Enuresis and sickle cell disease

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A scheme for thinking about wetting in children

WETTING +/- LUT SYMPTOMS

NIGHT
ENURESIS
DAY
DAYTIME INCONTINENCE (+/- ENURESIS)

MENORRHAGIA

MONOSX
WAKEABILITY
VASOPRESSIN

PATHOLOGICAL
FUNCTIONAL
KEEPING
STORAGE PHASE
VOIDING PHASE
ANATOMICAL
NEURO-PATHIC

STACCATO FRACTIONATED/
INTERRUPTED

BLADDER EMPTYING
COMPLETE
INCOMPLETE
COMPLICATED/UTI/CONSTIPATION
OTHER

Filling and emptying cycle of bladder

1. Bladder fills
Detrusor relaxes
2. First desire; 1/2 full
3. Urination inhibited until right time and place.
4. Micturition
Detrusor contracts
Sphincter relaxes
 voluntary control

Prevalence of primary nocturnal enuresis among different countries

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Prevalence of primary nocturnal enuresis with age and severity


Sickle cell disease and enuresis


Enuresis; ECH (n=48) Cheh, Brooke, Gathercole, Watanabe

Figure 4. Frequency of night time bed-wetting

Figure 2. Prevalence of enuresis and nocturia among children and young adults with sickle cell anemia, from ages 6 to 20 years.
Other sleep components

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Differences between enuretic and healthy children in sleep evaluation with SOGC scales</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enuretic: 57 (8-21)</td>
</tr>
<tr>
<td>DMG</td>
<td>14.92±3.25</td>
</tr>
<tr>
<td>TMD</td>
<td>5.65±3.32</td>
</tr>
<tr>
<td>AF</td>
<td>6.93±2.08</td>
</tr>
<tr>
<td>SWFD</td>
<td>14.63±4.36</td>
</tr>
<tr>
<td>DOWS</td>
<td>10.96±4.43</td>
</tr>
<tr>
<td>TSV</td>
<td>5.16±1.92</td>
</tr>
<tr>
<td>Total</td>
<td>59.51±12.05</td>
</tr>
</tbody>
</table>

DMG disorder is initiating and maintaining sleep, TMD sleep breathing disorder, AF disorder of arousal, SWFD sleep-wake transition disorder, DOWS disorder of excessive somnolence, TSV nocturnal polyphasicity


Mechanisms of action: alarms

- Alarm is triggered when urine comes into contact with sensor
- Body-worn and bedside systems
- Behavioural conditioning mostly based on reward (operant) but also negative effects (aversive)

Mechanisms contd

- In successful alarm treatment
  - 2/3 achieve dryness whilst sleeping through the night
  - 1/3 have nocturia as a means of achieving dryness
- Alarms increase
  - Nocturnal bladder capacity
  - Daytime bladder capacity

Other sleep components

- Adenotonsillectomy improves symptoms of nocturnal enuresis (n=107) in children with OSA
  - Cure 61.4%
  - Improvement 22.8%
    - Basha S Laryngoscope. 2005 Jun;115(6):1101-3
- Children with SCD have high rates of disordered sleep including high rates of OSA (10-79%)

PNE and Impaired Arousal Response

- Elevated arousal threshold associated with a reduced prepulse inhibition (PPI) of startle in enuretic patients, suggesting a dysfunction in the pontine tegmentum
  - Gnitz EM, 1999
  - Wolffa H, 1999
  - von Gontard, 2001
- Arousal disturbance and reduced ability to inhibit bladder activities and micturition during sleep may both originate from a common dysfunction in the brainstem

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Do alarms work? Cochrane review

• Alarms are more effective than control in RCTs

• Two thirds of children become dry during alarm use

• One half remain dry after treatment

Glazener CMA. Cochrane Review, Feb 2003

Nocturnal polyuria

• Nocturnal urine volume > 130% x Expected Bladder capacity (EBC)

