Narcolepsy and Hypersomnia

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With thanks to Neil Freedman, MD
and David Rye, MD, PhD
Once Upon a Time.....

Sleepy Patient
As the Story Progressed...

Sleepy Patient
And it Got Worse....

- Narcolepsy
- Idiopathic Hypersomnia
Kinda sorta sleepy

Tired with a blotchy rash

Extremely fatigued but not really “tired”

Falling asleep driving, but not while watching TV

Sleeping between 10 - 10.5 hours / day

Arthritis patients who have no energy

Red-heads who can’t stay awake

Extremely fatigued but not really “tired”

Lack of energy & precisely 64% N2 sleep

Looks sleepy, but not really, unless you listen to the spouse

Only tired after eating pizza with GERD

Dog owners sleepier than their pets

Apnea with 2+ MSLT REMs

30-50 arousals from sleep per hour

Left-handed sleepy shift-workers

Listless men married to energetic

Octogenarians with diurnal sleep attacks

Sleepy sleep doctors

Basic cable reality show stars with

Residents of Nebraska who can’t

“Two and a half men” starts with comorbid sleep drunkenness

Arthritis patients who have no energy

Tired lounge singers

Ex-NFL linemen with sleep inertia

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Central Disorders of Hypersomnolence

- Narcolepsy Type I and Type II
- Idiopathic Hypersomnia
- Associated with a Psychiatric Disorder
- Due to Medication or Substance
- Due to a Medical Disorder
- Kleine-Levin Syndrome
- Insufficient Sleep Syndrome

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Fortunately, that didn’t happen…
A 21 year old woman presents with long standing daytime sleepiness. She also reports intermittent lower extremity weakness that may be associated with laughter, though you are not able to reproduce it in clinic. She regularly sleeps 8-9 hours per night and has no symptoms of OSAS, or insomnia. Medications: None. Exam: Normal. An overnight PSG demonstrates:
- TST 8.5 hours
- REM latency of 70 minutes
- No abnormalities are observed
A multiple sleep latency test (MSLT) performed the following day demonstrates:
- Mean sleep latency (MSL) of 6.5 minutes and 1 sleep onset REM period during the first nap.
Question:

What other test would be most helpful to help confirm a diagnosis of narcolepsy?

A. HLA DQB1*0602
B. MRI of the brain
C. CSF hypocretin 1 (Orexin A) level
D. Maintenance of wakefulness test (MWT)
Question:

What other test would be most helpful to help confirm a diagnosis of narcolepsy?

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Narcolepsy

• Hallmark symptoms of Type 1 narcolepsy:
  – Excessive daytime sleepiness
  – Cataplexy (average time to onset from sleepiness ~ 4 years)
  – Hallucinations upon falling sleep or awakening from sleep (hypnagogic hallucinations)
  – Brief episodes of total paralysis upon falling asleep or awakening from sleep (sleep paralysis)
  – Disrupted sleep

• EDS is the most common initial symptom, occurring alone in ½ of patients

• >60% of patients present with only 1 hallmark symptom
• <10% of patients present with all 4 hallmark symptoms
Many Symptoms of Narcolepsy Stem from the Loss of Sleep-Wake Boundaries

Excessive Daytime Sleepiness
Disrupted Sleep
Hypnagogic Hallucinations
Automatic Behaviors

Cataplexy
Sleep Paralysis

Wake
NREM
REM
Narcolepsy Prevalence Varies among Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Cases per 100,000 Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>160</td>
</tr>
<tr>
<td>Europe</td>
<td>50</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>30</td>
</tr>
<tr>
<td>Israel</td>
<td>10</td>
</tr>
<tr>
<td>England</td>
<td>30</td>
</tr>
<tr>
<td>United States</td>
<td>40</td>
</tr>
</tbody>
</table>
Symptom Onset is Biphasic

Montpellier, France
(n = 317)

Montreal, Canada
(n = 202)

