



지 기 환

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Hypersomnia of Central Origin

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The principle manifestation of hypersomnia is inappropriate daytime sleepiness, common to all types of hypersomnias. Hypersomnias of central origin is a rare cause of excessive daytime sleepiness. Narcolepsy with or without cataplexy is the most well studied of the primary hypersomnias. Major aspects of this disorder will be discussed. Idiopathic hypersomnia is also part of the central hypersomnias. Although difficult to diagnose, certain characteristics of differentiation do exist. Kleine-levin syndrome as recurrent hypersomnia also is discussed.

Key Words: Primary hypersomnia, Narcolepsy, Cataplexy, Idiopathic hypersomnia, Kleine-levin syndrome

INTRODUCTION

The international Classification of Sleep Disorders the second edition classifies the hypersomnia of central origin as primary or secondary.¹ Narcolepsy with or without cataplexy, idiopathic hypersomnia with or without long sleep time and recurrent hypersomnia are main categories of primary hypersomnia. Author will focus on the primary hypersomnia.

1. NARCOLEPSY

Narcolepsy is the classical hypersomnia of central origin. The estimated prevalence of narcolepsy is between 0.03 to 0.05% of the population.^{2,3} Both sexes can be affected at any age, and mean age of onset is in the mid-twenties.

There is a bimodal distribution, with a peak around 15 and near 35 years of age.⁴ Narcolepsy with cataplexy is more common than without cataplexy.³ First-degree relatives have approximately 1% to 2% risk of developing narcolepsy.⁵ The classical narcolepsy tetrad is excessive daytime sleepiness (EDS), cataplexy, hypnagogic or hypnopompic hallucinations, and sleep paralysis. Sleep disruptions should be also considered as pentad of narcolepsy.

1) Clinical Manifestations

EDS is usually the most disabling symptoms of narcolepsy and varies in severity. Sleep attacks occur in bouts lasting seconds to minutes. Boring monotonous situations and calm will enhance the risk of falling asleep as opposed to doing exciting and challenging tasks. Naps are usually refreshing and lasting less than 30 minutes, can reduce the sleep drive for a few hours.⁶

Cataplexy is characterized by the loss or decrease of voluntary axial muscle tone. Events are provoked by intense emotional stimuli that are usually positive, such as laughter and surprise. Negative emotions such as anger may also be

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a trigger. Attacks may be generalized causing falls and potential injuries. More frequently, they will consist of localized muscle tone loss, manifesting as head dropping, jaw dropping, knee buckling, slurred speech, or blurred vision. However, respiratory muscles are never affected. The majority of cataleptic attack last seconds to a few minutes and the recovery is immediate and complete. Cataplexy may sometimes be followed by sleep. Status catalepticus, a very rare occurrence, can sometimes be triggered by abrupt withdrawal of medications, so-called rebound cataplexy.⁷

Sleep paralysis is a transient, generalized inability to move or to speak while being totally aware of one's surroundings and concurring events. Typically occurring at the transition between sleep and wakefulness, these events rarely last more than a few minutes. About two third of narcoleptic patients experience sleep paralysis and/or hypnagogic and/or hypnopompic hallucinations, but is not a pathognomonic as it can be present event in the normal subjects.⁶ Hypnopompic hallucinations are more typical than hypnagogic. Visual hallucinations are most common, but auditory or tactile forms can be encountered. About a 50% of narcoleptics report nocturnal sleep disturbances. Clinically, most patients complain of altered nocturnal sleep, reporting vivid dreams, fragmented sleep with multiple arousals, nocturnal eating, early awakenings, and overall unrefreshing sleep.⁷ Automatic behavior is present in half of narcoleptic patients.⁸ The patient continues an activity seemingly purposeful without memory or consciousness. Microsleep intrusions may account for this phenomenon.

