ARMC5 MUTATION IN A FAMILY WITH CUSHING SYNDROME DUE 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.**

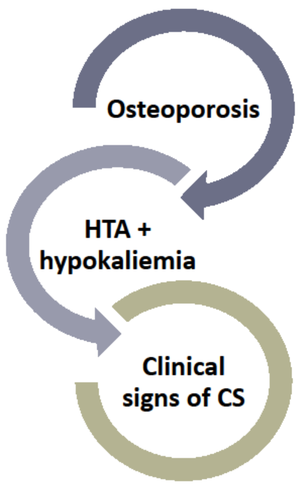
CLINICAL CASE

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**
- Rubeosis *and moon-like face*
- Central obesity
  - **Weight:** 75Kg
  - **Height:** 1.57 m
  - **BMI:** 30Kg/m2
- **Severe muscular atrophy**

Admitted to the ENDOCRINOLOGY DEPARTMENT for suspected CUSHING SYNDROME



LABORATORY WORK-UP

	BASAL	DEXAMETHASONE SUPRESSION TEST (0,5 mg 6/6h – 2 days)
Serum cortisol	21.4 ug/dL	21 ug/dL
Plasma ACTH	< 5 pg/mL	< 5 pg/mL
24-hour UFC	532 ug/day (r.v. 20-90)	592 ug/day
Midnight serum Cortisol	19.3 ug/dL	-

ABDOMINAL MRI

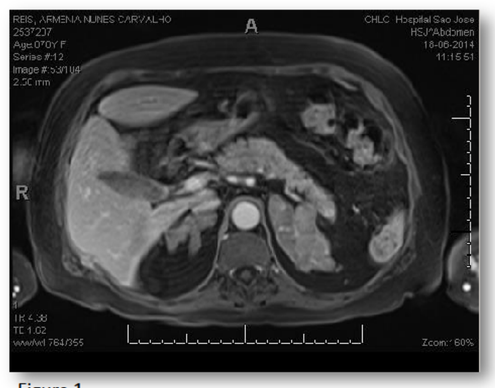


Figure 1.

Right gland:

55x54x30 mm

Left gland:

85x53x35 mm

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**

Figure 2.

Figure 3.

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 adrenals with maximal axis of 15 cm for both.
- **BILATERAL ADRENALECTOMY** (**right** gland – **68**g; **left** gland – **104**g)
- Pathology - **Cortical nodular hyperplasia.**

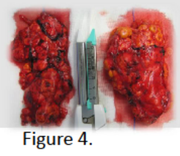
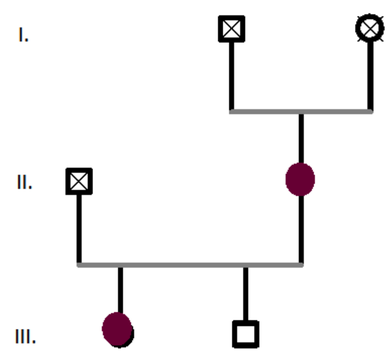
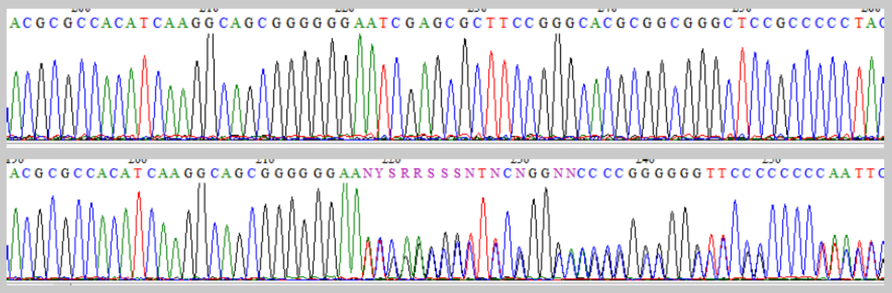


Figure 4.



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.I58Nfs*44)



COMMENTS

✓ 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 **meningeoma**, a watchful follow-up is required.

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Clinical Cases Pituitary/Adrenal

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