ARMC5 MUTATION IN A FAMILY WITH CUSHING SYMPODUE TO BILATERAL MACRONODULAR ADRENAL HYPERPLASIA

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INTRODUCTION

- Bilateral Macronodular Adrenal Hyperplasia (BMAH) is a rare and insidious etiology of Cushing’s syndrome (CS).
- BMAH is usually characterized by functioning adrenal macronodules and variable cortisol secretion.
- The asymmetric/asynchronous involvement of only one adrenal gland can also occur, making disease diagnosis a challenge.
- Familial clustering suggests a genetic cause that was recently confirmed, after identification of inactivating germline mutations in armadillo repeat containing 5 (ARMC5) gene.

CLINICAL CASE

A 70-year-old female patient, with no relevant medical history, was admitted due to left femoral neck fracture in May 2014, in Orthopedics Department. Submitted to total hip replacement on 20/05/2014. During hospitalization hypertension (HTA) and hypokalemia were diagnosed, both difficult to control.

PHYSICAL EXAMINATION

- Thin and dry skin with multiple bruises
- Ruborosis and moon-like face
- Central obesity
- Weight: 75Kg
- Height: 1.57 m
- BMI: 30Kg/m2
- Severe muscular atrophy
- Osteoporosis
- HTA + hypokalemia
- Clinical signs of CS

LABORATORY WORK-UP

<table>
<thead>
<tr>
<th></th>
<th>BASEAL</th>
<th>DEXAMETHASONE SUPPRESSION TEST (0:00 AM/8:00 AM)</th>
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</thead>
<tbody>
<tr>
<td>Serum cortisol</td>
<td>21.4 ug/dL</td>
<td>21 ug/dL</td>
</tr>
<tr>
<td>Plasma ACTH</td>
<td>&lt; 5 pg/mL</td>
<td>&lt; 5 pg/mL</td>
</tr>
<tr>
<td>24 hour UFC</td>
<td>532 ug/day (ex: 20-90)</td>
<td>592 ug/day</td>
</tr>
<tr>
<td>Midnight serum Cortisol</td>
<td>19.3 ug/dL</td>
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</tbody>
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ABDOMINAL MRI

Overt Cushing syndrome

BILATERAL MACRONODULAR ADRENAL HYPERPLASIA

TREATMENT

- BILATERAL ADRENALECTOMY (July/2014)
  - Right gland weight 62 g (Fig. 2)
  - Left gland weight 151 g (Fig. 3)

- Pathology - Cortical nodular hyperplasia

FAMILY HISTORY

In 2006 this patient’s 39-year-old daughter had been observed by one of the authors. - Severe clinical hypercortisolism
- ACTH < 5 pg/ml; UFC – 204 ug/24h; serum cortisol after low dose DST – 16.2 ug/dl;
- Abdominal CT scan: bilateral enlarged nodular adenals with maximal axis of 15 cm for both.
- BILATERAL ADRENALECTOMY (right gland – 68g; left gland – 104g)
- Pathology - Cortical nodular hyperplasia.

In this family context of severe bilateral disease, genetic study was performed.

Leucocyte DNA genotyping identified in both patients an ARMC5 mutation in exon 1 (c.172_173insA p.ISRNfs*44)

COMMMENTS

- The clinical cases herein described have an identical phenotype with severe hypercortisolism and huge adrenal glands, but different ages on diagnosis.
- Current knowledge of inheritance of this disease, its insidious nature and the well known deleterious effect of hypercortisolism favor genetic study of other family members.
- Since ARMC5, a tumoral suppressor gene, is expressed in many organs and recent findings suggest an association of BMAH and meningioma, a watchful follow-up is required.

BIBLIOGRAPHY