Secondary Narcolepsy: An Exploration of Cases and Pathophysiology

Scott Hollingshaus, MD
Sleep Medicine Fellow, University of Utah Hospital and Clinics; Salt Lake City, Utah

Objectives:
• Identify causes of secondary narcolepsy
• Describe HLA Class serotyping and its relationship to narcolepsy
• Identify location and projections of hypocretin producing cells in the brain
• List the possible ways in which the hypothalamus/hypocretin system can be disrupted thus leading to secondary narcolepsy
• Describe the use of COMA acronym related to carbon monoxide poisoning screening
Secondary Narcolepsy

An Exploration of Cases and Pathophysiology

Utah Sleep Society Conference
Friday, February 26, 2016

Scott Hollingshaus, MD
Goals and Objectives

• Goals
  • Understand the pathophysiology of narcolepsy and hypocretin deficiency
  • Become familiar with cases of Secondary Narcolepsy

• Objectives
  • Identify causes of secondary narcolepsy
  • Describe HLA Class II serotyping
  • Identify location of hypocretin cell bodies and major projections in the brain
  • Describe the use of the COMA acronym
Financial and Professional Conflicts

• None
Case 1
Case 1 (1880) by Dr. Gélineau

- Mr. G., age 38, a barrel seller with a nervous, volatile temperament, is always accompanied by his 13-year-old son because of frequent “sleep attacks”
- No history of syphilis or convulsions in his youth. He drinks moderately and suffered from acute rheumatism of the joints and [tenia capitis] five years previously. Otherwise healthy
- Three years prior he received a great punch to the head and shortly after that a log fell on his head, though it did not hurt much
- “In the past two years, when laughing out loud or when anticipating a good business deal in his profession, he would feel weakness in his legs, which would buckle under him”
- “If he experiences a deep emotion, whether painful or joyous, the need to sleep is even more urgent and sudden”
- He suffers up to 200 attacks daily
- His memory is not affected in the least. He is aware of the status of his business, and he is actively involved in taking care of it
Narcolepsy

“The disease I am about to describe is characterized by the occurrence of attacks of irresistible sleep without apparent cause, and curious attacks on emotion in which the muscles relax suddenly so that the victim sinks to the ground, fully conscious, but unable to move.”

- Dr. William John Adie (1926)
Narcolepsy Epidemiology

• Narcolepsy type 1 (narcolepsy with cataplexy)
  • Prevalence of 25 to 50 per 100,000 people (0.025% – 0.05%)
  • Incidence of 0.74 per 100,000 person-years
  • It is probably equally common in men and women
  • Typically begins between 12 and 25 years old, but may occur as early as five years of age or after 40 years of age
  • Bimodal age distribution at diagnosis with peaks at 15 years old and 35 years old.

• Narcolepsy type 2 (narcolepsy without cataplexy): Incidence estimated to be 20 to 34 per 100,000 people

• Secondary Narcolepsy: ?
# Narcolepsy Public Burden

**Table 2**  
Percentage share of narcoleptic patients and controls receiving healthcare, and income (after diagnosis).

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy</th>
<th>Controls</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient treatment</td>
<td>58.1</td>
<td>31.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inpatient treatment</td>
<td>28.8</td>
<td>13.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication</td>
<td>92.4</td>
<td>75.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Public health insurance</td>
<td>98.5</td>
<td>94.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Employment</td>
<td>50.2</td>
<td>60.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total public transfer income</td>
<td>62.1</td>
<td>51.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pension</td>
<td>19.2</td>
<td>19.7</td>
<td>0.980</td>
</tr>
<tr>
<td>Other public transfers</td>
<td>32.4</td>
<td>23.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sick pay (publicly funded)</td>
<td>16.5</td>
<td>11.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P*-value from Cochran-Armitage test, bootstrapped (by each expense type, irrespective of significance of share received).

**Table 3**  
Percentage share of partners and controls receiving healthcare, and income (after diagnosis).

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Controls</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient treatment</td>
<td>33.1</td>
<td>30.8</td>
<td>NS</td>
</tr>
<tr>
<td>Inpatient treatment</td>
<td>14.5</td>
<td>13.2</td>
<td>NS</td>
</tr>
<tr>
<td>Medication</td>
<td>81.5</td>
<td>75.1</td>
<td>&lt;0.001</td>
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<tr>
<td>Public health insurance</td>
<td>96.9</td>
<td>95.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Employment</td>
<td>65.5</td>
<td>68.6</td>
<td>NS</td>
</tr>
<tr>
<td>Total public transfer income</td>
<td>50.5</td>
<td>49.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pension</td>
<td>12.2</td>
<td>13.9</td>
<td>NS</td>
</tr>
<tr>
<td>Other public transfers</td>
<td>28.0</td>
<td>24.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sick pay (publicly funded)</td>
<td>14.2</td>
<td>15.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P*-value from Cochran–Armitage test, bootstrapped (by each expense type, irrespective of significance of share received).
Narcolepsy Public Burden

Fig. 1. Employment rate and corresponding income from employment (in euros) before and after a diagnosis of narcolepsy, compared with control subjects.