Periodic leg movements of sleep (PLMS) are common in the narcoleptic patients, occurring in more than 60% of them. Compared with age-matched controls, PLMS are more frequently observed in REM sleep, and this may be interpreted as further evidence of REM sleep instability and disruption in narcoleptic patients.⁹ REM sleep behavior disorder is commonly associated condition, present in 7 to 36% of the narcoleptic people. Obstructive sleep apnea is also more prevalent in narcoleptic patients than in the general population and may contribute to sleep fragmentations in some individuals.¹⁰

The occurrence of cataplexy can precede the presence of EDS by a few years, but this is unusual. About half of narcoleptic patients will have both at the time of diagnosis, and roughly 40% will develop cataplexy later. Most will have their first cataplexy within 10 years.⁸

2) Pathophysiology of Narcolepsy

HLA DQB1*0602 is specifically associated with narcolepsy. In narcolepsy with cataplexy, more than 90% of patients test positive for this marker.¹¹ In narcolepsy without cataplexy, the link is less certain, even though more than 40% have this HLA on blood typing. This allele is present in 12 to 34% of the general population, depending on ethnicity. The hypocretin/orexin neurons in the lateral hypothalamus broaden our understanding of the pathophysiology. These hypocretin peptides, especially hypocretin-1, bind to their own receptors in the brainstem monoaminergic system (locus coeruleus, dorsal raphe, ventral tegmental area), the cholinergic pedunculopontine nucleus, the his-

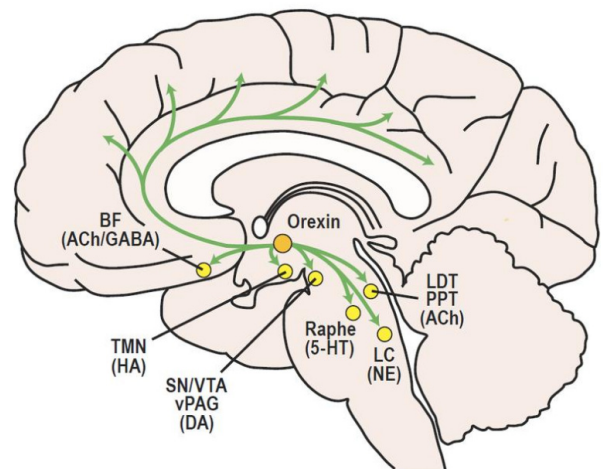


Figure 1. Schematic diagram of the hypocretineric/orexinergic system. Orexin releasing neurons in the lateral hypothalamus innervate all of the ascending arousal systems, as well as the cerebral cortex. Targets include the laterodorsal and pedunculopontine tegmental nuclei (LDT, PPT), locus coeruleus (LC), raphe nucleus, substantia nigra (SN), ventral tegmental area (VTA), ventral periaqueductal grey (vPAG), and tuberomammillary nucleus (TMN), all nuclei contribute to arousal. Each nucleus labelled with the neurotransmitter that it releases (ACh-Acetylcholine, NE-Norepinephrine, 5-HT-Serotonin, DA-Dopamine, HA-Histamine, GABA-γ-aminobutyric acid).

Figure adapted from España RA, Scammell TE. Sleep Neurobiology from a Clinical Perspective. Sleep, 2011;34(7):845-858.

taminergic tuberomammillary nucleus, the ventrolateral preoptic nucleus, and diffusely in the basal forebrain (Fig. 1).¹² CSF hypocretin levels are low or undetectable in patients with narcolepsy with cataplexy. Almost all these patients are also positive for HLA DQB1*0602. Histopathology showed a significant loss of the hypocretin neurons of the lateral hypothalamus.¹³ Cataplexy has been described as a condition similar to the REM sleep atonia. It was thought that this was the result of a REM dissociative process. The atonic process was attributed to the inhibition of the motor effector of the H-reflex, an electrical analog of the deep tendon reflex. It was inferred that the motoneurons of the anterior horn of the spinal cord were inhibited via a descending polysynaptic pathway, thus preventing any movement as is seen in REM sleep.¹⁴

