

Narcolepsy: Diagnostic Approaches and Clinical Decision Making for the Primary Care Physician

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Abstract: Narcolepsy is a serious neurological condition in which patients are overcome by persistent, excessive feelings of fatigue and drowsiness. In addition to chronic fatigue, patients with narcolepsy often succumb to intermittent, uncontrollable periods where they abruptly fall asleep during waking hours. In addition to episodic bouts of daytime sleeping, narcoleptics also exhibit cataplexy, sleep paralysis, and hypnagogic and hypnopompic hallucinations. Unfortunately, many individuals with narcolepsy remain undiagnosed and therefore, untreated, posing a risk to themselves and those around them. There is currently no cure for this lifelong disease. Nonetheless, narcolepsy can be effectively managed with medications, lifestyle changes, and the peripheral support of individuals such as family members, coworkers, and other casual relations.

intermittent nature of this devastating disease, often leads to significant psychosocial impairment for narcoleptics. Approximately 50% of adults with the disorder retrospectively report symptoms beginning as early as their teenage years.^{1,2} The average delay in the diagnosis of narcolepsy is usually greater than 10 years since only one-third of patients will exhibit all four of the classic symptoms. Moreover, narcoleptics have increased incidence of other sleep-related disorders like obstructive sleep apnea, restless leg syndrome, periodic limb movement disorders and rapid eye movement (REM) behavior disorder (RBD), which further camouflages the clinical picture.³⁻⁸ Thus, a high index of suspicion is required by primary care physicians for diagnosis and subsequent referral to a sleep specialist.

Pathophysiology

Despite certain similarities, narcolepsy is a far more complex and devastating condition than a sleep disorder.⁹ Although the exact etiology of narcolepsy remains unclear, recent studies suggest a combination of genetic predisposition, abnormal neurotransmitter functioning and sensitivity, and abnormal immune modulation as contributing to the development of the disorder.^{2,9,10,11} The hereditary basis of the disease stems from current findings which implicate human leukocyte antigen (HLA) subtypes as predisposing individuals to narcolepsy.^{10,12} There appears to be a link between variations on HLA genes on chromosome 6 and the development of narcolepsy. Specifically, human leukocyte antigen (HLA)-DR2 and DQB1*0602 antigens have been linked to

Kp Narcolepsy is a disabling neurological condition that is characterized by excessive daytime sleepiness (EDS), cataplexy, hypnagogic hallucinations, and sleep paralysis. The term "narcolepsy," which was coined by Dr. Gelineau in 1880, is derived from the Greek word 'nark' which means "seized by somnolence." Individuals with narcolepsy are often seized with intermittent, irrepressible urges to sleep at various times throughout the day. The overwhelming nature of these urges often render narcoleptics incapable of staying awake during episodes, leading them to fall asleep for periods lasting from a few seconds to minutes.

Despite being the second leading cause of EDS after sleep apnea, this debilitating condition is frequently underdiagnosed.¹ If left untreated, narcoleptics risk falling asleep any time during the day, underscoring the importance of controlling the condition for individuals who regularly operate dangerous machinery or rely on motor vehicles for regular transportation.¹ The increased risk of injury, along with the

Key Points

- Although pharmacologic therapy can be helpful in treating narcolepsy, the mainstay of therapy involves improved sleep hygiene and supportive therapy.
- The increased risk of injury, along with the intermittent nature of this devastating disease, often leads to significant psychosocial impairment for narcoleptics.
- The classic tetrad of excessive daytime sleepiness (EDS), hypnagogic hallucinations, sleep paralysis, and cataplexy is present in only 50% of patients with narcolepsy.

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the onset of narcolepsy, especially in cataplectic patients.¹³ The abnormalities in HLA complexes that accompany these genetic alterations are believed to initiate an autoimmune response against neurons in the central nervous system that are responsible for the production of hypocretin, a peptide neurotransmitter that plays a critical role in regulating appetite, energy homeostasis, neuroendocrine regulation, and sleeping patterns.¹⁴⁻¹⁸ Recent studies have demonstrated significantly reduced numbers of hypocretin-producing neurons as well as levels of hypocretin in narcoleptic patients.^{14,15} Although a similar mutation on chromosome 12 in canines exhibits similar dysfunction in hypocretin production, no such mutation has been linked to the development of human narcolepsy.¹⁹ While a strong link exists between genetic changes and narcolepsy, hereditary transmission is not the only causative agent in narcolepsy development. Furthermore, in cases where genetic transmission is the primary cause, no mode of inheritance has yet to be identified in patients with familial forms of narcolepsy.¹³