Fig. 2. Percentage receiving social security and the corresponding social security income before and after a diagnosis of narcolepsy.
Narcolepsy Symptoms

**Nighttime**
- Episodes of hypnagogic hallucinations
- Short sleep latency
- Disruption of the Rapid Eye Movement (REM)/Non-REM (NREM) cycle and its distribution
- Disruption of nocturnal sleep with awakenings
- Motor and behavioral disturbances during sleep.
- Sleep paralysis

**Daytime**
- Daytime sleepiness
- Cataplexy (episodes of motor weaknesses induced by emotions)
Narcolepsy Type I - Diagnostic Criteria

Criteria A and B must be met

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months

B. The presence of one or both of the following:
   1. Cataplexy and a mean sleep latency of $\leq 8$ minutes and two or more sleep onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT
   2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either $\leq 110$ pg/mL or $<1/3$ of mean values obtained in normal subjects with the same standardized assay
Hypocretin-1 (Orexin-A)

- Discovered by two groups in 1998
- Produced exclusively by a group of several thousand neurons localized in the posterior/lateral hypothalamus
Possible Causes of Hypocretin Deficiency

• Ischemia
Blood Supply to Hypothalamus

- Most plentiful blood supply in the brain
- Receives blood from all four major arteries as they join in the Circle of Willis
- Ischemia to the hypothalamus is extremely rare
Possible Causes of Hypocretin Deficiency

- Ischemia
- Inflammation
- Mass effect damage
- Trauma
- Autoimmune
Case 2
Case 2

• 20-year-old Mr. M from Iceland
• Christmas 1918- He had an ordinary attack of influenza (Spanish Flu)
• Summer 1919- He described a tickling in the epigastrum when he laughed
• He then developed excessive daytime sleepiness
• It was followed by a period of diplopia and delirium with auditory and visual hallucinations
• After this he noticed that whenever he laughed or got excited he would fall down
• Subsequently he found his face losing expression, he had trouble with drooling, could no longer read, could not concentrate, and developed a tremor
• These symptoms got a little better after 1922, but he still had the falling attacks
• He was evaluated in 1925 and diagnosed with encephalitis lethargica
• At time of evaluation he mainly complained of insomnia at night and excessive sleepiness in the day. He continued to have the falling attacks and on was observed during evaluation

The Lancet 1926
Encephalitis Lethargica (von Economo disease)

• First described in 1917 by the neurologist/psychiatrist Constantin Baron von Economo and Jean-René Cruchet

• Symptoms include high fever, sore throat, headache, lethargy, double vision, delayed physical and mental response, sleep inversion and catatonia

• Following the 1918 influenza pandemic (H1N1) there was an outbreak of encephalitis lethargica associated with postencephalitic parkinsonism

• Peak incidence in 1921

• Over 1 million cases and 500,000 deaths

• 1/3 died, 1/3 recovered completely, and 1/3 developed long-term neurological symptoms

• Etiology is uncertain and has been referred to as the greatest medical mystery of the 20th century

• Possible viral cause or post infectious autoimmune

Journal of clinical virology 2014
HLA-DQ06:02

- HLA-DQB1 belongs to the Human Leukocyte Antigen (HLA) class II beta chain paralogues
- Heterodimer consisting of an alpha (DQA) and a beta chain (DQB), both anchored in the membrane
- Expressed in antigen-presenting cells (B lymphocytes, dendritic cells, macrophages)
- Plays a central role in the immune system by presenting peptides (antigens) derived from extracellular proteins to T-lymphocytes causing multiplication of T-helper cells, which in turn stimulate antibody-producing B-cells to produce antibodies to that specific antigen
- DQA1*01:02 - DQB1*06:02 is the most common DQ type among European Americans (14.27%)
- 98% of patients with Narcolpesy type I have this allele

Tissue Antigens 2003
Maternal DQ haplotype
A1  B1

Given 2 parental haplotypes -
There are 4 potential isoforms.

