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Research Article

Rare Association of Congenital Adrenal Hyperplasia Due To 17α-Hydroxylase Deficiency and Adrenal Myelolipoma

Suely Santos*

*Universidade Federal do Estado do Rio de Janeiro, Brazil

Corresponding author: Suely Santos, Universidade Federal do Estado do Rio de Janeiro, Brazil.

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Abstract

Congenital Adrenal Hyperplasia (CAH) comprises a group of autosomal recessive disorders caused by pathogenic variants in genes encoding adrenal steroidogenesis enzymes. 17α-hydroxylase deficiency (17-OHD) is the rarest form of CAH, accounting for approximately 1% of all cases. It is characterized by impaired androgen synthesis, resulting in arterial hypertension, hypokalemia, primary amenorrhea, and absence of secondary sexual characteristics. We report the case of a 46,XX female patient with primary amenorrhea, sexual infantilism, and arterial hypertension. Laboratory evaluation revealed reduced levels of 17-OH-progesterone, cortisol, and androgens, along with elevated LH, FSH, ACTH, and deoxycorticosterone. Genetic testing identified compound heterozygous pathogenic variants in the CYP17A1 gene: c.286G>T (p.Arg96Trp) and c.1084C>T (p.Arg362Cys), confirming the diagnosis of CAH due to 17α-hydroxylase deficiency. Inadequate clinical follow-up resulted in multiple complications, including ischemic stroke, osteoporosis with femoral fracture, and the development of bilateral adrenal myelolipomas, an uncommon finding in this form of CAH. Due to progressive tumour growth, left adrenalectomy was required. This case highlights the importance of early diagnosis and treatment adherence to prevent potentially severe complications. The association between 17α-hydroxylase deficiency and adrenal myelolipomas is rare and reinforces the need for careful clinical and radiological surveillance in patients with inadequate disease control. Molecular analysis was essential for diagnostic confirmation, therapeutic guidance, and genetic counseling..

Keywords: Congenital Adrenal Hyperplasia, 17alpha-hydroxylase Deficiency, Adrenal Myelolipoma.

Introduction

Congenital adrenal hyperplasia (CAH) due to 17α-hydroxylase deficiency (17α-OHD) (OMIM #202110) was first described by *Biglieri, et al.* in 1966 in a patient who presented with systemic arterial hypertension (SAH), hypokalemic alkalosis, almost absent aldosterone levels, amenorrhea, and normal height [1]. In 1967, Goldsmith *et al.* reported a 46,XX woman with clinical manifestations of SAH, primary amenorrhea, and the absence of secondary sexual characteristics caused by a defect in 17α-hydroxylation [2]. Later, in 1970, the first case of a male with the pseudohermaphroditism phenotype was reported, characterized by ambiguous external genitalia and prominent breast development during puberty, yet without hypertension and hypokalemia [3].

Congenital adrenal hyperplasia is a group of potentially lethal diseases with an autosomal recessive inheritance pattern that causes multiple imbalances in the adrenal steroidogenesis pathway due to various enzyme deficiencies [4]. The most common form of CAH, accounting for roughly 90–95% of cases, is caused by a deficiency of the enzyme 21-hydroxylase [5]. The second most common cause, representing about 5% of cases, is a deficiency of the enzyme 11β-hydroxylase. Moreover, CAH resulting from 17α-OHD is the rarest form, comprising approximately 1% of all cases [6], and caused by pathogenic variants in homozygosity or compound heterozygosity in the CYP17A1 gene, located at locus 10q24.32 [7]. This gene encodes the steroid 17α-hydroxylase (or steroid 17α-monooxygenase), which possesses both 17α-OHD and 17,20-lyase activity. Through these pathways, the adrenal glands and gonads synthesize 17α-hydroxylated glucocorticoids (17α-hydroxylase pathway) and sex steroids (17,20-lyase pathway) [8,9,10].

The clinical manifestations of CAH as a result of 17α-OHD typically include SAH, hypokalemia, and primary amenorrhea with the lack of secondary sexual characteristics in females. Phenotype severity is related to the extent of enzyme activity [11]. The incidence of CAH due to 17α-OHD is estimated at 1 in 50,000 births worldwide [12].

