Sleep and Rasopathies

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Brief Overview of Pediatric Sleep

- Truly multidisciplinary
- A discipline better defined as the study of sleep and wakefulness

- Varies greatly through the life span and rapidly changing through childhood

- Pediatric normative values and even more so studies of subpopulations are greatly lacking
The basics

- **Definition**: Sleep is a reversible state of unresponsiveness
- **Function**: Undeniably necessary for
  - brain development
  - Behavioural / emotional function
  - memory consolidation
  - organ/organelle function
Sleep Homeostatic Process (s) & Circadian Process (c)

(Borbely and Achermann, 1999)
The Circadian Rhythm

- **Biological clock**
  - Present in most living organs
  - Functions autonomously

- Sets the ~ 24.3 hr rhythm in humans
  - Genes/proteins: Per, Cry, Clock & BMAL1

- Entrains to external cues daily for 24 hr day
  - Light is the most important cue
Synchronizing the Circadian Rhythm

- Melatonin
  - Regulated by the suprachiasmatic nucleus
  - Entrained by light

(Reiter, 1994)
Efficient sleep & disorders

- General:
  - Refreshed and awake for daytime activity
    - Occurs at desirable times
      - Circadian disorders
      - *Environmental/behavioral/psychiatric insomnias*
      - Hypersomnolence disorders
    - Free of disruptions (see later)
Sleep log
Actigraphy
Polysomnogram (PSG)
Hypnogram – normal child

(Stores, 2009)
Hypnogram
Abnormal

INSOMNIA HYPNOGRAM

INCREASED SLEEP LATENCY
Case 1

- 13 year old girl with Costello syndrome and longstanding history of sleep onset insomnia and co-sleeping
- History of controlled reflux, stable Chiari malformation without brainstem compromise. No overt signs of pain, sleep disordered breathing or leg movements
- Exam typical of Costello syndrome, but with overt anxiety, consistent with generalized anxiety disorder
Case 1

- Sleep study was not performed because of predicted intolerance of the procedure.
- GI did not believe nocturnal reflux as major cause, nighttime reflux medications adjusted empirically without improvement in sleep.

- **Treatment**: Melatonin failed, trial of SSRI (lexapro) with significant improvement in sleep onset and long periods sleeping alone.
Anxiety and insomnia

- Anxiety is a common feature of rasopathies, often comorbid with AD/HD
- Familial history of anxiety disorders is an important risk factor, as well as multiple medical encounters
- Insomnia is a very common feature of childhood anxiety disorders
Anxiety and insomnia

- Menifestation of anxiety around sleep
  - Early childhood:
    - “sleep phobia”, fear of dark, often together with separation anxiety (disorder)
    - Child’s temperament may mask it as sleep resistance
    - Co-sleeping is common and perpetuating
  - Later childhood:
    - Compensatory behaviours such as reading, texting, other activities instead of sleeping
Anxiety and insomnia

- **Daytime effects:**
  - Hypersomnia: excessive napping, or hyperactivity
  - Increased anxiety and worsening behaviours
  - Poor school performance

- **Treatment:**
  - Multidisciplinary approach, age dependent
    - Psychological assessment
    - Normalizing daytime behaviours
      - Limit sleeping in
      - Limit naps
      - Increase exercise
Anxiety and insomnia

- **Treatment**
  - **Sleep onset**
    - Bedroom is for sleep only
    - Bedtime rituals
    - Transitory objects in younger child
    - Limit excitement around bedtime
      - Calming activities can be personal and counterintuitive
    - Gradual weaning of parental presence
    - “Cold turkey” and letting child “cry it out”
Anxiety and insomnia

- Treatment
  - Medications:
    - As last resort
    - Melatonin: also has hypnotic effect
      - Dose: 0.3 mg – 9mg in teens
    - Anxiety specific medications: SSRIs
    - Rarely: tricyclic antidepressants, trazodone
  - Caveat:
    - Anxiety can be comorbid with ADHD and appropriate treatment can reverse insomnia, rarely stimulants are given at night with good control of insomnia
Behavioural insomnias

- **Sleep onset association:**
  - Child falls asleep only in parents presence

- **Limit setting type:**
  - Parent loses ability to soothen child to sleep

- **Sleep resistance:**
  - More common in intellectually normal children
  - Can be a result of perpetuating habits (co-sleeping, TV, games in room)
  - Behavioural treatment is effective but takes time
Chiari Malformation and Sleep In Children - Overview

