Renal Tubular Disorders
Case discussions
Detlef Bockenhauer
Objectives

• Physiology of sodium and water transport
• Clinical consequences of disturbed transport
Case 1

- 11-months old girl referred for assessment of hyponatraemia, first noted incidentally during investigations for viral illness and confirmed several times subsequently
- Examination: well perfused, BP: 90 mmHg

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<tr>
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<tbody>
<tr>
<td>Sodium</td>
<td>121</td>
<td>45</td>
<td>mmol/l</td>
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<tr>
<td>osmolality</td>
<td>249</td>
<td>252</td>
<td>mOsmol/kg</td>
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<tr>
<td>Creatinine</td>
<td>0.017</td>
<td>&lt;1.0</td>
<td>mmol/l</td>
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Diagnosis?

- Too much water?
- Too little salt?
Case 1

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• Examination: well perfused, BP: 90 mmHg

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Key message

Sodium is reabsorbed to preserve intravascular volume and in response to renal perfusion

Kidney does not sense or detect serum sodium concentration
SIADH
Syndrome of inappropriate ADH

Key features:
- Hyponatremia
- Hypoosmolality
- Urine osmolality > 100 mosmol/kg
- Patient clinically euvoletic
Family History

- Mother and maternal grandmother were known to have had hyponatraemia. Maternal uncle has developmental delay and recurrent hyponatraemia (often with seizures).
- Mum and grandmother “don’t drink”
Diagnosis?

- Nephrogenic Syndrome of inappropriate antidiuresis
- X-linked inherited
- Gain-of-function in AVPR2: R137C/L
- Females usually less affected
<table>
<thead>
<tr>
<th></th>
<th>II-1</th>
<th>II-2</th>
<th>II-3</th>
<th>III-1</th>
<th>III-2</th>
<th>III-3</th>
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<tbody>
<tr>
<td>Age [years]</td>
<td>8</td>
<td>62</td>
<td>10</td>
<td>65</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>P-Na [mmol/l]</td>
<td>146</td>
<td>126</td>
<td>145</td>
<td>141</td>
<td>134</td>
<td>120</td>
</tr>
<tr>
<td>P-Osm [mosmol/kg]</td>
<td>297</td>
<td>ND</td>
<td>295</td>
<td>300</td>
<td>274</td>
<td>252</td>
</tr>
<tr>
<td>P-Creatinine [mg/dl]</td>
<td>0.53</td>
<td>0.75</td>
<td>0.51</td>
<td>0.84</td>
<td>0.62</td>
<td>0.68</td>
</tr>
<tr>
<td>U-Na [mmol/l]</td>
<td>116</td>
<td>80</td>
<td>161</td>
<td>122</td>
<td>81</td>
<td>31</td>
</tr>
<tr>
<td>U-Osm [mosmol/kg]</td>
<td>1070</td>
<td>485</td>
<td>978</td>
<td>741</td>
<td>437</td>
<td>543</td>
</tr>
<tr>
<td>U-AVP [log pg/min/Cosm]</td>
<td>1.64</td>
<td>ND</td>
<td>1.39</td>
<td>0.59</td>
<td>ND</td>
<td>0.37</td>
</tr>
<tr>
<td>Genetics</td>
<td>WT</td>
<td>R137C</td>
<td>WT</td>
<td>R137C</td>
<td>R137C</td>
<td>R137C</td>
</tr>
</tbody>
</table>
Treatment

• Intuitive by patients!
• Increased osmotic load during infancy (urea)
Conclusions

- SIADH is the most common cause of hyponatraemia
- SIADH is associated with elevated urine sodium excretion
- Kidneys do not sense sodium concentration, just perfusion
- A $U_{\text{osm}}=P_{\text{osm}} (>100 \text{ mosm/kg})$ in the face of hyponatraemia and water overload is inappropriate
- Treatment: fluid restriction, AVPR-blockers (vaptans), urea, ?nothing
And now for something completely different
Case 2

- 2-week old neonate transferred to GOSH renal ward
- Born at 32-wk gestation
- Pregnancy complicated by polyhydramnios (2 amniocentesis)
- Postnatal: polyuria (200 ml/kg/d) and severe electrolyte disturbance
- 3rd child of healthy parents, 1st cousins
Examination

