REVIEW ARTICLE

Narcolepsy and other Disorders of Excessive Sleepiness

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The French physician Gelineau used the term narcolepsy in 1880 to describe irresistible sleep attacks and "astasia" which has all the features of what was later to be named cataplexy. Reports of a large series of patients in the last century brought the entity of narcolepsy/cataplexy to the attention of the medical profession. Sleep attacks, cataplexy, sleep paralysis and hypnagogic hallucinations were all grouped under the term narcoleptic tetrad by Yoss and Daily in 1957. In 1960 Vogel discovered sleep onset rapid eye movements (SOREMs). Honda et al. discovered the presence of HLA-antigens in 100% of Japanese narcoleptics in 1983. Finally, the discovery of hypocretin or Orexin systems, reports of canine and mouse models of narcolepsy and hypocretin-1 deficiency in the cerebrospinal fluid of human narcolepsy/cataplexy patients (Mignot et al.; Nishino et al.) brought narcolepsy research to the forefront of the molecular neurobiology field.

Epidemiology of Narcolepsy

The prevalence of narcolepsy is estimated to be approximately 1 in 2000 persons in the United States, 1 person in 600 in Japan and 1 in 500,000 individuals in Israel. There is, however, a distinct lack of good epidemiologic studies in different parts of the world.

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Genetic Factors of Narcolepsy

Approximately 1-2% of the first-degree relatives of narcoleptic patients compared with 0.02-0.18% in the general population manifest the illness, indicating a 10-40 times higher prevalence than existing in the general population. Most cases of human narcolepsy are sporadic, but some are dominant. Twin studies of narcolepsy document lack of a strong genetic influence. The majority of monozygotic twins were discordant for narcolepsy; only 25-31% have concordance, suggesting an influence of environmental factors in the etiology of narcolepsy. Narcolepsy is thought to be recessive in Doberman Pinschers and Labrador Retrievers but multifactorial in poodles. Histocompatibility leucocyte antigens (HLA) are closely associated with narcolepsy in 95-100% of cases in white and Japanese patients. HLA DQB1 *0602 has been established as the narcolepsy gene along with allele DQA1*0102, located nearby on chromosome 6 across all ethnic groups. In African Americans with narcolepsy DR2 antigen is found in only 65%; however, DQ1 is present in more than 90% of cases. It should be remembered, however, that cases of narcolepsy not carrying HLL-DR2 or DQ1 antigens have been reported. Furthermore, 12-38% of the general population carry the same HLA alleles but narcolepsy is present in only 0.02-0.18% of the population; therefore, HLA DQB1*0602 is neither necessary nor sufficient to development of narcolepsy.

Pathogenesis of Narcolepsy/Cataplexy Syndrome

The most exciting recent development is the pathologic role played by the newly discovered hypocretin (Orexin) peptidergic systems in the lateral hypothalamus. Mutation of the hypocretin receptor 2 gene in dogs (Lin et al.) and

pre-prohypocretin knockout mice (Chemelli et al.) produced the phenotype of human narcolepsy. It is also noted that most cases of human narcolepsy and cataplexy have decreased hypocretin-1 in the cerebrospinal fluid. In addition, depletion of hypocretins is noted in narcoleptic brains at autopsy (Thannickal et al.), and mutation of the pre-prohypocretin gene has been identified in one child with severe narcolepsy (Peyron et al.). Therefore, the contemporary theory for pathogenesis of narcolepsy/cataplexy suggests that the condition results from a depletion (? Degeneration or autoimmune disorder) of the hypocretin neurons in the lateral hypothalamus, and thus narcolepsy/cataplexy can be considered a hypocretin (Orexin) deficiency syndrome. The association of narcolepsy with HLL DQB*0602 haplotype suggests the possibility of an autoimmune disorder causing depletion of the hypocretin neurons. However, all attempts to find evidence of autoimmune disorder in narcolepsy have so far failed. There is no evidence of inflammatory processes or immune abnormalities, presence of classical autoantibodies or an increase of oligoclonal bands in the cerebrospinal fluid in these patients. The other typical findings which may be noted in autoimmune disorders, such as alterations in the erythrocyte sedimentation rate, serum immunoglobulin levels, C-reactive protein and complement levels, and lymphocyte subset ratios are found to be normal in these patients. However, findings of increased levels of streptococcal antibodies in narcoleptic subjects in some reports and evidence of gliosis in the autopsied lateral hypothalamus in one report (Thannickal et al.) indicate that further exploration for possible immune-related disfunction in narcolepsy is needed.

