Narcolepsy in Children

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Internal Medicine/Pediatrics/Sleep Medicine
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Special thanks to Judith Owens MD MPH
Disclosures

- No conflicts of interest
- Some off label medication use will be discussed
BABY -
WHILE SLEEPING WITH
MAMA
PAPA
Pediatric Sleep Medicine

- Dr. Dominic Gault
- Jennifer MacLean NP
- Referral based practice
- Pediatric Sleep Labs (6 beds +/- 1), open lab
- Greenville, SC
Tonight I'm sleeping with mum or I will cry all night, understood?
Objectives

- Discuss challenges in the diagnosis of narcolepsy in children
  - Defining EDS in children
  - Differential diagnosis of EDS
  - Secondary narcolepsies
  - Clinical presentation
  - Overview of Therapy
- Review epidemiologic studies of N-C in childhood
Range of “normal” sleep duration much greater in 2yo (10.8-15.6 hrs/24) compared to 12 yo (8.0-10.7 hrs)

Iglowstein et al. Pediatrics 2003
"Normal" Daytime Napping Patterns

% Napping

- Weissbluth
- Iglowstein
- Crosby - AA
- Crosby - C

6M 12M 2Y 4Y 6Y 8Y
**EDS in Children**

- **Mood dysregulation:** irritability, mood instability, less positive mood
- **Behavioral problems:**
  - Internalizing
  - Externalizing (aggressiveness, hyperactivity, impulsivity)
- **Neurocognitive deficits**
  - Attention
  - Executive functions (organization, self-monitoring, planning)
  - Memory
  - Verbal creativity
- **Performance deficits**
  - Poor academic functioning
  - Social impairments
  - Family dysfunction
# Prevalence of EDS in Pediatrics

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Age</th>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>Neveus, 2001</td>
<td>1413</td>
<td>6-10</td>
<td>4%</td>
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<tr>
<td>Yang, 2005</td>
<td>1457</td>
<td>9-19</td>
<td>6.5%</td>
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<tr>
<td>Wang, 2013</td>
<td>912</td>
<td>6-14</td>
<td>20%</td>
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Differential Diagnosis of Hypersomnia in Children

- Chronic insufficient sleep
- Prolonged sleep need (“long sleeper”)
- Primary sleep disorders (OSAS, RLS/PLMD)
- Circadian rhythm disorders
- Psychiatric disorders
- Conversion disorder
- Drug and toxin effects
- Substance abuse

- Nocturnal seizures
- Medical conditions disrupting sleep; eg, asthma, atopic dermatitis, chronic pain
- Brain tumors
- Post-encephalitis or post-viral
- Post-concussion syndrome
- Kleine-Levin syndrome
- Idiopathic hypersomnia

- Narcolepsy
  - With or without cataplexy
  - Primary vs secondary
NARCOLEPSY
sexier than you thought

VERY DEMOTIVATIONAL.COM
Narcolepsy

- With (Type 1) or without (Type 2) cataplexy
- N+C prevalence is 25 to 50 per 100,000, equally common in men/women
- Typically begins in teens and early twenties
- N-C less studied but estimates 20 to 34 per 100,000
- Second most common cause of disabling daytime sleepiness (after OSA)
- Onset highest in the spring
Pathophysiology

- Loss of orexin/hypocretin
- Orexins released during wakefulness, helps with stabilizing wakefulness and preventing inappropriate transitions into sleep (REM/non REM)
- N+C -> specific loss of hypothalamic neurons that produce orexins (but adjacent neurons normal)
- DQB1*0602 present in 95% of N+C patients
- Only 25% affected monozygotic (identical) twins are concordant for narcolepsy
Secondary Narcolepsies in Children

- Associated with:
  - Pituitary or hypothalamic surgery
  - Brain tumors
  - Head injury, viral illness, encephalitis
  - Chemotherapy, cranial irradiation
  - Autoimmune thyroiditis

- Congenital syndromes:
  - Prader-Willi
  - Niemann-Pick type C
71% can’t get through the day without falling asleep
77% indicated they have difficulty interacting with family or friends
84% report not being able to perform as they wish at work or in school
32% with symptoms < 15 yo
But the diagnosis made before age 15 in only 4%

Challamel 1994
NARCOLEPSY
It can strike at any time!
"My daughter has seen more than 15 specialists over the past 5 years and they couldn't find anything wrong. It took the right doctor asking the right question to pick up on something that prompted a sleep study."

