Narcolepsy

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Narcolepsy

A central nervous system disorder that is an important cause of persistent sleepiness.

The second most common cause of disabling daytime sleepiness after sleep apnea.
Clinical features
Neurobiology
Evaluation
Treatment
1862 - Gelineau applied the term "narcolepsy" to a clinical syndrome of daytime sleepiness with

- hypnagogic hallucinations
- sleep paralysis
- cataplexy
Narcolepsy affects 1 in 2000 people in Western Europe and North America

Equal prevalence in men and women
Narcolepsy...

- Typically begins in the teens and early twenties, but can occur as early as age 5 or after age 40
- The symptoms may worsen over the first few years and then persist for life
- Half of all patients report that symptoms interfere with job, marriage, or social life
• Can be considered a disorder of state control-

• Elements of sleep intrude into wakefulness, and wakefulness intrudes into sleep

• This state instability results in characteristic symptoms
Excessive daytime sleepiness —

- All patients with narcolepsy have chronic sleepiness
- Over 24 hours, they do not sleep more than normal controls, but they are prone to fall asleep throughout the day, often at inappropriate times
- “Sleep attacks”
- Often improved temporarily by a brief nap
- Patients with untreated narcolepsy typically have ESS scores above 15
Associated Features...

- Hypnagogic hallucinations
- Sleep paralysis
- Cataplexy
Hypnagogic hallucinations

- Vivid, often frightening hallucinations that occur just as the patient is falling asleep
- Likely result from a mixture of REM sleep dreaming and wakefulness
Sleep paralysis

• A complete inability to move for a minute or two just after awakening

• Episodes of sleep paralysis may be accompanied by hypnagogic hallucinations
Cataplexy

• Sudden episodes of bilateral muscle weakness leading to partial or complete collapse

• Often triggered by strong emotions such as laughter, anger, or excitement

• Episodes of cataplexy last one to two minutes, and are not associated with impairment of consciousness

• Sixty percent of narcoleptic individuals develop cataplexy
Other symptoms...

- Maintenance insomnia
- Higher than expected incidence of other sleep disorders
- Slightly higher incidence of adult onset diabetes, obesity, and migraine headaches
Neurobiology

- Loss of function of the neuropeptide orexin (hypocretin)
- Made by neurons in the lateral hypothalamus
- Excitatory effects on postsynaptic neurons through the ox1 and ox2 receptors
Neurobiology

- The orexins are synaptically released during wakefulness.
- Increase the activity of many brain regions involved in the promotion of wakefulness.
- Locus coeruleus, raphe nuclei, and the tuberomammillary.
- Help stabilize wakefulness, preventing inappropriate transitions into REM or non-REM sleep.
• Animal models first identified the importance of orexin in narcolepsy

• People with narcolepsy also have orexin deficiency

• About 90 percent of narcoleptics with cataplexy have little or no detectable orexin in their spinal fluid

• Autoimmune or neurodegenerative process results in a loss of orexin neurons

• Narcolepsy without cataplexy may be a separate disease- they usually have normal CSF orexin levels
GENETIC FACTORS

- Usually sporadic, but genetic factors play important role
- Most narcoleptics (50 to 90 percent) have HLA DR2 and DQ1
- Environmental factors appear to be even more important: only about 25 percent of affected monozygotic twins are concordant for narcolepsy
- On rare occasions, narcolepsy runs in families.
Secondary narcolepsy

- Narcolepsy is usually caused by a sporadic, possibly autoimmune, process
- Midbrain injuries can produce similar results, though affected patients usually lack the full narcolepsy syndrome
Secondary narcolepsy

- Tumors, vascular malformations, and strokes have all been reported to cause secondary narcolepsy, most likely due to direct injury to the orexin neurons or their projections.

- All patients with secondary narcolepsy have obviously abnormal neurologic exams, with cognitive, motor, and/or eye movement deficits.

- Thus, neuroimaging is unnecessary in narcoleptic patients with a normal bedside neurologic exam.
CLINICAL EVALUATION

- Complete evaluation includes an overnight polysomnogram (PSG)
- Multiple Sleep Latency Test (MSLT)
- Nocturnal PSG and the MSLT are standard, electrophysiological diagnostic procedures to measure the amount and type of sleep that occurs during a specified time period
MSLT

• A patient is given four or five opportunities to nap every two hours
• On average, healthy subjects fall asleep in about 10-15 minutes
• People with narcolepsy often fall asleep in less than five minutes
• The naps of narcoleptics often include REM sleep
• Occurrence of sleep onset REM periods (SOREMs) in two or more naps is an essential feature in establishing the diagnosis of narcolepsy
• False negative 20 to 30 percent of the time

• Should be repeated if the history is strongly suggestive of narcolepsy

• May be less sensitive for the diagnosis of narcolepsy in older adults because sleep latency increases and SOREMs become less frequent with age
• False positives: SOREMs can occur with other disorders that increase REM sleep pressure:

  - sleep deprivation
  - untreated sleep apnea
  - circadian phase delay
Drug Effects...

