Hypersomnias of Central Origin

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Conflict of Interest

I do not have any conflict of interest to report

Objectives

1. To identify the clinical features of central hypersomnias
2. To review the ICSD-2 criteria for narcolepsy and idiopathic hypersomnia
3. To discuss the PSG and MSLT findings in these two conditions
WHY DO WE SLEEP?

Baron Constantin von Economo - 1916

NOTES

The Neurobiology of Sleep
Clifford B. Saper, MD, PhD, FAAN, FRCP
Continuum, 2013
Mechanism of Sleep

- Sleep promoting substances
  - Adenosine
  - Muramyl peptides
  - Prostaglandin D2
- Interaction between inhibitory neurons (anterior hypothalamus) and excitatory neurons (posterior hypothalamus and brainstem)
- Thalamus
Stages of Sleep

• NREM
  – Synchronization of low frequency EEG activity (0.5-15 Hz)
  – Generated by cerebral cortex and thalamus
  – Thalamus inhibits signals to the cortex. (behavioral quiescence and suppression of conscious processes.

• REM
  – Suppressed motor output
  – Rapid eye movements

Hypersomnias

• Insufficient sleep
• Medications
• Medical Conditions
• Psychiatric condition
• Substance use
• Other sleep disorder
  – Sleep disordered breathing

Hypersomnias of Central Origin

Sleepiness is due to a dysfunction in the Central Nervous System

1. Narcolepsy with/without cataplexy
2. Idiopathic Hypersomnia with/without long sleep time
3. Kleine-Levin Syndrome
ICSD-2 Criteria for Narcolepsy with Cataplexy

- Excessive daytime sleepiness present for at least 3 months.
- Definite history of cataplexy, (loss of muscle tone triggered by laughter or strong emotions).
- Should be confirmed by MSLT preceded by an overnight PSG consisting of at least 6 hours of sleep. A sleep latency of 8 minutes or less plus two or more sleep-onset REM periods are considered abnormal. Alternatively, a decreased CSF hypocretin level (<110 pg/mL) can be used.

Pathophysiology

- Loss of Hypocretin containing neurons
- Low CSF level of hypocretin
  - 10% have normal hypocretin level
- Positive HLA DQB1*0602
  - Present in up to 30% of normal population
- Low familial prevalence

ICSD-2 Criteria for Narcolepsy without Cataplexy

- Excessive daytime sleepiness present for at least 3 months.
- Cataplexy is absent or very doubtful.
- Must be confirmed by MSLT preceded by an overnight PSG consisting of at least 6 hours of sleep. A sleep latency of 8 minutes or less plus two or more sleep-onset REM periods are considered abnormal.
Pathophysiology

• 10% have low hypocretin level
• 40% test positive for HLA DQB1*0602
• Low familial prevalence

Features in Narcolepsy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Notes</th>
<th>Percentage in Narcolepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataplexy</td>
<td>Never occurs in normal people</td>
<td>50%</td>
</tr>
<tr>
<td>Sleep paralysis</td>
<td>More common in narcolepsy with cataplexy</td>
<td></td>
</tr>
<tr>
<td>Hypnogogic Hallucinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fragmented Sleep</td>
<td>Can occur in normal people</td>
<td></td>
</tr>
<tr>
<td>Automatic behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleepwalking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OSA</td>
<td>OSA is more common in narcolepsy than in general population. Remember hypocretin suppresses appetite</td>
<td>20%</td>
</tr>
<tr>
<td>RBD</td>
<td></td>
<td>10%</td>
</tr>
</tbody>
</table>

Associated Conditions

1. Periodic Leg Movements of Sleep (PLMS)
   a. Up to 60% of patients with narcolepsy
   b. May occur during REM sleep
   c. Associated with more sleep disruption
2. REM sleep Behavior Disorder
   a. 7-36% patients
   b. REM sleep without atonia

Reference:
Primary Hypersomnias of Central Origin
Samir Mahfota, MD; Clete A. Kushida, MD, PhD, RPSGT
Continuum (Minneap Minn) 2013;19(1):67-85
NOTES

- _______________________________________
- _______________________________________
- _______________________________________
- _______________________________________
- _______________________________________
- _______________________________________
- _______________________________________
- _______________________________________

Polysomnographic Findings

- Short sleep latency (3.1 +/- 2.9 mins)
- Sleep Onset REM
- Sleep Disruption with frequent awakenings

Hypnogram SOREMP

RomyNotes Atlas of Polysomnography
Hypocretin Levels

Sleep Medicine Reviews (2005) 9, 269–310 Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system
Seiji Nishino,a,* Takashi Kanbayashi b