Different DQ isoforms bind
different peptides

Nucleus

Paternal DQ haplotype
A1  B1

PNAS 2004
The Lancet, Neurology 2015
Case 3
Case 3

- A previously healthy 3-year-old girl presented with ataxic gait, inability to bear weight, and frequent falls one week after antibody-confirmed varicella zoster
- Occasional and temporary loss of tone with apparent generalized weakness, ptosis, and paucity of facial movements and speech
- Loss of tone with head drops could be induced by clinical examination, which suggested emotionally stimulated cataplectic events
- She had flat affect, irritability, and hypersomnia
- Frequent nocturnal arousals heralded by eyelid flickering, upper limb posturing in extension or flexion, shouting out, and fearful appearance developed
Case 3 - Workup

- MRI brain and spinal cord were normal
- EEG was normal
- Ammonia, amino acids, cortisol, adrenocorticotropin, and CSF studies were normal
- Paraneoplastic panel was negative
- Cerebrospinal fluid hypocretin of 174 pg/mL
- MRI of the pelvis showed a paraspinal mass measuring 5.9 x 3 x 3.8 cm lateral to L2-L4 vertebral bodies consistent with a sympathetic chain mass
- Urinary catecholamines were initially normal, but elevated on repeated testing
- Ultrasound-guided biopsy confirmed poorly differentiated neuroblastoma without MYC-N
Treatment with dexamethasone in conjunction with chemotherapy

- Rapid resolution of hypersomnia and the cataplectic events
- Gradual resolution of ataxia and return of independent weight-bearing and speech
- Moderate tumor shrinkage was achieved and complete surgical resection was possible after six cycles of chemotherapy
Possible Paraneoplastic Syndrome

Peptides 2000
Hypocretin 1 (Orexin-A)

PNAS 2004, Sleep Medicine Reviews 2005
Hypocretin 1 (Orexin-A)

Neurons project widely to the olfactory bulb, cerebral cortex, thalamus, hypothalamus, and brainstem, and more densely to the locus coeruleus, tuberomamillary nucleus, raphe nucleus, and bulbar reticular formation.

Sleep Medicine Reviews 2005, Encyclopedia of Sleep 2013
### Table 1. Relative density of gephyrin-immunoreactive fibers in various regions of the rat brain

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Fiber density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>++</td>
</tr>
<tr>
<td>Layers 1–2</td>
<td>++</td>
</tr>
<tr>
<td>Layer 4</td>
<td>++(+)</td>
</tr>
<tr>
<td>Layers 5-6</td>
<td>++</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td></td>
</tr>
<tr>
<td>Accumbens nucleus</td>
<td>++</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>++(+)</td>
</tr>
<tr>
<td>Putamen nucleus</td>
<td>++</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>++</td>
</tr>
<tr>
<td>Neostriatum</td>
<td>++</td>
</tr>
<tr>
<td>Amygdala</td>
<td>++</td>
</tr>
<tr>
<td>Parolfactory cortex</td>
<td>++(+)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>++</td>
</tr>
<tr>
<td>Ammoniakoepalatal area</td>
<td>++</td>
</tr>
<tr>
<td>Anterior cingulate area</td>
<td>++</td>
</tr>
<tr>
<td>Basal nucleus</td>
<td>++</td>
</tr>
<tr>
<td>Cerebellar nucleus</td>
<td>++</td>
</tr>
<tr>
<td>Midbrain</td>
<td>++</td>
</tr>
<tr>
<td>Septum</td>
<td>++</td>
</tr>
<tr>
<td>Lateral geniculate nucleus</td>
<td>++</td>
</tr>
<tr>
<td>Medial geniculate nucleus</td>
<td>++</td>
</tr>
<tr>
<td>Ventral tegmental area</td>
<td>++</td>
</tr>
<tr>
<td>Midbrain</td>
<td>++</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>++</td>
</tr>
<tr>
<td>Nucleus accumbens, core</td>
<td>++</td>
</tr>
<tr>
<td>Nucleus accumbens, shell</td>
<td>++</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>++</td>
</tr>
<tr>
<td>Fundus of the striatum</td>
<td>++</td>
</tr>
</tbody>
</table>

### Table 1. Continued

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Fiber density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zona incerta, rostral</td>
<td>++(+)</td>
</tr>
</tbody>
</table>