- Decreased peripheral perfusion
- Wt: 1.68 kg
- Length: 44 cm
- HC: 29 cm
- BP: 68 mmHg systolic
# Biochemistries

<table>
<thead>
<tr>
<th>Parameter</th>
<th>admission</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>Na (mmol/l)</td>
<td>116</td>
<td>133-146</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>2.1</td>
<td>3.5-5.5</td>
</tr>
<tr>
<td>Cl (mmol/l)</td>
<td>59</td>
<td>100-108</td>
</tr>
<tr>
<td>HCO₃ (mmol/l)</td>
<td>&gt;40</td>
<td>20-30</td>
</tr>
<tr>
<td></td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Venous pH</td>
<td>7.8</td>
<td>7.37-7.43</td>
</tr>
<tr>
<td>Ca (mmol/l)</td>
<td>1.99</td>
<td>2.17-2.44</td>
</tr>
<tr>
<td>Mg (mmol/l)</td>
<td>0.55</td>
<td>0.66-1.00</td>
</tr>
<tr>
<td>Creatinine (mcmol/l)</td>
<td>116</td>
<td>16-33</td>
</tr>
</tbody>
</table>
Diagnosis

• Bartter syndrome
• Also has sensorineural deafness
• Bartter type 4
• Homozygous mutation in Barttin p.Pro151Leufs*27
Treatment

- Salt! up to 14 mmol/kg/d
- Potassium up to 13 mmol/kg/d
- NSAID (indomethacin, celecoxib)
Further course

<table>
<thead>
<tr>
<th>parameter</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (mmol/l)</td>
<td>116</td>
<td>173</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>1.4</td>
<td>6.9</td>
</tr>
<tr>
<td>Cl (mmol/l)</td>
<td>56</td>
<td>125</td>
</tr>
<tr>
<td>Creatinine (mcmol/l)</td>
<td>29</td>
<td>182</td>
</tr>
<tr>
<td>pH</td>
<td>7.58</td>
<td>7.90</td>
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“Renal Apnoea”

• Recurrent desaturations
• Inability to extubate after GA for central line insertion
Polysomnography
More complications

• Hypophosphataemic rickets

<table>
<thead>
<tr>
<th>test</th>
<th>Value [unit]</th>
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</thead>
<tbody>
<tr>
<td>PO4</td>
<td>0.3 mmol/l</td>
</tr>
<tr>
<td>PTH</td>
<td>56 pmol/l</td>
</tr>
<tr>
<td>ALP</td>
<td>1226 IU/l</td>
</tr>
<tr>
<td>TmP/GFR</td>
<td>&lt;0.8 mmol/l</td>
</tr>
</tbody>
</table>
....and more complications

- Severe developmental delay
- Failure-to-thrive
- Stuck in hospital
How to move forward?

- Palliative care
- Titration with HCl
- Nephrectomy(ies)
- amiloride
Amiloride action

Principal cell

MRCR

Aldo

2K⁺

Na-K-ATPase

K⁺

ENaC

ROMK

H⁺

H-ATPase

blood

urine

intercalated cell

blood
Pathophysiology
Bartter syndrome affects tubuloglomerular feedback

- MD cells are TAL cells
- ↓ chloride reabsorption leads to renin/angiotensin activation via Prostaglandins
- COX-2
- Patients have serum renin & aldosterone and urine PGE2
Amiloride justification

• JG apparatus is “short circuited”, as no chloride reabsorption
• => prostaglandin=>renin=>aldosterone independent of volume status
• Volume homeostasis must be maintained by adequate salt supplementation
Course since

• Blood pH <7.6
• Improved mental state
• No further phosphate supplementation
• Discharged home age 12 months (2 months after starting amiloride)

• Severe developmental delay
• CKD stage 3 (eGFR 30 ml/min)
Conclusions

• Disorders of water are primarily reflected in Na concentration
• Renal Na handling regulates volume/BP
• Renal sodium transport is molecularly linked to multiple other transport pathways
• Disorders of renal sodium handling clinically manifest with altered BP and secondary electrolyte abnormalities
And now for something completely different
Case 3

