

Causes of Hypersomnia – Narcolepsy

M.V. Padma Srivastava

Department of Neurology

All-India Institute of Medical Sciences, New Delhi

ABSTRACT

The causes of hypersomnia or excessive daytime sleepiness (EDS) besides volitional sleep deprivation and obstructive sleep apnea are principally due to primary central nervous system abnormalities. Most common amongst these is Narcolepsy, a primary disorder of the neural control of wakefulness and sleep. The recent discovery of hypocretin/orexin deficiency as the main cause of narcolepsy will lead to important therapeutic advances for patients with narcolepsy and further to understanding of the control of sleep and wakefulness in general. Importantly, the excessive daytime sleepiness is not due to psychiatric conditions, but rather is always due to sleep deprivation or an underlying diagnosable and treatable sleep disorder.

Key words : EDS, Sleep, Narcolepsy

Volitional sleep deprivation and obstructive sleep apnea are the most common causes of hypersomnia. The remaining causes are primarily due to primary central nervous system abnormalities, the most common of which is narcolepsy, a primary disorder of the neural control of wakefulness and sleep.

NARCOLEPSY :

It is the prototypic example of dissociated sleep-wake phenomenon in which components of one state, ie rapid eye movement (REM) sleep, appear in another (wakefulness) (1).

Narcolepsy is a relatively frequent disorder with a prevalence of 0.09%. A clear genetic component is indicated by the fact that over 90% of individuals with narcolepsy carry the HLA DR15 and HLA DQ6 gene, which is found in less than 30% of the general population. Siblings of individuals with narcolepsy have a 60-fold increased likelihood for developing the disease. Narcolepsy is thought to result also from abnormal neurotransmitter functioning and sensitivity and abnormal immune modulation (1,2,3).

The male to female ratio in narcolepsy is 1.64:1. The usual age of onset of narcolepsy is adolescence or early adulthood, although it ranges from early childhood to senescence (3 to 72 years of age), with a primary peak in the teens and a lesser peak in the early 30s.

Signs and Symptoms :

Manifestations of narcolepsy are as follows: (1,2)

1. EDS
2. Cataplexy
3. Hypnagogic hallucinations
4. Sleep paralysis

Excessive Daytime Somnolence (EDS) :

EDS is the primary symptoms of narcolepsy with unwanted and unanticipated sleep episodes lasting seconds to minutes and occurring at inappropriate times, particularly during periods of reduced environmental stimulation, such as reading, watching television, riding in or driving or attending a class or meeting. During periods of excessive sleepiness, a brief (10 to 30 minute) nap is frequently very refreshing, if only for a short period of time. The symptom of sleepiness is accompanied by failing performance due to impairment of sustained attention, at times reflected in a complaint of impaired memory. The apparent memory disturbance is secondary to impaired attention (1,2,4).

Ancillary symptoms of narcolepsy include cataplexy, hypnagogic hallucinations, and sleep paralysis.

Cataplexy :

Cataplexy, which occurs in 65% to 70% of these patients, comprises of sudden loss of muscle tone, typically triggered by emotion such as laughter,

anger, excitement, delight or surprise. The muscle weakness of cataplexy may be complete, resulting in the patients falling or being forced to sit, much more commonly, the weakness is milder and more focal, taking the form of facial sagging, slurred speech or localized weakness of an extremity. Cataplexy may never occur in 30% of patients with narcolepsy or may precede the onset of EDS (1,2,4).

Hence the salient features of Cataplexy are:

1. If severe and generalized, cataplexy may cause a fall.
2. More subtle forms exist with only partial loss of tone (eg., head nod and knee bucking)
3. Respiratory and extraocular movements are preserved.
4. Cataplexy is usually triggered by emotions (especially laughter and anger)

Sleep Paralysis :

Sixty percent of individuals with narcolepsy experience sleep paralysis upon awakening from REM sleep (usually from a dream). At times, this frightening manifestation consists of total-body paralysis, with sparing of respiration and of eye movements, lasting from seconds to minutes (1,2,4).

The salient features of Sleep paralysis are:

1. Usually the patient is unable to move upon awakening.
2. Less commonly, the patient is unable to move upon falling asleep with consciousness intact.

3. Paralysis is often accompanied by hallucinations
4. Respiratory and extraocular muscles are spared
5. Paralysis occurs less frequently when the person sleep in an uncomfortable position
6. Paralysis can be relieved by sensory stimuli (eg. touching or speaking to the person)

Hallucinations :

Hypnagogic (at sleep onset) and hypnopompic (upon awakening) hallucinations are noted in 12% to 50% of cases. The hallucinations are extremely vivid and often frightening dreams that occur during the transition between wakefulness and sleep. They may be associated with total body paralysis and sensations of oppression and dread. These hallucinations are more frightening than conventional dreams because the dream imagery arises from the real (waking) environment, making differentiation between reality and dreaming difficult (1,2,4,5).

