A 14 y/o middle school student is brought in by his parents because of moderate sleepiness for the last year. He often falls asleep in classes, when doing homework, and when watching TV. On several occasions, he has awoken convinced there was a threatening stranger in his room. At a birthday party, he was telling a funny story, and then he transiently "looked drunk" with slurred speech for about 30 sec.

Symptoms of Narcolepsy

1) Excessive daytime sleepiness
2) Cataplexy: brief, emotionally-triggered episodes of muscle weakness in ~50%
3) Other REM sleep-like phenomena
   - Sleep paralysis in 40-80%
   - Hypnagogic and hypnopompic hallucinations in 40-60%

4) Fragmented sleep in >50%
5) Associated sleep disorders
   - Obstructive and central sleep apnea in 10-20%
   - Periodic limb movements in 40-60%
   - REM sleep behavior disorder in in 10-30%
   - Sleepwalking, sleeptalking, night terrors in ~20%
6) Mild obesity:
   - Sometimes rapid weight gain in months after onset
   - Adult BMI increased by ~15% on average

Demographics

- Prevalence 1:2,000 in US; male = female

Sleepiness in narcolepsy

- May be mild to severe
- Varies over the day
- Most apparent when sedentary, bored, or relaxed
- “Sleep attacks” rare
- Automatic behavior common
- Brief naps often help reduce sleepiness for 1-2 hours

Cataplexy

- Muscle weakness triggered by strong emotions - esp. laughter and joking, but also intense frustration or anger
- Consciousness is preserved
- Frequency varies from a few episodes/yr to several/day
- Clonic inhibitory movements leading to loss of motor neuron activity for a few seconds to a few minutes
- Severe episodes are bilateral and generalized, leading to a fall
- Partial cataplexy can affect only the face, voice, or a limb

Negative motor symptoms

- Head drop (18-82%)
- Ptosis plus tongue protrusion (51-82%)

Plazzi, Brain 2011

Positive motor symptoms

- Eyebrow raising
- Perioral and tongue movements

Plazzi, Brain 2011

Generalized hypotonia (31-47%) with interictal forced squatting unsteady gait in 26%

Plazzi, Brain 2011
Positive motor symptoms

Stereotyped motor behavior

Dyskinetic–dystonic movements

Lab findings in narcolepsy

- Overnight Polysomnogram
  - helps rule other sleep disorders (OSA, PLMS, etc)
  - verify > 6 hours sleep prior to a MSLT
  - short sleep latency, short REM latency

- Multiple Sleep Latency Test (MSLT)
  - short sleep latencies (< 8-10 min)
  - episodes of sleep-onset REM sleep (SOREMs)
  - ≥ 2 SOREMs is usually diagnostic of narcolepsy

New ICSD-3 Definitions of Narcolepsy

Narcolepsy Type 1 (“Narcolepsy with cataplexy”)
- EDS for at least 3 months.
- At least two of the following:
  - Definite cataplexy
  - Positive MSLT
  - Low CSF hypocretin-1 (≤110 pg/ml or <1/3 of normal)

Narcolepsy Type 2 (“Narcolepsy without cataplexy”)
- EDS for at least 3 months.
- Positive MSLT

*: Positive MSLT: mean sleep latency of ≤5 minutes and ≥2 SOREMPs. A SOREMP (≤15 min) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

Low hypocretin/orexin levels in narcolepsy

Loss of hypocretin/orexin neurons in narcolepsy with cataplexy

Limitations of the current definitions

- Very dependent on the MSLT
  - ≥2 SOREMS occur in 13% of men and 6% of women.
  - ≥2 SOREMs and MSLT latency ≤ 6 min occurs in 6% of men and 1% of women.
  - Are these false positives, or is narcolepsy without cataplexy much more common than we think?
  - MSLT can be falsely negative ~20% of the time (anxiety, meds, etc)

- Cataplexy can develop months or years after EDS.
- Cataplexy decreases with age.

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What is narcolepsy without cataplexy (N-C)?

- Forme fruste of narcolepsy with cataplexy?
  - Two patients with N-C had moderate (33-85%) loss of the hypocretin neurons.
  - ~20% of N-C patients have low CSF hypocretin levels (<110 pg/ml).
  - ~13% of N-C patients have intermediate CSF hypocretin levels (between 110-200 pg/ml).
  - N-C are less likely to have 0602.
  - Maybe this reduces the severity of cell loss.
  - About 1/3 of N-C with intermediate of low CSF hypocretin develop cataplexy 1-26 years later.

- A problem downstream of hypocretin peptides?
  - Perhaps it’s like type 1 and 2 diabetes mellitus:
    - Severe phenotype with ligand deficiency
    - Moderate phenotype with ligand insensitivity

- Unrelated to hypocretin signaling?


