

Central Disorders of Hypersomnolence

Placeholder – chapter table of contents

Adequate alertness is necessary for well-being and performance in modern society. Sleepiness predisposes an individual to develop serious performance decrements in multiple areas of function and have potentially life-threatening domestic, occupational, and vehicular accidents. This section includes a group of disorders in which the primary complaint is daytime sleepiness not caused by a circadian rhythm sleep-wake disorder or disturbed sleep due to another untreated sleep disorder such as sleep apnea. These and other comorbid sleep disorders may be present, but they must be adequately treated before a diagnosis in this category can be established, with the exception of narcolepsy type 1, which can be diagnosed without exclusion of other causes if hypocretin (orexin) deficiency is confirmed. Insufficient sleep syndrome is a behavioral reduction of usual sleep time resulting in daytime sleepiness. Although not a central disorder per se, it is included in this section as a key component of the differential diagnosis of hypersomnolence. In this nosology, the term hypersomnolence is used to describe symptoms including excessive sleepiness and increased sleep duration, whereas hypersomnia refers to specific disorders such as idiopathic hypersomnia.

Daytime sleepiness is defined as the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep. Sleepiness may vary in severity and is more likely to occur in sedentary, boring, and monotonous situations that require little active participation. Although patients are often aware of increasing sleepiness before falling asleep, they may do so with little or no prodrome (i.e., "sleep attacks"). Temporary resolution of sleepiness by short naps is a variable trait among central disorders of hypersomnolence and may be useful in guiding diagnosis and clinical decision-making. In most patients, excessive daytime sleepiness is also accompanied by impairment of sustained attention. In some persons with hypersomnolence, sleepiness is accompanied by significant increases in the total daily amount of sleep without any genuine feeling of restoration or by pronounced sleep inertia (i.e., great difficulty in waking up from sleep with impaired performance and reduced vigilance during the sleep-to-wake transitional state). It has been suggested that the word "hypersomnia" should be reserved for this phenotype. However, historically the terms hypersomnolence and hypersomnia have been frequently used interchangeably. In young children, sleepiness may present as excessively long night sleep or the recurrence of previously discontinued daytime napping. Children may also present with inattentiveness, emotional lability, hyperactive behavior, or decreased performance in school. In most cases, excessive sleepiness is a chronic symptom and must be present for at least three months before the diagnosis can be established.

The severity of daytime sleepiness can be quantified subjectively using severity scales such as the Epworth Sleepiness Scale and objectively using the Multiple Sleep Latency Test (MSLT). These measures do not

always correlate with each other and must be used with appropriate clinical judgment. When applied in clinical settings, the MSLT is sensitive to sleep deprivation and circadian effects. It has not been validated as a diagnostic test in people who are habitually awake throughout the night and sleep during the day. Normal and abnormal ranges of sleep latencies have not been established when this test is administered at times other than the hours between 8:00 a.m. and 6:00 p.m. Normative data are not available for preschool children.

The MSLT measures the physiological propensity to fall asleep in quiet situations. In diagnosing central disorders of hypersomnolence, the MSLT should be conducted according to standardized procedures, as defined in the American Academy of Sleep Medicine (AASM) recommended protocol. In particular, patients should be encouraged to sleep as much as possible during the week and, especially, during the night prior to the MSLT. Delaying wake-up time and subsequent MSLT start time may be appropriate in some patients (e.g., with delayed sleep phase syndrome). It is recommended that an adequate sleep-wake rhythm and duration is documented by sleep log and actigraphy, whenever possible, for one to two weeks before the MSLT. Actigraphy, in addition to sleep logs, typically provides more accurate information about the presence of sleep deprivation or circadian rhythm disorders than sleep logs alone. MSLT mean sleep latencies should be considered along a continuum, with smaller values reflecting increasing sleep propensity. However, in this section, a mean MSLT sleep latency of eight minutes or less defines pathological sleepiness for diagnostic purposes. This value is the best cutoff in diagnosing narcolepsy with cataplexy, with approximately 90% of patients with narcolepsy having a latency below this level. The presence of multiple sleep-onset rapid eye movement periods (SOREMPs) during the MSLT is a more specific finding in narcolepsy than is a mean sleep latency less than or equal to eight minutes. However, SOREMPs can also be observed with insufficient sleep, circadian rhythm disorders (including delayed sleep phase disorder or shift work), sleep-related breathing disorders, using or withdrawing from certain substances/medications, or in normal persons. Thus, the results of an MSLT should be carefully considered in the context of the patient's history and clinical complaints, and not be relied upon solely for diagnosis. Insufficient sleep and circadian rhythm disorders as cause for abnormal results should be excluded to prevent misdiagnosis. The average amount of sleep required for healthy adults is seven or more hours, although clinicians should keep in mind that some individuals require more than 7-8 hours to be adequately rested. The recommended sleep requirements for pediatric populations are greater than those required for adults and vary by age.

The Maintenance of Wakefulness Test (MWT) measures the ability to remain awake during the daytime in a darkened, quiet environment. It is usually administered to assess response to treatment, particularly in the context of driving or for security positions. It is not currently used in the diagnostic criteria that define central disorders of hypersomnolence. A 24 to 32-hour continuous sleep recording or an actigraphic recording of at least one week can be helpful to diagnose patients with idiopathic hypersomnia and narcolepsy. However, universal standards and methodologies for these diagnostic tests in central disorders of hypersomnolence are not yet established. In all cases in which a diagnosis of a central disorder of hypersomnolence is considered, a review of other sleep, medical, and psychiatric disorders, as well as substance and medication use, should be performed.

Narcolepsy is divided into narcolepsy type 1 and narcolepsy type 2 rather than narcolepsy with and without cataplexy. This distinction is predicated on the concept that the presence of hypocretin (orexin) deficiency is a fundamental marker of the most precisely defined category of narcolepsy type 1. Because some patients without cataplexy will also have low cerebrospinal fluid (CSF) hypocretin-1 levels, the use of the terms “narcolepsy with cataplexy” or “narcolepsy-cataplexy”, which have been used historically, may be inappropriate. This nomenclature does not imply that the presence or absence of cataplexy is unimportant clinically nor that measuring CSF hypocretin-1 levels is obligatory.

The continuation of idiopathic hypersomnia as a single diagnostic construct is discussed in the appropriate section, with recognition that this lumping approach has been challenged by recent studies. Scientifically-guided delineation of all disorders in the narcoleptic borderland (i.e., other than narcolepsy type 1) is challenging given the absence of definitive pathophysiologies that reliably segregate these disorders. The nosology is subject to change in future editions as research advances.

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Narcolepsy Type 1

ICD-9-CM code: 347.01

ICD-10-CM Code: G47.411

Alternate Names

Hypocretin deficiency syndrome, narcolepsy-cataplexy, narcolepsy with cataplexy.

Diagnostic Criteria

Criteria A and B and C must be met

- A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep.
- B. The presence of one or both of the following:
 1. Cataplexy (as defined under Essential Features)¹ and either:

- i. Mean sleep latency of ≤ 8 minutes and two or more sleep-onset REM periods (SOREMPs) on an MSLT performed in accordance with current recommended protocols² or:
 - ii. A SOREMP (within 15 minutes of sleep onset) on nocturnal polysomnogram.
 - 2. CSF hypocretin-1 concentration, measured by radioimmunoassay, is ≤ 110 pg/mL (using a Stanford reference sample) or $<1/3$ of mean values obtained in normal subjects with the same standardized assay.³
- C. The symptoms and signs are not better explained by chronic insufficient sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, mental disorder, or medication/substance use or withdrawal.

Notes

1. *Typical* cataplexy is most strongly associated with narcolepsy type 1 (NT1). Although some patients with NT1/hypocretin deficiency may present with *atypical* cataplexy features, presentations that include only *atypical* cataplexy should raise a higher index of doubt regarding a diagnosis of NT1. Clinical judgment is required. Further guidance regarding distinguishing typical from atypical cataplexy is included in the *Essential Features* section below.
2. See references - AASM Recommended Protocols for the MSLT and MWT in Adults. Sleep logs are required, accompanied by actigraphy, whenever possible, prior to in-laboratory sleep testing to evaluate for insufficient sleep and circadian rhythm disturbances.
3. If hypocretin deficiency is verified, the diagnosis of NT1 should be made regardless of other comorbidities that could potentially be related to clinical symptoms, given the definitive nature of this finding.

Essential Features

Narcolepsy type 1 (NT1) is a disorder primarily characterized by excessive daytime sleepiness and signs of REM sleep dissociation, the most specific of which is cataplexy. It is now firmly established that narcolepsy type 1 is caused by a deficiency of hypothalamic hypocretin (orexin) signaling. Patients with low or undetectable concentrations of hypocretin-1 in the CSF compose a specific disease population with a single etiology and relatively homogenous clinical and polysomnographic features. Patients with sleepiness and low or absent CSF hypocretin-1 levels are classified as having narcolepsy type 1, even if they do not manifest cataplexy.

Excessive Daytime Sleepiness Excessive daytime sleepiness is the cardinal symptom, and often the most disabling. Patients with narcolepsy type 1 experience repeated daily episodes of an irrepressible need to sleep or lapses into sleep. Most patients awaken refreshed after a sleep episode but begin to feel sleepy again after variable periods. Sleepiness is most likely to occur in monotonous situations that require no active participation, for example, watching television or riding in a car. Physical activity may temporarily suppress the urge to sleep. In some cases, sleepiness manifests as sudden irresistible sleep “attacks” that

may occur in unusual situations such as eating or walking. Such sleep attacks often occur on a background of overall sleepiness. Even when seemingly awake, most narcolepsy patients have impaired sustained attention, sometimes in combination with automatic behavior, such as writing gibberish or interrupting a conversation with a completely different topic. Sleepiness and impaired sustained attention often have serious impacts on the ability of the patient to function properly in educational, social, and occupational situations.

Cataplexy As patients are rarely examined during an attack of cataplexy, its presence needs to be established based on the clinical interview. Cataplexy is defined as more than one episode of generally brief (< 2 minutes), usually bilaterally-symmetrical, sudden loss of muscle tone with retained consciousness. The episodes are precipitated by strong emotions, usually positive, with almost all patients reporting some episodes precipitated by emotions associated with laughter. The finding of a transient reversible loss of deep tendon reflexes during an attack, if observed, is an important diagnostic finding. In children (and rarely adults), cataplexy may present close to disease onset as facial (or generalized) hypotonia with droopy eyelids, mouth opening, protruding tongue, or gait unsteadiness, which sometimes are not clearly related to emotion. Facial and masticatory movements may occur. It is essential to use child-appropriate contexts and language when trying to elicit a history of cataplexy in children. Video footage may be helpful.

The cataplexy phenotype differs widely between patients, ranging from sporadic partial cataplexy triggered by laughter to frequent complete cataplexy brought about by various emotions. Partial attacks can be very subtle and sometimes only recognized by experienced observers such as the patient's partner. When attacks are longer in duration, a bilateral loss of muscle tone in the face, neck, or legs (e.g., buckling knees), with or without involvement of the arms, is typically experienced; Head drop is a common complaint, and facial weakness may lead to sagging of the jaw and dysarthria. Respiratory muscles are not involved, although patients sometimes describe shortness of breath when symptomatic. Complete attacks build up over several seconds and may progress to complete weakness and collapse. Positive motor phenomena such as dyskinesia or muscle twitching, particularly of the face, have been reported in pediatric NT1. Although many emotions can potentially lead to cataplexy, those associated with mirth are usually the most potent. Laughing out loud, telling a joke, and making a witty remark are typical examples. The frequency of cataplexy is variable, ranging from less than one episode per month to more than twenty per day. Cataplexy is generally short-lived, and partial attacks may last only seconds. Attacks lasting more than two minutes are exceptional. However, if a particular trigger continues, consecutive attacks may merge to form what seems to be one long episode. Sudden withdrawal of anticataplectic medication, especially antidepressants, can result in "status cataplecticus," in which long-lasting attacks happen almost continuously.