The following are also common features of narcolepsy:

1. A tendency to take short and refreshing naps during the day; these may be accompanied by dreams.
2. Trouble sleeping at night
3. Nocturnal compulsive behaviours (sleep related eating disorder and nocturnal smoking)
4. Obesity

Features of Narcolepsy in children are :
(6)

1. Restlessness and motor over activity may predominate
2. Academic deterioration, inattentiveness and emotional lability are common
3. At disease onset, children with narcolepsy and cataplexy may display a wide range of motor disturbances that do not meet the classic definition of cataplexy.
4. Motor disturbances may be negative (hypotonia) or active.
5. Motor disturbances may resolve later in the course of the disorder.

Diagnosis :

The DSM-5 defines narcolepsy as recurrent episodes of irrepressible need to sleep, lapsing or napping occurring within the same day. These must have been occurring at least three times per week over the past 3 months. There must also be presence of at least one of the following (1,2,5).

1. Episodes of cataplexy occurring at least a few times per month
2. Hypocretin deficiency
3. REM sleep latency < 15 minutes or a mean sleep latency < 8 minutes and two or more sleep-onset REM periods (SOREMPs).

Narcolepsy can be categorized as mild, moderate or severe based on the frequency of cataplexy, need for naps, and disturbance of nocturnal sleep. In

addition, the DSM-5 identifies five subtypes as follows:

1. Narcolepsy without cataplexy but with hypocretin deficiency
2. Narcolepsy with cataplexy but without hypocretin deficiency
3. Autosomal dominant cerebellar ataxia deafness and narcolepsy
4. Autosomal dominant narcolepsy, obesity and type 2 diabetes
5. Narcolepsy secondary to another medical condition

Whenever possible, the diagnosis of narcolepsy should be confirmed by polysomnography (PSG) followed by a multiple sleep latency test (MSLT). The MSLT should show sleep latency 8 minutes or less and 2 or more SOREMPs. An alternative criterion is a CSF hypocretin level of 110 pg/ml or lower. The hypersomnia must not be explained as another sleep, neurologic, mental or medical condition, or induced by medicine/substance use.

Pathophysiology :

Narcolepsy is thought to result from genetic predisposition, abnormal neurotransmitter functioning and sensitivity, and abnormal immune modulation. Current data indicate certain human leukocyte antigen (HLA) subtypes and abnormal hypocretin (orexin) neurotransmission, which leads to abnormalities in monoamine and acetylcholine synaptic transmission, particularly in the pontine reticular activating system (3,7).

Understanding of the neurochemistry of narcolepsy began with research involving narcoleptic dogs. In these animal models, the disorder is transmitted in an autosomal recessive fashion with full penetrance and is characterized mainly by cataplexy. Muscarinic cholinergic stimulation increases cataplexy in these animals, and cholinergic blockade eliminates the symptom. Nicotinic agents have no effect on the cataplexy (8).

Receptor subtypes such as the alpha-1-noradrenergic receptor appear to mediate cataplexy. Prazosin, an alpha-1-antagonist, worsens symptoms in canine and human subjects. The pons is not the only neuroanatomic site that is responsible for mediating cataplexy. The mesocorticolimbic dopaminergic system also has been implicated. This connection with the limbic system in part explains the relationship of cataplexy to emotion.

The centrality of hypocretin transmission in the pathophysiology of narcolepsy was demonstrated when hypocretin knockout mice displayed cataplexy and sleepiness. Further evidence for impaired hypocretin functioning in humans was found with the discovery of low levels of hypocretin in the CSF of narcoleptic patients (9,10).

Subsequently, abnormal immune modulation was associated with the clinical development of narcolepsy in children in Scandinavia and Finland. After vaccination against H1N1 influenza virus with a vaccine using a potent ASO3

adjuvant, narcolepsy in Finish children increased 8 to 12 fold. All affected children who underwent HLA typing were found to have the HLA DQB*0602 allele (3,7).

REM Sleep :

Dysfunction and inappropriate regulation of REM sleep are thought to exist in narcolepsy. Neuroanatomic control of REM sleep appears to be localized to the pontine reticular activating system.

The brain contains REM-on cells, which fire selectively during REM sleep periods, and REM-off cells, for which the converse holds true. Most REM-on cells function through cholinergic transmission whereas REM-off cells are noradrenergic or serotonergic. In narcolepsy, monoamine-dependent inhibition of REM-on cells may be defective (5,4).

Symptoms can be viewed as REM sleep components intruding into wakeful states. For example, cataplexy and sleep paralysis represent an intrusion of REM sleep atonia, whereas hallucinations represent an intrusion of dreams.