- In general, in normal children, Chiari malformations do not cause sleep apnea, severe cases can.
- Chiari can be progressive and present later in childhood, yearly surveillance may be needed.
- Chiari can cause obstructive or central sleep apnea or both.
- In Costello syndrome, Chiari is form a different cause, from abnormal brain growth (Gripp, 2010).
  - May explain why Chiari decompression is not always helpful.
Efficient sleep & disorders

- **General goals:**
  - Refreshed and awake for daytime activity
    - Occurs at desirable times
      - Circadian disorders
      - Environmental/behavioral/psychiatric insomnias
      - Hypersomnolence disorders
  - Free of disruptions
    - Environmental/behavioral/psychiatric insomnias
    - Parasomnias
    - **Respiratory related arousals**
    - Movement related arousals
    - Systemic disease complications
Case 2

- 8 year old boy with Cardiofaciocutaneous syndrome and new onset disrupted sleep
- Past medical history:
  - Limited intellectual abilities
  - Frequent ear infections
  - Seasonal allergies
  - GE Reflux
- History of present illness:
  - New onset mouthbreathing, snoring and restless sleep, new onset daytime sleepiness and worsening school performance
- Family history:
  - Father with sleep apnea
Case 2

- **Physical exam:**
  - Mouthbreathing
  - Tonsils are enlarged 3+, restricted pharyngeal inlet

- **Overnight polysomnogram:**
  - Difficult study
  - Apnea index: 5/hr
  - Sleep efficiency: 65%
  - Wake time after sleep onset (WASO): 120 mins
  - O2 nadir: 94%
    - Obstructive sleep apnea
Case 2

- **Treatment:**
  - Adenotonsillectomy without complications

- **Follow up**
  - Resolution of sleep disruption in 6 weeks
  - Improvement in daytime performance in 8 weeks
Respiratory disruption: Obstructive sleep apnea

- **Definition:**
  - Limitation of airflow to lungs in presence of respiratory effort
  - In central apnea: no presence of effort

- **Prevalence of obstructive sleep apnea**
  - Approximately 2-3% of children
Obstructive sleep apnea

- **Risk factors:**
  - General
    - Genetic
    - Obesity
    - Hypotonia
  - Anatomical
    - Upper airway obstruction
    - Episodic/seasonal inflammation
    - Adenotonsillar hypertrophy
    - Redundant nasopharyngeal soft tissue
    - Anomalies: large tongue, retrognathia, depressed midface
  - Neurological
    - Diminished neuromuscular dilatation of airway
  - Exacerbating/complicating circumstances
    - reflux, asthma, heart disease
Obstructive sleep apnea

**Evaluation:**
- Assess severity of daytime function:
  - May not correlate with severity of OSA
  - May persist after treatment
- Evaluation of nighttime dysfunction:
  - Overnight polysomnogram is the gold standard
Obstructive sleep apnea: Overnight polysomnogram

- Normative values are difficult to establish
  - Especially in the obese and
  - Developmentally delayed

- **In general in children:**
  - Apnea hypopnea index > 1 is abnormal
  - 1-5: mild; 5-10: moderate; 10+ is severe
  - However:
    - Look at wake after sleep onset, sleep efficiency
    - REMs percent decrease
    - Respiratory parameters
Obstructive sleep apnea

Treatment

- **Goals:**
  - Restore nighttime normative sleep and respiratory function
  - Restore daytime wakefulness
  - **Eliminate chances of recurrence**

- **Medical:**
  - Sleep hygiene, psychological/medical causes of sleep disruption need to be addressed
  - Discourage permitting sleep position
  - Weight loss (5-10%)
  - Treat allergic symptoms
  - Facial, orthodontic devices
  - Positive pressure airway support
    - nCPAP, BiPAP
  - May use stimulants after compliance with nighttime treatment is ascertained
Obstructive sleep apnea

Treatment

- **Surgical:**
  - In general, tonsilloadenoidectomy is curative in majority of cases
  - Other surgical procedures to reduce redundant nasopharyngeal tissue
  - Advanced craniofacial reconstruction
  - Tracheostomy is rarely necessary

- **Follow up:**
  - Long term follow up is crucial
Obstructive sleep apnea

Complications

Neuropsychiatric
  Largely behavioural
    Rebellious
    Aggressive
    Hyperactivity (Beebe, 2006)

Academic effect less prominent
  Short term memory processes more vulnerable in younger children (Gozal, 2007)
Obstructive sleep apnea

- **Complications**
  - **Injury**
    - May be at risk for increased accidents
  - **Cardiovascular**
    - Inflammatory cytokines also elevated in children (Gozal, 2007)
    - Blood pressure increases are seen in children (Marcus, 1998)
    - May exacerbate cardiomyopathy in Costello Syndrome (Peppard, 2000)
Obstructive sleep apnea