### Table 2. Relative density of gephyrin-immunoreactive fibers in various regions of the rat brain

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Fiber density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locus coeruleus</td>
<td>+++++</td>
</tr>
<tr>
<td>Nucleus of the solitary tract</td>
<td>+++++</td>
</tr>
<tr>
<td>Rapha nuclei</td>
<td>+++++</td>
</tr>
<tr>
<td>Raphe dorsalis</td>
<td>+++++</td>
</tr>
<tr>
<td>Raphe median</td>
<td>+++++</td>
</tr>
<tr>
<td>Raphe magnus</td>
<td>+++++</td>
</tr>
<tr>
<td>Raphe pallidus</td>
<td>+++++</td>
</tr>
<tr>
<td>Raphe obscurus</td>
<td>+++++</td>
</tr>
<tr>
<td>Raphe linearis</td>
<td>+++++</td>
</tr>
<tr>
<td>Raphe pontis</td>
<td>+++++</td>
</tr>
<tr>
<td>Substantia nigra, compact part</td>
<td>+++++</td>
</tr>
<tr>
<td>Substantia nigra, reticular part</td>
<td>+++++</td>
</tr>
<tr>
<td>Substantia nigra, lateral part</td>
<td>+++++</td>
</tr>
<tr>
<td>Ventral tegmental area</td>
<td>+++++</td>
</tr>
<tr>
<td>Central grey</td>
<td>+++++</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>+++++</td>
</tr>
<tr>
<td>Mesencephalic reticular formation</td>
<td>+++++</td>
</tr>
<tr>
<td>Interpeduncular nucleus</td>
<td>+++++</td>
</tr>
</tbody>
</table>

### Brainstem

- **Abducens nucleus (VI)**
- **Oculomotor nucleus (III)**
- **Trochlear motor nucleus (IV)**
- **Trigeminal motor nucleus (V)**
- **Facial motor nucleus (VII)**
- **Mental nuclei of the vagus (X)**
- **Hypoglossal nucleus (XII)**
- **Somatosensory nuclei**
- **Superior colliculus**
- **Inferior colliculus**
- **Mesencephalic nuclei**
- **Parabigeminal nuclei**
- **Olfactory nuclei**
- **Central nuclei, dorsal**
- **Central nuclei, ventral**
- **Lateral lemniscus**
- **Pons tegmentum (oral, ventral, and caudal)**

### Other brainstem nuclei

- **Nucleus prepositus hypoglossi**
- **Nucleus ambiguus**
- **Nucleus cuneatus (oral, ventral, and caudal)**
- **Cerebellum (cortex and nuclei)**
- **Epencula**
Case 4
Case 4

- 19-year-old woman complains of one year of headache
- MRI revealed a capsuled tumor 30 mm in maximum dimension compressing the surrounding tissues in the intrasellar space
- Shortly after the diagnosis, she underwent transnasal resection of the craniopharyngioma
1 Week Post-op

- Diabetes insipidus and panhypopituitarism
- Short term memory deficit
- Left hemiparesis and left lateral visual field defect
- Excessive daytime sleepiness lasting throughout the day
- Cataplexy with sudden loss of knee strength triggered by laughter or surprise once or twice each day
- Sleeping >10 hours at night
- Frequent naps in the daytime with durations of 1 to 4 hours
Sleep Evaluation (age 22)

- She had no history of other neurologic, psychiatric or sleep disorders, or a family history of sleep disorders.
- Height: 157 cm, Weight: 50 kg, BMI: 20.3
- HLA typing showed the presence of DRB1*0101/0901 and DQB1*0303/0501
- Orexin concentration in her cerebrospinal fluid was 70.8 pg/ml
- Total sleep time 517 min
- REM latency 3.5 min
- Percentage of REM stage sleep 38.1%
- AHI = 0/hr
- Multiple sleep latency test (MSLT)
  - mean sleep latency was 1.0 min
  - 4/4 Sleep onset REM periods (SOREMPs)

Internal Medicine (Tokyo) 2012
Repeat Imaging

- MRI revealed expansion of the 3rd ventricle, and atrophy of the pituitary gland as well as a cavity forming in the whole hypothalamus
MRI-tractography Imaging

Figure 4. Left panel: Tractographic image of the patient. A lack of neuronal fiber connections between the hypothalamus and the frontal lobe can be seen. Right panel: Image of a normal control, a 20-year-old woman.
CSF Levels of Hypocretin by Age
Hypocretin and Narcolepsy

Roles of Hypocretin (Orexin)
Case 5
Case 5

- A previously healthy 53-year-old-man presents with alterations in alertness
- Unexplained, unintentional weight loss
- Severe excessive sleepiness
- Subjective fevers and night sweats
- MRI shows hypothalamic lesion
- Hypothalamic biopsy demonstrates non-caseating granulomas
- Infectious diseases are excluded
- Diagnosed with neurosarcoidosis
- No other body involvement noted on PET
- Admitted to the hospital for treatment
Imaging
In the Hospital