Other neurochemical dysfunctions that arise in the setting of narcolepsy involve malfunctioning of the dopamine system.^{7,20} The brains of narcoleptic patients commonly demonstrate monoaminergic (dopamine and norepinephrine) hypoactivity.^{2,21} Canine studies have revealed that inducing cholinergic stimulation can induce cataplexy in narcolepsy.²² These neurochemical findings offer insight into why recent trials using atropine, an anticholinergic agent, and selegiline, a monoamine oxidase B inhibitor, have shown promise in treating narcoleptic patients.²³ By blocking monoamine oxidase B, selegiline increases the release of dopamine and concomitantly protects dopaminergic neurons by increasing the levels of cyclic adenosine monophosphate (AMP) with the net effect of improved symptoms in narcoleptic patients.^{20,23-25} Further, atropine's inhibition of cholinergic pathways has demonstrated decreased cataplexy in canine models and offers promise for future treatment of narcoleptic patients with similar clinical findings.^{20,22}

Epidemiology

The incidence of narcolepsy is 0.02-0.18%.^{26,27} First-degree relatives have 10-40 times greater risk than the general population.²⁸ Males and females are equally affected with the age-of-onset distribution being biphasic. The highest peak occurs at 15 years, while a less pronounced peak occurs at 36 years.²⁶⁻²⁸

Clinical Presentation

Narcoleptic patients do not sleep more than normal controls over 24 hours. However, the instability of the sleep-wake state control results in the repetitive intrusion from REM sleep into wakefulness and vice versa. The classic tetrad of EDS, hypnagogic hallucinations, sleep paralysis, and cataplexy is present in only 50% of patients with narcolepsy.²⁹

Cataplexy remains the only pathognomonic sign for narcolepsy.²⁹ Nonetheless, narcolepsy is classified according to one of the following: narcolepsy with cataplexy, narcolepsy without cataplexy, or secondary/ symptomatic narcolepsy. The common clinical findings of narcolepsy are discussed in detail below.

Excessive Daytime Sleepiness (EDS)

EDS is the primary symptom of narcolepsy characterized by persistent sleepiness. EDS arises secondary to fragmented nocturnal sleep and sleep attacks resulting from REM intrusion into wakefulness. These attacks occur in the setting of persistent drowsiness and differ from the EDS seen in obstructive sleep apnea (OSA) patients. The distinguishing feature between the EDS of OSA and the variant seen in narcolepsy is that daytime naps commonly have a refreshing, rejuvenating effect on the OSA patient, but not on the narcoleptic.³⁰ Furthermore, the narcoleptic patient can fall into a napping state during normal activities such as eating and talking. This can result in severe disability, particularly when falls or traumas ensue.^{31,32}

Cataplexy

Cataplexy is an abrupt neurological attack that often accompanies narcolepsy. It manifests as muscle weakness which lasts for a few minutes or longer.³³ Muscular weakness in cataplexy commonly affects facial muscles, intraocular muscles, and the knees.³³ Depending on the muscles affected, patients with cataplexy may complain of diplopia, blurred vision, inability to raise the head, sagging jaw, dysarthria, drooping of the head, persistent knee buckling, and other physical findings (Table 1).^{34,35} Notwithstanding the wide range of possible complaints, patients with cataplexy are usually alert and oriented even in instances where their inability to appropriately respond to verbal stimuli is impaired.³⁶ Further, irrespective of its severity, cataplexy never results in hearing impairment or any form of auditory dysfunction.³⁷ The most characteristic form of cataplexy is triggered by strong emotions like laughter, anger, or fear. Instances in

Table 1. Physical findings in patients with cataplexy³⁴

Complete atonia
Areflexic partial paralysis of muscles
Areflexic complete paralysis of muscles
Knee buckling
Facial sagging
Eyelid sagging
Jaw sagging
Dysarthria
Blurred vision
Arm weakness
Head drooping
Sensation of weakness

which heightened emotional states dominate, such as during orgasms, may also precipitate the onset of cataplexy.^{35,37} Positive emotions are more likely than negative emotions (e.g. anger) to produce a cataplectic attack.²⁷ Cataplexy is seen in approximately 70% of narcoleptic patients, and its presence strongly suggests the diagnosis of narcolepsy.³⁸ A higher index of suspicion is warranted as partial cataplectic symptoms like head drop, jaw drop, slurred speech, bilateral ptosis, or dropping things occur.³⁴