- Born at 35 wk gestation, pregnancy complicated by “probable hydramnios”
- Stays 2 weeks in hospital due to jaundice, “somewhat unwell” and hypoglycaemia
- Multiple tests carried out, including urine amino acids => “Hartnup disorder”
- Sent home. Repeat urine at 1–y of age “diagnosis of Hartnup seemed confirmed”
- No rash, no ataxia
Further course

- At 2-years of age, delay in motor development noted: not walking
- Nicotinamide commenced and advised to avoid sunlight, but no improvement.
- Develops clinical rickets and commenced on colecalciferol: no improvement.
- Commences 1,25-OH Vit D and referred to Otto Wolf and Martin Barrett for suspected diagnosis of cystinosis age 3y
Admission GOSH age 3.5y

- Healing rickets
- Hepatomegaly and raised transaminases
- Normal slit lamp examination (no cystine crystals)
- Fasting hypoglycaemia
- Renal Fanconi syndrome with aminoaciduria, glycosuria, phosphaturia
Laboratory Investigations

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<td>K</td>
<td>3.9</td>
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<tr>
<td>Cl</td>
<td>106</td>
</tr>
<tr>
<td>tCO2</td>
<td>17</td>
</tr>
<tr>
<td>urea</td>
<td>7.1</td>
</tr>
<tr>
<td>Creatinine</td>
<td>57</td>
</tr>
<tr>
<td>PO4</td>
<td>1.5</td>
</tr>
<tr>
<td>ALP</td>
<td>2323</td>
</tr>
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On: NaBicarb, Calcium, Phosphate and 1,25 VitD

- Normal: glycogenolytic enzymes, caeruloplasmin, heavy metals, WBC cystine
- Cr-EDTA GFR: 57 ml/min/1.73m2
- Liver biopsy: “no abnormality seen, except for lowish glycogen content”
US kidney

Age: 4 years

9 years
DMSA scan
Further course

• Diagnosis of “idiopathic autosomal recessive renal Fanconi Syndrome”
• Has occasional fainting episodes after prolonged fasting
• Transferred to RFH age 17 y
Renal biopsy age 25 y
Assessing the children

- 1\textsuperscript{st} child referred age 2 months due to risk of RFS
- All investigations normal
- Discharged age 6 months
- Reassured parents that children were unlikely affected due to presumed recessive inheritance
2\text{nd} \text{ child}

- Born at 32 wk gestation, birth weight: 1.53 kg
- Hypoglycaemia
- Persistent hyponatraemia and hypophosphataemia
- Transferred to GOSH age 3 months
Admission GOSH

• Normal examination
• Investigations:

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<td>108</td>
<td></td>
</tr>
<tr>
<td>tCO2</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>urea</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>creatinine</td>
<td>22</td>
<td>600</td>
</tr>
<tr>
<td>Ca</td>
<td>1.60</td>
<td>3.36</td>
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<tr>
<td>PO4</td>
<td>1.21</td>
<td>19.3</td>
</tr>
<tr>
<td>(TRP:39%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALP</td>
<td>937</td>
<td></td>
</tr>
<tr>
<td>glucose</td>
<td>2.2</td>
<td>+</td>
</tr>
<tr>
<td>albumin</td>
<td>22</td>
<td>0.072</td>
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Renal US
Further history

• Diazoxide, 1-alfa, PO4, KCl supplementation
• Difficulty feeding
• Biochemically stable, but poor growth
• Routine genetics screen for HI
• mutation in HNF4A: c.187C>T; p.R63W identified
• Subsequently confirmed also in the mother
• HNF4A: mutations usually cause HI/MODY1 (with neonatal HI), but R63W (prev. R76W) also causes RFS

Novel Presentations of Congenital Hyperinsulinism due to Mutations in the MODY genes: *HNF1A* and *HNF4A*

Diana E. Stanescu, Nkecha Hughes, Bernard Kaplan, Charles A. Stanley, and Diva D. De Leo´n

(*J Clin Endocrinol Metab* 97:E2026–E2030, 2012)
Insulin secretion

Bell GI, et al, Nature 2001;414;788-91
conclusions

• Striking improvement in diagnosis of rare diseases
• Intriguing role of R63 in PT function
• Recent biopsy suggests mitochondrial dysfunction