• EBC = Age (years) x 30mls + 30mls
  – (Age/years +1) X 30mls
  – Hjalmas formula

Glazener CMA. Cochrane Review, Feb 2003

Diurnal variation in plasma vasopressin and urine production

Vasopressin levels pg/ml

- Non enuretic child
- Enuretic child

Urinary excretion rate ml/hr

- Non enuretic child
- Enuretic child

Using Desmopressin

Desmopressin safety; clinically sig hyponatraemia

• Desmospray; licence for enuresis removed.
• Desmopressin can be used for as long as symptoms persist - reassess every 3 months (minimum one week off treatment)
• Desmopressin does not suppress endogenous vasopressin after 24/52 tmt Knudsen UB Urol Res 1991

Desmopressin

• Analogue of vasopressin (anti diuretic hormone)
• Potent antidiuretic
• Concentrates urine
• No direct bladder effect
• No direct cardiovascular action

Desmopressin safety; clinically sig hyponatraemia

• Medline search 1972-2006
• Post marketing safety data Ferring 1972-2005
• Ten million children used desmopressin world wide
  – Approx 5 million intranasal (intro 1972)
  – Approx 5 million oral formulation (intro 1987, melt 2005)
• Sig hyponatraemia= headache, nausea, vomiting, altered consciousness, seizure due to water intoxication

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Clinically sig hyponatraemia; desmopressin

- Intranasal preparation
  - 172 reports
  - 145 PMS
  - 27 additional Medline
- Pharmacokinetics
  - 6-24 hours (prolonged effect in some children) Dehoorne J Urol 2006
- Oral preparation
  - 6 reports
  - Duration of action is dose dependent with optimal dose giving 8-10 hours duration

Desmopressin in SCD

- Only one study comments on its use in very small numbers; in six out of ten patients it was successful
- No contraindication to its use as long as child can adhere to fluid restriction limitations

Safe use of desmopressin

- Fluid restriction before bed
  - Sporting activity at night
- Caution coexistent conditions
  - Cystic fibrosis
  - DaV
  - ADHD
  - Prader Willi
- Supervision of younger children
- Caution with prodromal symptoms; headache, nausea, vomiting
  - Thumfart J Urol 2005

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Reduced nocturnal bladder capacity

- Small bladder (monosymptomatic)
- Overactive bladder (OAB/non-monosymptomatic)
  - Daytime LUT symptoms in addition to enuresis
  - Nocturnal OAB

Urgency: overwhelming desire to pass urine +/- incontinence. Counteracted by various holding manoeuvres including Vincents Curtsey.

Management of OAB

<table>
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<th>Bladder retraining</th>
<th>Drug therapy</th>
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<tr>
<td>Regular fluid intake</td>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Timed regular voiding</td>
<td>- Oxybutynin</td>
</tr>
<tr>
<td>Correct toileting position</td>
<td>- 1-2mg/day</td>
</tr>
<tr>
<td>Charts</td>
<td>- XL formulation</td>
</tr>
</tbody>
</table>

- Tolterodine
  - 1-2mgbd
  - XL prep
- Titrate slowly
- R constipation first

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Bladder capacity in SCD

- Only one study addresses bladder capacity in SCD +/− enuresis n=31
  - Two matched groups all with SS, Jamaica
  - 8-13 years
  - Overnight urinary osmolality and volumes not statistically different
  - Enuretics had smaller FBC (ave 291 vs 395)p 0.005

  Readett D Archives of Disease in Childhood 1990; 65: 615-618

Causative factors

- Attribution by parents:

  Jordan SS; Mississippi 2005

New challenges in managing enuresis in SCD

- Establish epidemiology including severity and current classifications
- Establish underlying mechanisms specific to SCD
  - Sleep disorders
  - Polyuria
  - Bladder parameters
- Establish effective management pathways for SCD + enuresis
  - Desmopressin sensitivity
  - Alarm response
  - Combinations
Thank you