- No dream enactment, snoring, apneic spells, cataplexy, hallucinatory episodes or sleep paralysis
- Sleep fragmentation is present
- Physical examination reveals a lethargic, thin man
- He awakens intermittently to verbal stimuli
- He holds a very short attention span of approximately 5-to-10 seconds, lapsing back to sleep.
- During the course of hospitalization, he develops acute hypercapnic respiratory failure of unclear origin

JCSM 2015
Labs

- CSF
  - Hypocretin is 0 pg/mL
  - 2 RBC and 3 WBC
  - No evidence for demyelination
  - Negative for coccidiomycosis, cryptococcus, JC virus, toxoplasmosis, VDRL, varicella PCR, HSV1/2 PCR, mycobacterial PCR, acid fast stain and culture, bacterial culture, viral culture, and fungal culture

- HLA DQB1*0602 was negative

- Blood gas showed respiratory acidosis with a pH of 7.29, PaCO2 = 91 mm Hg, PaO2 = 50 mm Hg, HCO3 = 42.6 mmol/L

- Sleep study not done as patient is not stable
Hypocretin and Breathing

PNAS 2007, Progress in Brain Research 2012
Hypocretin Response to Danger

Fig. 9. Orexin is required for the cardiovascular and behavioral responses during the resident–intruder test.
Case 6
Case 6

- A 30-year-old previously healthy man not taking any drugs, without a history of alcohol or drug misuse admitted with symptoms and signs of brain stem encephalitis
- Three months before admission, he had a febrile illness with fever 39°C, severe headache and double vision
- Physical exam shows a bilateral weakness of eye abduction and convergence, a vertical nystagmus at upward gaze and a slightly unsteady gait
- An inflammatory lesion was assumed, and steroids were given

Journal of neurology, neurosurgery, and psychiatry 2007
Case 6 Continued

• Six months later, double vision had partially subsided
• Severe fatigue and hypersomnia evolved
  • prolonged night sleep
  • continually reduced alertness
  • episodes of sleep attacks
• Developed isolated cataplexy-like episode
• Now has episodes of sleep paralysis
• Hallucinations while falling asleep or while awakening several times per month
• His wife reported violent motor activity and screaming during sleep
• No psychiatric symptoms were reported
• Epworth score was 13

Journal of neurology, neurosurgery, and psychiatry 2007
Repeat Exam and Labs

- Horizontal gaze-evoked nystagmus to both sides, with double vision
- Smooth pursuit was saccadic
- Vestibulo-ocular reflex was incompletely suppressed
- Halmagy test was abnormal to both sides
- Multimodal evoked potentials and electroencephalogram were all normal
- Cerebrospinal fluid (CSF)
  - 2 cells/mm³
  - protein 36 mg%
  - without oligoclonal bands
  - Hypocretin 266 pg/ml
  - Leptin 0.43 ng/ml
- HLA studies were negative for DRB1*1501 and DQB1*0602

Journal of neurology, neurosurgery, and psychiatry 2007
PSG and MSLT

• PSG showed two episodes of violent motor activity, mainly in the legs, and screaming during REM sleep
• REM sleep muscle atonia was partially preserved, but phasic activity was abnormally increased and also included proximal muscles
• The sleep profile was fragmented
• AHI 1/hr
• The multiple sleep latency test showed a sleep latency of 5 min
• Two short REM episodes 17 and 13 min after the onset of sleep

Journal of neurology, neurosurgery, and psychiatry 2007
Possible Common Pathway for RBD and Narcolepsy

- Important for the generation of REM sleep, including muscle atonia, postural tone, locomotion, and startle reaction
- Origin of the cholinergic component of the ascending reticular activating system
- Comprises the magnocellular and dorsal raphe nuclei (B, C), with the rostrally adjacent nuclei reticularis pontis caudalis, coeruleus, laterodorsal tegmental, and pendunculopontine nuclei. They form the anatomical basis of a complex interaction between cholinergic and catecholaminergic cell groups producing the aroused, yet atonic state of REM sleep, as proposed in the “reciprocal interaction hypothesis”
- Major synaptic target of the hypocretin-containing neurons

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Journal of neurology, neurosurgery, and psychiatry 2007
Case 7
Case 7