Sleep Paralysis

Sleep paralysis describes the inability to move while asleep or awakening with intact consciousness. It is present in about 33% of patients with narcolepsy and seems to occur with greater frequency in individuals with a past history of abuse.^{39,40} These episodes are very alarming, particularly when they happen for the first time, and are associated with a feeling of being unable to breathe.³⁹ Despite persistent complaints of inability to breathe in such patients, diaphragmatic activity and air exchange usually remains adequate during such episodes.⁴⁰

Sleep-Related Hallucinations

Sleep-related hallucinations may occur during the onset of sleep (hypnagogic) or during awakening (hypnopompic). Both hypnagogic and hypnopompic hallucinations are most commonly visual in nature; however, auditory, tactile, or multisensory events have also been reported in association with narcolepsy.⁴¹ Unfortunately, given the association with visual and auditory hallucinations in other systemic disorders, the presence of hypnagogic and hypnopompic hallucinations pose

a challenge to clinicians and represent a common reason for wrongly prescribed antipsychotics.^{42,43}

Automatism

Automatism describes the sudden, persistent, oscillating desire to sleep.⁴⁴ Automatism, which is indicative of severe sleepiness, occurs in up to 80% of patients with narcolepsy.⁴⁴ Patients with automatism appear to be awake but lack complete awareness and often demonstrate extremely inappropriate behavior during such spells.⁴⁴ The state of pseudoawakeness that characterizes automatism may result in patients being misdiagnosed with partial complex seizures.⁴ Further, the abnormal behavior overlapping lack of complete awareness that has been reported in many patients during automatism spells has led to the misdiagnosis of psychogenic dissociative fugue.⁴⁴

Differential Diagnosis

Although the classic complex of symptoms in narcolepsy is easily recognizable, it is rarely present in an analogous manner clinically. This lack of uniform clinical presentation can pose a challenge to clinicians who lack a basic understanding of this disease. Hence, we have divided the differential diagnosis for each symptom in the complex (Table 2). 12

Diagnostic Workup

History & Examination

Narcolepsy with cataplexy is a clinical diagnosis based on a detailed history and analysis of normal sleep patterns.^{13,20} Additional testing may be warranted in order to confirm the

Table 2. Differential diagnosis of narcolepsy according to symptom complex

Excessive daytime somnolence (EDS)	Cataplexy	Sleep paralysis	Hypnagogic/hypnopompic hallucinations
Untreated obstructive sleep apnea	Drop attacks	Isolated/physiological response	Psychoses
Behaviorally induced insufficient sleep syndrome	Syncope	Periodic paralysis (channelopathies)	Sleep onset rumination
Idiopathic hypersomnia with or without long sleep time	Transient ischemic attacks	Part of familial sleep paralysis	Space-occupying lesion of temporo-occipital cortex (stroke, tumor, abscess)
Hypersomnia due to medical conditions (chronic obstructive pulmonary disease, congestive heart failure, peptic ulcer disease)	Akinetic seizures	Upper brain stroke (top of the basilar syndrome)	
Hypersomnia due to neurological conditions (stroke, fatal familial insomnia, diencephalic tumors)	Periodic paralysis (channelopathies)		
Hypersomnia due to psychiatric conditions (psychosis, anxiety, bipolar)	Psychological/psychiatric disorders		
Hypersomnia due to drugs/toxins (alcohol, sedatives/hypnotics)	Cataplectic-like episodes (may happen in normal individuals)		

diagnosis, determine the severity, or exclude other sleep disorders.^{13,45} Patients with primary narcolepsy do not have any specific general physical and neurological findings on examination.^{13,20,45} Thus, a detailed physical examination is warranted if findings are equivocal on history in order to arrive at an accurate diagnosis and exclude secondary causes of narcolepsy. Specifically, the history and initial physical examination can be critical in ruling out sleep apnea as a cause of the symptoms in patients with suspected narcolepsy.²⁰ Thus, the clinician is encouraged to thoroughly look for any physical signs that may be indicative of obstructive sleep apnea such as obesity or physical/anatomic causes of upper airway obstruction.⁴⁶ Presently, no single definitive diagnostic test exists for the diagnosis of narcolepsy⁴⁶; however, the following is an overview of the techniques and procedures that have proven to be the most effective in assessing all patients suspected of having narcolepsy.^{20,46}