Clinical manifestations

The onset in most cases occurs in adolescents and young adults, with a peak incidence between the ages of 15 and 20 years. The second peak is observed after the second decade, and rare cases have been described in children younger than 5 years and adults older than 50 years. The International Classification of Sleep Disorders (ICSD-2) divides narcolepsy into three types: narcolepsy with cataplexy, narcolepsy without cataplexy and secondary narcolepsy. The major clinical manifestations of narcolepsy include narcoleptic sleep attacks (100%); cataplexy (60-70%); sleep paralysis (25-50%); hypnagogic hallucinations (20-40%); disturbed night sleep (70-80%); and automatic behavior (20-40%) [Table 1].

Table 1: Clinical features of Narcolepsy

Major Manifestations
o Narcoleptic sleep attacks: 100%
o Cataplexy: 70%
o Sleep paralysis: 25-50%
o Hypnagogic hallucinations: 20-40%
o Disturbed night sleep: 70-80%
o Automatic behavior: 20-40%
Comorbid Conditions
o Sleep apnea: up to 30%
o PLMS: 10-60%
o RBD: up to 12%

The classic sleep attack is an irresistible and uncomfortable desire to fall asleep in inappropriate circumstances and at inappropriate places (e.g., while talking, driving, eating, playing, walking, running, working, sitting, listening to lectures or watching television or movies, during sexual intercourse, or when involved in boring or monotonous circumstances). These spells last for a few minutes to as long as 20-30 minutes. The patient generally feels refreshed upon waking. There is wide variation in the frequency of attacks occurring anywhere from daily, weekly, monthly or every few weeks to months. Attacks generally persist throughout the patient's lifetime, although fluctuations and rare temporary remissions may occur. The patients often show a decline in performance at school and work and encounter psychosocial and socio-economic difficulties as a result of sleep attacks and excessive daytime somnolence.

Cataplexy is characterized by sudden loss of tone in all voluntary muscles but respiratory and ocular muscles are spared. The attacks are triggered by emotional factors such as laughter, rage or anger more than 95% of the time. Attacks may be complete or partial and rarely unilateral. Most commonly the patient may momentarily have head nodding, sagging of the jaws, buckling of the knees, dysarthria or loss of voice, but sometimes they may slump and fall forward to the ground for a few seconds. Attacks generally last for a few seconds to a minute or two. Consciousness is retained completely

during attacks. Neurological examination during these brief spells reveals flaccidity of the muscles and absence or markedly reduced muscle stretch reflexes. H reflex and F responses are decreased or absent. Cataplexy is present in 60-70% of patients with narcolepsy. Generally cataplectic spells occur months to years after the onset of sleep attacks, but occasionally it may be the initial manifestation. It is a lifelong condition but is generally less severe and may even disappear in old age. Rarely, status cataplecticus occurs particularly after withdrawal of anti-cataplectic medications. EEG shows evidence of wakefulness during brief cataplectic spells; however, if attacks last longer than 1-2 minutes, the EEG shows REM sleep.

Sleep paralysis generally appears months to years after the onset of narcoleptic sleep attacks in about 25-50% of patients. A sudden paralysis of one or both sides of the body or one limb occurs either during sleep onset (hypnagogic) or on awakening (hypnopompic) in the morning. The patient is unable to move or speak and is often frightened or fearful although he or she retains consciousness. The attacks last from a few minutes to 15-20 minutes.

