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Case Report

# 21-Hydroxylase Deficiency Presenting as Bilateral Adrenal Masses in a Phenotypically Male but Genetically Female Patient

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**Abstract**

A 59-year-old male was investigated for bilateral adrenal masses. At birth he had a phallus and partial fusion of the labioscrotal folds and was raised as male. At puberty he menstruated and 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. Genetic testing of the 21-hydroxylase gene revealed a compound heterozygoticity for the mutations p.I172N and p.Q318X. Following left adrenalectomy histology revealed a diffusely hyper plastic adrenal cortical zone with regions of myelolipoma transformation. In patients with Congenital Adrenal Hyperplasia there is an increased frequency of adrenal adenomas and myelolipomas related to the chronic stimulation of the adrenal cortex by ACTH and adrenal androgens. Adrenal myelolipomas are benign and biochemically inactive neoplasms. Measurement of17-hydroxyprogesterone in cases of adrenal enlargement can lead to the diagnosis of Congenital Adrenal Hyperplasia.

**Keywords:** 21-Hydroxylase deficiency; Congenital adrenal hyperplasia; Adrenal myelolipoma

## Introduction

Recently, there have been reported several cases of the classic form of Congenital Adrenal Hyperplasia (CAH) diagnosed in adult life, only after the incidental discovery of adrenal masses on Computed Tomography (CT). Here we report a 59-year-old phenotypically male but genetically female patient with the Simple Virilizing (SV) form of 21-Hydroxylase Deficiency (21-OHD), previously undiagnosed who presented with bilateral adrenal masses, described as myelolipomas on CT.

## Methods and Results

A 59 year-old male, followed by the Hematological Department of our Hospital for polycythemia was referred to the Endocrinological Department for the investigation of bilateral adrenal masses found incidentally on abdominal CT. The adrenal masses measured 5 cm on the right and 8 cm on the left adrenal (Figure 1), both with features characteristic for myelolipoma. Family history was not contributory.

The patient was assigned the male gender and raised as a man, since at birth he had a phallus and partial fusion of the labioscrotal folds.He was considered bilaterally cryptorchid and hypospadias.He reported being the taller boy among his classmates initially, but stopped growing at the age of 10. At the age of 15 the patient menstruated and the karyotype testing identified the 46, XX chromosomal sex. The patient at that time strongly refused a gender reassignment and was submitted on multiple operations in another hospital, for the creation of a scrotum and the restoration of hypospadias.The uterus andthe ovaries were removed and prosthetic testes were placed in the scrotum. The patient denied any clinical symptoms suggestive of adrenocorticaldeficiency. To be noticed, most of the details regarding the diagnosis at the age of 15 were reported by the patient's sister. The patient himself hid his genetic sex and did not accept to undergo any special psychological test. However, he looked quite concordant psychologically with the gender of assignment, he had worked as a cook in the merchant fleet and he even had had an unsuccessful marriage. On physical examination he had a male appearance with sparse beard and male type baldness; his height was 138 cm, weight 73 kg, and body mass index 38.3 Kg/m$^2$. He had a phallus with a 5 cm length and a 2.5 cm circumference, a well formed scrotum with very hard, clearly prosthetic testis of 15 ml volume. The urethral orifice was at the top of the phallus. Gynecomastia was also present. Hormonal laboratory dataare summarized in Table 1.

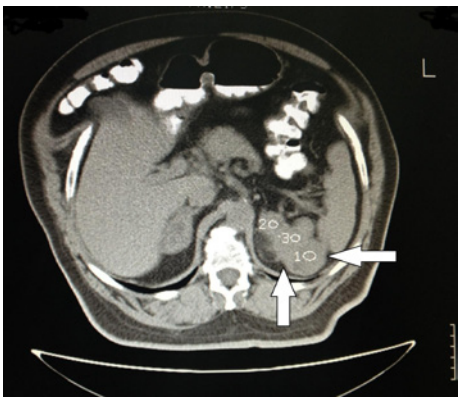


**Figure 1:** Adrenal CT of the patient. The left adrenal mass is seen. The Housfield Units are 1-3 with >60% washout at 15'.




