Narcolepsy
UPDATES

Rose A. Franco, MD
Associate Professor of Pulmonary, Critical Care
and Sleep Medicine
Medical College of Wisconsin

Disclosure

• No conflicts of interest
**Narcolepsy Type 1 (Narcolepsy with Cataplexy)**

(ICD-9 347.01/ICD-10 G47.411)

- Profound sleepiness almost daily for >3 months

**PLUS:**
- hypocretin-1 CSF levels <110 pg/mL (1/3 normal control mean)
- HLA-DQB1*0602 positive

**OR (and)**

- Definite Cataplexy
  - Sudden bilateral brief episodes of loss of muscle tone triggered by emotion with Preserved consciousness

**PLUS**
- MSLT with MSL <8 minutes, ≥2 SOREM
  (one SOREM can be used from PSG)
- 1 week of actigraphy and a sleep log proceeding MSLT highly recommended

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**Narcolepsy: Historical**

- Westphal (1877) and Fisher (1878) first description of Narcoleptics
  - Hereditary component noted
- Gelineau (1880) “Narcolepsy” as specific disorder
- Loewenfeld (1902) “Cataplexy”
Von Economo (1930)

• 1917-1927 epidemic of encephalitis lethargica
• Studies allowed localize area of brain critical for wakefulness as the posterior hypothalamus
• He correctly proposed region in the posterior hypothalamus as lesioned in human narcolepsy
  — Von Economo et al. J Nerv Ment Disease 1930

Classic Narcolepsy Tetrad

• Large case series in the 1920s-1950s lead to the classic clinical description that we know as narcolepsy today
  — Hypersomnia/Sleep Attacks
  — Sleep Paralysis
  — Cataplexy
  — Hypnogogic Hallucinations
Link to REM sleep

- Vogel 1960 first reported SOREM
  - Vogel G. Arch Gen Psychiatry 1960
- Rechtschaffen and Dement confirmed later
- Hishikawa (with above) studied EEG during sleep paralysis and hypnagogic hallucinations
  - Sleep and Altered States of Consciousness. Baltimore, Williams and Wilkins. 1967
  - Dissociated REM sleep
- MSLT became the standard for diagnosis
  - Richardson et al. Electroencephalogr Clin Neurophysiol 1978
  - Carskadon et al. Sleep 1986

Animals models for study

- Stanford Doberman 1976
- Intracerebral and CSF measurements of acetylcholine, monoamines, metabolites and receptors allowed evolution of hypothesis of a pontine monoaminergic cholinergic imbalance
  - Baker et al. Brain Mechanisms of Sleep 1985
- Dopaminergic abnormalities in the amygdala lead to consideration for its role in cataplexy
- Demonstrated presynaptic activation of adrenergic mediated antiscatpetic effects of antidepressants
  - Nishino et al. Sleep 1993
Nature vs Nurture

• Recognition of inheritance
• 1-2% Narcolepsy with Cataplexy are familial (20-40X RR)
• 1980s HLA-DR2 in most narcoleptics
  – Japanese (Honda, Juji, and Asaka first described)
  – German
  – French
  – Canadian

• Most HLA associated disorders are autoimmune in nature
• Is Narcolepsy too an autoimmune disorder?

Next steps

• Presence of Narcolepsy without HLA-DR2 positivity lead to debate on autoimmunity theory
• HLA-DQB1*0602 more tightly linked with narcolepsy
  • Mignot et al Sleep 1994
• Homozygotes for 0602 and heterozygotes for 0602/0301 carry highest risk of narcolepsy
  • Mignot et al. Sleep 1999
Critical Discovery

- Hypocretins 1, 2/Orexins A, B identified 1998
  - DeLecea et al Proc Natl Acad Sci 1998
  - Sakurai et al Cell 1998
- Receptors for the Hypocretin peptides were also identified
  - Sakurai et al Cell 1998
- Lateral Hypothalamus>>>hypocretin discrete activity
- Broad reaching connections suggested complex physiologic regulation
- Dense projections to monoaminergic cells in locus coeruleus suggested role in sleep regulation
- Narcolepsy animal lines (canine-hypocretin receptor mutation, knockout mouse for preprohypocretin gene) confirmed link with narcolepsy
  - Chemelli Cell 1999
Canine Gene identified