Hypnagogic hallucinations occur either during the onset of sleep or on awakening in the morning in 20-40% of narcoleptic patients, generally appearing years after the onset of sleep attacks. Most commonly, these hallucinations are vivid and visual and often fearful; sometimes auditory, vestibular or somesthetic phenomena may occur. In 30% of the patients, 3 of the 4 major manifestations of the narcoleptic tetrad are seen, and in approximately 10% of cases, all 4 major features occur together.

Disturbed night sleep is noted in 70-80% of patients. Automatic behavior is observed in 20-40% of patients, and during this episode, the patient repeatedly continues to perform a single function, such as speaking or writing in a meaningless manner or driving on the wrong side of the road or to a strange place, and then does not recall the episode. These episodes of automatic behavior may result from partial sleep episodes, frequent lapses or "micro-sleeps."

Patients with narcolepsy may also have important comorbid conditions [Table 1]: sleep apnea, periodic limb movements in sleep (PLMS) and REM sleep behavior disorder (RBD). Sleep apnea is noted in approximately 30% of narcoleptic patients, and most commonly it is central apnea, but obstructive or mixed apneas also occur. Associated sleep apnea may aggravate sleep attacks. It is important to diagnose obstructive sleep apnea in these patients because they may require additional treatment with continuous positive airway pressure (CPAP) for relief of apnea and excessive daytime sleepiness. RBD generally occurs in men with narcolepsy in about 12% of patients. Narcolepsy and RBD most commonly emerge in tandem. Treatment of narcolepsy/cataplexy with stimulants and tricyclic medications or selective serotonin reuptake inhibitors (SSRI) may induce or exacerbate RBD. PLMS may be seen in 10-60% of narcoleptic patients.

Differential diagnosis and other causes of excessive sleepiness

The most common conditions that should be differentiated from narcoleptic sleep attacks are listed in Table 2. Table 3 lists all causes of excessive daytime sleepiness, and many of these conditions may also resemble narcoleptic sleep attacks.

Table 2: Differential diagnosis of narcoleptic sleep attacks

- Obstructive sleep apnea syndrome
- Sleep deprivation
- Insufficient sleep syndrome
- Alcohol-and drug-related hypersomnolence
- Periodic hypersomnolence
- Medical, neurologic, and psychiatric disorders causing hypersomnolence
- Idiopathic hypersomnia
- Circadian rhythm sleep disorders

Table 3: Causes of excessive daytime sleepiness

Physiological causes
Physiological causes
Sleep deprivation and sleepiness related to lifestyle and irregular sleep-wake schedule
Pathological causes
Primary sleep disorders
Obstructive sleep apnea syndrome
Central sleep apnea syndrome