- **Complications:**
  - **Neurological:**
    - Increased seizure frequency
    - Increased headaches (Bruni, 2004)
      - More likely as a function of daytime sleepiness
      - Multifactorial, complex
    - Cerebral blood flow velocity increases (Hill, 2006)
    - Intracranial pressure increases during apneas (Jennum, 1989)
Sleep apnea in Costello syndrome

- Della Marca, 2006

<table>
<thead>
<tr>
<th>Upper airways evaluation</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Nasal papillomata</td>
<td>+</td>
</tr>
<tr>
<td>Adenoid hypertrophy</td>
<td>−</td>
</tr>
<tr>
<td>Tonsils size</td>
<td>++</td>
</tr>
<tr>
<td>Macroglossia</td>
<td>+</td>
</tr>
<tr>
<td>PAS (mm)</td>
<td>10</td>
</tr>
<tr>
<td>MP-H (mm)</td>
<td>15</td>
</tr>
<tr>
<td>Mallampati class</td>
<td>2</td>
</tr>
<tr>
<td>Fujita’s class</td>
<td>3</td>
</tr>
</tbody>
</table>

“+” indicates presence; “−” indicates absence. For tonsils size: 0, tonsils not visible; +, tonsils visible; ++, mild tonsillar hypertrophy; ++++, moderate tonsillar hypertrophy; ++++, tonsils touching each other. Mallampati’s classes: 1, soft palate, fauces, uvula, and pillars seen; 2, soft palate, fauces, and uvula seen; 3, soft palate and base of uvula seen; and 4, soft palate not visible. Fujita’s classes: 1, only retropalatal narrowing; 2, retropalatal and retrolingual narrowing; 3, only retrolingual narrowing. PAS, posterior airways space; MP-H, mandibular planus—hyoid bone distance, measured on lateral Rx of the skull performed for cephalometry. Endoscopy: yes, performed; no, not performed.
Sleep apnea in Costello syndrome

- Della Marca, 2006
- 7/10 patients had OSA
- Causes:
  - Unlike in general population not adenotonsillar hypetrophy, nor were papillomata, but macroglossia
  - Fujita class III
Sleep apnea in Costello syndrome

- Della Marca, 2006

**Possible pathophysiology:**

- Decreased elastin and increased fibroblast deposition in soft tissue leading to collapsing nasopharyngeal wall (Haoki, 2005)

- Balooning of the muscle fibers leading to weakness (Mori, 1996)

- Adenotonsillectomy only helped 2/3 patients.
Sleep apnea in Noonan syndrome

Case Report

Life-Threatening Obstructive Sleep Apnea Caused by Adenoid Hypertrophy in an Infant with Noonan Syndrome

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1 IP Santé, 94200 Ivry sur Seine, France
2 Pediatric Pulmonary Département, AP-HP, Hôpital Armand Trousseau, 75012 Paris, France

Adenoidectomy is a commonly performed surgery in children, even though its effectiveness is still under investigation. However, in children with risk factors such as age under 3 years old, associated comorbidities, or severe obstructive sleep apneas, a high postoperative respiratory morbidity is possible. We report the case of a 15-month-old boy with Noonan syndrome and a complex clinical history, who presented with a life-threatening obstructive sleep apnea due to hypertrophy of the adenoids which resolved completely after adenoidectomy.
Efficient sleep & disorders

- **General goals:**
  - Refreshed and awake for daytime activity
    - Occurs at desirable times
      - Circadian disorders
      - Environmental/behavioral/psychiatric insomnias
      - Hypersomnolence disorders
  - Free of disruptions
    - Environmental/behavioral/psychiatric insomnias
    - Parasomnias
    - Respiratory related arousals
    - Movement related arousals
    - Systemic disease complications
Movement related arousals

- Epilepsy
  - Some mainly occur in sleep
    - Rolandic seizures
    - Occipital lobe seizures
    - Nocturnal frontal lobe seizures
    - Electrographic status epilepticus in sleep
- Periodic limb movement disorder
- Rhythmic movement disorders in sleep
- Tics
  - Very rarely seen in sleep
  - Simple tics
  - Do not significantly disrupt sleep
Case 3

- 5 year old girl with Neurofibromatosis type 1 and sleep maintenance insomnia and morning headaches

- Family history of restless legs syndrome

- History of restlessness in sleep, unlike other sibs without NF, mild snoring rarely
Case 2

- Suspected PLMD, ferritin 12 ug/ml, responded to oral iron in 1 week.

