PARADOXICAL INCREASE IN URINARY CORTISOL EXCRETION IN CHILDREN WITH PRIMARY PIGMENTED NODULAR ADRENAL DISEASE

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Background

Pediatric Cushing syndrome is a rare disorder and its diagnosis is always a challenge to the clinicians. The hypercortisolism can be classified as ACTH-dependent (Cushing disease) and ACTH-independent. The latter group comprises several hereditary conditions. One of them is primary pigmented nodular adrenocortical disease (PPNAD) which occurs isolated or as part of Carney Complex (CNC). It is known that adult patients with Cushing syndrome due PPNAD exhibit a paradoxical increase of urinary cortisol excretion in response to dexamethasone. However, this finding was never described in children or adolescents, before clinical manifestations of hypercortisolism became evident.

Case report

Identification

Two monozygotic twin sisters and their first-degree cousin, followed in our outpatient consultation since the age of 4, belonging to a large Azorean family with CNC (Fig 1), heterozygous for the mutation S147F, substitution of serine (S) with glycine (G) at position 147, in the gene of PRKAR1A. The twin’s mother died at age of 28-year-old due to adrenal carcinoma arising in the context of PPNAD.

Case 1 and 2
• The twins exhibit strong spotty skin pigmentation (lentigines) including the vermillion borders of the lips, conjunctival and vaginal mucosa. One of them also has a blue nevus.
• At the age of 13-years-old they started complaining of Cushing syndrome: olygomenorrhea/amenorrhea, weight gain, high blood pressure and hirsutism.
• Imaging of the heart and adrenal glands were normal.

They were submitted to bilateral adrenalectomy and the histologic examination confirmed the diagnosis of PPNAD. Now they are clinically well, on fludrocortisone and hydrocortisone substitution.

Case 3
• She doesn’t exhibit lentigines or cutaneous manifestations of hypercortisolism (Fig 7).
• At 13-year-old she started olygomenorrhea and menorrhagia.
• Imaging of the heart and adrenal glands were normal.

Laboratorial Tests

<table>
<thead>
<tr>
<th>Basal Values</th>
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<td>Absence of the normal circadian variation of cortisol.</td>
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<tr>
<td>Low or undetectable ACTH and late night cortisol above 5 µg/dl.</td>
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<tr>
<td>Elevated urinary cortisol.</td>
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Dexamethasone Test (DT)

| Absence of cortisol suppression (Fig 8). |
| Paradoxical increase in urinary cortisol excretion: >50% over basal values (Fig 9). |

Conclusion

As in most adults a paradoxical increase in urinary cortisol excretion in response to oral dexamethasone, is also found in children with PPNAD. When this increase is over 50% it is pathognomonic of PPNAD. The laboratory testing allowed for timely treatment, before complications of Cushing’s syndrome appeared.