Narcolepsy: Differential diagnosis

- EDS and SOREMs can be seen with many conditions that disrupt sleep, especially REM sleep
  - SOREMs and EDS very common with shift work
  - Also occurs with insufficient sleep, OSA, PLMs, etc

- EDS, SOREMs, and cataplexy can occur in:
  - Prader-Willi Syndrome
  - Niemann-Pick type C
  - Hypothalamic and midbrain lesions

- No need for MRI, etc if neuro exam is normal

What causes the loss of hypocretin neurons in narcolepsy?

- Most narcoleptics do not have mutations in the genes coding for hypocretin or its receptors.
- 90% of narcoleptics with cataplexy have HLA DQB1*0602 compared to only 12-25% of the general population. Also associated with HLA DQA1*0102 and the less specific marker DR2.
- Only 1/3 of monozygotic twins will both develop narcolepsy.
- Risk of affected child only ~ 1%.

What causes narcolepsy?

- Brains of narcoleptics may have gliosis in the lateral hypothalamus, but no increase in microglia or local TNFα production.
- CSF shows no increase in protein or oligoclonal bands.
- HLA DQB1*0602 and other genes may confer a susceptibility for some individuals to develop narcolepsy. Possibly, these individuals are more likely to develop an autoimmune attack against the hypocretin neurons.

Some narcolepsy patients have high levels of antibodies against Trib2

- Tribbles homolog 2 is expressed in hypocretin neurons and other neurons.
- Higher anti-streptolysin O titers 1-3 years after narcolepsy onset


Anti-DNAse B also increased in first 3 years

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Narcolepsy onsets more common in spring & summer

Han, et al, 2011

N=629 Chinese patients (86% children)

Narcolepsy after H1N1 vaccine in Finland


8-12-fold increase in narcolepsy in children in Finland and Sweden with Pandemrix or Arepanrix (brands with potent ASO3 adjuvant)

All 0602+. Onset ~40 days after vaccine

Autoimmunity: Summary

- DQB1*0602 found in 50-90% of people with narcolepsy
- ASO and Trib2 titers are increased in some patients with narcolepsy, especially in the first years after onset. Thus far, there is no clear evidence that these antibodies are pathogenic
- Narcolepsy can be triggered by some H1N1 vaccines, but no need to alter normal vaccination plans.
- An autoimmune process is looking more likely.

Narcolepsy from a hypothalamic stroke

Scammell, et al, 2001

Secondary narcolepsy

- Caused by lesions of the posterior and lateral hypothalamus or midbrain
  - Tumors (esp. gliomas, craniopharyngiomas).
  - Demyelination (esp. anti-aquaporin 4)
  - Strokes
  - Inflammation
- Patients always have
  - Excessive amounts of sleep
  - Overt neurologic deficits (e.g. abnormal eye movements, focal weakness, pituitary dysfunction, obesity)
- May disrupt the hypocretin neurons or their connections to REM- and wake-regulatory regions

Treatment of narcolepsy: Non-pharmacologic approaches

- One or two 15-20 min naps are often helpful (e.g. during and after school)
- Adequate amount and good quality nighttime sleep
- Sustained vigilance can be difficult, so consider accommodations in school:
  - Occasional breaks to walk around
  - Nap(s) at school, short-acting stimulant before nap
  - More time on tests
  - Help taking notes
A 20 y/o woman presents with 3 years of severe daytime sleepiness. ESS=16. She sleeps ~11 hours each night and on vacation can easily sleep 14 hours every day. She often sleeps through 2 alarm clocks and does not feel rested in the morning or after taking naps. PSG shows 10.5 hours of sleep, with sleep efficiency 92% and normal amounts of all stages. AHI=4.

MSLT shows sleep in all 5 naps with average sleep latency of 5.5 min and 1 SOREM.

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### Treatment of excessive sleepiness: Amphetamines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>10-30 mg BID or 20 mg SR qAM with 10-20 mg qPM</td>
<td>Irritability, headaches, insomnia, GI upset, arrhythmias, anxiety, psychosis</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>5-30 mg BID or 10 mg SR qAM with 10-20 mg qPM</td>
<td>Same, reduced appetite</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>5-20 mg BID</td>
<td>Same</td>
</tr>
</tbody>
</table>

No large trials of any narcolepsy meds in children.

### Treatment of excessive sleepiness: Newer agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafinil</td>
<td>100-400 mg qAM or 200 mg BID</td>
<td>Few side effects, headache, nausea, nervousness, insomnia, rash</td>
</tr>
<tr>
<td>Armodafinil</td>
<td>150-250 mg qAM</td>
<td>Same</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>2.25-4.5 g qhs and 3-4 hours later</td>
<td>Sedation, nausea, dizziness, worse OSA, weight loss</td>
</tr>
</tbody>
</table>

IVIG is still experimental.