Typical versus atypical cataplexy The initial diagnosis of cataplexy is usually made based on history. Therefore, distinguishing features of typical cataplexy from atypical cataplexy and events that are not compatible with cataplexy is essential. Typical cataplexy is most frequently manifested as partial cataplexy. Classically, this may involve bilateral loss of muscle tone in the face, neck, or legs (e.g., buckling knees), with or without involvement of the arms. Sudden and particularly positive emotions (e.g., laughing

out loud, telling an amusing joke/story), making a witty remark, unexpectedly meeting a familiar acquaintance, or, less frequently, anger may trigger an episode. These episodes typically last for up to 1 minute but are usually less than 30 seconds. Occasionally episodes are fleeting. The frequency of cataplexy can be quite variable, but episodes usually occur at least once per month (if untreated). During typical cataplexy, consciousness is preserved, and there is an abrupt return of muscle tone after the attack. While events are stereotypical for individuals, the extent of progression and extension into involved muscles, as well as the duration of episodes, may vary.

While less frequently observed than partial cataplexy, some patients experience complete cataplexy. It is uncommon for patients to have only complete cataplexy without episodes of partial cataplexy (see below). Attacks of complete cataplexy begin like partial attacks with similar triggers. Bilateral progressive loss of muscle tone generally starts in the face or neck and builds over seconds, leading to inability to stand and a subsequent fall if not prevented. Like partial typical cataplexy, consciousness is preserved, and there is an abrupt return of muscle tone after the attack. Occasionally patients may fall asleep during complete cataplexy, particularly if the episode is prolonged.

Variations of typical cataplexy may be observed. These include occasional spontaneous episodes (which occur primarily in the evening and are enhanced by sleepiness), attacks having asymmetrical (but not unilateral) severity, facial twitching, or jerky arm movements. Patients with one of the following characteristics are considered to have atypical cataplexy, which is much less strongly associated with hypocretin-1 deficiency and the NT1 diagnosis: 1) attacks never triggered by laughing, mirth, or joking; 2) prolonged attacks in adults (e.g., >3 minutes) in the absence of an ongoing precipitant; 3) absence of clear precipitants for episodes or only negative emotions (such as anxiety, fear, a sudden, startling noise) as triggers; 4) purely unilateral attacks; 5) hyperacute generalized muscle weakness without build-up over seconds, leading to falls and injuries; 6) prolonged recovery (several minutes) needed to recover after a single attack; 7) uncertainty regarding the preservation of consciousness; or 8) exclusively generalized attacks without a history of partial episodes. If two or more of these characteristics are present, the episodes should not be labeled as cataplexy.

Features that would not be compatible with cataplexy for the diagnosis of narcolepsy type 1 include the following: 1) loss of consciousness from the start of the attack; 2) duration greater than 10 minutes in the absence of a precipitating trigger; 3) remaining deep tendon reflexes of the involved limb when elicited during an observed attack; or 4) clear signs of attacks other than cataplexy (e.g., typical aura experience of epilepsy or typical prodromal signs that may be experienced during vasovagal syncope).

For specific features observed in children, see Developmental Issues.

Associated Features

In addition to sleepiness and cataplexy, patients with narcolepsy type 1 often report several other symptoms, none of which are specific to the disorder. Many patients report disrupted nighttime sleep, which can sometimes be of major concern. Although difficulty with sleep onset is rarely a problem, an inability to maintain continuous sleep is very common. Thirty-three to eighty percent of narcolepsy patients have hypnagogic hallucinations or sleep paralysis. Hypnagogic hallucinations are vivid dreamlike experiences occurring during the transition from wake to sleep. Typically, hypnagogic hallucinations have a multimodal or “holistic” character, often combining visual, auditory, and tactile phenomena. Hypnopompic hallucinations are similar but occur during sleep-to-wake transitions. Sleep paralysis describes the disturbing temporary inability to move voluntary muscles at sleep-wake transitions. Despite being awake and conscious of the sleeping environment, it is impossible for subjects to move their limbs or even open their eyes. The experience may last for several minutes and can be very distressing. Hypnagogic hallucinations may occur together with sleep paralysis. Patients may also experience vivid dreams that are bizarre, frightening, complex in structure, or perceptually vivid. They suffer more frequent nightmares than healthy people. Delusional dreaming may occur wherein patients mistake the memory of a dream for a real experience. Lucid dreaming has also been reported to be more frequent. Finally, symptoms may include ptosis, blurred vision, and diplopia, presumably because of sleepiness.

Epidemiological studies have shown that obesity is common in narcolepsy type 1. Around disease onset, an unexplained increase in body weight is often observed, particularly when disease onset is more acute, as is often the case in children. Obesity (defined as a body mass index ≥ 30 kg/m²) occurs more than twice as often in narcoleptic populations as in control groups. An increased frequency of several other sleep abnormalities has been described in narcolepsy, including sleep talking, periodic limb movements of sleep, sleep-related breathing disorders, and REM sleep behavior disorder. There is an increased prevalence of depressive symptoms, although there are conflicting reports on how often these symptoms qualify as clinical depression. There is an increased prevalence of anxiety disorders in patients with narcolepsy; panic attacks or social phobias occur in about 20%. Attention problems are an expression of daytime sleepiness. However, there is also debate whether the NT1 patients who meet the criteria for an attention-deficit hyperactivity disorder (ADHD) diagnosis (up to 30%) have comorbid ADHD. Alternatively, their symptoms may merely reflect major attention problems as an expression of excessive daytime sleepiness. More than half of patients report severe fatigue, which should be distinguished from sleepiness.

Clinical and Pathophysiological Subtypes

Narcolepsy type 1 due to a medical condition In these cases, the condition is presumably caused by another central nervous system (CNS) disorder, for example, an autoimmune or paraneoplastic disorder associated with anti-Ma2 or antiaquaporin-4 antibodies, or tumors or other lesions of the hypothalamus. Some genetic disorders such as Nieman Pick type C, Norrie’s disease, and Prader-Willi syndrome can have a narcolepsy-like phenotype with cataplexy (typically with pediatric onset). NT1 phenotype can be observed in individuals with DNMT1 mutations. However, hypocretin levels are not always decreased in

these cases, suggesting different etiologies for the phenotype. In addition, undetectable hypocretin-1 levels have been reported in association with sleepiness after severe head trauma.

The condition must fulfill the criteria for NT1 and be attributable to another medical disorder.

Narcolepsy without cataplexy with low CSF Hcrt-1 levels NT1 should be diagnosed, even in the absence of cataplexy, if diagnostic criteria A and B2 are fulfilled.

Demographics

Estimating NT1 prevalence is challenging because it typically relies on the presence or absence of cataplexy rather than CSF hypocretin measures. In most countries where prevalence has been well studied, narcolepsy with cataplexy affects 0.02-0.03% of the population. The prevalence of narcolepsy without cataplexy but with hypocretin deficiency is unknown. Both sexes are affected, possibly with a slight preponderance of males.

Underdiagnosis and a long diagnostic delay are still common in most countries. Narcolepsy without cataplexy but with hypocretin deficiency is more common in persons of African descent.

Predisposing and Precipitating Factors

Several unproven precipitating factors have been suggested in case reports, including head trauma, sustained sleep deprivation, unspecified viral illness, and sudden changes in sleep-wake patterns. Several studies have pointed to seasonal patterns in the onset of narcolepsy, which may point to a specific environmental trigger. More recent studies have shown an increase in antibodies against beta-hemolytic streptococcus, which were highest around the onset of narcolepsy and decreased with disease duration. This observation suggests that streptococcal infections may constitute an environmental trigger. There have been reports of narcolepsy type 1 occurring after influenza infection or vaccination. In 2010, an increased incidence of narcolepsy was reported following vaccination with a specific H1N1 vaccine, Pandemrix.™ Currently, neither a definite causal association nor mechanism has been established.

Familial Patterns

At the genetic level, narcolepsy with cataplexy is closely associated with the human leukocyte antigen (HLA) subtypes DR2/DRB1*15:01 and DQB1*06:02. These two alleles are always found together in White and Asian people, but in people of African descent, DQB1*06:02 is more specifically associated with narcolepsy with cataplexy or hypocretin deficiency. Almost all patients with typical cataplexy are positive for DQB1*06:02, compared with 12% to 38% of the general population with this HLA subtype. Other subtypes also have less striking associations. For example, DQB1*03:01 is associated with increased susceptibility to narcolepsy, whereas subtypes such as DQB1*05:01, DQB1*06:01, and DQB1*06:03, are

protective in the presence of DQB1*06:02. Genome-wide association studies in narcolepsy have also identified associations with polymorphisms in T cell receptor genes and other genes regulating immune responses.

There is a low prevalence of familial cases; the risk of NT1 in first-degree relatives of affected individuals is approximately 1% to 2%. This finding indicates a ten-fold to forty-fold increase in risk compared to the general population prevalence. This increased risk cannot be explained solely by HLA gene effects, suggesting the existence of other genetic factors. Multiplex families with more than two affected members are uncommon. In some cases, normal CSF hypocretin levels have been found in these families, and the association with HLA DQB1*06:02 is weaker than in sporadic narcolepsy.

Onset, Course, and Complications

Onset usually occurs after five years of age, typically between 7 and 25 years. A bimodal distribution in the age at onset has been described in some populations, with a first peak occurring at adolescence (age 15 years) and a second smaller one at the age of 35 years. An onset under 4 years of age is extremely uncommon.

Sleepiness is usually the first symptom to manifest. Cataplexy most often presents simultaneously or within one year of onset. However, in rare cases, cataplexy may precede the onset of sleepiness or commence up to 40 years later. Hypnagogic hallucinations, sleep paralysis, and disturbed nocturnal sleep often manifest later in the course of the disease. There may be an abrupt symptom onset in days to weeks, particularly in children.

When left untreated, NT1 is often socially disabling and isolating. Patients tend to fail in school and are often dismissed from their jobs. Driving may be avoided for fear of a motor vehicle accident. The inability to maintain sleep at night may further contribute to a loss of control over patients' schedules. Depression and weight gain also are common.

In most cases, symptoms gradually develop over several months to years. When the clinical picture has fully developed, there are usually only minor fluctuations in severity over time. Cataplexy may lessen with age or occasionally increase in frequency and severity.

Developmental Issues

In recent years, increasing attention has been given to the clinical presentation of narcolepsy in childhood. The clinical presentation in children may be different from that of adults. In young children, sleepiness may be difficult to assess and may express itself as excessively long night sleep or the recurrence of previously discontinued daytime napping. Moreover, children may paradoxically present with hyperactive behavior, behavioral problems, or decreased performance in school. Inattentiveness, lack of energy,

insomnia, bizarre hallucinations, or a combination thereof can lead to a psychiatric misdiagnosis of attention deficit-hyperactivity disorder, schizophrenia, depression, or autism spectrum disorder. In this population, ancillary symptoms such as sleep paralysis or hypnagogic hallucinations may also be difficult to confirm, depending on the child's verbal ability. Disease onset can be abrupt in days to weeks which is unusual in adults. Precocious puberty and obesity may develop around the time of symptom onset. REM sleep behavior disorder or REM sleep without atonia may be manifest at the time of symptom onset. There are reports of increased prevalence of schizophrenia in children and adolescents with NT1. Cataplexy may be very severe around disease onset and appear phenotypically different from typical episodes seen in adulthood. In addition to typical attacks triggered by positive emotions, children can also present with weakness involving the face, eyelids, and mouth not always clearly associated with emotion. A hypotonic ataxia-like gait may accompany this finding and likely represents static cataplexy (without emotional trigger) in pediatric NT1 cases.

Together with tongue protrusion, this characteristic pattern has been termed "cataplectic facies." Children with cataplexy may also display positive motor phenomena, ranging from perioral dyskinetic or dystonic movements to frank stereotypies.

Establishing the NT1 diagnosis in children may be complicated because of difficulties performing the MSLT. If successfully performed, criteria different from those applied in adults have been suggested: at least 2 SOREMPs or a mean sleep latency ≤ 8.2 minutes. However, these diagnostic cut points have not been replicated, and the generalizability is uncertain. If the MSLT shows equivocal results or cannot be performed, CSF hypocretin-1 measurements are of value, as hypocretin-1 levels are low or undetectable very shortly after disease onset in children.