Narcolepsy due to Medical Condition

REM Sleep Behavior Disorder and Narcoleptic Features in Anti–Ma2-associated Encephalitis
SLEEP, Vol. 30, No. 6, 2007
Yaroslau Compta, MD Alex Iranzo, MD; Joan Santamaría, MD; Roser Casamitjana, PhD; Francesc Grau, MD

ICSD-2 Criteria for Idiopathic Hypersomnia with Long Sleep Time

1. Almost daily excessive daytime sleepiness occurring for at least 3 months.
2. Documented prolonged nocturnal sleep of at least 10 hours with laborious awakening
3. Nocturnal PSG has excluded other causes of daytime sleepiness.
4. PSG documents a short sleep latency and a prolonged sleep period of greater than 10 hours.
5. An MSLT performed after the overnight PSG will show a mean sleep latency of less than 8 minutes and fewer than two sleep-onset REM episodes.
ICSD-2 Criteria for Idiopathic Hypersomnia without Long Sleep Time

1. Almost daily excessive daytime sleepiness occurring for at least 3 months.
2. Normal nocturnal sleep of at least 6 hours and less than 10 hours with laborious morning or end-of-nap arousals.
3. Nocturnal PSG excludes other causes of daytime sleepiness.
4. PSG documents a normal sleep period of greater than 6 hours but less than 10 hours.
5. An MSLT performed after the overnight PSG will show a mean sleep latency of less than 8 minutes and fewer than two sleep-onset REM episodes.

Pathophysiology

- 50% to 60% of cases had at least 1 relative affected [autosomal dominance?]
- Most studies found normal levels of CSF hypocretin-1
- possibility of a dysfunction of aminergic arousal systems
- decreased CSF levels of histamine
- Increased Spindles

Chronic Hypersomnia
Dauvilliers and Billiard
Sleep medicine Clinics 1 (2006) 79-88
Klein-Levin Syndrome

- 1 in a million
- Peak in the second decade
- Precipitating factor in 9 out of 10 cases
- PSG not different
- MSLT inconsistent
- MRI and CT normal
- SPECT: decreased perfusion in thalamus during an event
Kleine–Levin syndrome: a systematic review of 186 cases in the literature
I. Arnulf, 1, 4 J. M. Zeitzer, 1 J. File, 1 N. Farber 3 and E. Mignot 1, 2
Brain, 2005

### Event at KLS onset

<table>
<thead>
<tr>
<th>Event at KLS onset</th>
<th># pat</th>
<th>Onset [%]</th>
<th>Recur [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>None Reported</td>
<td>66</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>Infection or Fever</td>
<td>72</td>
<td>42.8</td>
<td>8.9</td>
</tr>
<tr>
<td>Unspecified Fever, flu like</td>
<td>42</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Upper Resp. Tract infection</td>
<td>20</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Tonsillitis, sore throat, cough</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Streptococcus identified</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Asian Flu, Chicken Pox and mono Enterovirus, post typhoid vaccine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol or marijuana</td>
<td>7</td>
<td>4.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Head Trauma</td>
<td>4</td>
<td>2.4</td>
<td>0</td>
</tr>
<tr>
<td>Sleep deprivation, stress</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Menses or lactation</td>
<td>6</td>
<td>3.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Local/general anesthia</td>
<td>6</td>
<td>3.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Physical exertion</td>
<td>6</td>
<td>3.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>

### Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients/Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersomnia</td>
<td>168/168</td>
<td>100</td>
</tr>
<tr>
<td>Cognitive disorders</td>
<td>98/102</td>
<td>96</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>66/66</td>
<td>100</td>
</tr>
<tr>
<td>Confusion</td>
<td>24/47</td>
<td>51</td>
</tr>
<tr>
<td>Amnesia</td>
<td>24/50</td>
<td>48</td>
</tr>
<tr>
<td>Derealization</td>
<td>22/93</td>
<td>24</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>13/93</td>
<td>14</td>
</tr>
<tr>
<td>Delusions</td>
<td>15/93</td>
<td>16</td>
</tr>
<tr>
<td>Eating Behavior Disorder</td>
<td>125/157</td>
<td>80</td>
</tr>
<tr>
<td>Hyperphagia</td>
<td>97/125</td>
<td>78</td>
</tr>
<tr>
<td>Craving for sweets</td>
<td>15/125</td>
<td>12</td>
</tr>
<tr>
<td>Increased Drinking</td>
<td>10/125</td>
<td>8</td>
</tr>
<tr>
<td>Binge eating</td>
<td>7/125</td>
<td>8</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>6/125</td>
<td>5</td>
</tr>
<tr>
<td>Depression</td>
<td>41/86</td>
<td>48</td>
</tr>
<tr>
<td>Irritability</td>
<td>76/86</td>
<td>88</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>67/155</td>
<td>43</td>
</tr>
<tr>
<td>Compulsion to sing, write, pace</td>
<td>17/59</td>
<td>29</td>
</tr>
</tbody>
</table>
Subjective Measures of Sleepiness

