Pathogenesis of nocturnal enuresis

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Disclaimer:
• Teaching and research collaboration with Ferring
• CI in solifenacin and mirabegron studies (Astellas)
OUTLINE

✓ Pathogenesis of nocturnal enuresis

• Terminology
• The three factor model
  • Sleep – new understanding?
  • Reduced bladder capacity
  • Nocturnal polyuria
• Genetics
Nocturnal enuresis pathogenesis
- Simple model still holds water

Nocturnal enuresis is caused by a mismatch between nocturnal urine volume and nocturnal bladder capacity

+ Inability to awaken when this occurs
The role of sleep

- Are they “deep sleepers” ??
Nocturnal enuresis
- Conventional sleep studies

Nørgaard et al, 1989:
Sleep EEG is normal (manual scoring). Enuresis occurs in all sleep stages.

Hunsballe et al, 1997:
No difference in EEG by manual scoring. Tendency to more delta band energy (computer).

Neveus et al, 1998:
Enuresis occurs predominantly in nonREM sleep. No correlation between enuresis events and EEG.
Arousal and Nocturnal Enuresis

*Kirk et al, 1996:* Normal children are also unable to wake up when the bladder is overfilled (< 12 yrs).

*Wolfish et al, 1998:* 61% of normal children were unable to wake up to acoustic stimuli (120 dB).

Fewer enuretic children (9 vs. 39%) were able to wake up to acoustic stimuli.

*Yeung et al, 2010:* “Our results suggest an interaction between bladder overactivity and brain arousability” (“bladder–brain dialogue”).

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**Table 1. Sleep Architecture and the Cortical Arousal Index in Children with Enuresis and Normal Controls.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Nocturnal Enuresis (N=35)</th>
<th>Normal Controls (N=21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>9.5</td>
<td>10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep stage (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>45</td>
<td>NS</td>
</tr>
<tr>
<td>Light (stages 1 and 2)</td>
<td>57</td>
<td>50</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Deep (stages 3 and 4)</td>
<td>26</td>
<td>30</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Rapid eye movement</td>
<td>16</td>
<td>20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cortical arousal index†</td>
<td>6.32</td>
<td>3.90</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* NS denotes not significant.
† The cortical arousal index ranges from 1.12 to 12.48, with a higher score indicating more frequent cortical arousals.
Sleep and PLMS
- The new black?

_Dhondt et al, J Urol, 2009:_
Periodic Limb Movement during Sleep and increased cortical arousal is common in treatment resistant NE.

_Dhondt et al, ICCS 2014:_
PLMS is associated with reduced QoL
PLMS/Cortical arousal is associated with reduced daytime performance
6 months desmopressin tx in pts with NP increases daytime performance.

The role of sleep – a paradigm shift?

- Are they “light sleepers”?
- With poor sleep quality?
- With day-time consequences?
The role of the bladder

Reduced bladder capacity (MVV):

MVV < 65% of EBC

EBC = 30 x (age + 1) (ml)
NB: Is correct only if first morning voided volume is disregarded!!

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal bladder capacity</th>
<th>Reduced Bladder capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>180 ml</td>
<td>&lt; 117 ml</td>
</tr>
<tr>
<td>6 years</td>
<td>210 ml</td>
<td>&lt; 136 ml</td>
</tr>
<tr>
<td>7 years</td>
<td>240 ml</td>
<td>&lt; 156 ml</td>
</tr>
<tr>
<td>8 years</td>
<td>270 ml</td>
<td>&lt; 175 ml</td>
</tr>
<tr>
<td>9 years</td>
<td>300 ml</td>
<td>&lt; 195 ml</td>
</tr>
<tr>
<td>10 years</td>
<td>330 ml</td>
<td>&lt; 214 ml</td>
</tr>
<tr>
<td>DAY</td>
<td>NIGHT</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>DAY 1</td>
<td>Cystoscopy Suprapubic cat.</td>
<td></td>
</tr>
<tr>
<td>DAY 2</td>
<td>Urodynamic investigation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overnight monitoring</td>
<td></td>
</tr>
<tr>
<td>DAY 3</td>
<td>Overnight monitoring</td>
<td></td>
</tr>
<tr>
<td>DAY 4</td>
<td>Provocative tests cystometries</td>
<td></td>
</tr>
<tr>
<td>DAY 5</td>
<td>Urodynamic investigation</td>
<td></td>
</tr>
</tbody>
</table>

Nocturnal bladder function in enuresis

Jens Peter Norgaard, Doctoral thesis, AU, 1992
Nocturnal bladder function in enuresis

Only 2/32 had reproducible bladder instability

Significant correlation between enuresis volume and daytime bladder capacity

Enuresis episode could be provoked in any sleep stage
# Daytime bladder function in enuresis

<table>
<thead>
<tr>
<th></th>
<th>Non (N=55)</th>
<th>Partial (N=15)</th>
<th>Full (N=10)</th>
<th>Anova</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mic. freq.</td>
<td>5.1 ± 1.5</td>
<td>5.2 ± 1.4</td>
<td>5.2 ± 1.4</td>
<td>N.S.</td>
</tr>
<tr>
<td>AVV</td>
<td>112 ± 4.7</td>
<td>131 ± 11</td>
<td>143 ± 12</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Morn. mict</td>
<td>157 ± 77</td>
<td>259 ± 78</td>
<td>278 ± 79</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>MVV/age</td>
<td>0.69 ± 0.3</td>
<td>1.02 ± 0.4</td>
<td>1.00 ± 0.2</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

Case - Michael, 7 years
- a new enuresis subtype?

