Recent Advances in the Understanding of Narcolepsy: Diagnosis, Pathophysiology and Treatment

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Narcolepsy Network Annual Meeting, Atlanta, October, 2013
Narcolepsy – Diagnostic Criteria DSM5

- A. Recurrent periods of an irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day. These must have been occurring at least three times per week over the past 3 months.

- B. The presence of at least one of the following:
  1. **Episodes of cataplexy**, defined as either (a) or (b), occurring at least a few times per month:

     a. In individuals with long-standing disease, brief (seconds to minutes) episodes of sudden bilateral loss of muscle tone with maintained consciousness that are precipitated by laughter or joking.

     b. In children or in individuals within 6 months of onset, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers.
2. **Hypocretin deficiency**, as measured using cerebrospinal fluid (CSF) hypocretin-1 immunoreactivity values (less than or equal to one-third of values obtained in healthy subjects tested using the same assay, or less than or equal to 110 pg/mL).

   (Low CSF levels of hypocretin-1 must not be observed in the context of acute brain injury, inflammation, or infection.)

3. Nocturnal sleep polysomnography showing rapid eye movement (REM) sleep latency less than or equal to 15 minutes, or a multiple sleep latency test showing a mean sleep latency less than or equal to 8 minutes and two or more sleep-onset REM periods.
Narcolepsy Subtypes– Diagnostic Criteria

- **347.00 (G47.419)** Narcolepsy without cataplexy but with hypocretin deficiency: Criterion B requirements of low CSF hypocretin-1 levels and positive polysomnography/multiple sleep latency test are met, but no cataplexy is present (Criterion B1 not met).

- **347.01 (G47.411)** Narcolepsy with cataplexy but without hypocretin deficiency: In this rare subtype (less than 5% of narcolepsy cases), Criterion B requirements of cataplexy and positive polysomnography/multiple sleep latency test are met, but CSF hypocretin-1 levels are normal (Criterion B2 not met).

- **347.00 (G47.419)** Autosomal dominant cerebellar ataxia, deafness, and narcolepsy: This subtype is caused by exon 21 DNA (cytosine-5)-methyltransferase-1 mutations and is characterized by late-onset (age 30-40 years) narcolepsy (with low or intermediate CSF hypocretin-1 levels), deafness, cerebellar ataxia, and eventually dementia.
Narcolepsy Subtypes—Diagnostic Criteria

DSM5 (cont)

- **347.00 (G47.419) Autosomal dominant narcolepsy, obesity, and type 2 diabetes:** Narcolepsy, obesity, and type 2 diabetes and low CSF hypocretin-1 levels have been described in rare cases and are associated with a mutation in the myelin oligodendrocyte glycoprotein gene.

- **347.10 (G47.429) Narcolepsy secondary to another medical condition:** This subtype is for narcolepsy that develops secondary to medical conditions that cause infectious (e.g., Whipple's disease, sarcoidosis), traumatic, or tumoral destruction of hypocretin neurons.
Narcolepsy - Severity Criteria (DSM5)

- **Mild**: Infrequent cataplexy (less than once per week), need for naps only once or twice per day, and less disturbed nocturnal sleep.

- **Moderate**: Cataplexy once daily or every few days, disturbed nocturnal sleep, and need for multiple naps daily.

- **Severe**: Drug-resistant cataplexy with multiple attacks daily, nearly constant sleepiness, and disturbed nocturnal sleep (i.e., movements, insomnia, and vivid dreaming).
Hypersomnia Disorders  
– Diagnostic Criteria ICSD3

- 347.00 (G47.4) Narcolepsy Type I (Narcolepsy with Cataplexy):
- 347.00 (G47.419) Narcolepsy Type 2. (Narcolepsy without cataplexy)
- Idiopathic Hypersomnia
- Kleine-levin Syndrome
- Hypersomnia due to a medical, psychiatric disorder or medications.
- Behaviorally-Induced insufficient sleep syndrome.
Narcolepsy– Diagnostic Criteria ICSD3

- 347.00 (G47.4) Narcolepsy Type I (Narcolepsy with Cataplexy):
  Excessive sleepiness for 3 months
  At least 1 of the following:
  1. Cataplexy, and
     on MSLT, MSL <8 mins >2 SOREMPs
     (one SOREMP may be on the preceding night’s PSG)
  OR

  2. CSF CSF hypocretin-1 levels <110 pg/ml or 1/3 rd the baseline normal levels, and
     on MSLT MSL <8 mins >2 SOREMPs
     (one SOREMP may be on the preceding night’s PSG)

In children actigraphy is required before the MSLT.

- 347.00 (G47.419) Narcolepsy Type 2. (Narcolepsy without cataplexy)
  Positive polysomnography/ multiple sleep latency test are met, but
  No cataplexy is present

A. The patient has daily periods of irrepresible need to sleep or daytime lapses into sleep occurring for \( \geq 3 \) months

- Note: In young children, narcolepsy may sometimes present as excessively long night sleep or by resumption of previously discontinued daytime napping

(In children actigraphy is required before the MSLT.)
Narcolepsy Diagnostic Criteria
Type 1 Narcolepsy (ICSD3)

B. The presence of $\geq 2$ of the following:

1. Cataplexy

2. Mean sleep latency of $<8$ minutes and $\geq 2$ sleep-onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREM (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT.