“Hallucinations with sleep attacks in the classroom is really disturbing.”
Narcolepsy Tetrad/CHESS

- Cataplexy
- Hypnagogic/Hypnopompic Hallucinations
- Excessive Daytime Sleepiness
- Sleep Paralysis
- ? Pentad…Sleep Disruption
Cataplexy

- sudden, brief loss of muscle strength or control caused by strong emotions
- Head drop/facial droop
- Triggered by strong emotions such as happiness, laughter, surprise
- Usually last <2min
- No loss of consciousness
Video Examples of Cataplexy

http://www.youtube.com/watch?v=R6_hwbp97eU (20-30s)

http://www.youtube.com/watch?v=qVu-IcLoZtU (2:20)
Hypnagogic Hallucinations

- Vivid dream-like events that occur while falling asleep (more common) or waking up (hypnopompic).
- Different from psychosis in that patients are usually aware it was not real, seems dream-like.
Excessive Daytime Sleepiness

- Inability to stay awake and/or alert
- Sudden lapses into drowsiness/microsleeps
- Patients can complain of fatigue, difficulty concentrating, irritability
Sleep Paralysis

- Inability to move or speak while falling asleep
- Usually scary/disturbing to patients
- Can have subjective sense of dyspnea
Sleep Disruption

- Fall asleep quickly but frequent brief awakenings (sleep fragmentation)
- Can lead to non-restorative sleep
Age Influences Expression of Narcolepsy with Cataplexy

- Case-control study of 157 patients with narcolepsy and 164 controls
  - First symptom before age 12 in 12%, 13 to 20 years in 42%
  - Daytime sleepiness first symptom 66%
  - Cataplexy appeared soon after EDS in 53%
  - Cataplexy first occurred in 48% during childhood or adolescence
  - Peak frequency of onset of sleepiness and cataplexy ages 15 to 19 yrs
  - Initial frequency of related symptoms (including cataplexy) lower with earlier age of onset EDS

1 Ohayon 2005
Sleepiness in Childhood Narcolepsy

- Sleep attacks may not be present
  - Constant low level or waxing and waning of sleepiness without discrete sleep episodes
- Sleep attacks may last longer (60-90 minutes)
  - May be refreshing or non-refreshing
  - Sleep drunkenness may be seen upon arousal
- Similar to adults with narcolepsy, naps tend to occur in sedentary situations
Sleepiness in Childhood Narcolepsy

- “Long sleeper” with increased sleep needs for age:
  - 30% of adult narcoleptics reported sleeping >10 hrs/night and still needing daytime naps at age 10yo
- “Deep sleepers”; if awakened during sleep act confused, may be verbally abusive and aggressive
- Extreme difficulty awakening in the morning
Other Symptoms Associated with Narcolepsy in Children

- Cognitive impairments
  - Significant difference verbal/performance scores WISC-III in 42% 7-16yo (N=12)\(^1\)
- Memory lapses
- Inattentiveness
- Impaired executive function
- Mood dysregulation
- Behavioral and psychosocial problems
  - One series of 16 patients with narcolepsy first presented with behavioral or emotional disturbances\(^2\)
  - 83% in clinical range total score CBCL; 75% internalizing scale\(^1\)

1Dorris 2008 2Dahl 1994
Other Symptoms Associated with Narcolepsy in Children

- Automatic behaviors
- Disturbed nocturnal sleep
- Periodic Limb Movements
- Parasomnias
- REM Sleep Behavior Disorder
  - May be presenting complaint\(^1\)
  - RBD in 3-17yo (N=15); 40% with EDS, 6% narcolepsy\(^2\)
- Obesity
- Precocious puberty\(^3\)

1Nevsimalova 2007 2Lloyd 2012 3Piazzi 2006
Features of Cataplexy in Children

- Knees, head/jaw most frequently affected\(^1\)
  - Eyelids, arms, trunk less frequent
- Falls in 43\%\(^1\)
- “Cataplectic facies”
  - “Semi-permanent” state facial (jaw/eyelid) weakness with superimposed occasional exacerbations in up to 1/3\(^1\)
  - Usually occurs close to clinical onset
  - Primarily affects the face, causing grimaces or jaw opening with tongue thrusting/protrusion
- Ptosis/blurred vision
- Slurred speech
- Gait disturbances
  - Low grade continuous LE hypotonia

\(^1\)Serra 2008
Serra L, et al 2008
Features of Cataplexy in Children

- May co-occur with complex motor behaviors at disease onset (hypotonia, dyskinesia, stereotypies)\(^1\)
- Emotional triggers less easily identified
- Patients may be less aware of/disturbed by symptoms
- May be misdiagnosed as “clumsiness”, atonic sx ("drop attacks"), conversion/malingering, syncope
- Video recording of attacks may be helpful

\(^1\)Piazzi 2011
Diagnostic Approach

- Clinical Diagnosis
- Polysomnogram and Multiple Sleep Latency Testing
- HLA testing
- Sleep log/Actigraphy
- CSF Orexin levels (Stanford)
- Rule out other causes of excessive daytime sleepiness
Multiple Sleep Latency Testing

- Protocol driven 5 nap opportunity
- Requires overnight polysomnography (at least 6 hours)
- Urine Drug Screen
- If not asleep, ends at 20mins, repeat every 2 hours
- Looking for Sleep Onset REM (2/5 or more)
- On average people fall asleep in 10-15min, narcoleptic patients usually fall asleep in <8min (often much shorter)
Challenges in Conducting and Interpreting MSLTs in Children

