**GLUCOCORTICOID RESISTANCE SYNDROME – CASE REPORT**

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**INTRODUCTION**

Glucocorticoid Resistance Syndrome (GRS) or Chrousos Syndrome is a rare familial or sporadic genetic condition, caused by mutations in the glucocorticoid receptor gene (GR). It is characterized by partial resistance of target tissues to cortisol action and subsequent activation of hypothalamic-pituitary-adrenal axis with compensatory elevation of ACTH that stimulates adrenal glands to hypersecretion of cortisol, mineralocorticoids and androgens. Clinical spectrum is very wide, varying from asymptomatic cases that only present laboratory alterations to more severe forms with arterial hypertension (AHT), metabolic alkalosis, hypokalaemia and virilization. Low levels of renin and aldosterone are due to inappropriate activation of mineralocorticoid receptors by cortisol in excess.

Currently, at least 17 inactivating mutations in exons 4-9 of NR3C1 gene, occurring in the ligand-binding domain and DNA-binding domain of GR α isoform, have been described as the cause of GRS. Most of these induce glucocorticoid resistance through more than one defect in the signal transduction cascade of glucocorticoids, which results in impaired transduction of glucocorticoid responsive genes.

**CASE REPORT**

**C.N.S.A.:** 19 years old (yo), black, partially autonomous, born and resident in Cape Verde

**Previous Medical History:**
- Delivery of term, eutonic
- Delayed psychomotor development
- Epilepsy diagnosed at 6 yo, treated with Carbamazepine until 14 yo, with no further convulsive episodes
- AHT diagnosed at 14 yo
- Normal puberty at adequate age

**Medication:**
- Nifedipine 20 mg/day; Atenolol 50 mg/dia

**Family History:**
- Maternal grandmother = AHT
- Paternal half-brother = Epilepsy, died from infectious disease (F)

**Endocrine Department in CCH:**

**Physical Examination:**
- Height 1.70m
- Weight 52 kg BMI 18
- BP 139/95 mmHg
- No features of Cushing Syndrome
- Normal adult secondary sexual development
- Body hair distribution adequate for age and sex
- No signs of hiperpigmentation
- Palpable and wide femoral pulses

**Laboratorial Evaluation**

<table>
<thead>
<tr>
<th>Test</th>
<th>Nov/2010</th>
<th>Apr/2012</th>
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<tbody>
<tr>
<td>ACTH (pg/ml)</td>
<td>111</td>
<td>121</td>
</tr>
<tr>
<td>Cortisol (μg/dL)</td>
<td>17.2</td>
<td>17.5</td>
</tr>
<tr>
<td>Noradrenaline (μg/dL)</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Adrenaline (μg/dL)</td>
<td>4</td>
<td>1</td>
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</tbody>
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**Cape Verde:**

- No occupying space lesions, bleeding or sequela.
- No abnormalities of renal arteries stenosis.
- No papillary features in the kidney, slight deviation of papillary stalk lateral without any direct or indirect signs of microadenoma.
- Echocardiogram Aug/2013
  - Preserved systolic function. Normal left ventricle. Abnormal movement of mitral valve chordae tendineae, with diastolic opening typical of rheumatic disease in the past. The opening is wide and without hemodynamic consequences.

**Cranial-CT:**
- 30/12/2011

**Abdominal-CT:**
- 30/12/2011

**Abdominal/Renal US:**
- 07/12/2009
  - No occupying space lesions, bleeding or sequela.
  - No abnormalities of the renal arteries stenosis.
  - No papillary features in the kidney, slight deviation of papillary stalk lateral without any direct or indirect signs of microadenoma.

**FUNCTIONAL TESTS**

Low-dose Dx
- 130
- 19.8
- 23

High-dose Dx
- 24.5
- <1.0
- 11.9

**Biochemical study suggestive of endogenous hypercortisolism, with preservation of the circadian rhythm of cortisol secretion.**

- No clinical features of hypercortisolism
- AHT

**Glucocorticoid Resistance Syndrome?**

- Probably pathogenic mutation.
- The deletion is predicted to introduce a premature “stop” codon, which results in a truncated protein with the loss of 6% of amino acids.
- Genetic study of relatives has not been done yet, since they live abroad.

**GENETIC STUDY:**

Frameshift mutation c.2159_2160delAA, in heterozygosity in the NR3C1 gene

Not yet described in the literature or data base.

**CONCLUSIONS**

Diagnosis of GRS is suggested by the finding of persistant elevated urinary cortisol in a young man with AHT without any other features of Cushing Syndrome. The elevation of cortisol and androgens, as well as the resistance to dexamethasone suppression depend on the severity of the defect in the signal transduction of glucocorticoids. A novel frameshift mutation in the gene NR3C1 responsible for GRS was identified in this patient. Further molecular and genetic studies of the patient and relatives are expected to be performed in order to identify the transduction defect involved and whether it is an inherited or de novo mutation.