21-Hydroxylase Deficiency Presenting as Bilateral Adrenal Masses in the Sixth Decade of Life in a phenotypically male but genetically female patient

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INTRODUCTION: 21-hydroxylase deficiency (21-OHD) is a common inherited disorder accounting for 90-95% of congenital adrenal hyperplasia (CAH) cases. Some cases may be diagnosed in adulthood after the incidental discovery of adrenal masses on computerized tomography (CT).

CASE REPORT: A 59 year-old male was investigated for incidentally discovered bilateral adrenal masses in an abdomen CT scan, measuring 5 cm on the right and 8 cm on the left adrenal (Fig.1). At birth he had a phallus and partial fusion of the labioscrotal folds and was was diagnosed with bilateral cryptorchidism and hypospadias. He was raised as a man. At the age of 15 the patient menstruated and the karyotype testing revealed the XX cromosomal sex. He underwent multiple operations for the creation of a scrotum and the restoration of hypospadias. The uterus and ovaries were removed and prosthetic testes were placed in the scrotum. He was not receiving any cortisone supplementation. On physical examination he had a male appearance with sparse beard male-type baldness, height was 138cm and weight 73Kg. He had gynecomastia and a 5 cm phallus with prosthetic testes. Laboratory evaluation (Table 1) and Synachten test results (Table 2) are shown on tables.

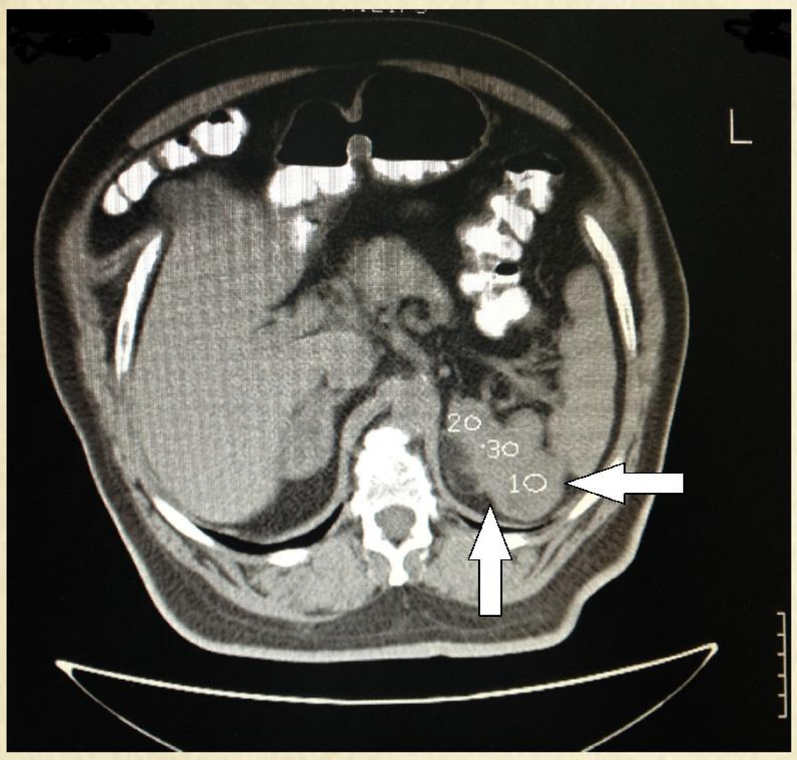

Figure. Adrenal CT of the patient. The left adrenal mass is seen. HU 1-3, >60% washout at 15'

Table 1. Laboratory evaluation

Hormone	Value	Normal range for women
Testosterone (ng/ml)	7.8	0.07-0.65
DHEAS (μg/dl)	420	22-263
E_2 (pg/ml)	144	5.7-102
ACTH (pg/ml)	80.5	7.3-63.3
PRA (ng/ml/h)	3.6	0.6-1.9
Aldosterone (pg/ml)	450	66-173

Table 2. Synachten test

Synachten test	Value	Normal Range	Value	Normal Range
	17(OH)P (ng/ml)		Cortisole (nmol/l)	
Time 0'	92	0.19-0.71	199	260-720
Time 30'	139	< 10	242	> 500
Time 60'	226		285	

Genetic testing of the 21-hydroxylase gene revealed a compound heterozygoticity for the mutations I172N and Q318X.

Q318X Mutation in exon 8:

- It causes complete loss of the enzymatic activity
- It is present in pseudogene CYP21A1P → gene conversion between the pseudogene and active gene during meiosis
- It is a common mutation worldwide in patients with 21-OH deficiency
- In the Greek population it is found in the 5.9% of patients with the classical, simple virilizing form.

I172N Mutation in exon 4:

- It leads to enzymatic activity of 2%
- It causes the salt wasting and the simple virilizing form of classical 21-OH deficiency
- In the Greek population it found in the 35.3% of patients with the classical, simple virilizing form

Following left adrenalectomy histology revealed a diffusely hyperplastic adrenal cortical zone, measuring in total 12x8x4 cm with regions of myelolipoma transformation

CONCLUSIONS: Long standing, untreated classic virilizing form of CAH may lead to extensive hyperplasia of the adrenal cortex. It is prudent to measure 17OHPG in cases with massive adrenal enlargement. Moreover we emphasize some issues for our patient: One is the until now asymptomatic deficiency in cortisol production, obviously owing to the minimum enzymatic activity of 21OH allowed by the I172N mutation. Moreover, this is one of the few cases in which diagnosis was missed at birth; The majority of cases are raised as females and do not have to undergo this sort of operations and psychosocial burden. Finally, individuals with CAH may be at increased risk of developing adrenal myelolipomas and ACTH may have a role in the development of these tumors.

References

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