- Cannot be interpreted if sleep was insufficient or disturbed before MSLT
  - Sleep needs greater in children
- Cannot be done reliably when patient on stimulants or antidepressants
  - Problematic in comorbid ADHD, mood disorders
- Difficult to interpret with comorbid sleep disorders (OSAS, PLMD)
- Difficult to perform very young children and patients with comorbidities
- Hyperactivity, anxiety and “last nap effect” may impact MSL
Challenges in Conducting and Interpreting MSLTs in Children

- False-negative rate of 16% in patients with N+C (adults)
- False-positive rate of 10-25% in adult patients with sleep disorders such as OSAS
  - Adolescents with early school times, sleep deprivation
- Limited normative values in children
Pediatric Norms for Multiple Sleep Latency Test (MSLT)

Mean sleep latency varies more with Tanner Stage of sexual maturity rather than chronological age

Tanner Staging Affects MSLs

Carskadon 1981
Normative Values for MSL in Prepubertal Children

- Conflicting normative MSL (age related?):
  - MSL Tanner stage 1 (mean age 11.7 y): 19 ± 1.6 min\(^1\)
  - MSL Preadolescents (mean age 6.7 y): 23.7 ± 3.0 min\(^2\)
- Cannot use adult normative MSL data (10.4 ± 4.3 min\(^3\)) to assess pre-pubertal children
- Consider abnormal MSL in pre-pubertal children if MSL <10 min

\(^1\)Carskadon 1998; \(^2\)Gozal 2001 \(^3\)Littner 2005
SOREMs in Pediatric Narcolepsy

- 16% of 10th graders with early school start times had $\geq 2$ SOREMPs\(^1\)
- Among 10 children with narcolepsy (mean age 8.4yo, range 7.8-16.8 y)\(^2\)
  - MSL $< 10$ min and $\geq 2$ SOREMPs seen on initial MSLT in 6 children
  - MSL $< 10$ min and $\geq 2$ SOREMPs seen on 2nd MSLT in 3 children repeated mean 14 mths (range 3-28 mths) later
  - MSL $< 10$ min and $\geq 2$ SOREMPs seen on 3rd MSLT in 1 child

\(^1\)Carskadon 1998; \(^2\)Kotagal 1996
**Pediatric Prevalence of N-C**

- **Series 125 pediatric pts with EDS**: 16% Narcolepsy dx’ed; 85% N-C
  - 85% with SDB; 25% with PLMs
- **Retrospective study of 51 children with N+C**: Severity cataplexy increased with peri- and post-pubertal onset
  - 94%-100% cases post-H1N1 narcolepsy + cataplexy

1 Vendrame 2008 2 Aran 2010 3 Partinen 2011 4 Dauvilliers 2010
Therapy-Non Pharmacologic

- Avoid certain drugs (benzos, opiates, antipsychotics, alcohol)
- Napping/Sleep Hygiene
- Psychosocial support/Community Education
- Caution about driving/operating heavy machinery
Therapy - Pharmacologic

- Modafinil (Provigil), Armodafinil (Nuvigil)
- Mechanism of action unknown
- Stimulant
- Monitor blood pressure
- Side effects - headache/dry mouth/nausea/anorexia
- Rare: Stevens-Johnson syndrome
- Adult dose 200mg-400mg
82% of respondents describe their untreated condition as severe—significantly impacts daily activities. With treatment, only 22% report the same severe impact on function.

41% of respondents reports substantial improvement with prescription medications in their ability to do important activities of daily living. Another 45% say they receive some improvement in their function.
Stimulants

- Methylphenidate (Ritalin)
- Dextroamphetamine
- Amphetamine-dextroamphetamine (Adderall)
- Lisdexamfetamine (Vyvanse)
SSRI’s/Tricyclics for Cataplexy

- Escitalopram (Lexapro) 10mg to 20mg
- Venlafaxine (Effexor) 37.5mg to 150mg
- Fluoxetine (Prozac) 20mg to 80mg
- Clomipramine 10mg to 150mg
- Protriptyline 5mg to 60mg
Sodium Oxybate (Xyrem)

- Gamma hydroxybutyrate (GHB)
- 2.5-4.5 g (adult dose) at bedtime, repeat in 4 hours
- For narcolepsy with cataplexy
- Can cause confusion/severe sedation/coma
- High salt load
- Central Pharmacy
Sodium oxybate: a retrospective study
Mansukhani M, Kotagal S. Sleep Med 2012; 606-10

- 15 subjects below the age of 18 years
- Followed for 3-90 months (mean 33)
- The median Epworth Sleepiness Score improved from 18 to 12 (p = 0.01)
- Estimated cataplexy frequency decreased from 38 / week (median) to < 1 / week
- Side effects in 6/15 (40%) subjects:
  - Nausea, alteration in daytime behavior, postural tremor, blurring of vision, night awakenings, body aches, dizziness
Narcolepsy Websites

- http://narcolepsynetwork.org/
- http://www.wakeupnarcolepsy.org/
- http://www.narcolepsyl ink.com
- http://www.unitenarcolepsy.org
If olive oil is made from olives, what is baby oil made of? OMG!
Thanks!
Questions/Comments?