Wie corticotropin releasing factor signaling
die Harnblase und den Dickdarm steuern kann

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EBDS – a multi-center controlled trial of standard treatment, placebo, oxybutynin, bladder training, and pelvic floor training, in children with functional incontinence

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Clinical classification in urge syndrome and dysfunctional voiding

In each branch, randomized interventions plus standard treatment

Before and after treatment:
- urodynamic studies
- Achenbach’s CBCL, fecal soiling questionnaire

Outcome: urinary continence with/without urinary tract infection
Comorbidity *versus* treatment outcome

After treatment, fecal incontinence dropped from 32% to 21% (*p*<0.02). Fecal incontinence did not influence treatment outcome.


After treatment, abnormal total behavior problem scores (18%) decreased to the level of the normative population. These scores did not correlate with treatment outcome.

Incontinence during treatment and follow up
Kaplan-Meier survival estimates

URGE SYNDROME
- Daytime wetting, n=92
- Night-time wetting, n=87

DYSFUNCTIONAL VOIDING
- Daytime wetting, n=92
- Night-time wetting, n=91

Prevalence of wetting, %
Follow up, months

p=0.08
p<0.001

Slow and steady resolution of incontinence during treatment and follow up.

Abnormal urodynamic patterns before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Urge syndrome (n=97)</th>
<th>Dysf. voiding (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detrusor overactivity</td>
<td>Before 33%</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>After 27%</td>
<td>56%</td>
</tr>
</tbody>
</table>

No significant change in pattern prevalence after treatment. After treatment, the abnormal patterns occurred *de novo* in >50%.

EBDS results: conclusions

Clinical diagnosis is a poor predictor for abnormal urodynamic patterns, and abnormal patterns occur *de novo* after treatment. It follows that cure was not linked to the interventions, aimed at abnormal urodynamics, but to standard treatment.

Standard treatment – explanation and remedial teaching – is a form of cognitive-behavioral therapy.

The gradual resolution of incontinence – a learning curve – is typical for response to cognitive-behavioral therapy.

EBDS: unexplained characteristics

Gender specificity (girls/boys ratio 3.7)
Variations of urodynamic patterns over time
Co-existence of urinary and fecal incontinence
Response to cognitive-behavioral therapy

EBDS: unexplained characteristics

Gender specificity (girls/boys ratio 3.70)
Variations of urodynamic patterns over time
Co-existence of urinary and fecal incontinence
Response to cognitive-behavioral therapy

In rodents, these characteristics are all hallmarks of the response to social stress, mediated by the corticotropin (CRF) signaling pathway: models for functional incontinence in children?
Topography of corticotropin releasing factor (CRF) signalling pathways

BN: Barrington's nucleus
LC: Locus coeruleus
PAG: para-aqueductal gray matter

CRF: a major neurotransmitter in Barrington's nucleus

[a] Rat brain section at level of Barrington's nucleus showing CRF-immunoreactive neurons (blue) and neurons labeled retrogradely from the lumbosacral spinal cord (brown).
[b] Lumbosacral spinal cord section with dense CRF-immunoreactive terminal fields (blue) within the parasympathetic motor neuron regions.

Social stress alters bladder urodynamics

[a] Control rat cystometry

[b] Cystometry in rat exposed to resident-intruder stress, with numerous non-voiding contractions, prolonged intermicturition intervals, and greater bladder capacity

# Social stress in rodents: response of bladder/colon

<table>
<thead>
<tr>
<th>STUDY CONTROLS</th>
<th>SEX</th>
<th>RODENT</th>
<th>STRESS</th>
<th>NUMBER BLOTS</th>
<th>BLOT SIZE</th>
<th>NUMBER PELLETS</th>
<th>COLONIC TRANSIT</th>
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</thead>
<tbody>
<tr>
<td>*Wood 2009</td>
<td>M</td>
<td>rat</td>
<td>Social defeat</td>
<td>decrease</td>
<td>increase</td>
<td>–</td>
<td>–</td>
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<td>Kiddoo 2006</td>
<td>M</td>
<td>rat</td>
<td>CRF agonist</td>
<td>decrease</td>
<td>increase</td>
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<tr>
<td>*Larauche 2009</td>
<td>M</td>
<td>rat</td>
<td>CRF agonist</td>
<td>–</td>
<td>–</td>
<td>increase(^1)</td>
<td>decrease(^1)</td>
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<tr>
<td>*Larauche 2009</td>
<td>M</td>
<td>mouse</td>
<td>CRF agonist</td>
<td>–</td>
<td>–</td>
<td>increase(^1)</td>
<td>decrease(^1)</td>
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<tr>
<td>Klausner 2005</td>
<td>F</td>
<td>rat</td>
<td>CRF</td>
<td>increase(^2)</td>
<td>decrease(^2)</td>
<td>–</td>
<td>–</td>
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</tbody>
</table>

\(^*\) mRNA expression and immunoreactivity in Barrington's nucleus

\([1]\) dose-dependent effects

\([2]\) reversible with CRF antagonist (astressin 1)
Models for responses of bladder (and colon) to social stress, mediated by the CRF signaling pathway

Gender specificity (girls/boys ratio 3.70)
Variations of urodynamic patterns over time
Co-existence of urinary and fecal incontinence
(Response to cognitive-behavioral therapy)

In rodents, stress-provoked responses of bladder (and colon) are gender-specific, and mediated by the CRF signaling pathway: homologous models are available, for urge syndrome in girls, and Hinman's syndrome in boys.
Segmental topography S1-S2 for motor innervation of detrusor and urethral sphincter/pelvic floor

Kontinenzschulung im Kindes- und Jugendalter

Protocoll zur Evaluation der Kurzschulung

Find indicators for social stress
Document wetting not for just 3 days, but continuously
Find the link for wetting and stress
**European Bladder Dysfunction Study, branch II**

Clinically diagnosed dysfunctional voiding (n=105)

<table>
<thead>
<tr>
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<th>standard treatment</th>
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<tbody>
<tr>
<td>Mnths</td>
<td>T0</td>
<td>T6</td>
</tr>
<tr>
<td>Girls</td>
<td>42</td>
<td>40</td>
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<tr>
<td>Boys</td>
<td>8</td>
<td>6</td>
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<tr>
<td>Total</td>
<td>50</td>
<td>46</td>
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Girls/boys ratio 3.7
## European Bladder Dysfunction Study branch I
Clinically diagnosed urge syndrome, branch I (n=97)

<table>
<thead>
<tr>
<th>Mnth</th>
<th>T0</th>
<th>T6</th>
<th>T18</th>
<th>T0</th>
<th>T6</th>
<th>T18</th>
<th>T0</th>
<th>T6</th>
<th>T18</th>
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<tbody>
<tr>
<td>Girls</td>
<td>20</td>
<td>17</td>
<td>12</td>
<td>22</td>
<td>21</td>
<td>18</td>
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<td>27</td>
</tr>
<tr>
<td>Boys</td>
<td>13</td>
<td>12</td>
<td>11</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>6</td>
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</tr>
<tr>
<td>Total</td>
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<td>24</td>
<td>30</td>
<td>29</td>
<td>25</td>
<td>34</td>
<td>34</td>
<td>31</td>
</tr>
</tbody>
</table>

Girls/boys ratio 3.7
Functional incontinence: two-tiered approach

EBDS results suggest that 50% of children with functional incontinence can be cured with explanation and ‘remedial teaching’ – the main components of standard treatment.


When this approach fails, a more continuous assessment of incontinence is indicated, as well as a full assessment of psychiatric co-morbidity.