Dauvilliers, Y et al. Neurology 2001;57:2029-33
Excessive Daytime Sleepiness

• Universal and most disabling symptom
• Typically the first symptom
• Transiently improved by nighttime sleep and daytime naps
  – As opposed to idiopathic hypersomnia
• May occur suddenly (sleep attacks)
• Despite EDS, the total sleep time per 24 hour period is similar to healthy adults
Cataplexy

- Sudden loss of bilateral muscle tone (partial or generaliz
- Full consciousness maintained during episode
  - Reflexes absent during episode
- Almost always associated with:
  - HLA DQB1-0602 + CSF hypocretin-1 deficiency
- Typically presents years (mean 1 to 5 yrs) after the onset of daytime sleepiness
- Typically triggered by emotion (not always)
  - Laughter most common
- Present in 60% to 90% of narcoleptics
- Virtually pathognomonic for narcolepsy
- Duration = Seconds to minutes
- Recovery is immediate and complete
Clinical Features are inadequate by themselves to diagnose Type 1 narcolepsy

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sensitive</th>
<th>Specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATAPLEXY</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>SLEEP PARALYSIS</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>HYPNAGOGIC/HYPNOPOMPIC HALLUCINATIONS</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>SLEEPINESS</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>DISRUPTED SLEEP</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>
Diagnostic Criteria for Narcolepsy Type 1

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- Daily sleepiness for ≥ 3 months
- The presence of one of the following:
  - Cataplexy AND a MSL < 8 minutes with ≥ 2 SOREMP on the MSLT
  - A SOREMP (within 15 minutes of sleep onset) on the preceding night’s PSG may replace one of the SOREMPs on the MSLT
- CSF hypocretin-1 concentration ≤ 110 pg/mL, or < 1/3 of mean values obtained in normal subjects
Reduced Number of Hypocretin Neurons in Narcolepsy with Cataplexy

• Specific loss of HCRT cells in the posterior and lateral hypothalamus
  – No significant difference in the number of melanin-concentrating hormone (MCH) neurons

• Presence of gliosis in HCRT cell region most consistent with a degenerative process
  – No clear evidence for immune activation

Thannickal, TC et al. Neuron 2000;27:469-74
Thannickal, TC et al. Sleep 2009;32:993-98
Mechanism of Disease and Hypocretin Deficiency Not Clear

• Possibly genetic
  – DQB1*0602 haplotype in 90% of narcolepsy 1
    • Only 25% of affected monozygotic twins concordant
    • Most familial cases (-) for HLA DQB1*0602

• Possibly autoimmune
  – Onset greatest in the spring / winter related viral infection
  – Association with polymorphisms in T cell receptor alpha genes
What causes hypocretin cell loss?
What causes hypocretin cell loss – molecular mimicry and H1N1?

Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland
Markku Partinen et al. PLOS One (2011)

Narcolepsy Onset Is Seasonal and Increased following the 2009 H1N1 Pandemic in China
Fang Han et al. Annals of Neurology (2011)
CNS HCRT-1 Deficiency is Highly Specific for HLA+ Narcolepsy Type 1

- Sensitivity = 87%
- Specificity = 99%
- PPV and NPV = 96%
- Normal levels in other sleep disorders
  - OSA, RLS, insomnia, idiopathic hypersomnia
- May be useful diagnostically for atypical presentations, non-diagnostic MSLT, children and patients on antidepressants

Diagnostic Criteria for Narcolepsy Type 2

• Daily periods of sleepiness for ≥ 3 months
• A MSL ≤ 8 minutes with ≥ 2 SOREMP on the MSLT
  – A SOREMP (within 15 minutes of sleep onset) on the preceding night’s PSG may replace one of the SOREMPs on the MSLT
  – Polysomnographically indistinguishable for Narcolepsy Type I
• Cataplexy is absent
  – CSF hypocretin-1 concentration, > 110 pg/mL, or > 1/3 of mean values obtained in normal subjects, or not measured
  – The hypersomnolence and or MSLT findings are not better explained by other causes