- A 54-year-old man was in his usual state of health prior to a trip to the Amazon River
- Upon his return to the United States, he found himself sleeping between 18 and 23 hours a day
- His past medical history was unremarkable; he took no medicines
- He described automatic behaviors but denied cataplexy, sleep paralysis, or hallucinations
- He was sleepy and appeared exhausted
- Epworth Sleepiness Scale score of 22
- His vital signs and general examination were unremarkable
- His neurological examination revealed ataxia and difficulty with tandem gait
- Magnetic resonance imaging of the brain showed a left lateral hypothalamic cystic lesion with an invaginated scolex, typical for neurocysticercosis
PSG and MSLT

- 2 weeks sleep diary showed an average of 22 hours of a sleep daily prior to the MSLT
- PSG arousal index was elevated at 60 per hour
- Sleep efficiency was reduced to 69%
- There were no significant sleep disorders
- Hypocretin levels were normal

Table 1—Results of the Multiple Sleep Latency Test Performed Under Standard Conditions.3

<table>
<thead>
<tr>
<th>Nap number</th>
<th>Sleep latency, min</th>
<th>SOREMP latency, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>No REM</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>15.5*</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>13.5</td>
<td>No REM</td>
</tr>
<tr>
<td>Mean sleep latency, min</td>
<td>6.5</td>
<td></td>
</tr>
</tbody>
</table>

*Not considered a sleep-onset rapid eye movement period (SOREMP) due to occurring more than 15 minutes after sleep onset.
• He was successfully treated with praziquantel for his neurocysticercosis, based on cyst calcification on follow-up neuroimaging.

• Dextroamphetamine treated his sleepiness, and regular daytime naps improved his alertness.

Figure 1—Sagittal T1-weighted magnetic resonance image showing a cysticerci lesion in the left lateral hypothalamus. An invaginated scolex can be seen within the cyst (arrow).
Neurocysticercosis

- Neurocysticercosis is a common central nervous system parasitic disease endemic to Central and South America
- Intestinal infection (taeniasis) is contracted from eating raw or undercooked pork containing *Taenia solium*
- Neurocysticercosis results when eggs are ingested from a host with taeniasis
- Gastric acids release invasive oncospheres from the eggs, which enter the bloodstream and encyst in the brain
- Symptoms depend on lesion location and often include seizures, headaches, and focal neurological deficits
- Magnetic resonance imaging is diagnostic when revealing lesions that are either cystic or calcified. A scolex may be seen
Case 8
Case 8

- A 51-year-old male engineer with no family history of narcolepsy
- He had been in excellent health without any sleep complaints until 1978
- In May 1978, surgical treatment was planned for a peptic gastric ulcer and hiatal hernia producing epigastric pain
- Anesthesia was induced by intravenous injection of sodium pentobarbital
- During intubation of the trachea his blood pressure fell rapidly and respiratory arrest and cardiocirculatory insufficiency occurred
- Cardiopulmonary resuscitation was successful, but he remained in a coma for 5 days
- Upon regaining consciousness, neurological examination yielded normal findings except for bilateral cerebellar incoordination

Annals of Neurology 1986
Physical Exam

• Mild incoordination of all four extremities
• Generalized hypotonia, depressed reflexes, and extensor plantar responses
• Cranial nerves, motor systems, and sensory system were normal
• Examinations during several cataplectic attacks revealed dysarthria, bilateral ptosis, worsening of the generalized hypotonia, and irregular saccadic ocular movements in both lateral and vertical directions
• Results of urinalysis, complete blood counts, blood chemistries, and endocrinological studies were within normal limits
• Histocompatibility testing showed that his HLA types were HLA-A11, A24, B35, B39, and Cw4
• Neuropsychological examination revealed cognitive and memory performance to be within the superior normal range (Wechsler Adult Intelligence Scale, 146; Wechsler memory quotient, 140)
Sleep Testing

- Low total sleep time and frequent awakenings
- Sleep stages were poorly defined with relative suppression of REM stages 3 and 4
- Numerous episodes of sleep-onset-stage REM during the nocturnal period and during daytime recovery sessions
- Episodes of sleep apnea, reductions in arterial oxygen saturation, electrocardiographic abnormalities, and nocturnal myoclonus were absent
- The patient was noted to fall asleep at inappropriate times such as prior to assigned nocturnal sleep intervals, during routine electroencephalographic recording, and during neurological examinations
- Several episodes of sleep paralysis were observed
Imaging

- MR imaging of the brain revealed small lesions (areas of white on T2 weighting), which appeared to represent multiple small infarctions involving ventral portions of the basis pontis and the raphe nuclei.
- region is supplied by the paramedian branches of the basilar artery.
Case 9
Case 9