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**Table 1:** Basic hormone levels of the patient.

| Hormone | Value | Normal Range for menopausal women |
|---|---|---|
| Testosterone(ng/ml) | 7.8 | 0.07-0.65 |
| DHEAS (μg/dl) | 420 | 22-263 |
| E2 (pg/ml) | 144 | 5.7-102 |
| ACTH (pg/ml) | 80.5 | 7.3-63.3 |
| PRA (ng/ml) | 3.6 | 0.6-1.9 |
| Aldosterone (pg/ml) | 450 | 66-173 |
| Synachten test | | |
| Time | 17(OH)P (ng/ml) | Cortisole(nmol/l) |
| 0' | 92 (Normal Range 0.19-0.71) | 199 (Normal Range 260-720) |
| 30' | 139 (Normal Range <10) | 242 (Normal Range >500) |

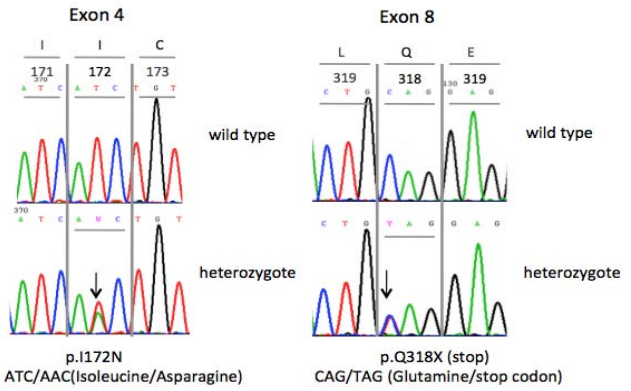


**Figure 2:** CYP21A2 GENE. The patient was found compound heterozygote for the mutations p.I172N and p.Q318X of the CYP21A2 gene. The specific genotype is associated with the classic simple virilizing form of 21-hydroxylase deficiency (C-SV CAH).

Karyotype showed 46, XX and genetic analysis of 21-hydroxylase gene revealed that the patient was a compound heterozygote for the mutations p.I172N and p.Q318X (Figure 2). DNA was extracted from peripheral blood leucocytes using standard methods. The *CYP21A2* gene was selectively amplified against the highly homologous *CYP21A1P* pseudogene in three different overlapping PCR fragments. All 10 exons, 9 introns, 420 bp of the 5′ untranslated region and 200 bp of the 3′ untranslated region of the *CYP21A2* gene were directly sequenced. Sequencing reactions were performed using the Applied Biosystems Big Dye terminator cycle sequencing kit and analysed on an ABI 3500 Genetic Analyzer.

The patient underwent a left adrenalectomy and the histology revealed a huge adrenal measuring in total 12x8x4 cm with diffusely hyperplastic adrenal cortex and regions of myelolipoma transformation (Figure 3).

## Discussion

CAH is a group of inherited, autosomal, recessive disorders characterized by impaired synthesis of cortisol and, in most instances, increased synthesis of adrenal androgens. The defect lays on mutations in several enzymes of the steroid pathway and its prevalence ranges

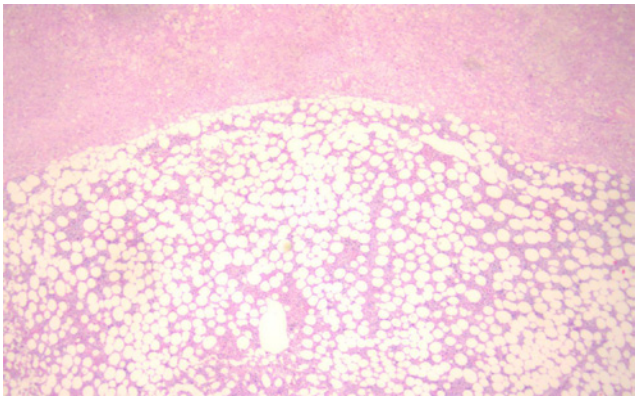

**Figure 3:** Hematocilin/ Eosin x 250: Hyperplastic adrenal gland cortex in the upper part of figure with myelolipoma loci in the lower part.