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Narcolepsy Type 2

• **Less** prevalent than narcolepsy with cataplexy
  – 15% to 25% of diagnosed narcoleptics
• Association with HLA DQB1*0602 **less** than with narcolepsy type 1:
  – 45% vs 90%
• CSF hypocretin 1 levels **normal**
  – Underlying pathophysiology of most patients with narcolepsy type 2 **not** known; ? A manifestation of several underlying pathologies?
• **Other:**
  – If cataplexy develops later or CSF hypocretin 1 levels are found to be deficient at a later date, reclassify as narcolepsy type 1
Narcolepsy Treatment

- Goal of therapy is to treat symptoms
  - Sleepiness
  - Cataplexy, if present
- Stimulant therapy typically improves, but does not resolve daytime sleepiness in many/most patients with narcolepsy
Treatment of Type 1 Narcolepsy

Behavioral Strategies

• Short, regularly scheduled naps
• Consistent sleep / wake schedule
• Exercise for at least 20 minutes per day at least 4 or 5 hours before bedtime
  – Regular exercise for prevention of obesity important in children with narcolepsy
• Avoid alcohol, caffeine and nicotine for several hours before bedtime

Treatment of Type 1 Narcolepsy
Pharmacologic Interventions

• **Excessive Daytime Sleepiness**
  – Modafinil (Provigil®) and Armodafinil (Nuvigil®)*
  – Amphetamine /dextroamphetamine (Adderall®)/ methamphetamine (Desoxyn®)*
  – Methylphenidate* (Ritalin®; Concerta®)
  – Sodium oxybate* (Xyrem®)
  – Selegiline (Emsam®)

• **Cataplexy**
  – Sodium oxybate*
  – Selegiline
  – Serotonin-norepinephrine reuptake inhibitors (SNRIs)
  – Tricyclic antidepressants (TCAs)
  – Selective serotonin reuptake inhibitors (SSRIs)

* Approved by the US FDA for the treatment of narcolepsy.
**Modafinil**

- Recommended as a **standard** by AASM for the treatment of daytime sleepiness
  - Supported by 14 studies
- Dosing: 100 to 400 mg daily
- Split-day dosing may be better for late day symptoms
- Half life = 15 hours
- May interact with birth control pills
  - Induces several cytochrome P450 enzymes
  - **Need to recommend alternative birth control methods during treatment**
- Pregnancy class C
- Should be taken without food

- Headache (10-26%)
- Nervousness/anxiety (3-20%)
- Nausea (5-11%)
- Dry mouth (3-7%)
- Insomnia (3-6%)
- HTN risk low
  - 1 study of OSA increased BP by 4%
- **Stevens Johnson**
Armodafinil

- Enantiomer of modafinil with longer half life
- FDA approved for the treatment of narcolepsy
- Dosing 150 to 250 mg once daily
- Data limited to 2 RCTs
  - Improved MWT, ESS and CGIC vs placebo
  - MWT increased 1.3 to 2.6 minutes vs placebo
- Side effects similar to modafinil
  - Headache most common (16 to 28%)
  - Dose related
Sodium Oxybate

- Recommended as a **standard** for EDS/Cataplexy
- **Mechanism**: GABA-B and own receptors
  - Actual mechanism in narcolepsy not known
- **Schedule III**
- Divided dosing 4.5 to 9 grams/night
  - One dose at bedtime, another 3-4 hours later
- **Important**:
  - Improvements are **dose dependent**
  - Tolerance typically does **not** develop
  - **No** significant adverse events upon abrupt discontinuation
  - **No** withdrawal or rebound cataplexy

- **Pregnancy category C**
- **Contraindications**:
  - Succinic semialdehyde dehydrogenase deficiency
  - Sedative hypnotics, ETOH, CNS depressants
- **Adverse Effects** (dose related)
  - **Most common**: Dizziness (12-34%), nausea (6-34%) and headache (23%)
  - **Other**: Enuresis, vomiting, anorexia, backpain, edema, acute confusional state, falls, elevated LFTs, weight loss