a. Stanford Sleepiness Score
b. Epworth Sleepiness Score
   i. Should not be used as substitute for objective measure of sleepiness
   ii. May correlate with OSA severity
   iii. Best use is to follow

Epworth Sleepiness Score

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of Dosing (0–3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
</tr>
<tr>
<td>Sitting, inactive in a public place (e.g., a theater or meeting)</td>
<td></td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in traffic</td>
<td></td>
</tr>
</tbody>
</table>


Epworth Sleepiness Score

d. Pittsburgh sleep quality index (PSQI)
   i. Inquires about sleep in the last month

d. Sleep Diaries

Epworth Sleepiness Score

f. Sleep Diaries

Epworth Sleepiness Scale

<table>
<thead>
<tr>
<th>Degree of Sleepiness</th>
<th>Scale Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling active, vital, alert, or wide awake</td>
<td>1</td>
</tr>
<tr>
<td>Functioning at high levels, but not at peak; able to concentrate</td>
<td>2</td>
</tr>
<tr>
<td>Awake, but tired; responsive but not fully alert</td>
<td>3</td>
</tr>
<tr>
<td>Somewhat foggy, let down</td>
<td>4</td>
</tr>
<tr>
<td>Fuzzy, losing interest in remaining awake; slowed down</td>
<td>5</td>
</tr>
<tr>
<td>Sleepy, woozy, fighting sleep; prefer to lie down</td>
<td>6</td>
</tr>
<tr>
<td>No longer fighting sleep; sleep onset soon; having dreams like thoughts</td>
<td>7</td>
</tr>
<tr>
<td>Asleep</td>
<td>X</td>
</tr>
</tbody>
</table>
Objective Measure of Sleepiness

1. Multiple Sleep Latency Test
   a. Measures tendency to fall asleep
2. Maintenance of Wakefulness Test
   a. Measures ability to stay awake in combination with history
   b. 40 minute protocol

BOTH must be performed under standardized conditions. BOTH have limitations

1. Suspected Narcolepsy or idiopathic hypersomnia
2. Not routinely indicated in the initial evaluation and diagnosis of obstructive sleep apnea or following treatment CPAP
3. Not routinely indicated for evaluation of sleepiness in medical and neurological disorders (other than narcolepsy), insomnia, or circadian rhythm disorders
4. Repeat MSLT testing may be indicated in the following situations: (a) when the initial test is affected by extraneous circumstances or when appropriate study conditions were not present during initial testing, (b) when ambiguous or uninterpretable findings are present, (c) when the patient is suspected to have narcolepsy but earlier MSLT evaluation(s) did not provide polygraphic confirmation.
Clinical Evaluation

Unexplained persistent sleepiness for more than 3 months

Clear Cataplexy

Triggers

Hallucinations

Narcolepsy with cataplexy MSLT

No or doubtful cataplexy

MSLT <8 min <2 SOREMPS Narcolepsy without cataplexy

TST >10 hours Idiopathic hypersomnia with prolonged sleep time

TST <10 Hours Idiopathic hypersomnia without prolonged sleep time

Recurrent Hypersomnia >2 episodes 2 days-4 weeks Not secondary

Medical Circadian OSA

Other Markers?

Clinical Research

Relationship Between Sleep Spindles and Hypersomnia

*Antonio Redol, 2Antonio Calleja, Thomas T. Moore and Michael E. Worden

*Sant Pau i Santa Creu Hospital, Barcelona, Spain.
Sleep Center, Community General Hospital of Capote Sampaio, New York, U.S.A., and MEND Health Science Center in Rome, New York, U.S.A.

- High number of spindles in hypersomnia group
- A low value of SS density does not rule out hypersomnia, but a density higher than 7.5 SS per minute supports the complaint of hypersomnia
Mean Spindle Density

Epoch from a patient with Idiopathic Hypersomnia

Characterization of REM Sleep Without Atonia [RSWA] in Patients with Narcolepsy and Idiopathic Hypersomnia

JCSM-In press

Lourdes M. DelRosso, M.D
Romy Hoque, M.D
Andrew L. Chesson Jr., M.D.