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### General considerations with wake-promoting drugs

- **Amphetamines**
  - Potential for anxiety, psychosis, mania
  - May disrupt sleep and suppress growth
  - Rebound hypersomnia common
  - Moderate abuse potential

- **Modafinil, armodafinil**
  - Interferes with birth control pills
  - Rare Stevens-Johnson Syndrome or other severe rash
  - Sometimes less potent than amphetamines
  - Low abuse potential

- **Sodium oxybate, GHB**
  - Very sedating, discuss home safety
  - Respiratory depressant, can worsen OSA
  - Overdose can cause coma and death
  - Large salt load
  - Some abuse potential

---

### Treatment of cataplexy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>75-150 mg XR qAM</td>
<td>Few side effects, dry mouth</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20-80 mg qAM</td>
<td>Same</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>10-150 mg qPM</td>
<td>Anticholinergic effects, somnolence, weight gain</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>3-4.5 g qhs and 3-4 hours later</td>
<td>Sedation, nausea, dizziness, worse OSA, weight loss</td>
</tr>
</tbody>
</table>

General warnings with antidepressants: Suicidality in young depressed patients, serotonin syndrome, neuroleptic malignant syndrome, interaction with MAOI's.

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### Idiopathic hypersomnia

- May occur with or without long sleep time (> or < 10 hrs). Total sleep may be over 12-14 hours.
- Naps generally long and unrefreshing. Sleep inertia common. Need help waking up.
- MSLT shows average sleep latency < 8 min and < 2 SOREMs.
- Prevalence ~1: 20,000
- Onset usually around age 10-30, develops over several weeks, then stable, resolves in 25%
- CSF hypocretin normal, but histamine may be decreased
- Need to consider subtle OSA, PLMS, insufficient sleep, delayed sleep phase, psychiatric illness, sedating meds, encephalopathy.
- Treatment: usual wake-promoting meds, may respond better to amphetamines

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A 17 y/o high school student presents with episodes of severe sleepiness. Over the last 2 years, he has had 6 episodes during which he needs to sleep 16 hours/day for periods of about 2 weeks. He becomes very hard to wake in the morning and is quite irritable and inattentive during these episodes. Between episodes, he is normal.

Kleine-Levin Syndrome

- Recurrent episodes of hypersomnia (TST 12-20 hrs/day) with deep, sustained sleep and sleep inertia
- First and subsequent episodes may be triggered by URI’s
- Episodes usually lasting 1-2 weeks, recur several times each year, with normal amounts of sleep and behavior in between
- Often have abnormal behaviors: hyperphagia (70-80%), hypersexuality (50%, mostly men), irritability (50%), aggression
- Cognitive abnormalities: confusion (50%), poor recall of episodes (90%), derealization (24%), hallucinations (40%). Apathy and depressed mood (80%).
- Onset in teens, and usually resolves in several years
- Very rare: 2-10/1,000,000
- 2-3x as common in men, 6x in Ashkenazi Jews, 1% familial

KLS: Differential diagnosis

- Psychiatric disorders (e.g. bipolar, SAD)
- Menstrual-related hypersomnia - sleepiness before menses, better with BCP
- Complex partial seizures- EEG abnormal
- CNS injury (hypothalamic or bilateral temporal lesions)- abnormal exam and other fixed deficits
- Idiopathic recurrent stupor (benzos or endozepine)- episodes last just a couple days
- Metabolic encephalopathies (e.g. liver failure, ornithine transcarbamylase deficiency, mitochondrial encephalopathies)- EEG abnormal and triggered by factors that worsen the encephalopathy

KLS: Diagnosis and treatment

- 24 hr PSG or actigraphy helpful
- MSLT can show >2 SOREMS in 20%
- Consider routine EEG or telemetry to help rule out seizures or encephalopathy
- Stimulants: Moderately helpful in 20-50%
- Lithium: 25-40% get better
- Amantadine: partial or good improvement in ~40%

Conclusions

- The diagnosis of narcolepsy requires EDS plus cataplexy or positive MSLT.
- Narcolepsy with cataplexy is caused by a loss of the hypocretin/orexin neurons.
- Sleepiness is usually treated with modafinil or methylphenidate. Cataplexy is best treated with venlafaxine or tricyclics. Sodium oxybate can improve both sleepiness and cataplexy.
- Other causes of hypersomnia include: Idiopathic hypersomnia, KLS, insufficient sleep, and psychiatric disorders. Also consider medical conditions and sedating meds.