or if those medications are not well tolerated. Some studies have suggested that sodium oxybate could be effective for excessive daytime sleepiness and sleep inertia in idiopathic hypersomnia.[30] However, systematic studies of the use of sodium oxybate in idiopathic hypersomnia with a strong methodology are lacking. Dextroamphetamine can also be used in the case of treatment-resistant idiopathic hypersomnia.[29] Sleep inertia is difficult to manage, and available medications are still unsatisfactory to reduce that symptom. Planned naps are seldom indicated in idiopathic hypersomnia, as they are often of long duration and not refreshing. It is also important to counsel patients with idiopathic hypersomnia about planning appropriate school and university schedules that allow for therapeutic napping, and, if possible, to plan for career work that is active and engaging. Clinicians must also frequently advocate for appropriate school and workplace accommodation for patients with

KEY POINTS

- The differential diagnosis of idiopathic hypersomnia must exclude chronic insufficient sleep syndrome, especially in long sleepers. The diagnosis of idiopathic hypersomnia requires the exclusion of other sleep, medical, and psychiatric comorbidities.
- Idiopathic hypersomnia is most frequently managed with psychostimulants, but evidence for their use in idiopathic hypersomnia remains poor, and medications are usually unsatisfactory in managing sleep inertia.

KEY POINTS

- Kleine-Levin syndrome is a recurrent hypersomnia associated with behavioral, psychological, and cognitive disturbances during episodes, with strictly normal sleep and functioning between episodes.
- Diagnostic criteria for Kleine-Levin syndrome are only clinically defined, and no reliable biomarker has yet been identified.

idiopathic hypersomnia, and avoiding early morning starts to better enable adequate sleep can be beneficial.

KLEINE-LEVIN SYNDROME

Kleine-Levin syndrome is a recurrent hypersomnia with an estimated prevalence of about 1 to 2 per million that affects young people during the second decade of life, especially young men (male to female ratio of 2:1).

Clinical Features

Kleine-Levin syndrome is characterized by relapsing-remitting episodes of severe hypersomnolence associated with behavioral and psychiatric disturbances, cognitive abnormalities, and hyperphagia or hypersexuality.[31,32] The median duration of an episode is 10 days, recurring every 1 to 12 months. A triggering factor, such as infection or alcohol intake, is often reported. During episodes, patients can sleep for 16 to 20 hours per 24 hours and are irritable if prevented from doing so. During their wake period, they are apathetic, confused, and slow in speaking and may have variable anterograde amnesia. Derealization is also typical (dreamlike and altered perception of the environment) as are hallucinations and delusions. Sleep, cognition, mood, eating, and sexual behavior are usually normal between episodes.

Pathophysiology

Kleine-Levin syndrome is likely a heterogeneous disease, with the underlying pathophysiology remaining unclear; however, some studies suggest recurrent primary hypothalamic dysfunction mediated by immune mechanisms.[33] Postmortem examinations have revealed inflammation of the hypothalamus, amygdala, temporal lobes, and thalamus. During episodes, functional brain imaging is abnormal, with metabolic changes in several brain regions (thalamus, hypothalamus, mesial temporal and frontal lobes).[34,35] The young age at onset and triggering factors, such as infection, suggest a possible autoimmune process. The hypothesized etiology that is most likely is a recurrent, transient, multifocal encephalopathy.[33]

Diagnosis

Diagnostic criteria for Kleine-Levin syndrome are only clinically defined, without any reliable biomarker yet identified. According to *ICSD-3*,[1] Kleine-Levin syndrome is diagnosed by the presence of all the following criteria:

- The patient experiences at least two recurrent episodes of excessive daytime sleepiness lasting 2 days to 5 weeks that recur usually more than once a year and at least every 18 months.
- Between episodes, mood, alertness, cognitive function, and behavior are strictly normal.
- During episodes, the patient has at least one of the following symptoms: cognitive dysfunction, altered perception, eating disorder (anorexia or hyperphagia), or disinhibited behavior (such as hypersexuality).
- The symptoms are not explained by another sleep disorder, other medical or psychiatric disorder (especially bipolar disease), or use of substance or medication.

If performed, 24-hour polysomnography shows prolonged total sleep time during episodes, and CSF cytology and protein are normal.[36] However, some studies showed that intraepisodic levels of CSF hypocretin-1 can be lower than interepisodic levels.[36]

Treatment Options

No medication has clearly demonstrated its efficacy in the treatment of

Kleine-Levin syndrome, and most practices are based on case reports, case series, or open-label trials.[31] Placebo-controlled trials are extremely difficult to perform because of the rarity of the disease. Symptomatic treatments are based on stimulants such as modafinil but can induce paradoxical agitation; they are of poor efficacy since cognitive and behavioral problems will remain despite improvement in the vigilance state. Moreover, the spontaneous disappearance of symptoms after a few days of evolution leads to difficulties in proper evaluation of the potential benefit of these drugs. Prophylactic treatments based on mood stabilizers such as lithium[37] or antiepileptic drugs (valproic acid, carbamazepine, phenytoin, gabapentin, and lamotrigine)[38] may be prescribed and have reportedly been effective to decrease the frequency and duration of episodes. The prognosis for Kleine-Levin syndrome is generally good, with a spontaneous resolution of the symptoms after a median of 14 years; therefore, routine pharmacologic management is sometimes not needed, especially when episodes are rare or lack major social impact. Patients should be allowed to rest in a safe and stress-free environment during an episode.

