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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 S147G, 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.

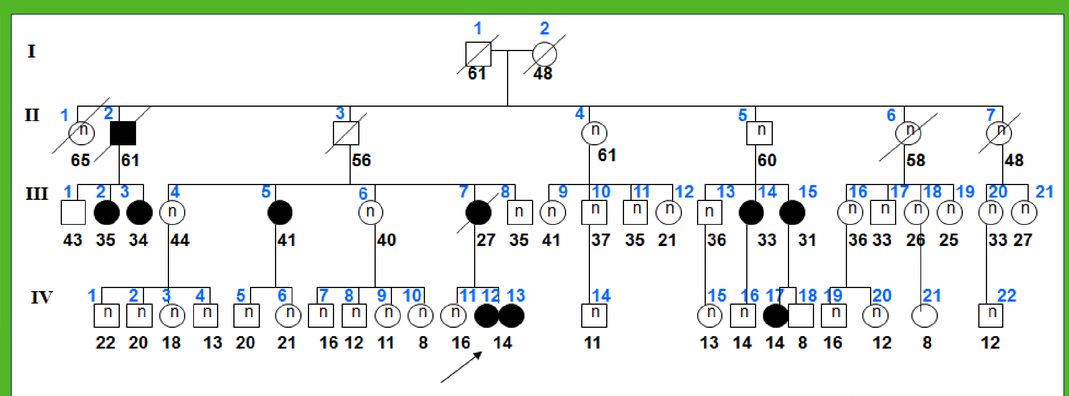


Figure 1 - Genealogic tree girls` family. Arrow indicates the index-cases. Circles are female members; Squares stand for males; Black symbols are PPNAD patients. Age of the subjects is shown bellow the symbols; Family members are numbered by generations above the symbol. Examined members who are normal are identified with (n) inside the symbol.

Case 1 and 2

- The twins exhibit strong spotty skin pigmentation (lentigines) including the vermilion borders of the lips, conjuntival 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 hyrsutism.
- Imaging of the heart and adrenal glands were normal.

Figure 2 - Identical twin sisters

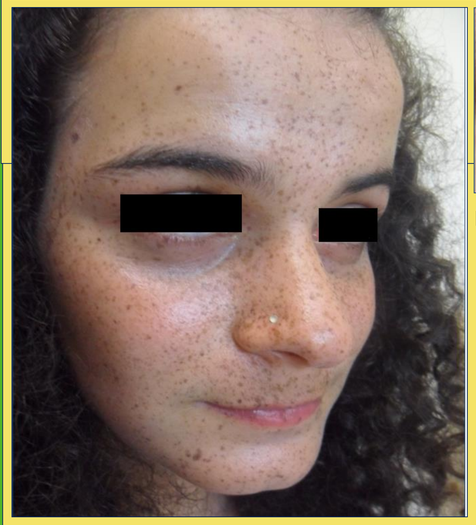


Figure 3 – Facial lentigines

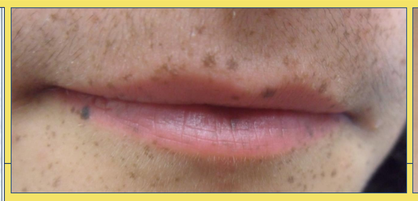


Figure 4 - Vermilion borders of the lips

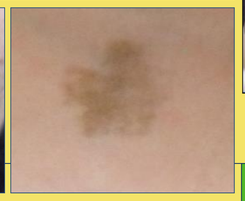


Figure 5 - Blue nevus

Figure 6 - Conjuntival pigmentation

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.

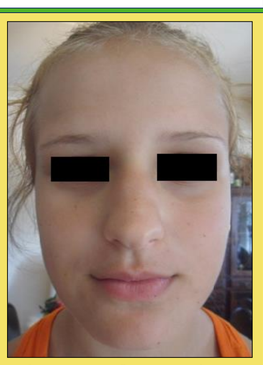
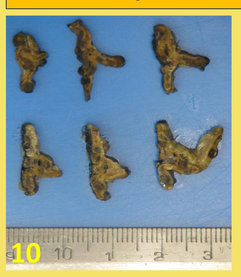


Figure 7 - face without lentigines.

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



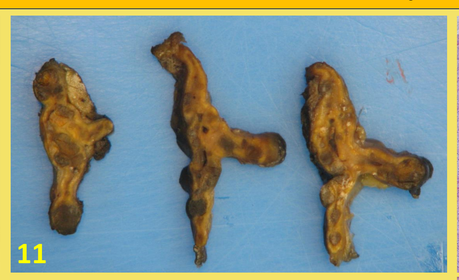
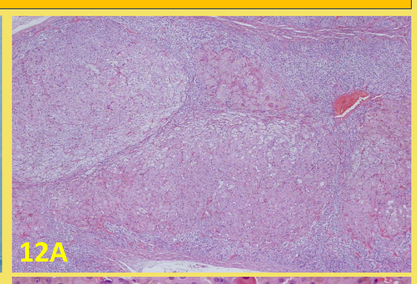


Figure 10 and 11 - Macroscopic aspect of adrenal glands: dark nodules scattered within the glands.