Hypocretin :

Hypocretin plays an important role in the pathophysiology of human narcolepsy. Patients with narcolepsy have been found to have little or no hypocretin in their CSF. Postmortem pathologic examination of the brains of people with narcolepsy with cataplexy has

demonstrated dramatically reduced numbers of hypocretin neurons. Hypocretin deficiency is theorized to produce instability of sleep and wake states, thereby preventing the persons from sustaining more continuous sleep or wakefulness. A large majority of patients with narcolepsy without cataplexy have normal CSF hypocretin levels (9,10).

Investigators have also found low levels of histamine (that helps maintain wakefulness) in the CSF of patients with hypocretin-deficient narcolepsy. They are also seen in narcolepsy patients with normal CSF hypocretin levels and in patients with idiopathic hypersomnia. Low CSF histamine levels have not been found in patients with hypersomnia secondary to obstructive sleep apnea syndrome. The CSF histamine level may serve as a biomarker reflecting the degree of hypersomnia of central origin (9,10).

CNS nuclei for wakefulness and the relevant neurotransmitters generated in those nuclei include the following:

1. Locus ceruleus – Norepinephrine
 2. Raphe nucleus – Serotonin
 3. Tubomammillary nucleus – Histamine
 4. Ventral tegmental area – Dopamine
 5. Basal forebrain – Acetylcholine
- These areas also inhibit REM sleep.

Hypocretin neurons thought to be autoexcitatory project from the lateral hypothalamus into these regions and serve

to maintain wakefulness. A deficiency of hypocretin neurons may decrease the threshold for transitioning between wakefulness and sleep. This is a proposed explanation for the sleepiness and REM intrusion into wakefulness found in narcolepsy (9,10).

Destruction of hypocretin-producing neurons appears to be an autoimmune process. A specific autoantigen against Tribbles homolog 2 (Trib2) have been found to be higher in narcolepsy patients with cataplexy than in normal controls. The autoimmune model of narcolepsy inspired trials of intravenous immunoglobulin therapy in narcoleptic patients with low levels of hypocretin – 1. In these trials, IVIG reportedly improved cataplexy and sleepiness in many cases, but the effects did not last long (11).

Genetic Factors:

The genetics of Narcolepsy are complex. The risk is as high as 40% in the first-degree relatives.

There is a striking association between narcolepsy and the HLA haplotype DQA1*01:02-DQB1*06:02. A genome wide association study proposed a protective variant DQB1*06:03. GWA studies in Caucasians with replication in 3 ethnic groups have revealed associations between SNP in the T cell receptor alpha locus and narcolepsy. This association further supports the autoimmune basis of narcolepsy (3,7).

An SNP in the purinergic receptor subtype P2Y₁₁ gene also appears to be associated with Narcolepsy. A GWA study that investigated 202 candidate genes in a replication study in 222 narcoleptic patients and 380 controls identified 6 genes that were associated with narcolepsy: NFATC2, SCP2, CACNA1C, TCRA, POLE and FAM3D (3,7).

Management :

Treatment of Narcolepsy has both nonpharmacologic and pharmacologic components. Sleep hygiene is important. Most patients improve if they maintain a regular sleep schedule, usually 7.5 to 8 hours of sleep per night. Scheduled naps during the day also may help (1,2,11).

Pharmacologic treatment of narcolepsy involves the use of central nervous system stimulants such as methylphenidate, modafinil, dextroamphetamine sulphate, methamphetamine and amphetamine. These medications help reduce daytime sleepiness, improving the symptom in 65% to 85% of patients. In patients for whom stimulant treatment is problematic, subjective benefit from treatment with codeine has been reported (1,2,11).

Methylphenidate was the stimulant most frequently used for treatment of narcolepsy. It improves sleep tendency in a dose-related fashion. Undesirable side effects include headache, nervousness, and gastrointestinal complaints. Nocturnal sleep may be impaired with a resulting decrease in total sleep time (11).

Modafinil is novel wake-promoting agent. The mechanism of action is not understood, but it does not appear to involve altering levels of dopamine or norepinephrine. Unlike traditional medications, modafinil does not appear to affect total sleep time or suppress REM sleep; the most common adverse effect is headache. Its safety in children has not been established (11).

Armodafinil has fewer side effects. It is indicated for the treatment of EDS associated with narcolepsy. The most common side effects are headache, nausea, dizziness and difficulty in sleeping (11).

Cataplexy in patients with narcolepsy can be treated with the CNS depressant sodium oxybate. Other agents that are used off-label for cataplexy are tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. The strongest evidence is for clomipramine, fluoxetine and sodium oxybate (11).

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