Note: If narcolepsy Type 1 is strongly suspected clinically but criteria B2 are not met, a possible strategy is to repeat the MSLT.

3. CSF hypocretin-1 concentrations measured by immunoreactivity either $<110$ pg/mL or $<\frac{1}{3}$ of mean values obtained in normal subjects with the same assay.

Narcolepsy Diagnostic Criteria
Type 2 Narcolepsy (ICSD3)

A. The patient has daily periods of irrepessible need to sleep or daytime lapses into sleep occurring for at least 3 months
   • Note: In young children, narcolepsy may sometimes present as excessively long night sleep or by resumption of previously discontinued daytime napping

B. Mean sleep latency of <8 minutes and ≥2 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 PSG may replace one of the SOREMPs on the MSLT. (In children actigraphy is required before the MSLT)

C. Hypersomnia not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder

Cataplexy in Narcolepsy

- Second most common symptom of narcolepsy\(^1,2\)
- Pathognomonic for narcolepsy\(^1\)
- Sudden and transient loss or reduction of muscle tone\(^1\)
- Triggered by strong emotions\(^1\)
  - Laughter, elation, surprise, anger
- Typically partial or localized (~75%)\(^2,3\)
- Usually short duration\(^1\)
- Frequency varies widely\(^1\)
- Narcolepsy with cataplexy can be socially disabling and isolating\(^1\)

\(^1\) American Academy of Sleep Medicine. The International Classification of Sleep Disorders. 2nd ed.; 2005.
\(^3\) Ahmed I, Thorpy M. Clin Chest Med. 2010;31(2)371-381.
This increase in histaminergic neurons in narcolepsy may be a compensatory response to loss of excitatory drive from the orexin neurons and may contribute to some symptoms such as preserved consciousness during cataplexy and fragmented nighttime sleep.

Increase of histaminergic tuberomammillary neurons in narcolepsy.
Valko P et al, Sleep 2013: (36) Suppl: A249
HLA in Narcolepsy

- HLA association:
  - It was first discovered that 100% Japanese narcoleptics were associated with HLA-DR 2 and DQ1 positive (Dw2)
  
  - Further genotyping/sequencing showed that the Dw2 haplotype was characterized as HLA DRB1*1501, DQA1*0102, DQB1*0602 90% of narcolepsy cases.

  - 67% of african-american patients are DR2 positive but nearly 100% DQB1*0602 positive.

  - Most patients with N/C who are DQB1*0602 positive have hypocretin deficiency.

  - HLA DQB1*0601 and HLA DQB1*0501 are protective.
A new gene for narcolepsy implicates the immune system in the cause of narcolepsy. GWA studies found association between narcolepsy and polymorphisms in the TRA@ (T cell receptor alpha) locus P<10 (-21)

ASO and ADB titers were highest close to narcolepsy onset, and decreased with disease duration. Elevated ASO and ADB titres were found in 51% and 45% of patients within 3 years of onset (P < 0.0005 cf controls).
Infections in Narcolepsy

- Population-based case-control study
- N = 45  DQB1*0602-positive  Cataplexy

<table>
<thead>
<tr>
<th></th>
<th>% of case</th>
<th>% Controls (n=95)</th>
<th>Adjusted OR</th>
<th>95% CI</th>
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<td>Strep throat</td>
<td>90.9</td>
<td>75.9</td>
<td>5.4</td>
<td>1.5-19.1</td>
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<tr>
<td>Pneumonia</td>
<td>18.2</td>
<td>19.9</td>
<td>1.0</td>
<td>0.3-3.0</td>
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<td>1.8</td>
<td>1.1</td>
<td>0.0-29.7</td>
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<tr>
<td>Inf. Mono</td>
<td>15.6</td>
<td>14.1</td>
<td>1.6</td>
<td>0.5-5.0</td>
</tr>
</tbody>
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H1N1 Infection in Scandanavia

8-12 fold increase in narcolepsy in children in Finland and Sweden with Pandemrix (brand with potent ASO3 adjuvant)
Genetic association, seasonal infections and autoimmune basis of narcolepsy. Singh AK, Mahlios J, Mignot E.
Narcolepsy

An autoimmune disorder in HLA DQB1*0602 and TCRalpha predisposed people possibly precipitated by an infection with an alteration in hypocretin production in the CNS
Narcolepsy Treatment

- **First line treatment** for narcolepsy Type 1 and Type 2: Sodium Oxybate

- **Second line**: Sleepiness: Modafinil or armodafinil
  - Cataplexy: Venlafaxine or atomoxetine

Sodium oxybate is the most effective medication for cataplexy and the only medication that can treat all the symptoms of narcolepsy.
Orexin gene therapy restores the timing and maintenance of wakefulness in narcoleptic mice.

Conclusion

- Narcolepsy with cataplexy (N/C) is associated with hypocretin loss (95%)
- Narcolepsy appears to be an autoimmune disorder.
- HLA DQB1*0602 and the T cell receptor gene association with N/C points to immune disorder
- An infection may be the commonest cause of precipitating narcolepsy
- Sodium oxybate is the most effective medication in narcolepsy
- Future treatments may target hypocretin and histaminergic systems.