Pathology and Pathophysiology

It is now firmly established that NT1 is caused by deficiencies in hypocretin signaling, most likely due to a selective loss of hypothalamic hypocretin-producing neurons due to an autoimmune process. Several animal models lacking hypocretin neurotransmission demonstrate narcolepsy, indicating a causal relationship. The vast majority of patients (about 95% with narcolepsy and typical cataplexy) have undetectable or low (i.e., < 110 pg/mL for values converted to Stanford values using a reference sample) levels of CSF hypocretin-1. Patients without cataplexy can be hypocretin deficient, although at a much lower frequency, and are thus also classified as narcolepsy type 1. The strong HLA association in narcolepsy has led to the hypothesis that autoimmunity is a likely etiological mechanism, potentially explaining the selectivity of neuronal destruction in the hypothalamus. However, definitive proof for autoimmunity has not been obtained.

Objective Findings

NT1 is essentially defined as a hypocretin deficiency syndrome. Objective measurements are required to make the diagnosis. This requirement is essential, as many patients require lifelong treatment with potentially addictive medications, underscoring the importance of objective confirmation of the diagnosis.

It is recommended, whenever possible, that the MSLT be preceded by at least one week of sleep logs, accompanied by actigraphy, whenever possible, to establish whether the results could be impacted by insufficient sleep or a circadian sleep-wake disorder. Because the circadian clock strongly gates the propensity of REM sleep, the MSLT is not an appropriate tool to use in the diagnosis of narcolepsy in shift workers. MSLT findings associated with a diagnosis of NT1 include a mean sleep latency of less than or equal to eight minutes (although it is very common to observe sleep latency below 5 minutes) and two or more SOREMPs. Recent data shows that a SOREMP within 15 minutes after the onset of nocturnal sleep is a highly specific finding in the absence of another sleep disorder. However, sensitivity is low, approximately 50%. For the correct interpretation of polysomnography and MSLT findings, the recordings should be performed with the following conditions: (1) the patient must be free of drugs that influence sleep propensity and architecture for at least 14 days (or at least five times the half-life of the drug and longer-acting metabolite). In certain situations, a urine drug screen may be warranted; (2) the sleep-wake schedule must have been standardized and, if necessary, extended to a minimum of seven hours in bed each night (ideally more and longer for children) for at least seven days before polysomnography (preferably documented by sleep log and, whenever possible, actigraphy); and (3) nocturnal polysomnography should be performed on the night immediately preceding the MSLT to rule out other sleep disorders that could mimic NT1 diagnostic features. In NT1 patients, MSLT results are usually consistent over time.

Sleep time during polysomnography should be curtailed as little as possible with the goal of at least seven hours asleep. The overnight polysomnogram may demonstrate an increase in the amount of stage N1 sleep, and there may be a disruption of the normal sleep pattern, with frequent awakenings. A high PLM index is common, and REM sleep without atonia may be present.

Measuring CSF levels of hypocretin-1 is a highly specific and sensitive test for NT1. The assay can be performed offsite through centralized laboratories if not available locally. Hypocretin-1 can be measured in crude CSF, using a commercially available radioimmunoassay. When using the Stanford reference sample, values less than 110 pg/mL are highly specific, although the immunoreactivity reflects both hypocretin-1 and metabolites/degradation products of hypocretin-1. Alternatively, a laboratory may elect to obtain control data themselves, in which case a level of less than 33% of mean control values is considered abnormal. Issues concerning the standardization of CSF hypocretin measurements remain, but extensive protocols are available. Low CSF hypocretin values are occasionally observed in seriously ill patients, especially when there is an alteration of the blood-brain barrier or high CSF protein content. In such cases, CSF hypocretin results should be interpreted with caution in the clinical context. An advantage of measuring hypocretin-1 levels to diagnose NT1 is that there are no known influences of sleep deprivation, circadian disturbances, disordered breathing, or medication use or discontinuation on the measured CSF levels.

HLA typing of narcoleptic patients with cataplexy almost always shows the presence of HLA DQB1*06:02 (and DR2 or DRB1*15:01 in White and Asian individuals), but this is not diagnostic for narcolepsy. Approximately 25% of the normal populations of European descent, 12% of the Japanese population, and 38% of persons of African descent are positive for DQB1*06:02. HLA typing could be considered when a lumbar puncture is contemplated to assess hypocretin-1 values: if the patient is HLA-negative, hypocretin-1 levels are most likely normal.

Differential Diagnosis

Assessment of possible cataplexy is often critical in establishing a diagnosis of narcolepsy type 1. Cataplexy should be differentiated from *syncope, transient ischemic attacks, drop attacks, akinetic seizure, neuromuscular disorder, vestibular disorder, psychological and psychiatric disorders, dozing and sleep paralysis*. Cataplexy must also be differentiated from *cataplexy-like episodes* that are occasionally observed in normal individuals. For example, feelings of muscle weakness are sometimes reported when healthy subjects laugh out loud. In genuine cataplexy, episodes most often occur with a significant frequency (e.g., at least three or more episodes) and are associated with loss of muscle tone. Improvement after initiation of antiepileptic agents may also favor a diagnosis of cataplexy.

Other central hypersomnolence disorders In the absence of cataplexy, NT1 can be diagnosed based on the presence of excessive daytime sleepiness and low CSF hypocretin-1 levels. When cataplexy is absent, and CSF hypocretin-1 levels are normal or unknown, *narcolepsy type 2* should be diagnosed. *Idiopathic hypersomnia* is differentiated from NT1 by the absence of cataplexy and normal CSF hypocretin. IH is not associated with SOREMPs characteristic of NT1. In contrast with patients who have narcolepsy, a subgroup of patients with idiopathic hypersomnia has a long duration of nocturnal sleep with sleep drunkenness and long, unrefreshing naps. In *insufficient sleep syndrome*, there is no cataplexy, and normalizing sleep time eliminates daytime sleepiness.

Other causes of sleepiness Sleepiness may be secondary to *obstructive sleep apnea, insufficient sleep, shift work, the effects of substances or medications, or other sleep disorders*. Many of these conditions can result in early-onset REM sleep as well. When cataplexy or hypocretin deficiency is present, these disorders do not preclude a diagnosis of NT1. When there is a questionable history of cataplexy in such cases, either comorbid conditions should be adequately treated before performing an MSLT or CSF hypocretin-1 should be measured.

Chronic fatigue syndrome and *depression* may mimic narcolepsy but do not show the typical MSLT findings. However, they may be comorbid in narcolepsy patients. *Malingering* and *substance abuse disorder* should be considered in patients who try to mislead the clinician to obtain stimulant medications.

Unresolved Issues and Further Directions

About 5 percent of patients with narcolepsy with typical cataplexy have normal hypocretin-1 levels in the CSF, which suggests that CSF levels do not perfectly reflect brain hypocretin neurotransmission or that narcolepsy with cataplexy can be caused by factors other than hypocretin deficiency. Many cases without hypocretin-1 deficiency are familial or secondary to other conditions.

Based on current knowledge, hypocretin-deficient narcolepsy with cataplexy is considered an immune-mediated disease, although the classical criteria for an autoimmune disorder are not (all) fulfilled. A T cell-mediated destruction of hypocretin cells is most likely. The role of B cells and autoantibodies is unclear.

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Narcolepsy Type 2

ICD-9-CM code: 347.00

ICD-10-CM Code: G47.419

Alternate Names

Narcolepsy without cataplexy.

Diagnostic Criteria

Criteria A-E must be met

- A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.
- B. A mean sleep latency of ≤ 8 minutes and two or more sleep-onset REM periods (SOREMPs) on an MSLT performed in accordance with current recommended protocols¹. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.^{2,3}
- C. Cataplexy is absent.⁴
- D. If CSF hypocretin-1 concentration is measured by radioimmunoassay, it is either > 110 pg/mL (when using a Stanford reference sample) *or* $> 1/3$ of mean values obtained in normal subjects with the same standardized assay.⁵
- E. The symptoms and signs are not better explained by chronic insufficient sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, mental disorder, or medication/substance use or withdrawal.

Notes

1. See references - AASM Recommended Protocols for the MSLT and MWT in Adults. Sleep logs are required, accompanied by actigraphy, whenever possible, prior to in-laboratory sleep testing to evaluate for insufficient sleep and circadian rhythm disturbance
2. The diagnostic value of a SOREMP on nocturnal polysomnography in the absence of MSLT SOREMPs is not established for NT2. However, it may help guide clinical decision-making, such as the need to pursue repeat or alternative testing.
3. Because the circadian clock strongly gates the propensity of REM sleep, narcolepsy type 2 should not be diagnosed in a shift worker without prior re-entrainment to a normal schedule.
4. If cataplexy develops later, the disorder should be reclassified as narcolepsy type 1.
5. If the CSF Hcrt-1 concentration is tested at a later stage and found to be either ≤ 110 pg/mL (when using a Stanford reference sample) or $< 1/3$ of mean values obtained in normal subjects with the same assay, the disorder should be reclassified as narcolepsy type 1.

Essential Features

Narcolepsy type 2 is characterized by excessive daytime sleepiness and abnormal manifestations of REM sleep on polysomnography/MSLT. Typical cataplexy is absent, although some atypical sensations of weakness triggered by unusual emotions such as stress and anger may be reported. Refreshing daytime naps are characteristic.

Sleepiness is most likely to occur in monotonous situations that require no active participation, for example, watching television or riding in a car. Physical activity may temporarily suppress the urge to sleep. In some cases, sleepiness manifests as sudden irresistible sleep “attacks” that may occur in unusual situations such as eating or walking. Often, such sleep attacks occur on a background of overall sleepiness. Even when seemingly awake, many have impaired sustained attention, sometimes in combination with automatic behavior, such as writing gibberish or interrupting a conversation with a completely different topic. Sleepiness and impaired sustained attention often have serious impacts on the ability of the patient to function properly in educational, social, and occupational situations.

An essential feature of the diagnosis is the presence of a mean sleep latency less than or equal to eight minutes and two or more SOREMPs on an MSLT (or one SOREMP on an MSLT and one on the preceding nocturnal polysomnogram). Because cataplexy is absent or atypical, the conditions for a valid MSLT are even more necessary in NT2 than in NT1, including adequate prior sleep time and normal circadian alignment, and no current or recent use of antidepressants and neuroleptic drugs. CSF hypocretin-1 concentrations ≤ 110 pg/mL or less than one-third of mean values obtained in normal subjects with the same assay exclude the diagnosis, but most patients with narcolepsy type 2 do not undergo CSF examination.

Associated Features

Sleep paralysis, hypnagogic hallucinations, or automatic behavior may be present. Memory lapses, automatic behavior, ptosis, blurred vision, and diplopia may be associated with sleepiness. REM sleep behavior disorder and lucid dreaming may occur. Nocturnal sleep disruption with frequent awakenings may be present but to a lesser extent than observed in narcolepsy type 1.

Clinical and Pathophysiological Subtypes

Narcolepsy type 2 due to a medical condition This condition fulfills the criteria for narcolepsy type 2 and is attributable to another medical disorder. Neurologic disorders associated with narcolepsy type 2 include tumors or sarcoidosis of the hypothalamus, autoimmune or paraneoplastic disorders associated with anti-Ma-2 or anti-aquaporin-4 antibodies, multiple sclerosis, myotonic dystrophy, Prader-Willi syndrome, Parkinson's disease, and head trauma. In disorders associated with both sleep apnea and narcolepsy type 2, such as myotonic dystrophy or Prader-Willi syndrome, a diagnosis of narcolepsy type 2 should only be made if abnormal MSLT findings persist after the sleep apnea is adequately treated, and

sleep insufficiency is excluded as a cause of symptoms. In all cases, especially with complex problems such as head trauma, clinical judgment should be used to determine if the development of narcolepsy was a mere coincidence or was triggered by the event or disorder.

Demographics

The exact prevalence of narcolepsy type 2 is uncertain. Difficulties in making the diagnosis and test characteristics of the MSLT complicate epidemiological studies. In particular, the MSLT demonstrates poor test-retest reliability and elevated rates of potential false positives on MSLT (especially in persons with shift work and sleep restriction). Prevalence estimates of 20 to 34 per 100,000 have been made for narcolepsy without cataplexy, with more recent U.S. insurance claims data suggesting a prevalence of 65 per 100,000. However, estimates in Europe have been far lower. Although both sexes can be affected, the prevalence may be slightly higher in females. The age of onset mirrors that of narcolepsy type 1.