- Dog gene studies.....Hypocretin Receptor 2 Gene (Hcrtr2) (autosomal recessive)
- Lin et al. 1999 Cell

Hypocretin deficiency in Human Narcolepsy with Cataplexy

- Human CSF levels very low, undetectable
- Nishino et al Lancet 2000
- Return to question.. Discrete cells produce the peptide, dropout occurs leading to symptomatic narcolepsy with cataplexy
  - Destroyed by autoimmune process in HLA associated Narcolepsy?
Narrowing in on the GENE in humans

• Narcolepsy associated with the TCR alpha locus
• Hallmayer et al. Nat Genet 2009
• TCRA locus role in T lymphocytes

Autoimmunity revisited: UK 2013

• Risk of narcolepsy in those receiving A/H1N1 2009 influenza vaccine.
• Of 245 cases reviewed 75 with narcolepsy (56 with also cataplexy)
• 11 received vaccine before onset, 7 within 6 months of vaccine developed symptoms
• OR 14.4 and 16.2
• Relative Risk from the self controlled cases was 9.9
• Attributable risk from the vaccination was 1 in 57,500 doses.
• Because of the variable delay in diagnosis the risk might be overestimated by more rapid referrals of vaccinated children.
  - BMJ 2013. Miller Et al
Animal models direct research into mechanisms

- Hypocretins central in regulation of the excitatory neurotransmitter system
- Respective roles of Hcrtr1 and Hcrtr2 and degeneration of amygdala and basal forebrain in the dog model
  - Lin et al. Cell 1999
- Murine model ataxin-3-orexin mouse
- Hcrt-neurons degenerate postnatally
  - Hara et al. Neuron 2001

Best animal model

- DTA-orexin mouse closest to human narcolepsy
- Doxycycline protects the orexin-neurons from degeneration
- Withdrawal leads to diphteria toxin fragment A expression in the Hcrt cells with cell death leading to typical narcolepsy and cataplexy
  — Nishino et al. Sleep Med Rev 2004
**Hcrt System and link to Histamine centers of wakefulness**

- Maintains wakefulness and muscle tone
  - Focal cells in lateral hypothalamus with Projections to spinal, brainstem, and forebrain regions
  - Dense projections to the histamine cell groups in Tuberomammillary region and locus coeruleus
  - Histamine linked to wakefulness
- Histamine receptor-3 (H3) inverse agonist (autoreceptor antagonist) decreases sleepiness in human narcoleptics
  - Lin et al Neurobiol 2008

**Link of Histaminergic system in Human narcolepsy**

- Intraventricular Hcrt is dependent on integrity of the H1 receptor
  - Huang et al. Proc Natl Acad Sci 2001
- Large increases in the number of histamine cells in the tuberomammillary region of human narcoleptics (not seen in animal models) suggests role of histamine cells is different in human narcolepsy
Histamine’s role in narcolepsy explored

- Measurement of histamine in CSF in human narcolepsy is below to low normal
- Increase in histaminergic cells does not result in increase levels of histamine
- Histamine plays a role in inflammatory response
- In Parkinsons disease, elevated histamine levels are hypothesized to cause the death of neurons in the substantia nigra
- Narcolepsy in humans has been linked with vaccination to H1N1, H1N1 infection and even streptococcus infection.
  - Authors suggest the increased number of HDC cells maybe residual of effect of histamine expression causing Hcrt cell loss
Summary of current understanding of Narcolepsy with cataplexy

• Caused by the loss of hypocretin cells in the hypothalamus
• Hypocretin-1 is best biologic marker (reduction) and can be measured in the CSF (not routine, false positives possible)
• HLA-DQB1*0602 in 92% Caucasians with narcolepsy (25% controls)
• Polymorphism of the T-cell receptor alpha gene and the purinergic receptor (P2RY11) gene are strong indications of autoimmune origin**