Department of Neurology, Louisiana State University School of Medicine Shreveport, Louisiana
Background

- 1987: Geisler, early REM onset, different REM density, distribution and phasic activity [controls]
- 1992: Schenck, excessive limb twitching and RWA in patients who do not meet criteria for RBD
- 2005: Nightingale, RBD increased in Narcolepsy
- 2007: Dauvilliers, RWA increased in the absence of RBD in Narcoleptic patients
- 2011: Franceschini, Video monitoring has shown mild motor activity as opposed to violent behaviors
Hypothesis

1. RSWA is predominant in patients with narcolepsy independent of cataplexy status
2. RSWA is present in patients with narcolepsy independent of REM Behavior Disorder.
3. RSWA is more prominent in narcolepsy as opposed to Idiopathic Hypersomnia

<table>
<thead>
<tr>
<th>PSG variable</th>
<th>Narcolepsy (n=8)</th>
<th>IH (n=8)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency</td>
<td>16-40 29-107</td>
<td>10-97</td>
<td>0.07</td>
</tr>
<tr>
<td>REM Latency</td>
<td>6-92 124.5-415.5</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>REM epochs</td>
<td>100-141-293 145.5-210</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>RSWA phase</td>
<td>25.4 11.9-53.9 4.6 0.64-0.98</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>RSWA tonic</td>
<td>10.5 6-37 0 0.1</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>RSWA total</td>
<td>42 22-70 5 1-12</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>TST</td>
<td>404-303-517 451 428-532</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>84-98 94 80-98</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>WAH</td>
<td>32 9.5-77 19.8 7.5-102</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>PLM</td>
<td>5.2 0-60 4.6 0-82</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

REM Onset

REM onset in Minutes

Narcolepsy
- With Cataplexy
  - n=4
  - P=0.01

Narcolepsy
- Without Cataplexy
  - n=4
  - P=0.375

Idiopathic Hypersomnia
- n=8
Characterization of REM Sleep Without Atonia in Patients with Narcolepsy and Idiopathic Hypersomnia using AASM Scoring Manual Criteria

Lourdes M. DelRosso, M.D.; Andrew L. Chesson Jr., M.D.; Romy Hoque, M.D.

JCSM in Press
Characterization of REM Sleep Without Atonia in Patients with Narcolepsy and Idiopathic Hypersomnia using AASM Scoring Manual Criteria
Lourdes M. DelRosso, M.D.; Andrew L. Chesson Jr., M.D.; Romy Hoque, M.D.
JCSM in Press
Case Report Neatherlands 2004

- 27 y/o woman
- Visits her GP
- CC:
  - Fatigue
  - Apathy
  - Loss of appetite
  - Depression
  - Excessive Sleepiness

Nederlandstijdschrift voor geneeskunde
By Hart, W

2 months later ER

- “Depressive & Flat affect”
- CC: fainting episodes, cramps in hands
- T 37.5 H 1.7m W HR 82 BP 120/85
- PE and neurological exam Normal
- Labs.
  - Mild normocytic anemia and borderline thrombocytopenia
  - Neg RF, ANA, ANCA, Anti Ds DNA, C3, C4, CH50, CRP
  - CRX, abd US NL
  - Urine culture + ECOli
- Treated Cipro 250 mg bid for 1 week

- Discharged home after 1 ½ week

3 months later...

- ER visit for worsening sleepiness and “inertia”
- SPE increased IgG and IgM
- Labs unchanged
- Neurologic Exam Normal
- CT scan head Normal
- MRI brain (next image)
- Discharged Home. NO diagnosis
2 months later

- Progressively Bed Ridden due to fatigue and sleepiness
- Admitted to hospital
  - Responsive to painful stimuli
  - T 39°C. HR100/min BP105/70 mmHg
  - Nystagmus, neck was soft. Hyperreflexia, No adenopathy. NL heart, lung and abd exam.

What Information are we missing?

- Chief complaint
- Sleep history
- Medications/allergies
- Past medical or surgical history
- Family history
- Review of symptoms
- Physical exam

Notes

- __________________________________________________
- __________________________________________________
- __________________________________________________
- __________________________________________________
- __________________________________________________
- __________________________________________________
Conclusions

• The tools for evaluation of hypersomnolence include subjective and objective measures.
• Medical, circadian, psychiatric, pharmacologic or social conditions must be ruled out.
• Narcolepsy has a specific pathophysiology and some markers that can help distinguish from idiopathic hypersomnia.
• More research is needed in IH.

Thank you