Predisposing and Precipitating Factors

As discussed below, approximately 15-20% of patients with narcolepsy but no cataplexy, particularly those with severely abnormal MSLT results, have low CSF Hcrt-1 levels, and almost all of these are positive for the HLA DQB1*06:02 antigen. This proportion has been estimated at 15% in one study in which all other causes of false-positive findings were carefully eliminated, and patients with atypical cataplexy were included. It is likely much lower in general clinical practice. Many of these subjects developed cataplexy over the years. These patients probably share a common pathogenesis with narcolepsy with cataplexy and should be classified as narcolepsy type 1. Reports indicate that narcolepsy without cataplexy but with hypocretin deficiency is more frequent in people of African descent. Underlying genetic and environmental factors associated with other patients with narcolepsy type 2 are unknown. Case reports have suggested environmental precipitating factors, but these factors have never been proven to trigger narcolepsy without cataplexy.

Familial Patterns

The detailed genetic pattern of narcolepsy type 2 is unknown. Relatives of patients with narcolepsy type 1 may be more likely to experience partial narcolepsy symptoms compatible with a diagnosis of narcolepsy type 2.

Onset, Course, and Complications

Onset typically occurs during adolescence. In a small portion of patients, cataplexy develops later in the course of the disease, necessitating a change in diagnosis to narcolepsy type 1. All these patients are HLA-DQB1*06:02 positive. Most of these patients, if tested, have absent or intermediate levels of CSF Hcrt-1 even before the development of cataplexy. In a cohort of patients with narcolepsy without cataplexy in whom CSF Hcrt-1 status was known, 33% of those with low levels later developed cataplexy, compared with 18% with intermediate levels and only 1% with normal levels.

When left untreated, narcolepsy type 2 is socially disabling and isolating. Patients tend to fail in school and are often dismissed from their jobs. Driving may be avoided for fear of a motor vehicle accident. The inability to maintain sleep at night may further contribute to a loss of control over patients' schedules. Depression is relatively common with an additional impact on quality of life. Weight gain may occur but less frequently than in NT1. There are limited data regarding spontaneous remission. However, one retrospective longitudinal study reported remission in 45% of patients with narcolepsy without cataplexy at 5 years.

Developmental Issues

NT2 seems to be less common in (young) children. In all pediatric cases, one should consider the possibility of an evolving disorder with the development of cataplexy over time. Once the patient develops clear cataplexy, the diagnosis should be changed to narcolepsy type 1. Limited information is available on narcolepsy type 2 that occurs prior to adolescence. The clinical presentation in children may be different from that of adults. In young children, sleepiness may be difficult to assess and may express itself as excessively long night sleep, or the recurrence of previously discontinued daytime napping. Moreover, children may paradoxically present with hyperactive behavior, behavioral problems, or decreased performance in school. Inattentiveness, lack of energy, insomnia, bizarre hallucinations, or a combination thereof can lead to a psychiatric misdiagnosis of attention-deficit/hyperactivity disorder, schizophrenia, autism spectrum disorder, or depression. Descriptions of the experience of sleep paralysis or hypnagogic hallucinations are very difficult to evoke in young patients and estimates of the prevalence of these symptoms are only available for NT1. In peripubertal children and adolescents, the diagnosis is often challenging. The most common causes of short sleep latencies, often with multiple SOREMPs on the MSLT, are chronic sleep deprivation and delayed sleep-wake phase disorder. Behavioral problems may be associated with the onset of the disorder, and the patient may hide symptoms. Hypocretin measurement can identify those younger patients with narcolepsy type 1 who have not yet developed cataplexy.

Pathology and Pathophysiology

Narcolepsy type 2 is most likely a heterogeneous disorder. A small portion of patients with narcolepsy without cataplexy have low (≤ 110 pg/ml) or intermediate (> 110 pg/mL but ≤ 200 pg/mL) CSF Hcrt-1 levels. However, the CSF Hcrt-1 status of most patients diagnosed with narcolepsy type 2 is unknown as

CSF hypocretin is rarely tested in these patients. Therefore, a subgroup of patients initially diagnosed with narcolepsy type 2 have yet unidentified hypocretin deficiency, presumably from loss of the hypocretin-producing neurons. These patients should be reclassified as narcolepsy type 1 upon the emergence of definite cataplexy or determination of their hypocretin deficiency. HLA DQB1*06:02 seems to be almost a prerequisite for hypocretin deficiency in this group. Hypocretin deficiency cannot be accurately predicted by laboratory tests (other than CSF Hcrt-1 level) in the majority of patients without cataplexy. Those with low CSF Hcrt-1 levels have a younger age of onset and shorter mean sleep latency with more SOREMPs on MSLT than those with normal levels. However, there is too much overlap between the groups for these differences to be helpful diagnostically in individual patients. The underlying pathophysiology of the remainder of patients who have normal CSF Hcrt-1 levels is unknown. Some may have partial hypocretin deficiency that is severe enough to cause sleepiness but not severe enough to result in cataplexy or low CSF Hcrt-1 levels. However, support for this hypothesis is lacking in that there are no major differences in clinical or polysomnographic findings in those positive or negative for HLA DQB1*06:02. In the only postmortem study of a case of narcolepsy without cataplexy (CSF Hcrt-1 status unknown), the number of hypocretin cells was decreased but not as much as in cases of narcolepsy with cataplexy.

In patients with normal CSF hypocretin who are unlikely to ever develop cataplexy (e.g., DQB1*06:02 negative individuals), pathophysiology and natural evolution are unknown. The disease may not always be lifelong. Further, as discussed below, it has recently been established that MSLT SOREMPs in these subjects may not be a stable trait, raising the question of whether a large portion of NT2 is truly distinguishable from patients with Idiopathic Hypersomnia. This issue is the object of intense research currently.

Objective Findings

The MSLT demonstrates a mean latency of less than or equal to eight minutes, typically less than five minutes, with two or more SOREMPs or one SOREMP and a SOREMP on the preceding polysomnogram. One to two weeks of sleep logs, with actigraphy, whenever possible, should precede the MSLT to establish whether the MSLT results are biased by insufficient sleep, shift work, or another circadian sleep disorder. Unfortunately, recent studies have shown that MSLT results in disorders other than NT1 often are inconsistent over time. Some patients fulfilling the criteria of NT2 may, over time, meet the criteria of idiopathic hypersomnia (IH) and vice versa, or not meet objective criteria for either NT2 or IH when retested. Test-retest reliability may be less than 50%. This poor reliability may be due to day-to-day variability in NT2 physiology, technical aspects of the PSG and MSLT testing, and, especially, inadequate attention to prior sleep time/schedule and medication/drug use.

Population-based studies have shown that approximately 4% to 9.5% of adults may have multiple SOREMPs during random MSLTs but shift workers and subjects with sleep deprivation or sleep apnea were included in the studies.

For the correct interpretation of polysomnography and MSLT findings, the recordings should be performed with the following conditions: (1) the patient must be free of drugs that influence sleep propensity and architecture for at least 14 days (or at least five times the half-life of the drug and longer-acting metabolite). In certain situations, a urine drug screen may be warranted; (2) the sleep-wake schedule must have been standardized and, if necessary, extended to a minimum of seven hours in bed each night (ideally more and longer for children) for at least seven days before polysomnography (documented by sleep logs, accompanied by actigraphy, whenever possible); and (3) nocturnal polysomnography should be performed on the night immediately preceding the MSLT to rule out other sleep disorders that could mimic the diagnostic features of narcolepsy type 2. Sleep time during polysomnography should be curtailed as little as possible, with the goal of at least seven hours asleep.

Only a minority of patients without cataplexy, almost all HLA-DQB1*06:02 positive, have hypocretin deficiency. In contrast, about a quarter of the general population is HLA-DQB1*06:02 positive by chance. Therefore, the HLA status of a patient cannot be used to diagnose narcolepsy type 2 nor to predict with high probability the patient's CSF Hcrt-1 levels. However, if lumbar puncture is contemplated to measure CSF Hcrt-1 levels, HLA typing could be performed first; if the patient is HLA negative, CSF Hcrt-1 levels will almost certainly be normal, rendering the lumbar puncture unnecessary.

Approximately 15-20% of narcoleptic patients without cataplexy have low (≤ 110 pg/ml) or intermediate (> 110 pg/mL but ≤ 200 pg/mL) CSF-Hcrt-1 levels. Again, if the CSF Hcrt-1 levels of such patients are low, they are classified as narcolepsy type 1. Indications for measuring CSF Hcrt-1 levels as a diagnostic procedure are the presence of disorders such as obstructive sleep apnea, confounding psychiatric diagnosis, or the use of psychotropic medications that may complicate interpretation of an MSLT.

Differential Diagnosis

Other central hypersomnolence disorders *Narcolepsy type 1* is diagnosed if cataplexy is present or the CSF hypocretin levels are known to be low, even in the absence of cataplexy. Patients with *idiopathic hypersomnia* may have mean sleep latencies on MSLT similar to those of narcolepsy type 2 but have fewer than two SOREMPs on MSLT and the preceding polysomnogram combined. In contrast to patients with narcolepsy, those with *idiopathic hypersomnia*, particularly those with long sleep, generally have higher nocturnal sleep efficiency. They also tend to have longer and unrefreshing daytime naps and frequent sleep inertia (prolonged difficulty awakening).

Other causes of sleepiness Sleepiness may be secondary to obstructive sleep apnea (OSA), insufficient sleep, shift work, the effects of substances or medications, or other sleep disorders. Many of these conditions can result in early-onset REM sleep, so their clinical and polysomnographic exclusion is essential before a diagnosis of narcolepsy type 2 is made. However, the presence of other sleep disorders

does not preclude a diagnosis of narcolepsy type 2 if daytime sleepiness and REM abnormalities persist after adequate treatment of the initial disorder.

Chronic fatigue syndrome and *depression* may mimic narcolepsy but do not show the typical MSLT findings. However, they may also be comorbid. *Malingering and substance abuse disorder* should be considered in patients who try to mislead the clinician to obtain stimulant medications.

Unresolved Issues and Further Directions

Excluding the minority of patients with definite hypocretin deficiency, who then qualify for NT1, the underlying biology of narcolepsy without the presence of cataplexy is unknown. Narcolepsy type 2 appears to be a heterogeneous condition. Some may develop narcolepsy type 1 over time, but sleep curtailment, circadian misalignment, or other unidentified conditions may also cause the phenotype. It is uncertain whether or not some patients have partial hypocretin deficiency not identifiable from CSF measurements. It also appears that some portion of patients fulfilling the criteria of NT2 may, over time, qualify for the criteria of IH and vice versa. Further advances in classification depend on answers to these unknowns. Further studies on the natural history of narcolepsy type 2 are needed to determine the cause of the hypersomnolence and the risk of development of cataplexy over time.

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Idiopathic Hypersomnia

ICD-9-CM code: 327.11

ICD-10-CM code: G47.11

Alternate Names

Idiopathic CNS hypersomnolence.

Diagnostic Criteria

Criteria A-F must be met

- A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.¹
- B. Cataplexy is absent.
- C. Polysomnography and MSLT findings are not consistent with a diagnosis of narcolepsy type 1 or 2.
- D. The presence of at least one of the following:
 1. The MSLT, performed in accordance with current recommended protocols², shows a mean sleep latency of ≤ 8 minutes.
 2. Total 24-hour sleep time is ≥ 660 minutes (typically 12–14 hours) on 24-hour polysomnographic monitoring (performed after correction of chronic sleep deprivation), or by wrist actigraphy in association with a sleep log (averaged over at least seven days with unrestricted sleep).^{3,4}
- E. Insufficient sleep is ruled out (if deemed necessary, by lack of improvement of sleepiness after an adequate trial of increased nocturnal time in bed, preferably confirmed by at least a week of wrist actigraphy).
- F. The symptoms and signs are not better explained by a circadian rhythm sleep-wake disorder or other current sleep disorder, medical disorder, mental disorder, or medication/substance use or withdrawal.

Notes

1. Severe and prolonged sleep inertia, known as sleep drunkenness (defined as prolonged difficulty waking up with repeated returns to sleep, irritability, automatic behavior, and confusion) and long (> 1 hour), unrefreshing naps are additional supportive clinical features.
2. See references – AASM Recommended Protocols for the MSLT and MWT in Adults. Sleep logs are required, accompanied by actigraphy, whenever possible, prior to in-laboratory sleep testing to evaluate for insufficient sleep and circadian rhythm disturbances.
3. In some cases, patients fulfilling other criteria may have an MSLT mean sleep latency longer than 8 minutes and total 24-hour sleep time shorter than 660 minutes. Clinical judgment should be used to decide if these patients should be considered to have idiopathic hypersomnia (IH). Great caution should be exercised to exclude other conditions that might mimic the disorder. Repeat testing at a later date is advisable if the clinical suspicion for IH remains high.
4. The total 24-hour sleep time required for diagnosis may need to be adapted to account for normal changes in sleep time associated with stages of development in children and adolescents, as well as for variability across cultures in all age groups.