Polysomnography & MSLT

An overnight polysomnogram (PSG) examination and a subsequent multiple sleep latency test (MSLT) is essential in the workup of narcolepsy.^{20,46,47} PSG accurately documents fragmented sleep patterns with a normal amount of REM sleep but a pattern of sleep onset REM.^{13,45} PSG is also helpful in excluding other sleep disorders; namely, obstructive sleep apnea.^{46,47} MSLT is usually performed one day after the nocturnal PSG recording.⁴⁷ In the MSLT, the patient is monitored during 4–5 naps which are taken at two hour intervals.⁴⁷ A MSLT of five minutes or less and at least two sleep-onset REM periods can be interpreted as a supportive test.⁴⁷ This criterion offers clinicians the highest specificity (99.2%) and positive predictive value (87%) for MSLT.⁴⁸ Mean sleep latency of less than 8 minutes during MSLT is used for the 2nd revision of the International Classification of Sleep Disorders (ICSD).⁴⁹ Overall, a patient with a mean sleep latency under 5 minutes can be said to suffer from the pathological sleepiness that accompanies narcolepsy.⁴⁶ Nonetheless, many patients without sleep apnea have also demonstrated similar sleep latencies during recent studies (Table 3).⁴⁶

Lab Studies

The clinical utility of HLA typing, including DQB1*0602 and DQA1*0602, is very restricted given the fact that, de-

pending on ethnicity, only 12–38% of the population is positive for these genetic variations.¹⁵ Therefore, HLA typing should not be used for the diagnosis of narcolepsy without cataplexy. Low cerebrospinal fluid (CSF) hypocretin-1 has been found consistently in narcolepsy with cataplexy patients with 90% sensitivity.^{9,14,15} Low CSF hypocretin-1 levels (< 110 pg/mL) were also included in the second revision of ICSD.^{9,14} The full clinical utility of evaluating CSF hypocretin-1 levels remains to be determined in evaluating narcolepsy without cataplexy (10%) and idiopathic hypersomnia patients.¹⁵

Imaging Studies

The clinical utility of magnetic resonance imaging (MRI) in diagnosing primary narcolepsy is limited. Nonetheless, MRI can play an important diagnostic role in patients with atypical symptoms or focal findings on the neurological examination.¹³ Structural lesions of the brainstem and diencephalon (hypothalamic hamartoma), which have been known to cause narcolepsy, can be identified with MRI.⁵⁰

Medical Management

Nonpharmacologic Treatment

Although pharmaceutical agents can significantly improve the course of narcolepsy, certain lifestyle changes and other nonpharmacologic adjustments can dramatically reduce complications associated with the disease.^{20,46} Regular consultation between the patient and his or her healthcare provider is essential to appropriately tailor lifestyle changes and thus, provide the patient with optimal management of the disease.²⁰

Among the most important recommendations for patients with narcolepsy is complying with a strict sleep schedule that provides the patient with at least 7–8 hours of sleep at night.^{9,20} Regularly scheduled daytime naps are also encouraged as a means of reducing daytime sleepiness in such patients.²⁰ Alerting family members, friends, and coworkers of potential signs of narcoleptic spells may significantly reduce injuries associated with sudden falls.^{9,20} Further, patients with narcolepsy should be encouraged to avoid operating motor vehicles or other dangerous equipment when feeling sleepy.^{9,20} Finally, regular exercise to maintain adequate physical fitness has been associated with increased daytime energy and improved sleeping patterns in individuals with narcolepsy.^{20,45,46} Ongoing collaboration with the patient’s physician as well as regular emotional support by loved ones can also improve the course of the disease in patients struggling to overcome the challenges it poses to them.

Pharmacologic Treatment

CNS stimulants such as methylphenidate, dextroamphetamine sulfate, methamphetamine, and amphetamine have shown promise in the treatment of EDS (Table 4).^{45,51} Meth-

Table 3. Mean sleep latency (SL) values obtained in recent studies⁴⁶

Conditions	Mean SL <5 min (%)	Mean SL <8 min (%)
Patients aged 18–29 yr	12	40
Patients aged 30–80 yr	10	30
Narcolepsy and cataplexy	87	93
Narcolepsy without cataplexy	81	97

Table 4. Pharmacologic treatment of narcolepsy^{45,51a}

CNS stimulants	TCAs or SSRIs	Sodium oxybate	Benzodiazepines
Improve sleep	Cataplexy	Cataplexy	Improve sleep
Cataplexy	Hypnagogic hallucinations		
	Sleep paralysis		

^aCNS, central nervous system; TCA, tricyclic antidepressant; SSRI, ●●●.

ylphenidate, the most frequently used stimulant in narcoleptics, functions by improving sleep tendency in a dose-related fashion.⁵¹ Adverse effects of methylphenidate include headache, irritability, nervousness, and gastrointestinal complaints. Further, methylphenidate often leads to qualitative impairment of nocturnal sleep and thus, decreases sleep time in some patients.^{45,46} Clinicians concerned with long-term use of methylphenidate are advised to instruct patients about the importance of abstaining from the medication at least one day each week (typically on a weekend).