- 37-year-old female radiology technologist at a local InstaCare with no history of sleep problems presented to the ED with acute carbon monoxide poisoning from a gas powered pump that was being used in the facility basement for recent flooding.
- She received 40 minutes of 100% oxygen prior to arriving at the ED but continued to be lightheaded with a headache.
- Blood carboxyhemoglobin in the ED was 13.7% and she was placed on 100% O2 via a non-rebreather mask for 4 hours.
- She did very well with this and had no symptoms, and so she was discharged to home.
- She did not receive hyperbaric therapy.
Evaluation

• 2 years later, at age 49, she is evaluated in the Sleep Disorders Centers
• Since her carbon monoxide poisoning, she is excessively tired and sleepy during the day
• She tries to sleep about ten hours per night and has no trouble falling asleep, but awakens unrefreshed
• She wakes up frequently during the night for brief repositioning
• She has now started to snore but is not aware of any apneic episodes
• She is not aware of any dream enactment
• She occasionally has a headache in the morning
• She denies any restless legs symptoms at night
Sleep Testing PSG + MSLT

Sleep Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Time (min.)</th>
<th>% TST</th>
<th>% TIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>15.0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Stage 2</td>
<td>157.5</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Stage 3</td>
<td>78.0</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Stage 4</td>
<td>0.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>REM</td>
<td>181.5</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td>Awake</td>
<td>26.0</td>
<td>---</td>
<td>6</td>
</tr>
<tr>
<td>Movement Time</td>
<td>0.0</td>
<td>---</td>
<td>0</td>
</tr>
</tbody>
</table>

Lights Out | Nap 1 | Nap 2 | Nap 3 | Nap 4 | Nap 5 | Mean
---|---|---|---|---|---|---
9:13 AM | 9:13 AM | 9:31 AM | 11:05 AM | 11:00 PM | 12:38 PM | 3:01 PM | 5:00 PM | ---
Sleep Onset | 9:13 AM | 11:05 AM | 9:00 PM | 3:02 PM | 5:02 PM | ---
Sleep On | 9:31 AM | 11:20 AM | 1:16 PM | 3:18 PM | 5:21 PM | ---
Time In Bed | 17.5 min. | 16.5 min. | 17.5 min. | 17.5 min. | 21.0 min. | 18.0 min.
Total Sleep Time | 17.0 min. | 15.0 min. | 16.0 min. | 15.5 min. | 18.5 min. | 16.4 min.
Sleep Latency | 0.0 min. | 1.0 min. | 1.5 min. | 1.5 min. | 2.5 min. | 1.2 min.
REM Latency | 4.5 min. | --- | --- | 13.0 min. | --- | 8.8 min.
Case 10
Case 10

- A 45-year-old female attorney presents with excessive daytime sleepiness and an Epworth score of 17/24
- She underwent sleep testing by PSG
  - No evidence of sleep apnea
  - Mild periodic limb movements
- Subsequent MSLT
  - Mean sleep latency of 3.4 minutes
  - No SOREMP
- Diagnosed with Idiopathic hypersomnia with comorbid depression
Interval History

• 2007 she moves into a new home
• she noted many new headaches lasting 5-7 days that her migraine medication did not help
• She felt flu-like for several weeks at a time and suffered periodic nausea and vomiting
• It was much easier to sleep all the time, and she would yawning throughout the day
• She was having extreme difficulty focusing or finishing tasks, particularly related to work and she started falling behind in case work and could not complete briefs
• She went from working in 2 other attorney group practices to working by herself, so she could have time to sleep more
• Complained of frequent dyspnea with profuse sweating at various times and getting dizzy easily
• She experienced pain with loud noises and she would avoid areas that had loud music or loud voices
• She had chest pain, frequently at night, during the last month that she was in the house
• Her youngest daughter, who lived with her, had similar problems
Interval History Continued

• She fell behind on bookkeeping and billing
• She did not earn enough to cover her bills and she eventually lost her health insurance and defaulted on her mortgage
• She leaves the home in 2011 and her daughter and son-in-law move in
• The CO detector in the home alarms and when the fire departments arrives 30 minutes later (windows and doors being open the whole time), the CO level is 161 ppm
• Improperly installed appliances and sub-standard ventilation are blamed for the elevated carbon monoxide levels
Repeat Evaluation

• In 2012 she returns to the Sleep clinic
• Headache is gone, but her daytime fatigue and sleepiness is much worse than previously
• Sleeping 12-14 hours a day
• Undergoes repeat PSG and MSLT in early 2015

AHI TST = 3/hr
Carbon Monoxide (CO)

- Colourless, odourless, and non-irritant gas
- Mixes evenly with room air and has no acidic or basic properties
- A product of incomplete combustion of carbonaceous matter and is
- Undetectable by human smell, taste or sight

**COMMON SOURCES**

- Improperly installed or poorly maintained cooking and heating appliances
- Exhaust of all internal combustion engines
  - Motor vehicles
  - Generators
  - Lawn mowers
  - Power tools
  - Small gasoline powered engines
Table 1 – Signs and symptoms of acute or chronic CO poisoning.