Essential Features

IH is characterized by excessive daytime sleepiness that occurs in the absence of cataplexy, is accompanied by no more than one SOREMP on MSLT and preceding polysomnogram combined and is not adequately explained by another disorder. Other disorders causing sleepiness must be carefully considered and excluded, especially insufficient sleep syndrome. Objective evidence of hypersomnolence must be demonstrated by an MSLT showing a mean sleep latency of ≤ 8 minutes or by polysomnography or wrist actigraphy showing a total 24-hour sleep time of ≥ 660 minutes. A prolonged and severe form of sleep inertia, historically known as sleep drunkenness, consists of prolonged difficulty waking up with repeated returns to sleep, irritability, automatic behavior, and confusion. It is reported in 36% to 66% of patients with IH in different series. Subjects typically do not easily awaken to alarm clocks and frequently use special devices or procedures to wake up. Naps are generally long, often more than 60 minutes, and described as unrefreshing by 46% to 78% of patients. Sleep efficiency on polysomnogram can be greater than 90%. Self-reported total sleep time is longer than in controls and is ≥ 10 hours in at least 30% of patients.

Associated Features

Associated symptoms which suggest a dysfunction of the autonomic nervous system may be present. These symptoms include headache, orthostatic disturbance, perception of temperature dysregulation, and peripheral vascular complaints (Raynaud-type phenomena with cold hands and feet). Memory and attention difficulties and depression may also accompany IH symptoms. Sleep paralysis and hypnagogic hallucinations may also be reported, but the frequency is uncertain (4% to 40% in various series).

Clinical and Pathologic Subtypes

IH is likely a heterogeneous condition with unknown pathophysiology, complicating pathologic subtyping. The 2005 2nd edition of the International Classification of Sleep Disorders divided IH into two disorders: IH with long sleep time and IH without long sleep time. The 3rd edition of the ICSD consolidated IH into one disorder. This consolidation of diagnostic entities was supported by some prior research that suggested that a division of the disorder based on the length of nocturnal sleep was questionable. Comparison of patients with ≥ 10 hours of sleep to those with < 10 hours showed no clear differences in Epworth Sleepiness Scale scores, MSLT mean sleep latencies, hypnagogic hallucinations, or sleep paralysis. However, other studies have demonstrated that patients with long sleep duration have higher rates of sleep drunkenness and unrefreshing naps, younger age of onset, lower body mass index, a higher percentage of women affected, and a tendency to an evening chronotype. A cluster analysis identifying more homogeneous subclassifications of central hypersomnias also found IH with long sleep time as an independent clinical entity while IH group without long sleep time and narcolepsy type 2 share substantial phenotypic overlap. Longitudinal data have suggested IH without long sleep time and NT2 may also have similar remission rates over time. Another clustering analysis identified a more severe hypersomnolence phenotype associated with longer sleep duration, more significant daytime sleepiness, sleep inertia,

functional impairment, and elevated depressive symptoms. Therefore, emerging data suggests IH with long sleep duration likely represents a more homogeneous IH entity.

Demographics

The prevalence of IH is difficult to determine with certainty but, based on comparison with narcolepsy prevalence in sleep centers and insurance claims data, it has been estimated to be around 0.002%-0.010%. Some studies have suggested a higher prevalence in women, particularly in IH with long sleep duration.

Predisposing and Precipitating Factors

In contrast to narcolepsy type 1, the disorder is not known to be HLA-associated, and no consistent precipitating factor has been identified.

Familial Patterns

A familial predisposition to this condition has been reported in almost 30% of IH patients, suggesting a genetic component.

Onset, Course, and Complications

The mean age of onset of IH in different series is 16.6–21.2 years. Once established, the disorder is generally stable in severity and long-lasting for the majority of patients; however, case series have reported spontaneous remission rates of 14-25%. One retrospective longitudinal study demonstrated remission rates of 32% at 5.5 years. Complications are primarily social and professional and include poor work or school performance, reduced earnings, and loss of employment.

Developmental Issues

IH frequently develops in adolescence. It is essential to exclude other causes of hypersomnolence in that age group, including delayed sleep-wake phase disorder, mood disorders, insufficient sleep, and use of recreational drugs. Early in the development of narcolepsy, SOREMPs may not be present on MSLT; therefore, some patients may need to be reclassified later as narcolepsy. If the 24-hour total sleep time is used to confirm the diagnosis of IH in a child or adolescent, values considered abnormal must reflect changes in sleep time associated with stages of development. Evolution is unknown, and the disease may not be lifelong in all patients.

Pathology and Pathophysiology

The pathophysiology of IH is not known. Neurochemical studies measuring monoamine metabolites in the CSF have been inconclusive. CSF hypocretin-1 concentrations in patients with IH are normal. However, alteration in histaminergic or dopaminergic signaling may be involved as well as altered homeostatic function. Some studies revealed longer circadian period length, explaining the tendency to evening chronotype and difficulties in awakening. Other investigations have suggested endogenous GABA-A receptor potentiation, though these findings have not been replicated. Arousal system deficiency is still a plausible factor, as some functional brain imaging studies suggest, although a clear neurochemical background has not been identified.

Objective Findings

Polysomnographic monitoring generally demonstrates cycles of NREM and REM sleep with normal REM latency. Total sleep time is often prolonged with, on average, shorter sleep latency, reduced slow wave sleep, and increased REM sleep. A significant effect of sex on sleep efficiency was found, with female sex being associated with lower sleep efficiency among pooled studies. Sleep apnea should be either absent or adequately treated before diagnosing this disorder, with particular attention to excluding significant respiratory effort-related arousals. The MSLT should not meet the diagnostic criteria for narcolepsy. The mean sleep latency on the MSLT is usually shorter than in controls but longer than in most patients with narcolepsy, averaging 8.3 and 7.8 minutes in two large studies.

Unfortunately, recent studies have shown that MSLT results in disorders other than NT1 often are not consistent over time. Some patients fulfilling the criteria of NT2 may, over time, qualify for the criteria of IH and vice versa, or not meet objective criteria for either NT2 or IH when retested. Test-retest reliability may be less than 50%. This poor reliability may be due to day-to-day variability in IH/NT2 physiology, technical aspects of the PSG and MSLT testing, or, in particular, inadequate attention to prior sleep time/schedule and medication/drug use.

In patients with MSLT mean latencies > 8 minutes and a long sleep phenotype, prolonged sleep monitoring should be performed by polysomnography (24 hours) or wrist actigraphy (seven days with unrestricted sleep) after correction of sleep deprivation, exclusion of other sleep disorders, and discontinuation of sedating medication, as required for an MSLT (see Narcolepsy—Objective Findings). Total 24-hour sleep time in adults (major sleep episode plus naps) must be \geq 660 minutes (note that the use of 24-hour PSG monitoring for the diagnosis of IH has been validated against controls, but the use of seven days of actigraphic monitoring has not been). A diagnostic threshold of 19 hours on a prolonged 32-hour bedrest protocol has also been proposed.

Differential Diagnosis

Insufficient sleep must be carefully excluded by extending the patient's sleep before testing. In individuals with physiologic sleep needs in excess of seven to eight hours, average sleep duration (e.g., seven hours/night in adults) may, in fact, be insufficient.

Other central hypersomnolence disorders *Narcolepsy type 2* is distinguished from IH by the presence of two or more sleep-onset REM periods on the MSLT or preceding PSG. It is essential to rule out other potential causes of hypersomnolence by historical information, physical examination, and, if indicated, laboratory testing, including brain imaging. These causes include *hypersomnia due to a medical disorder*, specifically *posttraumatic hypersomnia*, *residual hypersomnia following adequate treatment of sleep apnea*, and *sleep fragmentation due to pain*, all of which may mimic IH. *Hypersomnia due to a medication or substance* must be considered and ruled out by discontinuation of possible causative agents, if clinically appropriate. *Hypersomnia associated with a psychiatric disorder* should be considered in patients with a psychiatric condition, most typically depression. The complaint of excessive sleepiness and prolonged sleep may be similar to that of patients with IH, except that it may vary from day to day and is often associated with poor sleep at night. The MSLT in hypersomnia associated with a psychiatric disorder does not usually demonstrate a short mean sleep latency.

Other causes of sleepiness IH may be confused with *OSA*, especially when respiratory effort-related arousals (rather than apneas or hypopneas) are present.

Chronic fatigue syndrome is characterized by persistent or relapsing fatigue that does not resolve with sleep or rest. Patients clearly complain of fatigue rather than excessive daytime sleepiness, and the mean MSLT sleep latency is normal. *Long sleepers* feel fully refreshed and do not experience daytime sleepiness if they are allowed to sleep as long as they need. In contrast, patients with IH continue to feel sleepy regardless of prior sleep duration.

Unresolved Issues and Future Directions

There is a paucity of knowledge regarding the neurobiology of IH. Further research in this area and more precise characterization of clinical characteristics and treatment response are required. Given overlapping clinical phenotypes and similar course of illness for *Narcolepsy type 2* and IH without long sleep time, future research that clarifies the veracity of segregating these entities into separate conditions is also warranted. Additional research is also required to clarify the pathophysiological and genetic background of excessive sleep duration in IH.

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Kleine-Levin Syndrome

ICD-9-CM code: 327.13

ICD-10-CM code: G47.13

Alternate Names

Recurrent hypersomnia, periodic hypersomnolence.

Diagnostic Criteria

Criteria A-E must be met

- A. The patient experiences at least two recurrent episodes of excessive sleepiness and sleep duration, each persisting for two days to several weeks.
- B. Episodes usually recur more than once a year and at least once every 18 months.
- C. The patient has normal or near normal sleep and wakefulness, cognition, behavior, and mood between episodes, at least during the first years of the syndrome.¹
- D. The patient must demonstrate at least *one* of the following during episodes:
 1. Cognitive dysfunction
 2. Derealization
 3. Major apathy
 4. Disinhibited behavior (such as hypersexuality or hyperphagia)
- E. The symptoms and signs are not better explained by chronic insufficient sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, medical disorder, mental disorder, or medication/substance use or withdrawal.

Notes

1. Several new studies in a large series show that sleep duration is longer, cognition is mildly altered, and some psychiatric disorders may be evident in 15-20% of patients during inter-episodic periods over the longitudinal course of the disorder.

Essential Features

Kleine-Levin syndrome is characterized by relapsing-remitting episodes of severe hypersomnolence in association with cognitive, psychiatric, and behavioral disturbances. A typical episode starts abruptly and lasts a median 10 days (range, 2.5–80 days), with rare episodes lasting several weeks to months in 30% of patients. The first episode is often triggered by an infection or alcohol intake, with further episodes recurring every 1–12 months (median three months) for years. During episodes, patients may sleep as long as 16 to 20 hours per day, waking or getting up only to eat and void (incontinence is not observed). They remain arousable but are irritable if prevented from sleeping. When they are awake during episodes, most patients are exhausted, apathetic, confused, and slow in speaking and answering. Anterograde amnesia is typical. Major apathy is characterized by a severe reduction of usual motivated behaviors (e.g., neglecting phone calls, social networks, personal hygiene, and eating). Almost all report a dreamlike, altered perception of the environment, feeling it is unreal (derealization). Less commonly, patients eat ravenously (40–66%). They may exhibit hypersexuality (42–53%, principally men), childishness, depression (53%, predominantly women), and anxiety at being left alone and seeing strangers. Hallucinations and

delusions may also be reported (30%). Inter-episodic sleep, cognition, mood, and eating are normal, at least during the first years of the syndrome.

The disease typically resolves after a median of 14 years, except in adult-onset cases, when the course may be even more prolonged. The simultaneous occurrence of all these symptoms is the exception rather than the rule, with hypersomnolence being more characteristic at the disease onset and during the first part of the episodes, and disinhibited behaviors being evident during only a few episodes. Isolated recurrent hypersomnolence may be the only symptom in some cases. Amnesia, transient dysphoria, or elation with insomnia may signal the termination of an episode.