• Healthy, normal development. Familial history of enuresis.
• No daytime LUT symptoms.
• Phys ex: normal, Normal urinalysis.
• Desmopressin 240 mcg melt: no effect.

Bladder diary:
• MVV: 250 ml; (65% MVVage = 156 ml)
• No desmo: Nuvol: 320 ml (NP = 312 ml)
Michael on 240 mcg desmo melt

<table>
<thead>
<tr>
<th></th>
<th>Mandag</th>
<th>Tirsdag</th>
<th>Onsdag</th>
<th>Torsdag</th>
<th>Fredag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tør nat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>På toilet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Våd nat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sæt X</td>
<td>ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blevægt often</td>
<td></td>
<td>Blevægt morgen</td>
<td>Vandlading morgen</td>
<td>Blevægt often</td>
<td>Blevægt morgen</td>
</tr>
<tr>
<td>50 g</td>
<td>130 g</td>
<td>100 ml</td>
<td>50 g</td>
<td>200 g</td>
<td>100 ml</td>
</tr>
<tr>
<td>(b)</td>
<td>(c)</td>
<td>(d)</td>
<td>(b)</td>
<td>(c)</td>
<td>(d)</td>
</tr>
<tr>
<td>Udfyldes af lægen</td>
<td>Udfyldes af lægen</td>
<td>Udfyldes af lægen</td>
<td>Udfyldes af lægen</td>
<td>Udfyldes af lægen</td>
<td></td>
</tr>
<tr>
<td>Nat-urinvolumen = (c - b) + α + d</td>
<td>Nat-urinvolumen = (c - b) + α + d</td>
<td>Nat-urinvolumen = (c - b) + α + d</td>
<td>Nat-urinvolumen = (c - b) + α + d</td>
<td>Nat-urinvolumen = (c - b) + α + d</td>
<td></td>
</tr>
<tr>
<td>= 180 ml</td>
<td>= 250 ml</td>
<td>= 220 ml</td>
<td>= 160 ml</td>
<td>= 200 ml</td>
<td></td>
</tr>
</tbody>
</table>
Defect circadian bladder rhythm?
- normal day-time bladder capacity (MVV)
- isolated low nocturnal bladder capacity

Effect of reduced eNBC on desmopressin response

The role of nocturnal polyuria

Poulton, Lancet, 1952


Rittig et al, J Urol, 2010
Role of nocturnal polyuria
- definition

**ICCS Consensus:**
Definition based upon expected bladder capacity (ICCS, 2006):
\[ \text{Nuvol} > 130\% \text{ of MVV}_{\text{age}} \]

**Population based definition:**
\[ \text{Nuvol} = 20 \times (\text{age} + 9) \]

Nocturnal polyuria - mechanisms

- Genes
- Sleep, light activity, food
- Intrinsc circadian regulation

- AVP
- ANP
- Aldo
- AgII

- Hormones
- Renal factors

- Tubular reabsorption
- Urine concentration
- GFR
- Central blood volume
- Blood pressure

- Hemodynamic factors
- Renal factors
p-AVP during sleep

Conclusion:
Lower p-AVP levels during wet nights in patients with good response to dDAVP.


Rittig et al, J Urol, 2008
Sleep deprivation causes nocturnal polyuria

<table>
<thead>
<tr>
<th>Day</th>
<th>Night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis (mL/kg/h)</td>
<td><img src="image1.png" alt="Graph" /></td>
</tr>
<tr>
<td>U-osm (mOsm/kg)</td>
<td><img src="image2.png" alt="Graph" /></td>
</tr>
<tr>
<td>E-Na (mmol/kg/h)</td>
<td><img src="image3.png" alt="Graph" /></td>
</tr>
<tr>
<td>FE-Na(%)</td>
<td><img src="image4.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

- * denotes significant difference between day and night
Nocturnal polyuria - mechanisms

- Genes
- Sleep, light, activity, food
- Intrinsic circadian clock
- AVP
- AgII
- Aldo
- ANP
- Hormones
- Hemodynamic factors
- Blood pressure
- Central blood volume
- Urine concentration
- Renal factors
- Tubular reabsorption
- GFR
- Nocturnal polyuria

Central blood volume
Circadian regulation - could be a central pathogenic factor
Genetics aspects of enuresis
- Hunting for the enuresis gene
Genetic aspects of enuresis
- Linkage analysis

- Linkage to 4q, 8q, 12q, 13q, and 22q.

- Locus heterogeneity in nocturnal enuresis.

- More loci exists as families have been reported with no linkage in these regions.
Genetic aspects of enuresis
- Hunting for the enuresis gene
Take home messages

- Our understanding of NE pathogenesis is still developing...
- The role of deep sleep has been challenged.
- Circadian rhythm of bladder capacity is in focus (isolated low nocturnal bladder capacity).
- The increased understanding of pathogenesis has provided a basis for treatment
- Possible development of new treatments
Collaborators

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