- **Very low risk** of abuse, misuse and dependence
## Treatments for Cataplexy

<table>
<thead>
<tr>
<th>Agent/Class</th>
<th>Daily Dose Range</th>
<th>AASM Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Oxybate</td>
<td>4.5 to 9 grams</td>
<td>Standard</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>Various</td>
<td>Guideline</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Various</td>
<td>Guideline</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75 – 375 mg</td>
<td>Guideline</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>?</td>
<td>Guideline</td>
</tr>
<tr>
<td>Selegiline</td>
<td>5 -10 mg</td>
<td>Option</td>
</tr>
</tbody>
</table>

Morgenthaler, TI et al. Sleep 2007;30(12):1705-1711  
Wise, MS et al. Sleep 2007;30(12):1712-1727
Central Disorders of Hypersomnolence

- Narcolepsies
- Idiopathic Hypersomnia
- Associated with a Psychiatric Disorder
- Due to Medication or Substance
- Due to a Medical Disorder
- Insufficient Sleep Syndrome
- Kleine-Levin Syndrome

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Diagnostic Criteria for Idiopathic Hypersomnia

- Daily periods of sleepiness for $\geq$ 3 months
- Cataplexy is absent
- The MSLT demonstrates $\leq$ 2 SOREMPs or no SOREMPs if the REM latency on the preceding PSG was $\leq$ 15 minutes
- The presence of at least one of the following:
  - The MLST demonstrates a MSL of $\leq$ 8 minutes or
  - Total 24 hour sleep time is $> 660$ minutes on 24 hour PSG monitoring or by wrist actigraphy in association with a sleep log (averaged over at least 7 days without sleep restriction)
- The hypersomnolence and or MSLT findings are not better explained by other causes (including insufficient sleep syndrome)

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Idiopathic Hypersomnia

• Previously classified into “with and without long sleep time” – no longer
• Prevalence unknown
• Prolonged and severe sleep inertia common
• Unrefreshing naps and nighttime sleep periods
• A high sleep efficiency (> 90%) on the PSG is common
• No association with HLA DQB1*0602 or other HLA
• Normal CSF hypocretin 1 levels
• Family history in minority (34%)
• Spontaneous resolution described, but uncommon (14-25%)
PSG of Narcolepsy vs IH

Narcolepsy Type I

Idiopathic Hypersomnia
MSLT: MSL Greater in IH than Narcolepsy

- **Narcolepsy**
  - Mean Sleep Latency: $3.0 \pm 3.0$ (Mean $\pm$ 2 SD)

- **Idiopathic Hypersomnia**
  - Mean Sleep Latency: $6.2 \pm 3.0$ (Mean $\pm$ 2 SD)
Idiopathic Hypersomnia: Treatment

• Treatment approach similar to EDS with narcolepsy
• **No** FDA approved drugs for IH
  • Modafinil, armodafinil
  • Amphetamines and methylphenidate
• Possible role for clarithromycin or flumazenil

Morgenthaler, TI et al. Sleep 2007;30:1705-1711
Central Disorders of Hypersomnolence

- Narcolepsy Type I and II
- Idiopathic Hypersomnia
- Kleine-Levin Syndrome
- Insufficient Sleep Syndrome
- Due to a Medical Disorder
- Due to Medication or Substance
- Associated with a Psychiatric Disorder

Due to Medication or Substance Associated with a Psychiatric Disorder

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Question

Which one of the following statements is TRUE?

- A) Narcolepsy Type II is a disease whose pathophysiology has been well-characterized
- B) The number of sleep-onset REM periods (SoREMPs) can be used to distinguish Narcolepsy Type I from Narcolepsy Type II
- C) Patients with Idiopathic Hypersomnia tend to be sleepier (and more refractory to therapy) than patients with Narcolepsy Type I or Narcolepsy Type II
- D) There are no stimulant therapies that have been deemed to be safe in pregnancy
Question

Which one of the following statements is TRUE?