from 1:10,000 to 1:20,000 births [1]. 21-OHD is by far the most common among the various enzymatic deficiencies, accounting for 90-95% of CAH cases, leading to decreased production of cortisol and aldosterone [2]. There are 3 forms of 21-OHD, distinguished by the clinical expression of the disease: 1) the Salt-Wasting form (SW) that presents with adrenal crisis in the first weeks of life and virilization of the female newborn, 2) the Simple Virilizing form (SV), where there is only virilization of the external genitalia in the female infant, and 3) the milder, without any of the above features, Non Classical form (NC) [3]. The two classic phenotypes of CAH, the SW and SV forms, are diagnosed usually in the first weeks of life due to the adrenal crisis ensuing in the SW form, in addition to ambiguous external genitalia in the female newborn and the presence of ambiguous genitalia only in the SV form. The NC form is diagnosed during puberty due to early adrenarche or in early adult life with signs and symptoms of hyperandrogenism in women. All three forms are caused by mutations of the *CYP21A2* gene encoding 21-hydroxylase which converts 17-hydroxyprogesterone to 11-deoxycortisol and progesterone to deoxycorticosterone, the respective precursors for cortisol and aldosterone.

More than 100 mutations of the *CYP21A2* gene have been identified [4]. It is located on the short arm of chromosome 6, within the region of the major histocompatibility complex, at a short distance from a highly homologous (>95%) pseudogene, designated *CYP21A1P* [5]. Despite its high homology with *CYP21A2*, *CYP21A1P* is totally inactive. p.Q318Xmutation in exon 8 causes complete loss of the enzymatic activity of 21-OH and is present in *CYP21A1P*. Thus, the mutation is thought to be created by gene conversion between the *CYP21A1P* and the *CYP21A2* during meiosis. In the Greek population it is present in 14.3% of patients with the classic form, either SW or SV [6]. On the contrary, the p.I172N mutation in exon 4 leads to an enzymatic activity of around 2% of the wild-type *CYP21A2* gene [7] and it is found in the SW and the SV forms of classic 21-OH deficiency. In the Greek population it is present in 35.3% of patients with the SV form [6]. Therefore, our patient harbored two relatively common for the Greek population mutations of the *CYP21A2* gene, causing the classic form of CAH and since the phenotype is determined by the least harmful mutation, the clinical picture was that of the SV form.

Adrenal myelolipomas are rare, benign and biochemically inactive

neoplasms, of varied composition of adipose and hemopoietictissue. They frequently are diagnosed as adrenal incidentalomas, as they are usually asymptomatic, although they can grow very large and cause pressure symptoms to the surrounding structures, or even hemorrhage [8,9]. Diseases associated with increased ACTH, such as Cushing's disease, Addison disease and CAH have been associated with the development of myelolipomas [10]. Till now, no more than 40 cases of CAH associated with myelolipomas[10,11,12] have been described, frequently with very large size [11,13,14]. The patients may or may not been diagnosed with CAH prior to the detection of the adrenal masses. Bilateral or unilateral adrenalectomy is the treatment of choice.

There are three interesting issues in our case. Firstly, the absence of symptoms or signs of adrenal deficiency, despite the inadequate response of cortisol to Synacthen test, compatible with cortisol deficiency. It is conceivable that the minimal enzymatic activity of 21-OH allowed by the p.I172N mutation may have prevented the development of adrenal deficiency. Patients with the SV form maintain an adequate aldosterone production and normal sodium balance at the cost of increased plasma renin activity [15], as was the case in our patient. The enormous mass of the adrenal cortex may account for the increased levels of serum aldosterone.

Secondly, the development of gross enlargement of the adrenal cortex secondary to the minimal, yet long standing, elevation of ACTH. In patients with CAH, especially in those sub optimally treated, there is an increased relative frequency of adrenal adenomas and myelolipomas [16]. The most obvious cause would be the chronic stimulation of the adrenal cortex by ACTH and the adrenal androgens. Efforts to prove such a hypothesis have shown conflicting results, since some tumors from patients with CAH show increased expression of the ACTH and the androgen receptors, while others are not [17,18]. Therefore, the pathogenetic mechanisms involved in the formation of myelolipomas remain obscure. Nevertheless, it is prudent to measure 170HP in cases with adrenal enlargement, not only to obtain the correct diagnosis [19] but also to identify the very rare, still existing, patients with CAH who may harbor an adrenal carcinoma [20].

A third remarkable point in our case is the seemingly at least, absolute concordance of the patient's life. He chose a profession stereotypically more practiced by men and a female sexual partner. It is reported that patients like ours, diagnosed during puberty or as adults and reared as males, show male psychological and heterosexual orientation [8]. This case supports the option of choosing the male gender of rearing in severely virilized 46, XX infants with CAH.

## Statement of Ethics

Subject has given his informed written consent and the study protocol was approved by an appropriate ethics committee.

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