Onset and progression of disorder

• Initial symptoms not specific to narcolepsy, delays diagnosis
• MSLT may not provide diagnosis and can provide false positives (OSA, sleep deprived)
• Normal (3.9% with >1 SOREM)
• Idiopathic CNS hypersomnia overlap symptoms
Controlled study of phenotyping Narcolepsy

• Luca et al. European Sleep research Society 2013
  – Accurate Diagnosis requires full clinical presentation and critical interpretation of PSG and MSLT
  – Hcrt-1 concentrations important diagnostic tool (in questionable causes)
  – Gender may confound diagnosis (delays more in women)

MLST and REM latency as diagnostic in Narcolepsy/Cataplexy vs controls

<table>
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<tr>
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<th>Controls N=542</th>
<th>Narcolepsy N=542</th>
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<tbody>
<tr>
<td>Age</td>
<td>39.3</td>
<td>37.6</td>
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<tr>
<td>Gender (%M)</td>
<td>50</td>
<td>47</td>
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<tr>
<td>MSLT/MSL</td>
<td>11.5</td>
<td>2.6</td>
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<tr>
<td>MSLT # SOREMS</td>
<td>0.2</td>
<td>3.5</td>
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<tr>
<td>PSG REM Latency</td>
<td>116.7</td>
<td>51.2</td>
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<thead>
<tr>
<th></th>
<th>SOREMPs ≥2 and MSL&lt;8</th>
<th>REM latency ≤15</th>
<th>REM latency ≤15 or MSL&lt;8</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>93.5</td>
<td>51.3</td>
<td>94.9</td>
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<tr>
<td>Specificity</td>
<td>97.8</td>
<td>99.4</td>
<td>97.2</td>
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Anlauer et al. JAMA Neurol 2013
CURRENT DIAGNOSTIC CLASSIFICATION
ICDS-3

Narcolepsy

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**PLUS**

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Narcolepsy Type 2

- Hypersomnia >3 months
- MSL >8 minutes
- SOREM ≥2
- No cataplexy
- Hypocretin 1 levels >110pg/ml or not measured
  - 24% of those with MSLT above will have low hypocretin level
  - 45% will have HLADQB1*0602
  - 10% will develop cataplexy later
- If associated with a medical/neurologic condition use Narcolepsy type 2 due to a medical condition.

Narcolepsy Treatment: then and now

- Irradiation of the hypothalamic region
- Intrathecal air injections
- Canting off CSF
- Ephedrine
- 1935 Amphetamines (Prinzmetal/Bloomberg)
- 1960s Methylphenidate (Yoss and Daly)
- 1957 Tricyclics for cataplexy (Akimoto/Honda/Takahashi)
Modern medication mechanisms

• Presynaptic activation of dopaminergic transmission mediates wake promoting effects of modafinil/stimulants
  • Nishino et al. Sleep Research Online 1998
• Cholinergic hypersensitivity in basal forebrain, mesolimbic dopaminergic hypoactivity, and neuronal degeneration in the amygdala and forebrain also pathophysiological abnormalities
  • Nishino et al. J Neurosci 1995
  • Reid et al. Brain Res. 1996
  • Siegel et al. J Neurosci 1999

Amphetamines

• Derivatives of catecholamines that are more lipophilic allowing them to cross the BBB and enter the CNS easily
• Affect adrenergic, dopaminergic and also serotonergic synapses (balance based on chemical nature) (DA>NE>>5-HT)
• D isomers are more active than L isomers
• High doses can be cytotoxic to monoaminergic neurons in animals
• Increase BP, HR, sweating and cardiac complications
• Can precipitate psychosis
Methamphetamine

- Like amphetamines with increased lipophilic nature allowing better CNS penetration
- Highly addictive
- Very restricted