Adrenal myelolipoma is a benign, non-functional adrenal tumor composed of extramedullary adipose and hematopoietic tissue [13]. It represents about 6–16% of all adrenal incidentalomas and is the second most frequent, only behind adenomas [14]. Approximately 36% of patients with CAH may develop adrenal myelolipomas, particularly in bilateral and bulky forms . Symptoms are non-specific: dyspnea, low back pain, abdominal pain, fever, weight loss, or signs of compression [14]. Rupture usually occurs in tumors larger than 8 cm [15].

Case Report

A 17-year-old female, daughter of non-consanguineous parents, was born at term via vaginal delivery without gestational complications and exhibited normal neuropsychomotor development. She was referred to the gynaecology clinic for primary amenorrhea and the absence of secondary sexual characteristics.

The initial physical examination confirmed she had a height of 152 cm (P3–P15), a weight of 34.4 kg (P50), and was classified as Tanner M1 P1. Her bone age was consistent with that of a 12–3-year-old. Initial hormonal evaluation revealed elevated gonadotropins (follicle-stimulating hormone = 83.3 mUI/mL; luteinizing hormone= 43.2 mUI/mL; prolactin = 28.8 ng/mL). Estradiol was below 20 pg/mL, progesterone was 10 ng/mL, and thyroid stimulating hormone was 2.0 UI/L. The karyotype was 46,XX. A pelvic ultrasound indicated a hypoplastic uterus and ovaries.

During the preoperative period for diagnostic laparoscopy, the patient experienced a hypertensive episode, with a blood pressure of 160 × 100 mmHg. The procedure confirmed the presence of a hypoplastic uterus and ovaries. An ovarian biopsy revealed parenchyma with a preserved cortical layer that contained primary and some secondary follicles, which excluded the diagnosis of pure gonadal dysgenesis.

The combination of hypergonadotropic hypogonadism with SAH suggested a diagnostic hypothesis of 17α-OHD. Hormonal tests showed low levels of androgens (dehydroepiandrosterone sulfate = 1.39μg/dL; testosterone = 0.1pg/mL; androstenedione = 0.4ng/mL), 17-OH progesterone at 0.1 ng/mL, high adrenocorticotropic hormone (ACTH) at 487.1 pg/mL, corticosterone at 13.321 ng/dL, 11-deoxycortisol at 0.6 ng/mL, cortisol at 0.6 μg/dL, and serum potassium at 3.0 mEq/L (Table 1). Computed tomography scans of the sella turcica and adrenal glands were normal.

Table 1: Laboratory tests of the patient at the time of the diagnostic investigation.

Test	Results	Reference values
Follicle-stimulating hormone	83.3 mUI/mL	3-10 mUI/mL
Luteinizing hormone	43.2 mUI/mL	2-15 mUI/mL
Thyroid-stimulating hormone	2.0 mIU/L	0.45 to 4.5 mUI/L
Prolactin	28.8 ng/mL	4.8-23.3 ng/mL
Estradiol	<20 pg/mL	30-120 pg/mL
Progesterone	10 ng/mL	0.1-1.5 ng/mL
Testosterone	0.1 pg/mL	15-70 ng/dL
Dehydroepiandrosterone sulfate	1.39 μg/dL	35-430 μg/dL
Androstenedione	0.4 ng/mL	0.4-4.0 ng/mL
17-OH-progesterone	0.1 ng/mL	0.3-2.5 ng/mL
Cortisol	0.6 μg/dL	5-25 μg/dL
Adrenocorticotropic hormone	487.1 pg/mL	10-60 pg/mL
Corticosterone	13,321 ng/dL	100-1,000 ng/dL
11-Desoxycortisol	0.6 ng/mL	2-5 ng/mL
Potassium	3.0 mEq/L	3.5-5.0 mEq/L

Estrogen treatment began, and breast buds developed after three months. Menarche occurred at the age of 19, after which the dose of estrogen was increased. At age 21, she was in Tanner stage M2 P3, with irregular menstrual cycles. She was therefore referred to the medical genetics service at Gaffrée e Guinle University Hospital (Rio de Janeiro, Brazil) and underwent molecular tests. These tests identified the presence of pathogenic variants in compound heterozygosity in the CYP17A1 gene at c.286G>T (p.Arg96Trp) and c.1084C>T (p.Arg362Cys), confirming the CAH diagnosis due to 17α-OHD. Consequently, treatment with glucocorticoids, potassium replacement, and estrogens was maintained, initially controlling hypertension.