- On request, **overnight polysomnogram:**
  - Normal respiratory, sleep parameters
  - Periodic limb movement index: 17/hr
  - Periodic limb movement index with arousal: 1/hr

- **Diagnosis:**
  - Periodic limb movement disorder

- **Follow up:** continued iron supplements for 3 months, relapsed and remained well after restarting iron
Restless legs syndrome in Children

- A relatively recent disorder in pediatrics
- Common but severely underdiagnosed
- Difficult to identify in younger children
- Can be Primary
  - “Genetic”: one parent may have had RLS at some point in ~50% of cases
- Secondary: can be caused by many other illnesses, from spinal cord tumors to leukemia
- ~3% of children with growing pains may have restless legs syndrome
- It is an Unvoluntary movement disorder
  - Sensory stimulus, uncomfortable feeling or “urge” to move
    - Similar to Tics
  - Awake component of the movement spectrum:
    - Stereotypical movements, dystonia, myoclonic jerks
  - Asleep component
    - Periodic limb movement in sleep (PLMS)
Adult Restless Legs Syndrome

Definition

International RLS study group

**Essential diagnosis**

- Urge to move limb with or without unpleasant sensation in legs +/- arms
- Urge begins at rest
- Urge is relieved by movement, stretching, as long as the movement continues
- The urge must be worse at night
Pediatric Restless Legs Syndrome - Definitions

‘Definite’ pediatric restless legs syndrome
Meets adult ‘essential’ criteria and child can relate the discomfort in his own words or
Meets adult essential criteria and 2 of the 3:
1. Sleep disturbance for age
2. Biological parents with RLS
3. Polysomnographically documented periodic limb movement index above 5
Periodic limb movement in sleep
Periodic limb movement disorder (PLMD) in Children

Definitions

- PLMI>5/hr on PSG
- Restless sleep observed by co-sleeper
- Excessive daytime somnolence is rare, sleepiness is seen frequently
- Lack of sleep disordered breathing or medication effect
RLS
Epidemiology

- RLS
  - Less common in Asian populations, except Korea
  - RLS in general population: 5-10%
  - RLS: 8-17 years: 2%
  - Clinically significant RLS 8-11 yrs: 0.5%
  - 12-17 yrs: 1%
PLMS
Epidemiology

- PLMS
  - Abnormal in pediatrics: \( \geq 5/\text{hr} \)
  - Abnormal adults: \( \geq 15/\text{hr} \)

- Increases with age
  - After 50 years mean PLMI is over 20/\text{hr}
  - 31% over 50 years had PLMI over 10/\text{hr}
RLS/PLMD and Iron

- Mussio-Fournier and Rawak, 1940: RLS is a neurological disorder exacerbated during pregnancy
- Ekbom, 1945: association of RLS and iron deficiency
- Sun, 1998: low Ferritin cut off of: 50 mcg/L, Fe supplementation-Ferritin-Symptoms
- Early, 2000: low CSF ferritin and high transferrin with normal serum ferritin and transferrin
- Chervin, 2002: Association of ADHD/PLMD/RLS
- Simakajornboon, 2003: Fe supplementation for PLMD in children for 3 months
- Picchietti; Konofal; Oner, 2007: ADHD and/or PLMD/RLS and Fe deficiency
RLS/PLMD and Dopamine

- Akpinar, 1982: Levadopa therapy for RLS
  - Adults
  - 1st DBPC trial for RLS: Kaplan, 1993
  - 1st DBPC trial for PLMD: Walker, 1996

Children

- Open label for RLS/PLMD: Walters, 2000: PLMD in children with ADHD respond to dopaminergic medications with improvement in ADHD
RLS/PLMD Diagnosis

- **RLS:**
  - Clinical interview: scales
  - May use PSG as supportive evidence in
    - Children
    - Doubtful in those under 40 years of age
  - Treatment response

- **PLMD:**
  - Co-sleeper or parent interview
  - PSG with limitations, may need more than one night to capture increased leg movements (see next slide)
  - Actigraphy not established
  - Treatment response can also be supportive evidence
PLMS in RLS
PSG in Children (Picchietti, 2009)

Nonpharmacological:
- Avoid triggers: alcohol, drugs, caffeine, heavy exercise
- Light exercise may be effective
- Pressure stockings
- Anecdotal: cooling of spine/legs, etc.
- Fall asleep before peak symptoms

Pharmacological:
- Elemental iron is first line (3-6 mg/kg/day)
- Neurontin
- Dopaminergic medications with caution
  - augmentation