3) Diagnosis of Narcolepsy

Narcolepsy may be diagnosed on the ground of clinical history, but additional tests are essential to confirm the diagnosis. Nocturnal PSG followed by the multiple sleep latency test (MSLT) is a useful tool to assess the severity of sleepiness and diagnose other concomitant sleep disorders. The MSLT measures the physiologic sleep tendency to fall asleep in the absence of alerting factors. Overnight PSG should be preceded to ensure that the patient has slept sufficiently and is not sleep-deprived. Patients should be tapered off all medications, which may alter sleep architecture for a period of 2 weeks before MSLT. Five naps are scheduled during the day at 2-hour intervals. The first epoch of any sleep stage is defined as sleep-onset. Sleep onset REM periods (SOREMP) is defined as REM occurring within 15 minutes of sleep-onset. If no sleep has occurred, the nap is terminated after 20 minutes. The mean sleep latency shorter than 8 minutes is suggestive of pathologic sleepiness. At least two episodes of SOREMP and shortened mean sleep latency highly suggest narcolepsy.¹⁵

The PSG is also frequently abnormal in a narcoleptic patient. PSG may show a decrease of total sleep time, shortened sleep latency, fragmented sleep, REM sleep without atonia, PLMS, and sleep disordered breathing.

HLA DQB1*0602 shows a strong association with narco-

lepsy in the presence of cataplexy. However, narcoleptic patients without cataplexy have a greater chance of being HLA negative than positive, and that up to 30% of the general population can be HLA positive without having symptoms related to narcolepsy.¹¹ Hypocretin-1 measurement in the CSF is also available. Patients with narcolepsy-cataplexy will show a reduction (<110 pg/mL or one third of mean normal control values) or absence of detectable hypocretin.¹⁶ Other neurologic conditions have also been reported to show a decreased hypocretin level and low CSF hypocretin should be interpreted within the clinical context.

The ICSD-2 has two different sets of criteria for narcolepsy, depending on the presence or absence of cataplexy.¹ A clinical diagnostic question that often comes up in testing is whether to perform HLA typing and analysis of the CSF for hypocretin. In the presence of EDS and cataplexy along with a positive MSLT, the HLA assay and the study of CSF hypocretin level may not be necessary. However, if confronted with equivocal MSLT results and questionable cataplexy, it is helpful to confirm the diagnosis with the measurement of CSF levels of hypocretin-1.⁷

4) Treatment of Narcolepsy

(1) Excessive Daytime Sleepiness

As CNS stimulants, amphetamines and methylphenidate has been used.⁷ Recently, new drugs such as modafinil, premier nonamphetamine wake-promoting substance are introduced. Action mechanism of modafinil is not yet elucidated, but dopamine metabolism may give clues. Modafinil has no effect in the alertness changes on dopamine transporter knockout mice.¹⁷ Furthermore, when D1 and D2 receptors were blocked, modafinil lost its effect.¹⁸ Thus, the wake-promoting effect of modafinil might be related with adrenergic dopamine-dependent signaling. This interaction was present in the forebrain of the studied mice, also giving clues about the absence of efficacy of modafinil in treating cataplexy, thought to originate in the brainstem.¹⁹ Divided doses up to 300-400 mg are usual.

Sodium oxybate shows a consistent efficacy in narcolepsy. Its action mechanisms are unclear. Sodium oxybate is a naturally occurring substance and has its own receptors. It

also has an affinity for activating GABA_B receptors.⁷ EDS, cataplexy, and sleep disruptions can be efficiently managed with sodium oxybate.⁷ Combinations of modafinil and sodium oxybate may have synergism.⁷ Additionally, sodium oxybate consolidates sleep. It increases slow-wave sleep significantly, and probably regularizes the fragmented sleep of narcoleptic patients.^{20, 21} It is in a liquid form and twice nightly dosing the first dose is taken at bedtime and the second 2½-4 hours later, starting dose is 3 g in divided doses, and it can be increased up to 9 g.