Methylphenidate

- Blocks monamine uptake (DA>NE>>5-HT)
- No effect on reverse efflux or on vesicular monoamine transporter
- Short half life.
- Extended release formulations are less addicting
- Increased HR, BP, sweating
- Not cytotoxic in animal studies
Selegiline

- L-despreynl (aka)
- Monoamine oxidase B inhibitor conversion to L-amphetamine and L-metamphetamine
- Should not use in combination with amphetamines

Modafinil

- Mechanism Of Action (MOA) debated.
- Selective DA reuptake inhibitor.
  - Wisor et al J Neurosci 2001
- Does not affect REM sleep or reduce cataplexy
- R isomer longer half life.
- Slowly enters CNS. Lowers risk of abuse/addiction.
- Stevens Johnson Syndrome has been reported. (not available for pediatric use).
- May interact with low dose Birth Control but the claim is week resting on anecdotes.
Anti-cataplectic agents

- Protriptyline (TCA). Monoaminergic uptake blocker. Anticholinergic. Abrupt cessation induces severe rebound cataplexy
- Clomipramine (TCA).
- Duloxetine (SRNI). Longer half-life.
- Atomoxetine (NE reuptake blocker). Slightly stimulant, short half-life.
- Fluoxetine (SSRI). High therapeutic doses needed.

Sodium Oxybate

- May act via GABA-B or specific GHB receptors
  - Koek et al. 2008 Psychopharmacology.
- Reduces DA release.
- Induces slow wave sleep and REM sleep.
  - Broughton et al. 1979 Can J Neurol Sci
- Bi-nightly dosing with rare exceptions.
- Dosing Goal is consolidated sleep.
- May lead to psychiatric complications (anxiety most common) use in caution with pre-existing psychiatric issues.
- Unintentional OD have been reported.
- Unexplained deaths have been reported.
- Expensive.

- Immediate improvement in sleep.
- Gradual improvement in EDS and cataplexy (weeks to months).
- Studied in OSA without change in AHI.
  - George et al. 2011 Sleep Breath
  - Bi-nightly dosing with rare exceptions.
  - Dosing Goal is consolidated sleep.
Life considerations

- **Children**
  - Stimulants Reduce growth slightly
  - Modafinil not FDA approved
  - Documented hypocretin deficiency, sodium oxybate has been very effective
    » Lecendreux et al. Sleep 2012

- **Pregnancy and Breast feeding**
  - Amphetamines, methylphenidate, venlafaxine and modafinil all category C
  - Sodium Oxybate is category B
  - All are found in breast milk

Novel therapies

- **Hypocretin-1 peptide when infused to the CNS promotes wakefulness**
  - Hagan et al Proc Natl Acad Sci 1999
  - Fujiki et al Sleep 2003
  - Mieda et al Proc Natl Acad Sci 2004

- **Hypocretin-1 intranasal**
  - Hanson et al Drug Delivery Technol 2004

- **Histamine-3 antagonists**

- **Benzodiazepine antagonist-like agents**
  - Case series only.
  - David Rye (Emory University. Somnogen).
The future

• Cell Transplantation
  – Hypocretin neurons into the pontine reticular formation
    • Arias-Carrion et al. Sleep 2004, 2006

Gene Therapy

• Viral delivery of transgene allowing expression of hypocretin
  – Mieda et al Proc Natl Acad Sci 2004
• Appropriate vector and control over location of expression
Immunotherapy

- Attempts with IV steroids, IV immunoglobulins, and plasmaphoresis have been attempted in the last 12 years
- Equivocal results.

Narcolepsy

- Journey through history allows us to understand the need for well-defined nosology
- Advances in neurobiology and immunobiology are quickly providing a better understanding of the mechanism of disease
- Newer therapies have improved QoL for narcoleptics
- Early diagnosis is needed
- Readily available tests for diagnosis are not yet at gold standard level (MSLT) and HLA testing
- We await more discoveries that may one day allow early diagnosis and cure.
Thank You