Associated Features

Physical examination is unremarkable, except for general psychomotor slowing. Some patients complain of headache and sensory hyperesthesia (photo/phonophobia). Social and occupational impairment during episodes is often severe, with teenagers bedridden for days, but can be variable depending on the frequency, severity, and duration of episodes.

Clinical and Pathophysiological Subtypes

Menstrual-related Kleine-Levin syndrome (alternate name: menstrual-related hypersomnia) This descriptor is used when episodes are exclusively associated with menstruation (occurring just before or during menses), a condition reported in only 18 women worldwide. Hypersomnolence episodes in these cases have been associated with compulsive eating in 65%, sexual disinhibition in 29%, and depressive mood in 35%. Episodes last 3 to 15 days and recur less than three times a year. One boy with Kleine-Levin syndrome is reported to have a sister affected by menstrual-related hypersomnolence. Menstrual-related hypersomnia may be a variant of Kleine-Levin syndrome, although response to contraceptive doses of estrogen and progesterone, reported in some cases, suggests a reproductive endocrine disturbance.

Demographics

Kleine-Levin syndrome is rare, with a prevalence estimated at around 3 to 4 cases per million and a yearly incidence of 0.3 new cases per million. Around 1000 cases have been reported to date in the literature, from all countries in which the disease has been investigated. The disease starts during the second decade in 81% of patients, with a male/female ratio of 2:1. Adults and younger children may also be affected.

Predisposing and Precipitating Factors

Birth and developmental problems (found in one-third of patients) and Ashkenazi descent are risk factors for developing the syndrome. A genome-wide study in 844 patients with Kleine-Levin syndrome shows that gene polymorphisms in the TRANK1 region (chromosome 3) increase the risk of Kleine-Levin syndrome, but only in the presence of a perinatal injury. No robust association with HLA genotypes has been confirmed. A flu-like illness or an infection of the upper airway (and, more rarely, gastroenteritis) is often reported immediately prior to the onset of the first episode and, rarely, before relapses. Other less frequently reported triggering events include alcohol consumption, sleep deprivation, stress, travel, and head trauma.

Familial Patterns

Familial cases of Kleine-Levin syndrome are found in 8% of patients, including twins, parent-child, siblings, and uncle-nephew associations. There is no increased history of mood disorders in family members of patients. The familial form of Kleine-Levin syndrome is primarily present in the same generation and is clinically similar but slightly less severe than the sporadic form. Exome sequencing was unrevealing in 14 multiplex families.

Onset, Course, and Complications

Early adolescence is the usual age of onset. The course of Kleine-Levin syndrome is characterized by recurrent episodes of severe sleepiness, lasting up to several weeks, with normal functioning between episodes. Several long-term studies suggest an often-benign course, with episodes lessening in duration, severity, and frequency over a median course of 14 years. Male sex, age at onset younger than 12 years or older than 20 years, and the presence of hypersexuality during episodes predict longer disease duration. Complications are mainly social and occupational. In rare cases, affected individuals have experienced suicidal thoughts, choking while eating voraciously, or a car accident during an episode. After a mean of five years with KLS symptoms, 15-20% of patients have residual, mild sleep, cognitive or psychiatric symptoms during 'asymptomatic' periods. These symptoms may include longer sleep time, slower processing speeds, reduced attention and reduced retrieval strategies in episodic verbal memory, and mood and anxiety disorders.

Developmental Issues

Adolescents are affected in most cases. However, the onset of the condition has been reported in younger children.

Pathology and Pathophysiology

Postmortem examination of the central nervous system has been performed in only four cases, with inconsistent findings. One subject showed significant perivascular lymphocytic infiltrations in the hypothalamus, amygdala, and the grey matter of the temporal lobes; a second demonstrated similar infiltrations in the thalamus; and a third in the diencephalon and the midbrain, with a suggestion of mild localized encephalitis. In the fourth case, a smaller locus coeruleus and decreased pigmentation in the substantia nigra were reported. Magnetic resonance imaging was unremarkable. In contrast, functional brain imaging studies during episodes are frequently abnormal, showing hypometabolism in the thalamus, hypothalamus, hippocampus, and posterior associative cortex. Hypometabolism in the posterior associative cortex and hippocampus persist during asymptomatic periods in 70%. An autoimmune basis has been suggested because of the adolescent onset (which often occurs in conjunction with an infection) and the recurrent aspect of the disorder. Circadian abnormalities may also play a role.

Objective Findings

Routine electroencephalograms obtained during episodes have shown a general slowing of background electroencephalographic activity and often paroxysmal 0.5-2.0-second bursts of bisynchronous, generalized, moderate- to high-voltage 5- to 7-Hz waves. Polysomnography studies are often difficult to interpret, and results depend on the duration of recording (overnight vs. 24-hour monitoring) and the timing (at the beginning versus the end of episodes or at the onset of the disease or later in its course). Twenty-four-hour polysomnography demonstrates prolonged total sleep time (a mean 11–12 hours) and 18 hours or more in some reports. During nocturnal polysomnography in 17 children, nighttime slow wave sleep percentage was decreased during the first half of the episodes, and REM sleep decreased during the second half.

Results of the MSLT are highly dependent on the subjects' willingness to comply with the procedure and may either be normal or abnormal, showing short latencies or multiple SOREMPs. Actigraphy demonstrates a significant decrease in the amplitude (but not the phase) of rest-active rhythm during episodes. CSF cytology and protein are normal. CSF levels of hypocretin-1 are generally within normal range during episodes, although they have been reported to be one-third lower during symptomatic versus asymptomatic periods. Computed tomography scans and magnetic resonance imaging are normal. Brain functional imaging is abnormal in most cases, with hypoperfusion/hypometabolism of the thalamus, hypothalamus, posterior associative cortex, and hippocampus. Some hypermetabolism is occasionally found in the frontal lobe. These abnormalities are present during an episode of hypersomnolence and often between episodes. Hormone levels are normal, as are 24-hour secretory patterns.

Differential Diagnosis

Structural insults of the central nervous system Recurrent waxing and waning episodes of sleepiness may reflect a structural neurological disorder. *Tumors within the third ventricle* (such as colloid cysts, pedunculated astrocytomas, or, in some cases, craniopharyngiomas) may produce intermittent obstructions of ventricular flow, leading to headaches, vomiting, vague sensorial disturbances, and a paroxysmal impairment of alertness.

Other neurological and medical disorders *Encephalitis, hyperammonemic encephalopathy, multiple sclerosis, head trauma, porphyria, Lyme disease, basilar migraine, and complex partial status epilepticus* less frequently mimic symptoms of Kleine-Levin syndrome.

Mental disorders Recurrent episodes of sleepiness also are reported in the context of psychiatric disorders, such as *depression, bipolar disorder, seasonal affective disorder, and somatoform disorder*. However, the onset and offset of symptoms are less abrupt than in Kleine-Levin syndrome and persist to some extent between episodes.

Other causes of sleepiness Include *excessive sleepiness due to a medication or substance, OSA, narcolepsy, IH, and insufficient sleep*. However, in these disorders, the complaint of excessive sleepiness occurs daily and is usually not recurrent or periodic.

There is no evidence that Kleine-Levin syndrome occurs as a result of a seizure disorder.

Unresolved Issues and Future Directions

The pathophysiology of this disorder is not known. However, evidence suggests that a localized but multifocal encephalopathy occurs during episodes of Kleine-Levin syndrome, as functional imaging, and electroencephalography (EEG) slowing indicate thalamic, temporal, and frontal lobe involvement. The cause of these episodic abnormalities may be genetic, autoimmune, inflammatory, or metabolic.

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Hypersomnia Associated with a Medical Disorder

ICD-9-CM code: 327.14

ICD-10-CM code: G47.14

Alternate Names

Hypersomnolence Associated with a Medical Disorder.

Diagnostic Criteria

Criteria A and B and C must be met

- A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.
- B. The daytime sleepiness occurs as a consequence of a significant underlying medical or neurological condition.¹
- C. The symptoms and signs are not better explained by chronic insufficient sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, mental disorder, or medication/substance use or withdrawal.

Notes

1. Should polysomnography and MSLT be performed and criteria for narcolepsy fulfilled, a diagnosis of narcolepsy type 1 or type 2 due to a medical condition should be used rather than hypersomnia due to a medical condition.

Essential Features

Patients with this disorder have excessive nocturnal sleep, daytime sleepiness, or excessive napping that is attributable to a coexisting medical or neurological disorder. Daytime sleepiness may be of variable severity and may resemble that of narcolepsy (i.e., refreshing naps) or idiopathic hypersomnia (i.e., long periods of unrefreshing sleep). Sleep paralysis, hypnagogic hallucinations, or automatic behavior may be present. However, if the patient meets the diagnostic criteria for narcolepsy (based on cataplexy, PSG/MSLT findings, or CSF Hcrt-1 levels), then narcolepsy (type 1 or type 2) due to a medical condition should be diagnosed. In patients with both sleep-related breathing disorders and hypersomnia associated with a medical disorder, the latter diagnosis should only be made if the hypersomnolence persists after adequate treatment of the sleep-related breathing disorder. Hypersomnia due to a medical disorder is only diagnosed if the medical condition is judged to be the primary cause of the excessive sleepiness. Hypersomnolence is associated with many conditions, including metabolic encephalopathy, head trauma, stroke, brain tumors, encephalitis, systemic inflammation (e.g., chronic infections, rheumatologic disorders, cancer), genetic disorders, and neurodegenerative diseases.

Associated Features

Not applicable or known.

Clinical and Pathophysiological Subtypes

Many medical conditions can cause hypersomnolence.

Hypersomnia secondary to Parkinson’s disease and dementia with Lewy bodies One-third of patients with Parkinson’s disease complain of excessive daytime sleepiness, which may be related to the severity of the disease, depression, or a combination of neurodegeneration and medication. Significant hypersomnolence documented by MSLT has been reported in some cases of Parkinson’s disease and half of the cases of dementia with Lewy bodies. Hypersomnolence in Parkinson’s disease may be due to insufficient control of nocturnal symptoms, resulting in insufficient sleep and daytime sleepiness. Cases of hypersomnolence that are due to the side effects of dopaminergic agents should be coded as hypersomnia due to a medication or substance. In other cases, however, hypersomnolence is likely of central origin and should be classified in this section. Parkinson’s disease patients with an MSLT profile consistent with narcolepsy should be coded as narcolepsy due to a medical condition.

Posttraumatic hypersomnia Hypersomnolence appears to be common after traumatic brain injury (TBI), with one meta-analysis suggesting a frequency of 28% of TBI patients. In a prospective study, 42 patients with TBI slept on average one hour longer than healthy controls (a condition called “post-traumatic pleiosomnia”), and 59% of them had a mean sleep latency < 8 min on MSLT. Those with intracranial hemorrhage had a higher risk of posttraumatic hypersomnia. In some cases, this may be caused by injury to the hypocretin/orexin and histamine neurons or other wake-promoting neural systems.

Genetic disorders associated with primary central nervous system somnolence Genetic disorders such as Prader-Willi syndrome, myotonic dystrophy, fragile X, Moebius syndrome, Niemann Pick type C disease, and Norrie disease are associated with daytime somnolence, excessive sleep time, and abnormal MSLT. Several genetic disorders are associated with both sleep-related breathing disorders and hypersomnolence (e.g., myotonic dystrophy and Prader-Willi syndrome). In these cases, hypersomnia due to a medical disorder should be diagnosed only if the excessive sleepiness is still present after adequate treatment of the SRBD. Patients with Prader-Willi syndrome and myotonic dystrophy with an MSLT profile consistent with narcolepsy should be coded as narcolepsy due to a medical condition.

Hypersomnia secondary to brain tumors, infections, inflammation, or other central nervous system lesions Strokes, infections, tumors, sarcoidosis, or neurodegenerative brain lesions, especially in the hypothalamus, thalamus, or rostral midbrain, may produce daytime sleepiness. In patients with brain tumors, the sleepiness may be due to the tumor itself or the effects of treatment. Patients with multiple sclerosis and hypersomnolence may present abnormal MSLT or prolonged sleep time, with or without fatigue.

Hypersomnia secondary to endocrine disorder Hypothyroidism is the most recognized example of this condition.