(2) Cataplexy

Cataplexy is a unique characteristic of narcolepsy and a debilitating symptom. The aim of treatment is preventing muscle atonia because the loss of muscle tone and associated falls can lead to injuries.⁷ The first effective therapy was imipramine in 1960. The improvement in the cataplectic events led the introduction of this class of molecules, the tricyclic antidepressants (TCA), as the drug of choice for treating cataplexy. Agents altering norepinephrine

metabolism, such as the selective serotonin reuptake inhibitors (SSRIs), and the selective serotonin norepinephrine uptake inhibitors (SSNRI) also show efficacy.⁷

TCA, imipramine is the original agent used for treatment of cataplexy. Protryptiline and clomipramine are also available. Even though their overall mechanism of action may differ slightly, they still share the common feature of blocking norepinephrine reuptake as a mode of improving cataplexy. Doses well below the antidepressant dosage are efficacious. Anticholinergic properties may be troublesome. Fluoxetine is the most commonly prescribed of all SSRIs.⁷ The anti-cataplectic effect of this drug is less potent than that of the tricyclics, in large part because the affinity of the SSRIs is toward the serotonergic pathway. To achieve some therapeutic benefit, higher doses may be required. Venlafaxine is the drug most commonly used in SSNRIs.⁷ Doses lower than the ones used in depression are effective.²²

Management of narcolepsy is still symptomatic, not curative. In narcolepsy associated with cataplexy, sodium oxybate may be the drug of choice because of the oppor-

Table 1. Pharmacologic treatment of narcolepsy

Drug	Dosage	Half-life(h)	Common side effect
For Excessive daytime sleepiness			
<i>Stimulants</i>			
Methylphenidate	10-20 mg qd or bid (morning and noon) maximum 60 mg/d	-3 h	palpitation, tachycardia, elevated blood pressure, anorexia
<i>Waking promoting agent</i>			
Modafinil	100-200 mg qd or bid (morning and noon) maximum 400 mg/d	9-14 h	headache, nausea, insomnia
For Cataplexy			
<i>Tricyclic antidepressant</i>			
Imipramine	start with 10-25 mg at bedtime maximum 150 mg/d	5-30 h	dry mouth, constipation, drowsiness
Clomipramine	start with 10-25 mg at bedtime maximum 150 mg/d	15-60 h	dry mouth, constipation, drowsiness
<i>Selective serotonin reuptake inhibitor</i>			
Fluoxetine	start with 10-20 mg in the morning maximum 60 mg/d	24- 72h	nausea, insomnia, diarrhea
Fluvoxamine	start with 25-50 mg in the morning maximum 300 mg/d	15 h	nausea, insomnia, diarrhea
<i>Serotonin-norepinephrine reuptake inhibitor</i>			
Venlafaxine	start with 75 mg in the morning maximum 375 mg/d	4 h	nausea, constipation, somnolence, dry mouth, dizziness
Improving disturbed night time sleep, excessive daytime sleepiness, and cataplexy			
Sodium oxybate*	starting dose 1.5 g at bedtime and again 2-4 hours after sleep onset; usual effective dose 4.5-6 g/d; maximum 9 g/d	0.5-1 h	headache, nausea, dizziness, worsened sleep-disordered breathing

*Sodium oxybate is not available in Korea.

tunity to treat both symptoms at the same time.⁷ If EDS persists, then the addition of modafinil or another stimulant may be appropriate. In narcolepsy without cataplexy, either modafinil, another stimulant or sodium oxybate would constitute adequate first-line therapy. Sodium oxybate also enhances sleep consolidation and slow-wave sleep.^{7,20,21} However, sodium-oxybate is not commercially available in Korea. Table 1 lists the medications available in Korea that are prescribed for the treatment of narcolepsy.