OTHER CENTRAL HYPERSOMNIAS

In *ICSD-3*, three other central disorders of hypersomnolence are also defined: hypersomnia due to a medical disorder, hypersomnia due to a medication or substance or to stimulant withdrawal, and hypersomnia associated with a psychiatric disorder.[1]

In hypersomnia due to a medical disorder, the mean sleep latency on the multiple sleep latency test is fewer than 8 minutes, and excessive daytime sleepiness occurs as a consequence of a medical or neurologic condition. Some examples include brain tumors, residual excessive daytime sleepiness in patients with adequately treated sleep apnea, genetic disorders such as Niemann-Pick disease type C, or hypersomnolence secondary to Parkinson disease. If criteria for narcolepsy are fulfilled, the diagnosis is narcolepsy type 1 or narcolepsy type 2 due to a medical condition. Indeed, on rare occasions, narcolepsy can be caused by a broad injury of the hypothalamus or of the projections of the hypocretin neurons as a consequence of a cerebral lesion (tumor, stroke, sarcoidosis, demyelination) or paraneoplastic disorder.[39] Patients with myotonic dystrophy have a narcolepsy type 2 phenotype in 30% of cases.[40]

The diagnosis of hypersomnia due to a medication or a substance or to stimulant withdrawal should be considered when daytime sleepiness occurs in the setting of current medication or substance abuse or withdrawal from a wake-promoting medication or substance. Indeed, the chronology of the onset of excessive daytime sleepiness needs to be compatible with such conditions of drug intake or withdrawal. Stimulant abuse and the excessive daytime sleepiness due to their withdrawal is more frequent among adolescents and young adults.

Hypersomnia associated with a psychiatric disorder is a complex entity and subject to controversy. The mean sleep latency on the multiple sleep latency test is fewer than 8 minutes, and the patient also presents with a psychiatric condition. Hypersomnolence is indeed frequent in the context of mood disorders; however, the sleep latency on multiple sleep latency test is often normal.[41] A challenge for sleep specialists and psychiatrists is to differentiate psychiatric hypersomnolence from a central hypersomnia disorder with comorbid psychiatric

KEY POINTS

- The prognosis for Kleine-Levin syndrome is generally good, with a spontaneous resolution of the symptoms after a median of 14 years.
- Hypersomnia due to a medication or a substance, sleep deprivation, or a psychiatric disorder must always be considered in the differential diagnosis of narcolepsy type 2 and idiopathic hypersomnia.

symptoms. The current diagnostic tools seem to be limited in this combination of conditions, and further research is warranted.[42]

DIFFERENTIAL DIAGNOSIS

The differential diagnoses of excessive daytime sleepiness are numerous, and the most important and correctable is likely insufficient sleep syndrome. The clinician must carefully establish patients' sleep time on weekdays and weekends by personal or collateral history, sleep logs, or, sometimes, actigraphy, if needed. Extension of total sleep time during holidays or sometimes even on weekends results in resolution of symptoms. In a normal variant known as a *long sleeper*, habitual sleep is reported as refreshing, with normal daytime functioning, when the subject is allowed to sleep at least 9 or 10 hours per night, yet such individuals often report sleepiness when they are relatively sleep deprived and sleep less than their sleep requirement of 9 or 10 hours or longer. Shift workers may also present with excessive daytime sleepiness, even mimicking a narcolepsy type 2 phenotype.[43] It is also important to rule out other sleep disorders, such as obstructive sleep apnea or periodic limb movement disorder, or circadian disorders (such as delayed sleep-wake phase disorder), which can be responsible for excessive daytime sleepiness.

CONCLUSION

Central disorders of hypersomnolence are rare but disabling diseases, with a long delay before diagnosis, sometimes reaching several years (a median of 10 years for narcolepsy type 1).[44] The categorization is often difficult for sleep specialists, especially for hypersomnias outside the spectrum of narcolepsy type 1, as reliable biomarkers have not yet been discovered. It is important for clinicians to recognize the manifestations of central hypersomnia and to accurately diagnose and efficiently manage excessive daytime sleepiness to maximize the patient's quality of life and daily school or work performance and to minimize the risk of accidents.

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