Hypersomnia secondary to metabolic encephalopathy Hepatic encephalopathy, chronic renal insufficiency, adrenal or pancreatic insufficiency, exposure to toxins, and certain inherited metabolic disorders may result in hypersomnolence.

Residual sleepiness in patients with adequately treated OSA Six percent of patients with SRBDs report persistent sleepiness despite apparently adequate amounts of sleep and optimal treatment of their sleep apnea and other known sleep disorders. They may have moderately elevated Epworth Sleepiness Scale scores, but many have mean sleep latencies > 8 minutes on MSLT. They also report more fatigue, apathy, and depression. It is essential that SRBD is fully treated for at least three months. Control of the SRBD must be confirmed by a download of positive airway pressure (PAP) machine adherence data demonstrating optimal usage (preferably at least 7 hours a night) and control of SRBD. A polysomnogram demonstrating elimination of essentially all sleep-related breathing disorders on current PAP settings and evaluating for other causes of the symptom may be required. Other causes of sleepiness, such as insufficient sleep, narcolepsy type 1 or 2, idiopathic hypersomnia, hypersomnolence associated with psychiatric disorders, or hypersomnolence related to medications or drugs, must be eliminated.

Animal studies have suggested this residual sleepiness could be caused by hypoxic injury to monoamine systems, whereas human studies only reported hemispheric white matter structural alterations using diffusion tensor imaging in OSA patients with versus without residual sleepiness. Obesity may also contribute, and more research is needed to understand the underlying mechanism.

Demographics

Demographics reflect those of the underlying condition.

Predisposing and Precipitating Factors

Predisposing and precipitating factors reflect those of the underlying condition.

Familial Patterns

Familial patterns reflect those of the underlying condition.

Onset, Course, and Complications

Onset, course, and complications reflect those of the underlying condition.

Developmental Issues

Daytime naps are normal in children younger than 3-4 years; thus, it is challenging to differentiate physiologic napping from hypersomnolence in children younger than this age. Inattentiveness, mood swings, and learning difficulties often accompany childhood daytime sleepiness. The MSLT is technically and clinically feasible in developmentally normal children aged 5 years and older, but normative values may vary according to pubertal stages. Particular attention should be paid to genetic disorders in children.

Pathology and Pathophysiology

Pathology and pathophysiology reflect those of the underlying condition (see above).

Objective Findings

Nocturnal polysomnography may show normal or moderately disturbed sleep. In patients with metabolic encephalopathy, EEG abnormalities may be present, such as an increase in the amount of slow wave sleep or EEG triphasic waves. If performed, MSLT must show fewer than two SOREMPs, and mean sleep latency is typically less than eight minutes. A prolonged sleep time (>10-11 h) during 24-hour bed rest can also be observed.

Differential Diagnosis

See the differential diagnosis in previous hypersomnolence sections. The major challenge in establishing a diagnosis of hypersomnia due to a medical disorder is determining whether the associated medical or neurological disorder is truly causing the hypersomnolence.

Unresolved Issues and Future Directions

This area is understudied. Multiple complex neurological, metabolic, endocrine, and medication-related interactions with sleep and wake pathophysiology may be present. Further studies are needed to define the reciprocal relationships between sleep disorders and other diseases.

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Hypersomnia Associated with a Medication or Substance

ICD-9-CM code: 292.85 (drug-induced); 291.82 (alcohol-induced)

ICD-10-CM code: F11-F19 (see table in Appendix B for detailed coding instructions)

Alternate Names

Hypersomnia due to substance abuse, hypersomnia due to stimulant withdrawal, hypersomnia due to sedative abuse, toxic hypersomnia, toxic encephalopathy, hypersomnolence due to a medication or substance.

Diagnostic Criteria

Criteria A-C must be met

- A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep.
- B. The daytime sleepiness occurs as a consequence of current medication or substance use or withdrawal from a wake-promoting medication or substance.
- C. The symptoms and signs are not better explained by chronic insufficient sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, medical disorder, or mental disorder.

Essential Features

Patients with this disorder have excessive nocturnal sleep, daytime sleepiness, or excessive napping attributable to sedating medications, alcohol, or drugs of abuse. This diagnosis also includes hypersomnolence associated with withdrawal from amphetamines and other drugs. If narcolepsy or hypersomnolence existed prior to stimulant abuse, the diagnosis of hypersomnia due to a medication or substance should not be used.

Associated Features

Associated features reflect those of the medications or substances responsible.

Clinical and Pathological Subtypes

Hypersomnia due to sedating medications Sedation is a common side effect of many prescription medications, including benzodiazepines, non-benzodiazepine hypnotics, opioids, barbiturates, anticonvulsants, antipsychotics, anticholinergics, and some antidepressants and antihistamines. Sleepiness can also occur with some dopamine agonists such as pramipexole or ropinirole and many antiseizure medications. Though less common, sleepiness can also occur with nonsteroidal anti-inflammatory drugs, some antibiotics, antispasmodics, antiarrhythmics, and beta-blockers. Over-the-counter medications, such as valerian and melatonin, can produce sedation. Excessive sleepiness is especially common when these drugs are used in elderly patients or those with multiple medical conditions, or in combination. Some tolerance to the sedative effects can occur with time.

Hypersomnia due to substance abuse Daytime sleepiness can occur with abuse of alcohol, benzodiazepines, barbiturates, gamma hydroxybutyrate, opiates, and marijuana.

Hypersomnia due to stimulant withdrawal Daytime sleepiness is common with abrupt discontinuation of stimulants. In chronically heavy amphetamine users, sleepiness is most severe in the first week of withdrawal and can persist for up to three weeks; individuals may experience an increase in total sleep and daytime napping, but sleep may be fragmented and nonrestorative. In addition, significant depression often accompanies the hypersomnolence. In people who regularly consume coffee or other sources of caffeine, discontinuation can produce sleepiness, fatigue, and inattentiveness for two to nine days.

Demographics

Patients of any age can experience sleepiness from sedating medications. Stimulant abuse and the consequent sleepiness during withdrawal are most common in adolescents and young adults.

Predisposing and Precipitating Factors

Sleepiness from sedating medications may be more common in older patients and those with multiple medical problems.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

Onset, course, and complications reflect those of the medications or substances responsible.

Pathology and Pathophysiology

Pathophysiology reflects that of the medications or substances responsible.

Objective Findings

Polysomnography is generally unnecessary unless a concomitant sleep disorder is suspected. Polysomnography and MSLT results vary depending on the specific substance in question and the timing of the most recent intake. Some substances affect sleep structure and breathing during sleep and may cause central sleep apneas. With stimulant withdrawal, nocturnal polysomnography may show normal sleep, whereas the MSLT typically demonstrates a short mean sleep latency with or without multiple SOREMPs. A urine toxicology screen may be positive for the suspected substance. The diagnosis is often confirmed if symptoms resolve after the causal agent is removed.

Differential Diagnosis

Other sleep disorders associated with excessive sleepiness, especially *SRBDs*, *periodic limb movement disorder*, *narcolepsy*, *IH*, and *insufficient sleep syndrome*, should be ruled out.

Consideration should be given to drug screening as part of the MSLT protocol, as the use of or withdrawal from some medications or substances may affect MSLT results.

Although many psychotropic medications may result in daytime sleepiness, clinicians need to recognize that many psychiatric disorders also are associated with increased prevalence of other sleep disorders (e.g., insomnia, SRBD, circadian disorders, and movement disorders). Therefore, although sedative effects of the psychotropic agents may contribute to sleepiness, clinicians must maintain a high index of suspicion for other sleep-related etiologies. When other sleep disorders are identified, multiple diagnoses may be appropriate.

Unresolved Issues and Future Directions

Sedatives may have variable effects on sleep-related breathing disorders, and more research is needed to understand differences among varying compounds and inter-individual effects of these medications.

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Hypersomnia Associated With a Psychiatric Disorder

ICD-9-CM code: 327.15

ICD-10-CM code: F51.13

Alternate Names

Hypersomnia not due to a substance or known physiological condition, hypersomnolence associated with a psychiatric disorder.

Diagnostic Criteria

Criteria A-C must be met

- A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.
- B. The daytime sleepiness occurs in association with a concurrent psychiatric disorder.
- C. The symptoms and signs are not better explained by chronic insufficient sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, medical disorder, or medication/substance use or withdrawal.

Essential Features

Patients with hypersomnia associated with a psychiatric disorder may report excessive nocturnal sleep, daytime sleepiness, or excessive napping. In addition, they often feel their sleep is of poor quality and nonrestorative. Patients may be intensely focused on their hypersomnolence, and psychiatric symptoms may only become apparent after lengthy interviews or psychometric testing. Associated psychiatric conditions include mood disorders, conversion or undifferentiated somatoform disorder, and less frequently other mental disorders such as schizoaffective disorder, adjustment disorder, or personality disorders.

Associated Features

Common symptoms are poor work or school attendance, spending entire days in bed several times a week, or abruptly leaving work, school, or other activity because of a perceived need to sleep. Patients may also have social withdrawal, apathy, and feelings of low energy.

Clinical and Pathological Subtypes:

Hypersomnia associated with mood disorder Hypersomnolence in the context of depression is a frequent feature of atypical depression and bipolar II disorder (recurrent major depressive episodes with hypomanic episodes). In seasonal affective disorder, daytime fatigue, loss of concentration, increased appetite for carbohydrates, and weight gain are reported. Some depressed patients may stay in bed longer without a significantly increased amount of sleep (i.e., clinophilia), while others may demonstrate increased sleep duration relative to healthy sleepers.

Hypersomnia associated with a conversion disorder or somatic symptom disorder Pseudohypersomnia and pseudonarcolepsy, sometimes with pseudocatataplexy, have been described.

Demographics

Among studies evaluating patients consecutively referred for PSG/MSLT, hypersomnolence associated with a psychiatric disorder accounts for roughly 11% to 19% of hypersomnolence cases. Women have a higher prevalence than men, and the typical age range is between 20 and 50 years. In patients with major depression, the prevalence of hypersomnolence ranges from 5% to over 50%, depending on how hypersomnolence is defined. Hypersomnolence affects over 50% of patients with seasonal affective disorder.

Predisposing and Precipitating Factors

Not applicable or known.

Familial Patterns

Not known, except for the familial patterns of certain psychiatric disorders (e.g., bipolar II disorder).

Onset, Course, and Complications

The mean age of onset is usually in the third decade in both sexes. With major depression, hypersomnolence may persist even after the depressive episode improves, and persistent hypersomnolence is associated with an increased risk of recurrent depression. Complications are primarily social and occupational.

Developmental Issues

Hypersomnolence occurs in 10% to 20% of children with major depression, sometimes with insomnia, but sleep quality appears normal in most cases. Although sleep problems may develop at any stage of depression, they are most pronounced during the acute phase. Children and adolescents with depression who manifest insomnia or hypersomnolence generally manifest more pronounced symptoms, such as anhedonia and weight loss.

Pathology and Pathophysiology

The underlying cause is unknown. Although patients with this disorder report sleepiness, sleep studies may reveal little or no evidence of increased propensity to sleep. In some patients, fragmented nighttime sleep may contribute to their daytime sleepiness. Because of uncertainty about the nature of the relationship, the term “hypersomnia *associated with a psychiatric disorder*” is preferred to “hypersomnia *due to a psychiatric disorder.*”

Objective Findings

Nocturnal polysomnography can be variable but, on average, demonstrates modestly prolonged sleep time with normal sleep efficiency. Sleep latencies on the MSLT are often within normal limits, with approximately 25% of patients having mean sleep latency below 8 minutes but rarely below 5 minutes. In some instances, extended duration sleep-recording studies may show clinophilia. Psychiatric interviews and evaluations are essential to diagnose the associated psychiatric condition.

Differential Diagnosis

Other causes of sleepiness There are no definitive tests for diagnosing hypersomnolence associated with a psychiatric disorder. Therefore, it is essential to rule out other common causes of sleepiness such as *insufficient sleep, sedation from medications or substances, SRBD, periodic limb movement disorder, circadian rhythm disorders, and IH*. Insufficient sleep is associated with excessive daytime sleepiness,

impaired concentration, and lowered energy level, but a detailed history of the subject's current sleep schedule reveals chronic sleep deprivation.

Chronic fatigue syndrome This syndrome is characterized by persistent or relapsing fatigue that does not resolve with sleep or rest, but the main complaint is usually fatigue rather than sleepiness.