- A) Narcolepsy Type II is a disease whose pathophysiology has been well-characterized
- B) The number of sleep-onset REM periods (SoREMPs) can be used to distinguish Narcolepsy Type I from Narcolepsy Type II
- C) Patients with Idiopathic Hypersomnia tend to be sleepier (and more refractory to therapy) than patients with Narcolepsy Type I or Narcolepsy Type II
- D) There are no stimulant therapies that have been deemed to be safe in pregnancy
<table>
<thead>
<tr>
<th></th>
<th>Type 1 Narcolepsy</th>
<th>Idiopathic Hypersomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>1: 2,000</td>
<td>Unknown – rare (?) (1:400) ?</td>
</tr>
<tr>
<td><strong>Age of Onset</strong></td>
<td>Pre-pubertal Teens Twenties</td>
<td>Pre-Pubertal Teens Twenties Adulthood</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>Modestly Progressive Plateaus in 30s</td>
<td>More likely progressive</td>
</tr>
<tr>
<td><strong>Remissions</strong></td>
<td>NONE</td>
<td>RARE (15%)</td>
</tr>
<tr>
<td><strong>Heritability</strong></td>
<td>Minimal (4 x risk to $1^0$ relative)</td>
<td>Modest (~ 1/3 rd of subjects with $1^0$ relative)</td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
<td>Wake promoting agents (e.g., psychostimulants; modafinil; Xyrem®)</td>
<td>Wake promoting agents, possible role for sleep “lytics” (e.g., GABA$_A$ receptor antagonists) ?</td>
</tr>
<tr>
<td></td>
<td>Type 1 Narcolepsy</td>
<td>Idiopathic Hypersomnia</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Excessive Daytime Sleepiness</td>
<td>Imperative</td>
<td>Not as imperative</td>
</tr>
<tr>
<td>Daytime Sleep Duration</td>
<td>Minutes</td>
<td>Hours</td>
</tr>
<tr>
<td>Daytime Naps</td>
<td>With REM-sleep</td>
<td>ABSENT REM-sleep</td>
</tr>
<tr>
<td></td>
<td>(dreams)</td>
<td></td>
</tr>
<tr>
<td>Cataplectic Attacks</td>
<td>Most cases</td>
<td>ABSENT</td>
</tr>
<tr>
<td>REM-sleep dyscontrol</td>
<td>Many cases</td>
<td>RARE</td>
</tr>
<tr>
<td>Dampened sensorium or cognition</td>
<td>Exceptional</td>
<td>COMMON</td>
</tr>
<tr>
<td>Night-time Sleep</td>
<td>Normal Length &amp;</td>
<td>Prolonged &amp;</td>
</tr>
<tr>
<td></td>
<td>Restless</td>
<td>Very deep</td>
</tr>
<tr>
<td>Awakening from Sleep</td>
<td>Spontaneous</td>
<td>LABORIOUS</td>
</tr>
<tr>
<td></td>
<td>Type 1 Narcolepsy</td>
<td>Type 2 Narcolepsy</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Excessive Daytime Sleepiness</strong></td>
<td>3 months</td>
<td>3 months</td>
</tr>
<tr>
<td><strong>Cataplexy</strong></td>
<td>YES (60-95%)</td>
<td>NO</td>
</tr>
<tr>
<td><strong>MSL &lt; 8 minutes</strong></td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>≥ 2 SOREMPs</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td><strong>CSF Hypocretin &lt; 110 pg/ml</strong></td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>660’ of total sleep time (PSG + MSLT)</td>
<td>NO (normal)</td>
<td>Some (?)</td>
</tr>
<tr>
<td>660’ average total Sleep time 1 week</td>
<td>NO (normal)</td>
<td>N/A (?)</td>
</tr>
</tbody>
</table>
Thank you for your kind attention!