2. IDIOPATHIC HYPERSOMNIA

Idiopathic hypersomnia is a disorder of unknown etiology, characterized by unrefreshing sleep with difficulty waking up, either in the morning or after a daytime nap. This is still poorly understood, and diagnosis must be established with caution as exclusion of other causes of daytime sleepiness is mandatory. The exact prevalence is unknown, and no gender difference exists.⁷ The ICSD-2 classification differentiates long sleepers (more than 10 hours) and normal sleepers (4-10 hours).¹ Symptoms typically begin in the teenager or young adult. There seems to be a familial history of idiopathic hypersomnia.²³ However, linking to the HLA complex is not conclusive, and CSF hypocretin levels are normal. The cardinal manifestations of idiopathic hypersomnia are those of EDS, which is present despite adequate total sleep time and normal nocturnal sleep architecture. Patients report having difficulty getting up in the morning, feeling sleepy during the day, and wanting to go back to sleep. Sleep inertia is thus a common, but not pathognomonic symptom. Prolonged napping is usually un-refreshing. Little is known about idiopathic hypersomnia. Circadian dysfunction, abnormal melatonin secretion and abnormal homeostatic sleep drive have been postulated. With the discovery of hypocretin, a hypothalamic dysfunction has been proposed, but the evidence is still lacking. The ICSD-2 has elaborated the following set of diagnostic criteria. Sleepiness can be objectified with the Epworth Sleepiness Scale and the MSLT. To differentiate circadian rhythm disorder from idiopathic hypersomnia, actigraphy and sleep diaries are useful.⁷ In treatment, behavioral interventions should be considered.

Sleep hygiene may also be stressed. Increasing time spent in bed has not been proven useful. Pharmacologic intervention is in the same vein as narcolepsy, with the use of the available stimulants and wake-promoting agents such as modafinil. Melatonin has also been used with some success.

3. KLEINE-LEVIN SYNDROME

The best-known recurrent hypersomnia is Kleine-Levin syndrome (KLS). Recurrent hypersomnia is characterized by recurrent episodes of hypersomnia often associated with symptoms that typically occur weeks or months apart. KLS is classically described by the triad of hypersomnia, megaphagia, and hypersexuality. KLS is a rare disorder. Peak age of onset is in the second decade. Males outnumber females by a ratio of 2-4:1.^{1,24,25} Familial cases of the KLS are rare. Most of the KLS patients, the initial episode is preceded by a prodromal event, most commonly an infection or a fever. Alcohol use, sleep deprivation, stress, and travel are also frequently noticed. Less than 15% of the recurrent episodes are accompanied by a specific precipitating factor. Hypersomnia is the cardinal feature as daily sleep needs increase dramatically during the attacks, almost 12 hours to 18 hours per a day, waking or getting up only to eat and void.^{24,25} Other features include binge eating, sexual drive increase, cognitive impairment, autonomic symptoms, altered perception, and psychological changes. Men present more with hypersexuality and women with a depressed mood. The majority of episodes resolve within a month. Interval between episodes rarely exceeds 15 months. With time, the recurrent bouts become less frequent, less severe, and decrease in duration. The cure of KLS is questionable, but persistent remissions can occur, especially if the disease starts before adulthood, and if hypersexuality is absent.^{24,25} Major improvement has been reported in a limited number of patients with amantadine, lithium, lamotrigine, valproic acid and clarithromycin.^{7,26-29}

CONCLUSIONS

Primary hypersomnias of central origin represent a diverse group of different disorders. Those all have inappropriate and excessive daytime sleepiness. Narcolepsy with or without cataplexy is the prototypical hypersomnia. It is characterized by excessive daytime sleepiness, disturbed nocturnal sleep, sleep paralysis, hypnopompic more than hypnagogic hallucinations and/or cataplexy. Multiple sleep latency test after polysomnography shows short sleep latencies and two or more sleep-onset REM sleep periods. The recent progressions in the diagnosis and introduction of new medications have improved management of narcolepsy. CNS stimulants, wake-promoting agents and anti-cataplectic medication such as tricyclic antidepressants are widely used. Idiopathic hypersomnia is a sleep disorder characterized by excessive daytime sleepiness, with episodes of prolonged non-refreshing sleep, a prolonged major sleep episode, and great waking up either in the morning or at the end of a nap. It is a diagnosis of exclusion. Idiopathic hypersomnia is not well understood, but pharmacologic treatment is similar to that used for patients with narcolepsy, although the response has been variable. Kleine-Levine syndrome, a recurrent hypersomnia, is a rare disorder that is characterized hypersomnia, megaphagia and hypersexuality.

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