Modafinil is an alpha 1-agonist with wake-promoting qualities. It has also been used successfully in the treatment of narcolepsy.⁵² Although its mechanism of action does not appear to alter levels of dopamine or norepinephrine, it has shown both subjective and objective improvement in sleepiness in a recent multicenter trial.^{45,52} Unlike traditional medications, modafinil rarely affects total sleep time or suppresses REM sleep. A recent study found that despite yielding improvement in measures of sleepiness, modafinil does not generally normalize sleep and therefore, may be less effective than other stimulants for some patients.⁵² Modafinil has been approved by the Food and Drug Administration (FDA) for improving wakefulness in individuals with excessive sleepiness associated with narcolepsy, obstructive sleep apnea-hypopnea syndrome (OSAHS), or shift-work sleep disorder.^{14,52} Selegiline, a MAO-B inhibitor, has also demonstrated improved sleep cycles and reduced occurrence of cataplexy.^{24,51}

Tricyclic antidepressants (imipramine, clomipramine, protriptyline) or SSRIs (venlafaxine, fluoxetine) are prescribed to treat cataplexy, hypnagogic hallucinations, and sleep paralysis.⁵³

Sodium oxybate (γ -hydroxybutyrate) has been recently approved by the FDA for treating cataplexy. It may be better than traditional anticataplectic medications insofar as it also reduces EDS by preventing nocturnal fragmentation.⁵⁴ Further, sodium oxybate is tolerated better than other medications because it lacks the anticholinergic side effects that are associated with other forms of narcolepsy treatment.⁴⁵ Because of sodium oxybate's history of abuse as a recreational drug (date rape), the FDA approved it as a Schedule III Controlled Substance.

Finally, for consolidating nocturnal sleep, nighttime use of short-acting benzodiazepine hypnotics is sometimes attempted in refractory patients.^{45,51}

Complications

Narcolepsy is a lifelong disease that can be effectively managed with medications, lifestyle changes, and the peripheral support of individuals such as family members, coworkers, and other casual relations. Maintaining such relationships while complying with medical regimens is crucial to preventing complications of narcolepsy, many of which result in long-term disabilities and injuries. The following is a brief overview of possible complications that have been associated with narcolepsy:

1. Status cataplecticus (SC): SC describes the serious state that occurs in narcolepsy patients after they abruptly discontinue anticataplectic medications. SC results in frequent and persistent attacks of cataplexy that often render the patient helplessly immobilized and terrified.
2. Injuries from cataplectic attacks (i.e., secondary to falls).
3. Side effects from unnecessary medications (antipsychotics for hypnagogic hallucinations).
4. Increased incidence of other sleep disorders: OSA from weight gain, RBD from medication side effects/REM state, instability, or both.
5. Increased incidence of medical problems, such as type 2 diabetes.
6. Increased incidence of psychiatric problems, such as depression.
7. Negative social implications.

Future Directions

The presence of low CSF hypocretin-1 levels is a very specific finding for narcolepsy when compared with other sleep disorders.¹⁴ Measuring CSF hypocretin-1 levels is increasingly becoming a useful diagnostic tool for patients suspected of narcolepsy.¹⁴ Given the fact that most narcolepsy-cataplexy subjects tend to be hypocretin ligand deficient, hypocretin agonists may represent a promising target for future agents used in the treatment of narcolepsy.

Conclusions

Narcolepsy remains a far more serious condition than originally recognized given the potentially devastating impact it has on patients' quality of life. If left untreated, narcoleptics may develop the disabling tendency to involuntarily fall asleep at intermittent periods during the day. Although no cure exists for narcolepsy, its disabling symptoms can be controlled with appropriate, targeted therapy.

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Narcolepsy is a lifelong disease that can be effectively managed with medications, lifestyle changes, and the peripheral support of individuals such as family members, coworkers, and other casual relations.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

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1—Kindly spell out SSRI in Table 4 footnote.

2—Kindly check the currency of the corresponding authors' address and confirm whether the email address can be used for publication.