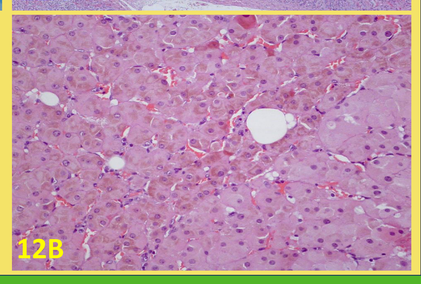


Figure 12 - Microscopic aspect of adrenal glands. **Figure 12A** (magnification 20x) **-** The cortex of the gland with eosinofilic nodules. Nodules are well delimited but not capsulated. **Figure 12B** (magnification 100x) - Cytoplasmic dark granules of lipofuscin.

Laboratorial Tests

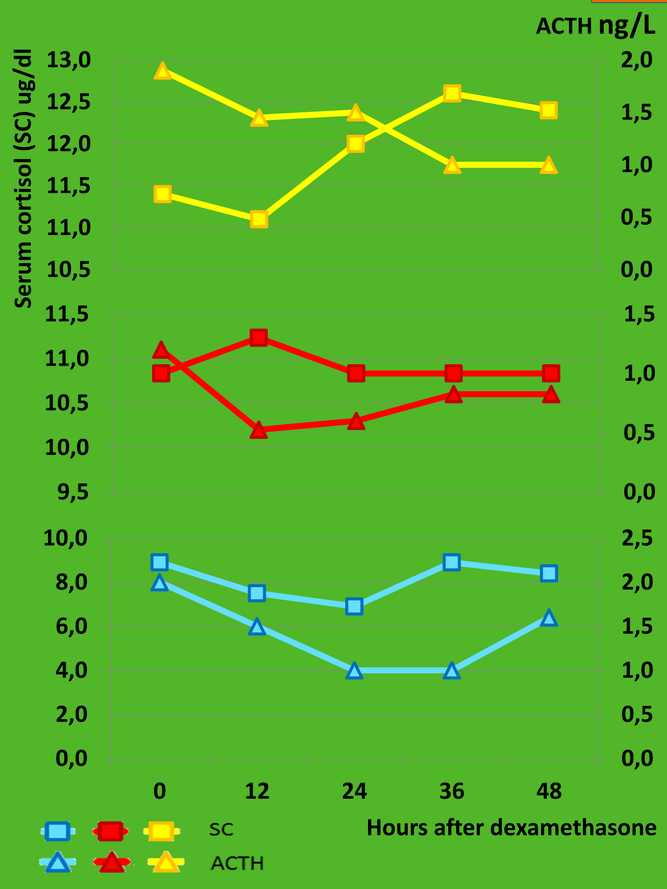


Figure 8 – Variation of serum cortisol and adrenocorticotropic hormone (ACTH) during the DT (oral administration of dexamethasone, 0.5 mg each 6 hours for 48 hours).

Basal Values

- Absence of the normal circadian variation of cortisol.
- Low or undetectable ACTH and late night cortisol above 5 µg/dl.
- Elevated urinary cortisol.

Dexamethasone Test (DT)

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

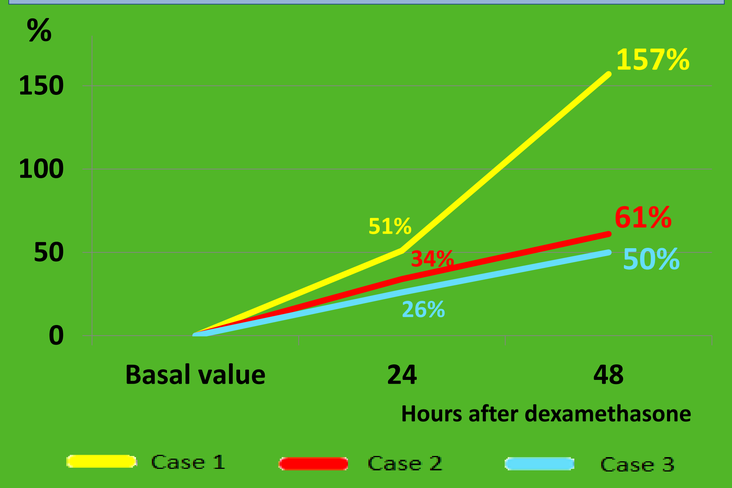


Figure 9 – Variation of urinary cortisol during DT.

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.