**Figure 2**—Periodic limb movements in sleep (PLMS) index (number/h) over the first 2 nights in cases with 5 or more PLMS per hour on at least 1 night (n = 15).
RLS/PLMD
Treatment

- **Nonpharmacological:**
  - Avoid triggers: caffeine, alcohol, heavy exercise, drugs (SSRI)
  - Timing of sleep in RLS
  - Exercise
  - Pressure stockings

- **Pharmacological:**
  - Elemental iron (3-6 mg/kg/day) + vitC
  - Neurontin
  - Dopaminergic medications
    - Beware of augmentation
Movement related arousals

- Epilepsy
  - Some mainly occur in sleep
    - Rolandoic seizures
    - Occipital lobe seizures
    - Nocturnal frontal lobe seizures
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- **Rhythmic movement disorders in sleep**
- Tics
  - Very rarely seen in sleep
  - Simple tics
  - Do not significantly disrupt sleep
Rhythmic movement disorders in sleep

- Very common in normal and even more common in delayed children, many types
  - Usually do not interfere with sleep quality
- In infants:
  - Head banging
- In young children:
  - Body rocking

- Della Marca, 2006
- **Costello syndrome:**
  - Rhythmic tongue movements
Epilepsy and Costello syndrome

- **Definition of a seizure:** abnormal paroxysmal event accompanied by abnormal EEG discharge
- **Definition of epilepsy:** two or more seizures

- Abnormal EEG in CS: ~30% (Okamoto, 1993)
- Seizures in CS: 20% (Delrue, 2003)
Leschziner, 2013

- PSQI and ESS were filled out by 100 adult patients
- ESS suggested hypersomnolence: 21%
- PSQI suggested poor sleep: 70%
- PLMD: 54%
- Sleep disordered breathing: 45%
- Morning confusion: 11%

- No circadian abnormalities
### Sleep In Neurofibromatosis 1

- Leschziner, 2013

### TABLE II. Responses to Questions 5a to 5i of the PSQI, Describing How Often the Subject Has Difficulty Sleeping Due to the Symptom in the Last Month

<table>
<thead>
<tr>
<th>Symptom causing trouble sleeping</th>
<th>Not during past month</th>
<th>Less than once per week</th>
<th>Once or twice per week</th>
<th>Three or more times per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannot sleep within 30 min</td>
<td>15</td>
<td>24</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td>Wake in night or early morning</td>
<td>10</td>
<td>19</td>
<td>24</td>
<td>47</td>
</tr>
<tr>
<td>Get up to use bathroom</td>
<td>28</td>
<td>19</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Cannot breathe comfortably</td>
<td>82</td>
<td>6</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Cough or snore loudly</td>
<td>75</td>
<td>7</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Feel too cold</td>
<td>67</td>
<td>17</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Feel too hot</td>
<td>44</td>
<td>15</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Bad dreams</td>
<td>59</td>
<td>23</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Pain</td>
<td>51</td>
<td>14</td>
<td>10</td>
<td>25</td>
</tr>
</tbody>
</table>
Sleep In Neurofibromatosis 1

- High PSQI score correlated with unemployment
  - Johnson, 2005
- Similar study in children with NF1
  - Poor sleep correlated with behavioural and cognitive effects
Efficient sleep & disorders

- **General goals:**
  - Refreshed and awake for daytime activity
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    - Movement related arousals
    - Systemic disease complications
Hypersomnolence disorders - Bird-eye view

- Secondary hypersomnolence:
  - Behavioural insomnia
  - Medical conditions
  - Medications/drugs
  - Sleep apnea, restless legs syndrome, PLMD, etc.

- Primary hypersomnolence:
  - Idiopathic hypersomnolence
  - Narcolepsy (primary or secondary)
Assessment of daytime sleepiness - Questionnaires

- Modified Epworth sleepiness scale
  - In African American children 2-18 years of age correlated with mean nocturnal SaO2
  - In Chinese children between 3-18 years of age correlated with AHI
Assessment of daytime somnolence

- PSG and Multiple sleep latency test (MSLT)
  - PSG to rule out sleep apnea
  - Multiple sleep latency test
    - to quantify somnolence
    - Differentiate idiopathic hypersomnolence from narcolepsy
  - SOREMPs
  - Normative for 6 yrs and under is not available
Closing remarks

- Sleep disorders are common and part of the phenotype in all rasopathies.

- The causes can be the common disorders but nuances and syndrome specific disorders and causes of sleep problems are slowly emerging.