- REM sleep-suppressing medications (TCAs, SSRIs) or withdrawal from these drugs also can produce SOREMs ("rebound" phenomenon)

- These drugs should be discontinued at least three weeks before the MSLT if possible
DIFFERENTIAL DIAGNOSIS

• With Cataplexy:
  - Hypothalamic lesions
  - Prader-Willi syndrome
  - Niemann-Pick disease type C
  - Norrie disease

• Without Cataplexy:
  - OSA
  - PLMD
  - Idiopathic hypersomnolence
TREATMENT

- Mainstays of therapy are
  - Stimulants for the treatment of sleepiness
  - REM sleep-suppressing medications for the treatment of cataplexy
- Napping and sleep hygiene
- Psychosocial support
• A few may get by with an occasional nap

• Most patients require a wake-promoting drug

• These drugs improve performance as measured by reaction time and simulated driving tasks

• Performance usually does not exceed 70 to 80 percent of normal control levels

• Goal is obtaining "normal" alertness throughout conventional waking hours
Modafinil

- Non-amphetamine "wake-promoting agent"
- Mechanism of action not well understood
- Reaches peak bioavailability in about two hours
- Well-tolerated
- No evidence of tolerance
Modafinil

- Large placebo-controlled clinical trials have shown significant improvements in Maintenance of Wakefulness Tests and Epworth Sleepiness Scale measurements.
- The drug is hepatically metabolized and induces several cytochrome P450 enzymes, thus decreasing the effectiveness of oral contraceptives.
- Women of childbearing age who use modafinil should employ another method of contraception.
• Typical dose is 200 to 400 mg given once in the morning

• May also be divided into early morning and mid-afternoon doses

• Side effects are uncommon but include headache, nausea, dry mouth, anorexia, and diarrhea

• The lack of sympathomimetic effects also makes modafinil a good choice for older patients who may have hypertension or heart disease
Amphetamines

- Used to control sleepiness since the 1930's
- Methylphenidate, Dextroamphetamine
- Very effective
- Sympathomimetic side effects can be troublesome
- Pemoline is no longer routinely used; can cause fatal hepatotoxicity
CATAPLEXY AND OTHER REM-RELATED SYMPTOMS

• About 30 percent of narcoleptics have cataplexy that warrants treatment.

• Brainstem circuits that generate REM sleep are strongly inhibited by norepinephrine and serotonin.

• Drugs that increase noradrenergic and serotonergic signaling suppress REM sleep and reduce cataplexy.
• Tricyclic antidepressants such as protriptyline or clomipramine

• Very effective, but anticholinergic side effects limiting (dry mouth and constipation)

• Newer antidepressants venlafaxine and fluoxetine are very effective and well tolerated

• Abrupt withdrawal from any of these antidepressants can trigger status cataplecticus - severe, nearly continuous cataplexy
Gamma hydroxybutyrate (GHB)

- 2002- Approved by the FDA for the treatment of cataplexy
- Especially useful in patients with severe cataplexy
- Can also improve daytime sleepiness
- GHB is a metabolite of GABA
- Mechanism of action in patients with cataplexy is unknown
Gamma hydroxybutyrate (GHB)

- Significantly decreases the frequency of cataplexy, and improves subjective daytime somnolence
- Adverse effects include nausea and dizziness in over 30 percent of patients
- 14 percent developed urinary incontinence and a similar number had a worsening of sleepwalking
Gamma hydroxybutyrate (GHB)

- Gained notoriety as a "date-rape" drug
- Has potential for abuse
- Anxiety, delirium and insomnia
- Overdosage can result in respiratory depression, coma, and death
SUMMARY

- Narcolepsy is characterized by excessive daytime sleepiness with REM sleep-related phenomena such as cataplexy, hypnagogic hallucinations, and sleep paralysis.

- Narcolepsy with cataplexy is usually due to a loss of the hypothalamic neuropeptide orexin/hypocretin, but the cause of narcolepsy without cataplexy remains unknown.

- The diagnosis is typically established by a detailed clinical history and an MSLT demonstrating short sleep latencies and REM sleep on two or more naps.
RECOMMENDATIONS

• General therapeutic measures include sound sleep hygiene, scheduled daytime naps, and avoidance of drugs that can produce daytime sleepiness or insomnia.

• Drug therapy is helpful in most patients and should be targeted toward specific symptoms.

• Excessive daytime sleepiness can be treated with modafinil or amphetamine-like compounds. REM-suppressing antidepressants and GHB often produce excellent control of cataplexy, sleep paralysis, and hypnagogic hallucinations.