Conservative treatment of neonatal Cushing’s syndrome in McCune Albright syndrome, a 2 year follow-up

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Introduction
McCune Albright syndrome (MAS) is defined by the classic triad of precocious puberty, fibrous dysplasia of bone and café au lait skin pigmentation. However, the clinical spectrum is often more variable due to mosaic distribution of the postzygotic GNAS-mutation.

Hypercortisolism occurs in a minority (5%) of patients. It is most frequently caused by nodular adrenal hyperplasia and can be life-threatening. Decisions on whether clinical management should be conservative or should involve active intervention are challenging.

Patient description
We report a male neonate (birth weight 2560 grams; -2.5sd) with café au lait skin pigmentation as described in MAS and neonatal cholestatic liver disease of unknown origin.

At the age of 4 months he developed a Cushingoid appearance, failure to thrive (height 54.4cm -3.2 sd and weight for height 3800gr -1.0sd) and hypertension (Figure 1 and 2).

Blood and saliva GNAS mutational analysis were both negative, but a mutation could be confirmed in tissue obtained during previous liver biopsy.

Discussion
In view of the present case, conservative treatment can be considered in neonatal Cushing syndrome in MAS. Brown et al reported a lower likelihood of spontaneous resolution in patients with liver disease [2]. Why spontaneous resolution occurs in some cases is a matter of further research. Probably this is the result of apoptosis of the mutated cells in the fetal zone of the adrenal cortex after the postnatal period [4]. Adrenal function must be monitored closely.

Diagnostic work-up at the age of 4 months showed elevated saliva cortisol levels (table 1), normal urinary cortisol excretion (220 – 240 nmol/l ref value 90-450 nmol/l). Cortisol levels were unsuppressed after a low and high dose dexamethasone test suggesting an adrenal origin (table 2). MRI showed unilateral enlargement of the adrenal gland.

Metyrapone treatment was initiated at the age of 6 months with a maximum dose of 65 mg/kg/day. However, treatment response was difficult to assess and as reports raised concerns towards the effect on white matter [3], after 6 months treatment was stopped. Subsequently, growth and biochemistry were regularly assessed while the clinical condition allowed a conservative approach.

At the age of 15 months height growth spontaneously improved (from 3.5 SD to -2SD; target height -0.8sd). There were no signs of other hormonal involvement in MAS (normal thyroid function and IGF1 levels). A low dose ACTH test (1 ugr) by the age of 1.5 years showed a adequate adrenal reserve (0.59 umol/l) at 60 min. Saliva cortisol levels normalized (table 1). There were no signs of developmental delay and blood pressure normalized. At the age of 2.8 years signs of fibrous dysplasia, requiring orthopedic treatment was diagnosed. Furthermore elevated serum aminotransferases persisted without liver failure.

Table 1: Saliva cortisol levels

<table>
<thead>
<tr>
<th>Time</th>
<th>Ref values</th>
<th>Age of 4 months</th>
<th>Age of 2.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning</td>
<td>9-29 nmol/l</td>
<td>26 nmol/l</td>
<td>9.5 nmol/l</td>
</tr>
<tr>
<td>Midday</td>
<td>4-12 nmol/l</td>
<td>28 nmol/l</td>
<td>11 nmol/l</td>
</tr>
<tr>
<td>Midnigh</td>
<td>1-6 nmol/l</td>
<td>22 nmol/l</td>
<td>6.1 nmol/l</td>
</tr>
</tbody>
</table>

Table 2: Results after dexamethasone suppression test before Metyrapone treatment

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Age of 4 months</th>
<th>ACTH</th>
<th>Serum cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>4 ng/l</td>
<td>0.60 umol/l</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>3 ng/l</td>
<td>0.59 umol/l</td>
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</table>

Conclusion
Conservative treatment of neonatal Cushing syndrome in MAS allows partial or complete recovery of Cushing syndrome, although close monitoring is required.

References