- Narcolepsy
- Idiopathic hypersomnolence
- Circadian rhythm sleep disorders
  - Jet lag
  - Delayed sleep phase syndrome
  - Irregular sleep-wake pattern
  - Shift work sleep disorder
  - Non–24-hour sleep-wake disorders
- Periodic limb movement disorder
- Restless legs syndrome
- Insufficient sleep syndrome
- Inadequate sleep hygiene
- Recurrent or periodic hypersomnia
  - Kleine-Levin syndrome
  - Idiopathic recurrent stupor
  - Catamenial hypersomnia
  - Seasonal affective depression
  - Occasionally secondary to insomnia
- General medical disorders
  - Hepatic failure
  - Renal failure
  - Respiratory failure
  - Electrolyte disturbances
  - Cardiac failure
  - Severe anemia
  - Endocrine causes
  - Hypothyroidism
  - Acromegaly
  - Diabetes mellitus
  - Hypoglycemia
  - Hyperglycemia
- Psychiatric or psychological causes
  - Depression
  - Psychogenic unresponsiveness or sleepiness
- Neurological causes
  - Brain tumors or vascular lesions affecting thalamus, hypothalamus, or brainstem
  - Post-traumatic hypersomnolence
  - Multiple sclerosis
  - Encephalitis lethargica and other encephalitides and encephalopathies including
    - Wernicke's encephalopathy
  - Cerebral trypanosomiasis (African sleeping sickness)
- Neurodegenerative disorders
  - Alzheimer's disease
  - Parkinson's disease
  - Multiple system atrophy
  - Myotonic dystrophy and other neuromuscular disorders causing sleepiness secondary to sleep apnea
- Medication-related hypersomnia
  - Benzodiazepines
  - Nonbenzodiazepine hypnotics, e.g., phenobarbital, zolpidem
  - Sedative antidepressants, e.g., tricyclics, trazodone
  - Antipsychotics
  - Nonbenzodiazepine anxiolytics, e.g., buspirone
  - Antihistamines
  - Narcotic analgesics including tramadol (Ultram)
  - Beta blockers
  - Toxin and alcohol-induced hypersomnolence

Idiopathic hypersomnia with or without long sleep time

Idiopathic hypersomnia closely resembles narcolepsy syndrome. This is a disorder of excessive daytime sleepiness of presumed CNS cause (but not proven) that is associated with normal (6-10 hours) or prolonged (more than 10 hours) nocturnal sleep documented by history, actigraphy, sleep logs or polysomnography. The condition occurs insidiously generally between the ages of 15 and 30 years. The sleep pattern in idiopathic hypersomnia is different from narcolepsy. The patient generally sleeps for hours, and the sleep is not refreshing. Because of

excessive daytime sleepiness, the condition may also be mistaken for sleep apnea. The patient, however, does not give a history of cataplexy, snoring or repeated awakenings throughout the night. Some patients may have automatic behavior with amnesia for the events. Physical examination uncovers no abnormal neurological findings. This is a very disabling and lifelong condition. The differential diagnosis of idiopathic hypersomnia should include other causes of excessive daytime somnolence (see Table 3). Unlike narcolepsy, there is no clear association between idiopathic hypersomnia and HLA antigens.

Symptomatic or secondary narcolepsy/cataplexy may be occasionally associated with diencephalic and midbrain tumors, multiple sclerosis, strokes, cysts, vascular malformations, encephalitis, cerebral trauma, and paraneopastic syndrome with anti-Ma2 antibodies. Symptomatic narcolepsy cases associated with cataplexy may develop in children affected with Niemann-Pick Disease Type C.

Differential diagnosis of cataplexy

Cataplectic attacks may be mistaken for partial complex seizures, absence spells, atonic seizures, drop attacks and syncope (Table 4). A partial complex seizure, however, is characterized by an altered state of consciousness unlike cataplexy. In addition, patients with partial complex seizure may have generalized tonic-clonic movements, post-ictal confusion and may show epileptiform discharges in the EEG. Absence spells are characterized by staring with vacant expression lasting from a few seconds to 30 seconds and an altered state of alertness, and is associated with characteristic 3 Hz spike and waves in the EEG. Atonic seizures are accompanied by transient loss of consciousness and EEG evidence of slow spike and wave or multiple spike and wave discharges. Narcoleptic sleep paralysis should be differentiated from isolated physiologic and familial sleep paralysis in which other manifestations of narcolepsy are absent. Automatic behaviors should be differentiated from the automatisms observed in partial complex seizures and psychogenic fugue. History, physical examination and EEG should be helpful in differentiating these conditions.