Symptoms:
Headache, dizziness, nausea, vomiting, irritability, weakness, fatigue, syncope, angina, ‘flu-like’ symptoms.
Depression, anxiety, irritability, recurrent infections and hair changes are reported more commonly in ‘chronic’ exposures.

Signs:
Ataxia, agitation, impairment of consciousness, respiratory failure, tachycardia, tachypnoea, hypotension, myocardial ischaemia and infarction. ST depression, prolonged QT interval, atrial fibrillation, pneumonia, high blood sugar, lactic acidosis. Cerebral edema and metabolic acidosis develop in serious cases.

Less common features:
Skin blisters, rhabdomyolysis, acute renal failure, pulmonary oedema, retinal haemorrhages, cortical blindness, choreoathetosis and mutism.

Neuropsychiatric features:
Memory loss, depression, anxiety, disorientation, apathy, mutism, irritability, inability to concentrate, personality change, Parkinsonism, including urinary and/or faecal incontinence, gait disturbance, dementia, psychosis, hallucinations, seizures, coma and death.

Fluctuating signs and symptoms are the rule.

| TABLE 1.—Frequency of Symptoms in Patients Exposed to Carbon Monoxide (26 Patients) |
|---------------------------------|-----------------|----------------|
| Symptom                        | Patients        | Percent       |
| 1. Fatigue                     | 24              | 92            |
| 2. Headaches                   | 22              | 85            |
| 3. Trouble thinking            | 20              | 77            |
| 4. Dizziness                   | 19              | 73            |
| 5. Nausea                      | 15              | 65            |
| 6. Trouble sleeping            | 15              | 65            |
| 7. Heart pounding              | 14              | 54            |
| 8. Shortness of breath         | 14              | 54            |
| 9. Numbness or tingling        | 12              | 46            |
| 10. Chest pain                 | 9               | 35            |
| 11. Decreased vision           | 9               | 35            |
| 12. Diarrhea                   | 9               | 35            |
| 13. Unusual spells             | 9               | 35            |
| 14. Abdominal pain             | 7               | 27            |
Incidence of CO Poisoning

• One study found overall ED incidence to be 28/10,856 (0.0026%) and 11 of those 28 were only found because “extra” testing

• Estimated that up to 75% of cases go undiagnosed in the community

• A prospective observational study of 1758 patients presenting to an emergency department with chest pain, exacerbation of chronic obstructive pulmonary disease (COPD), non-traumatic headache, seizures or flu-like symptoms found that 4.3% of these patients had unexpected COHb levels, which was defined as over 2.5% in non-smokers and over 5% in smokers
Neuropsychiatric Sequelae of CO Poisoning

• Cognitive function may be impaired with COHb levels as low as 5%
• Neuropsychiatric sequelae have been shown to occur in up to 50% of the patients with measured COHb levels of greater than 10%
• 50 - 75% of the patients with delayed neuropsychiatric sequelae recovered after one year, but some did have persistent memory disturbances
• Neurological abnormalities can be found years after acute CO poisoning, occurring in 37% of patients observed six years after being poisoned
• A serum S100B protein level of more than .165 mg/L independently predicts the development of delayed neuropsychiatric sequelae (sensitivity 90%, specificity 87%) after acute CO poisoning
Screening for CO Poisoning

**C:** Cohabitees/companions: is anyone else in the property affected (including pets)?

**O:** Outdoors: do your symptoms improve when out of the building? [better outdoors]

**M:** Maintenance: are your fuel-burning appliances and vents properly maintained?

**A:** Alarm: do you have a carbon monoxide alarm?
Conclusions

• Secondary Narcolepsy can arise from multiple neurologic insults targeted at the hypocretin system.
• HLA typing is not diagnostically helpful in these cases
• Hypocretin levels may be normal
• Carbon monoxide poisoning can be both acute or chronic
• Screening patients with complaints that could be consistent with carbon monoxide poisoning or neurologic sequelae will help identify these patients
Citations


Citations (Cont)


Citations (Cont)