Unresolved Issues and Future Directions

The lack of consistent concordance between subjective feelings of sleepiness and objective MSLT findings raise multiple issues. It is unclear to what extent these patients are objectively sleepy or, instead, suffer from decreased energy, psychomotor slowing, or lack of interest that confines them to bed. More research is needed to create an effective definition of hypersomnolence in this population and develop tools for measuring it. Distinguishing hypersomnolence associated with a psychiatric disorder from IH with comorbid psychiatric illness is often challenging, and future research identifying reliable factors that distinguish these disorders is required. Finally, future efforts should define the mechanisms underlying complaints of excessive sleepiness in patients with psychiatric disorders.

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Insufficient Sleep Syndrome

ICD-9-CM code: 307.44

ICD-10-CM code: F51.12

Alternate Names

Behaviorally-induced insufficient sleep syndrome, insufficient nocturnal sleep, chronic sleep deprivation, sleep restriction.

Diagnostic Criteria

Criteria A-F must be met

- A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep or, in the case of prepubertal children, there is a complaint of behavioral abnormalities attributable to sleepiness.
- B. The patient's sleep time, established by personal or collateral history, sleep logs, or actigraphy¹ is usually shorter than expected for age.²
- C. The curtailed sleep pattern is present on most days for at least three months.
- D. The patient curtails sleep time by such measures as an alarm clock or being awakened by another person and generally sleeps longer when such measures are not used, such as on weekends or vacations.

- E. Extension of total sleep time results in the resolution of the symptoms of sleepiness.
- F. The symptoms and signs are not better explained by a circadian rhythm sleep-wake disorder or other current sleep disorder, medical disorder, mental disorder, or medication/substance use or withdrawal.

Notes

1. If there is doubt about the accuracy of personal history or sleep logs, then actigraphy should be performed, preferably for at least two weeks.
2. In the case of long sleepers, reported habitual sleep durations may be normal based on age. However, these sleep durations may be insufficient for these patients.

Essential Features

Insufficient sleep syndrome occurs when an individual persistently fails to obtain the amount of sleep required to maintain normal levels of alertness and wakefulness. The individual is chronically sleep-deprived as a result of failure to achieve necessary sleep time due to reduced time in bed. There is a U-shaped relationship between age and average sleep time, with the minimum in middle-aged individuals. Examination reveals an unimpaired or above-average ability to initiate and maintain sleep. Physical examination reveals no medical explanation for the patient's sleepiness. A detailed history of the sleep pattern reveals a substantial disparity between the patient's sleep needs and the amount obtained. The significance of this disparity often goes unappreciated by the patient. Sleep time that is markedly extended on weekend nights or during holidays compared to weekday nights is also suggestive of this disorder. A therapeutic trial of sleep extension can reverse the symptoms. In individuals with physiologic sleep needs in excess of seven to eight hours, average sleep duration (e.g., seven hours/night in adults) may, in fact, be insufficient. Patients with insufficient sleep syndrome may experience sleep paralysis and hypnagogic hallucinations as well due to early entry into REM sleep.

Associated Features

Depending upon chronicity and extent of sleep loss, individuals with this condition may show irritability, concentration and attention deficits, reduced vigilance, distractibility, reduced motivation, anergia, dysphoria, fatigue, restlessness, incoordination, and malaise. Secondary symptoms may become the main focus of the patient, serving to obscure the primary cause of the difficulties. Daytime sleepiness typically results when psychologically and somatically normal individuals chronically obtain less sleep than they physiologically require. Chronic sleep restriction may be associated with metabolic syndrome (obesity, diabetes mellitus type 2, hypertension, cardiovascular and coronary heart diseases) and negatively impacts executive functioning. Situational factors such as demands of the family and work schedule may, on occasion, make it very difficult to obtain adequate sleep.

Clinical and Pathophysiologic Subtypes

Not applicable or known.

Demographics

Insufficient sleep syndrome affects all ages and both sexes. It may be more frequent in adolescence when sleep need is high yet sleep times may be curtailed by early school start times, social/academic pressures to stay awake late, or preference for later bedtime resulting in chronic restricted sleep. Cultural factors may also influence sleep duration. Students from different countries report sleep time that varies between six and eight hours per night.

Predisposing and Precipitating Factors

Social and psychological factors may impact nocturnal sleep length and daytime sleepiness. Cultural habits such as the *siesta* may enhance evening alertness at the expense of reducing nocturnal sleep efficiency. Also, the evening preference chronotype predisposes to complaints of insomnia and insufficient sleep. The association of evening chronotype with insufficient sleep persists after controlling for sex, age, and sleep duration.

Familial Patterns

Not applicable or known.

Onset, Course, and Complications

This condition results in increased daytime sleepiness, diminished concentration, lower energy level, and malaise. If unchecked, insufficient sleep syndrome may predispose to depression and other psychological difficulties, as well as poor work performance and withdrawal from family and social activities. Abuse of stimulants may also occur. Traffic accidents or work-related injuries may result.

Developmental Issues

Insufficient sleep syndrome is a common problem in adolescents and may be associated with adverse outcomes in their somatic and psychosocial health, school performance, and risk-taking behavior. It

should be differentiated from delayed sleep phase disorder, the effects of recreational drug use, and school avoidance behavior. In addition, an increased predisposition to substance use and accidents in teens may be consequent to insufficient sleep.

Pathology and Pathophysiology

Symptoms are due to normal physiological and psychological responses to sleep deprivation. Sleep restriction studies in normal volunteers have shown that even mild sleep restriction (for example, six hours of nocturnal sleep per night) results in a corresponding decrease in performance and increased sleepiness. Sleep restriction to four hours per night (i.e., an extension of wakefulness to 20 hours per day) greater likelihood of impaired performance on a psychomotor vigilance task likely due to a greater buildup of homeostatic sleep drive during the waking hours. The effects of sleep deprivation on neurobehavioral performance measures may vary with the nature of the task. In some long sleepers, it is essential to be aware that extending sleep to nine or more hours often improves performance. The diagnosis of insufficient sleep syndrome may be especially difficult to make in individuals with an unusually long physiological sleep requirement.

Objective Findings

Actigraphy combined with sleep diaries maintained for a 2- to 3-week period may be helpful by documenting total time in bed, sleep latency, total sleep time, and sleep efficiency. Polysomnography and MSLT are not required to establish a diagnosis of insufficient sleep syndrome. Instead, sleep time is extended first, and the patient is reevaluated. If a therapeutic trial with a more extended sleep episode eliminates the symptoms, insufficient sleep syndrome is diagnosed.

Polysomnography, when performed, reveals reduced sleep onset latency and high (i.e., greater than 90%) sleep efficiency. When extended sleep is permitted, prolonged sleep time with slow wave sleep rebound may be seen and REM sleep onset latency may become longer. Noting a disparity between reported sleep at home and observed total sleep time in the sleep laboratory can be helpful.

The MSLT reveals excessive sleepiness, with stage N1 sleep occurring in most naps, with short sleep latency. Stage N2 sleep occurs in more than 80% of MSLT naps. SOREMPs can occur.

Differential Diagnosis

Other central hypersomnolence disorders Insufficient sleep syndrome may be confused with *narcolepsy* because an abnormal MSLT (possibly including two SOREMPs) can be observed as the result of acute or

chronic sleep deprivation. The confusion may be most frequently encountered in adolescents or young adults.

Other causes of sleepiness The differential diagnosis of insufficient sleep syndrome includes other *central disorders of hypersomnolence (e.g., idiopathic hypersomnia), long sleeper or short sleeper, SRBD, circadian rhythm sleep disorders, insomnia disorder, affective disorder, and periodic limb movement disorder.*

Unresolved Issues and Future Directions

The correlation between subjective sleepiness, performance-test decrements, and MSLT-measured sleepiness after sleep deprivation is poor. Short sleepers often have a higher NREM sleep pressure, as measured by EEG delta power, than long sleepers, even if they do not complain of daytime sleepiness. Susceptibility to sleep deprivation varies among individuals, with some being consistently more tired and experiencing more significant performance decrement after even a mild degree of sleep deprivation.

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Isolated Symptoms and Normal Variants

Long Sleeper

A long sleeper is an individual who consistently sleeps substantially more in 24 hours than does the typical person of their age group. The usual definition of long sleep is a consistent duration of 10 hours or more for adults, but many epidemiologic studies have employed cutoffs of 8–10 hours. In children and

adolescents, the variant definition should be when sleep time is at least two hours longer than age-specific norms. However, more variable thresholds have been utilized in the research literature. A consistent daily pattern, documented by a carefully kept sleep log (preferably confirmed by actigraphy), showing 10 or more hours of sleep per night over a minimum of seven days is desirable for identifying the long sleeper. In general, long sleepers seek medical help when they develop sleepiness as a result of being forced to curtail their sleep time to less than their required amounts. The variant implies that there is no complaint of excessive daytime sleepiness when long sleepers fulfill their sleep need. The long sleep pattern typically begins in childhood, is well established by early adolescence, and persists throughout life. Because of occupational or educational demands, many long sleepers function reasonably on nine hours of sleep per night during the work or school week, with increases to 12 or more hours on weekends and holidays.

About 2% of men and 1.5% of women report sleeping at least 10 hours per night; 8.4% of 19,000 adults in the United States report sleeping more than 9 hours per day. The prevalence in this survey was higher in women. Epidemiologic studies have consistently found increased mortality, incident diabetes mellitus, cardiovascular diseases, stroke, coronary heart disease, and obesity associated with long sleep, compared to average-duration sleep. However, it is unclear whether most subjects were naturally long sleepers or had disorders resulting in excessive sleep duration. Most of these studies are based on questionnaires, and very few have used objective measures. Among long (>9 h) sleepers, 25% experience excessive daytime sleepiness, and 19% have daytime impairment (more often women and those with heart diseases and mood disorders). The data suggest that a 9-hour sleep duration may represent a threshold for increased risk of medical and mental disorders, especially mood disorders, and associated daytime consequences. In subjects older than 60 years, sleep duration longer than 9.5-10 hours is associated with male sex, low education, no physical exercise, more physical diseases, and lower cognitive status (suggesting long sleep could be an early sign of neurodegeneration). As measured by wrist actigraphy, long sleep duration is associated with retirement, unemployment, being separated/divorced, and the use of antidepressants. Long sleep duration is associated with decreased energy expenditure, increased sedentary time, and obesity-related factors associated with inflammation and a pro-thrombotic state. Higher C-reactive protein and interleukin-6 concentrations are also observed in this population. On the other hand, genetically determined long (>9 h) sleep has a protective effect against atrial fibrillation and heart failure in adults and obesity in children and adolescents.

Long (> 9 hours) sleep duration has a high heritability (44%) and concordance between monozygotic twins, which is higher if they live together. Genome-wide studies favor a polygenic origin of sleep duration, with the influence of clock and other genes (DEC2, K+ channel regulatory proteins genes). Long sleepers presumably represent the extreme high end of the normal sleep duration continuum.

Long sleep is typically normal in architecture and physiology with normal sleep efficiency and timings. Long sleepers, like short sleepers, have normal absolute amounts of N3 sleep unless there is chronic sleep restriction preceding polysomnography, in which case the absolute amount of N3 is increased. Amounts of N2 and REM sleep are somewhat higher than normal. The affected individual has no problem with time distortion or the ability to accurately gauge the quantity or quality of sleep. No sleepiness is evident on the MSLT if individuals have obtained their usual sleep amounts for several nights before the procedure.

It is important to differentiate the long sleeper from patients with narcolepsy, idiopathic hypersomnia, sleep-related breathing disorders, or medical causes of hypersomnolence. Many pathologic causes of increased sleep have an acute or subacute onset, may not be present in childhood, and rarely show the stable course of the long sleeper. Nevertheless, differentiation from pathologic conditions of hypersomnolence may be difficult in the child or adolescent because the normal continuum of sleep duration is somewhat longer in these age groups. The correct determination is often made by exclusion of specific diagnostic features associated with other conditions and by the absence of complaints concerning the quality of the individual's awake-state functioning when adequate sleep is obtained (e.g., during long holidays). In particular, the differentiation of a true long sleeper from a patient with idiopathic hypersomnia may be difficult. In the long sleeper, sleeping long hours is refreshing, and sleepiness disappears when long hours of nocturnal sleep are enforced.

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