Table 4: Differential diagnosis of cataplexy

- Partial complex seizure
- Absence spells
- Atonic seizure
- Drop attack
- Syncope

Laboratory Assessment

The two most important laboratory tests for the assessment of narcolepsy/cataplexy and idiopathic hypersomnia are overnight polysomnographic (PSG) studies followed by multiple sleep latency tests (MSLT) the next day. Overnight PSG findings in narcolepsy/cataplexy patients include short sleep latency, excessive disruption of sleep with frequent arousals, and excessive body movements. SOREMs are noted in approximately 40-50% of patients. Some narcoleptic patients may have associated sleep apnea, PLMS and RBD. In idiopathic hypersomnia, overnight PSG shows sleep with normal sleep stages and cycling.

MSLT showing a mean sleep latency of less than 8 minutes is most commonly noted in narcolepsy. SOREMs in 2 or more of the 4-5 recordings in the MSLT are highly suggestive of narcolepsy, although abnormalities of REM sleep regulatory mechanism and circadian rhythm sleep disturbances also may lead to such findings. In idiopathic hypersomnia MSLT shows a mean sleep onset latency of less than 8 minutes without any SOREMs.

Maintenance of wakefulness test (MWT) is a variant of MSLT and measures a patient's ability to stay awake. MWT is important for monitoring the effects of treatment in narcolepsy but is not as good as MSLT in measuring daytime sleepiness.

HLA typing may be performed as most narcoleptic patients are positive for HLA DQB1*0602. The test is not diagnostic of narcolepsy because of the high prevalence of these HLAs in the non-narcoleptic population and reports of HLA-negative narcoleptics. Cerebrospinal fluid hypocretin 1 has been found to be markedly reduced in most patients with narcolepsy/cataplexy with positive DQB1*0602 patients. In patients with narcolepsy without cataplexy, hypocretin may be low normal and this is also found to be low normal in some other neurological conditions. Neuroimaging studies should be performed for suspected secondary or

symptomatic narcolepsy.

Treatment of Narcolepsy/Cataplexy Syndrome

For narcoleptic sleep attacks, administration of stimulants such as modafinil, methylphenidate, dextroamphetamines, and methamphetamines is the treatment of choice (Table 5). In 65-80% of patients, significant improvement of excessive daytime sleepiness can be obtained. The most common initial choice is modafinil, a novel wake-promoting agent. If this fails, methylphenidate is the drug most commonly used in newly diagnosed narcolepsy.

For treatment of cataplexy and other symptoms (Table 5) such as sleep paralysis and hypnagogic hallucinations, tricyclic antidepressants or serotonin reuptake inhibitors (e.g., fluoxetine) have been used with success. Sodium oxybate in two divided nightly doses have been used recently in treating cataplexy and narcoleptic sleep attacks.

Table 5 : Treatment of Narcolepsy – cataplexy syndrome

- For Sleep attacks
  - o Modafinil: 200 mg / day
  - o Methylphenidate: 5 mg bid; maximum 50 mg/d; rarely 100 mg / d
  - o Dextroamphetamine: 5 mg q d or bid; up to 50 mg / d
  - o Melphamphetamine: 5 mg q d or bid; up to 50 mg / d
  - o Mazindol: 2 mg q d or bid; up to 8 mg/d
- For Cataplexy, sleep paralysis and hyponagogic hallucinations
  - o Fluoxetine: 20 mg q d; up to 60 mg / d
  - o Gamma-hydroxybutyrate (sodium oxybate):3 - 9 gm in two divided doses: 1st dose at bedtime and 2nd dose 2 hours later
  - o Venlafaxine: 150 - 300 mg /d
  - o Viloxazine: 150 - 200 mg /d
  - o Clompramine: 75 - 125 mg /d
  - o Imipramine: 75 - 150 mg /d

Non-pharmacologic treatment includes general sleep hygiene measures, short daytime naps and participation in narcolepsy support groups which should be combined with drug treatment. Associated conditions such as sleep apnea should be treated appropriately with CPAP, and RBD should be treated with small doses of clonazepam (0.5 to 2 mg at night). Treatment of idiopathic hypersomnia is similar to stimulant treatment for narcolepsy but is unsatisfactory.

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