Paediatric Cushing Disease: one patient’s path to cure

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Objectives

History:
- 15 years old boy, diagnosed with Cushing’s syndrome elsewhere
  - Initial signs and symptoms ≥2 yrs
  - Weight gain, growth arrest, skin changes, emotional lability, poor memory for recent events, eye problems
  - Numerous inconclusive investigations for 6 mo – Metformin therapy
  - TSS – unsuccessful (no further treatment)
  - Presented 2 mo after TSS with escalating deterioration

Physical examination:
- Weight 71.0 kg (SDS 1.25), height 148.1 cm, (H SDS -2.67, TH SDS -1.16), BMI 32.37 kg/m² (SDS 2.96)
  - Central obesity, “moon” face, buffalo hump
  - Skin changes: acne, striae, hypertrichosis, bruises, flush, acanthosis
  - Eye changes: discrete exophthalmos
  - Pubertal: Tanner stage IV, TV 15 ml
  - BP 115/89 mmHg, HR 84/min

Investigations: proved CD and localised hypophyseal corticotroph adenoma (Tables 1 & 2)
- Cortisol – morning and midnight values, disturbed circadian rhythm
- Coupled plasma ACTH/cortisol – inappropriately elevated
- UFC – increased
- Overnight Dexamethasone suppression test (8 mg)
- IPSS – basal ACTH ratio central/periphery >2/1 and left/right >1.5

First time in the country

Management:
- Oral Ketoconazole (2x200mg) + planned for a second TSS
- Liver toxicity after 3 weeks on Ketoconazole and deterioration, related to the hypercortisoaemia
  - increased BP, hypokalemia and tendency towards hyponatraemia, incipient heart decompensation
- Decision for bilateral adrenalectomy (BA), due to the rapid health decline – lack of other oral adrenolytics in the country

Results

Table 1. Hormonal investigations - presentation and follow-up (FU) - 6/9 months

<table>
<thead>
<tr>
<th>Name</th>
<th>Presentation</th>
<th>FU 6 mo</th>
<th>FU 9 mo</th>
<th>Ref. range</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>601.94 (awake)</td>
<td>460.5</td>
<td>490.3</td>
<td>&lt;50</td>
<td>nmol/l</td>
</tr>
<tr>
<td>Cortisol</td>
<td>977.5</td>
<td>755.9</td>
<td>50.5-550</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>117.0</td>
<td>228</td>
<td>572</td>
<td>&lt;46</td>
<td>pg/ml</td>
</tr>
<tr>
<td>UFC</td>
<td>1012.0</td>
<td>233.8</td>
<td>320.5</td>
<td>55.5-286</td>
<td>mg/kg/24h</td>
</tr>
<tr>
<td>IGF</td>
<td>159.0</td>
<td>193</td>
<td>595</td>
<td>237-996</td>
<td>ng/ml</td>
</tr>
<tr>
<td>LH</td>
<td>0.52</td>
<td>3.0</td>
<td>2.73</td>
<td>0.5-5.3</td>
<td>mIU/ml</td>
</tr>
<tr>
<td>FSH</td>
<td>4.0</td>
<td>4.0</td>
<td>4.34</td>
<td>0.3-8.2</td>
<td>mIU/ml</td>
</tr>
<tr>
<td>Testosterone</td>
<td>4.3</td>
<td>10.1</td>
<td>11.9</td>
<td>2.95-41.66</td>
<td>mIU/ml</td>
</tr>
<tr>
<td>TSH</td>
<td>1.6</td>
<td>1.3</td>
<td>2.65</td>
<td>0.4-4</td>
<td>mIU/ml</td>
</tr>
<tr>
<td>FT4</td>
<td>14.4</td>
<td>13.8</td>
<td>13</td>
<td>10.3-24</td>
<td>pmol/l</td>
</tr>
<tr>
<td>Prolactin</td>
<td>72.7</td>
<td>89.3</td>
<td>92.4</td>
<td>53-360</td>
<td>pmol/l</td>
</tr>
</tbody>
</table>

Table 2. IPSS

<table>
<thead>
<tr>
<th>Basal investigation</th>
<th>ACTH (pg/ml)</th>
<th>Cortisol peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>right</td>
<td>left</td>
</tr>
<tr>
<td>Sinus petrosus inferior</td>
<td>46.7</td>
<td>183</td>
</tr>
<tr>
<td>V. jugularis int. supp.</td>
<td>48.5</td>
<td>105</td>
</tr>
<tr>
<td>V. jugularis int. inf.</td>
<td>50.4</td>
<td>53</td>
</tr>
<tr>
<td>Central/periphery ratio</td>
<td>4.7/1</td>
<td></td>
</tr>
<tr>
<td>Lateralisation ACTH at S. petr. Inf. L/R</td>
<td>3.4/1</td>
<td></td>
</tr>
</tbody>
</table>

Preparation for the BA:
- Preoperatively treated with i.v. Etomidate
- 24 hours prior BA in block-replace regimen (Methylprednisolone, when desired Cortisol levels of 100-200 nmol/l reached)
- No previous experience in the country

Laparoscopic BA

Postoperatively
- Hydrocortisone, Fludrocortisone and antihypertensives
- Uneventful postoperative period

First weeks after the BA
- Elevated BP
- Swelling of the legs
- Anxiety attacks

FU at 6 months
- Weight reduction -8 kg (SDS 0.17)
- No catch-up growth (1 cm/6 mo, SDS -2.79)
- Advancing pubertal development (TV 20 ml)
- BP normalised
- Overcoming depression and anxiety
- GH deficiency
  - ITT and GT GH peak <10ng/ml (5.9 and 8.44 respectively)
  - BA 14 yr 10 mo
  - Started GH therapy (1.5 mg/day)

FU at 9 months
- Catch-up on GH (3 cm/3 mo)
- Two more anxiety attacks, blurred vision (left)
- Further levated ACTH
  - no signs of Nelson’s syndrome (MRI – no change, no hyperpigmentation)
- Normal TSH, gonadotrophins and testosterone

Conclusions

Treatment of paediatric CD and its related complications is complex. Many factors can change the therapeutic course, including the lack of medications and experience in smaller centers. Multidisciplinary approach and collaboration with experts in the field are crucial for a successful outcome.