Nevertheless, the patient discontinued follow-up and returned at age 37 with symptoms of amenorrhea, hypertension, persistent hypokalemia, osteoporosis, and a history of ischemic stroke at age 33, which resulted in spastic hemiparesis on the right side. A transesophageal echocardiogram revealed an ostium secundum-type atrial septal defect, which was surgically corrected. A next-generation sequencing panel was performed for hereditary thrombophilia, which identified a heterozygous pathogenic variant in the prothrombin gene (G20210A).

At age 38, she sustained a femoral neck fracture associated with osteoporosis and underwent hip arthroplasty. Treatment was resumed with glucocorticoids, as well as oral calcium, vitamin D, and potassium replacement. At age 39, she began experiencing severe low back pain. A total abdominal computed tomography scan revealed a heterogeneous mass in the left adrenal gland with a fatty component (12.9 × 8.7 cm) and a smaller lesion on the right (4.9 × 3.8 cm). She underwent a left adrenalectomy, and a histopathological examination confirmed adrenal myelolipoma (Figure 1). During follow-up, the patient required two hospital admissions for post-streptococcal acute diffuse glomerulonephritis, with impaired renal function. Following the initiation of monthly benzathine penicillin treatment, antistreptolysin O levels and nitrogenous waste products normalized, except for serum potassium, which remained subnormal.

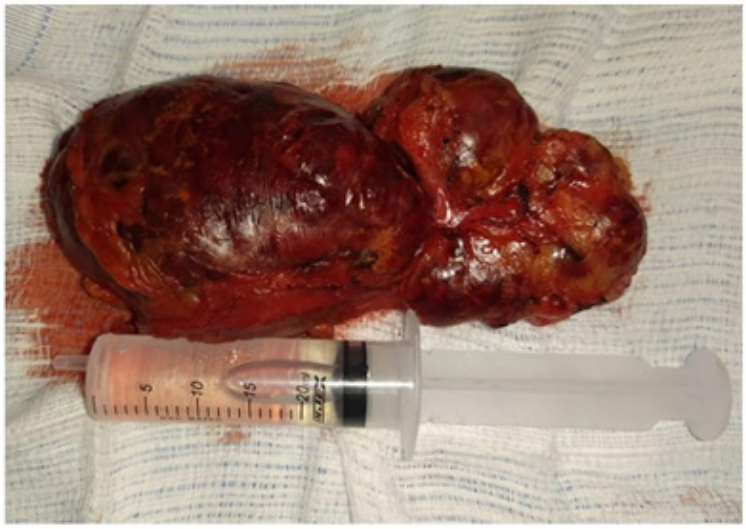

Figure 1: Surgical specimen of the left adrenal gland showing a large mass consistent with myelolipoma. Its size relative to a 20-mL syringe suggests dimensions >12 cm. Histopathological examination confirmed mature adipose tissue and hematopoietic elements, characteristic of adrenal myelolipoma.

Discussion and Final Considerations

17α-Hydroxylase deficiency is a rare form of CAH, accounting for less than 1% of all cases. It is caused by pathogenic variants in homozygosity or compound heterozygosity in the CYP17A1 gene, leading to inadequate synthesis of cortisol and sex steroids. The clinical presentation is variable and depends on the residual activity of the deficient enzyme. Generally, patients exhibit hypergonadotropic hypogonadism, SAH, hypokalemia, and delayed puberty in both males and females, with ambiguous genitalia occasionally observed to varying degrees [11]. In 46,XY individuals, varying degrees of ambiguous genitalia may occur, whereas there is a female phenotype with primary amenorrhea and absence of secondary sexual characteristics in 46,XX individuals.

Furthermore, 17α-OHD leads to accumulated corticosterone and deoxycorticosterone, which possess potent mineralocorticoid activity. These steroids are responsible for the absence of clinical manifestations of adrenal insufficiency and SAH and hypokalemia, secondary to sodium retention, potassium excretion, and suppression of plasma renin activity [11].

In the presented case, diagnosis was initially guided by primary amenorrhea, with a diagnostic hypothesis of gonadal dysgenesis, which was ruled out after an ovarian biopsy showed primordial follicles. The results of the 46,XX karyotype excluded structural alterations of the X chromosome. The presence of SAH and hypokalemia required the investigation of CAH, which was confirmed through hormonal tests and molecular analysis, revealing pathogenic variants in compound heterozygosity in the CYP17A1 gene (p.Arg96Trp and p.Arg362Cys) [12,16,17].

Another notable aspect is the development of bilateral adrenal myelolipoma, particularly the large mass in the left adrenal gland. Myelolipoma is a benign neoplasm composed of mature adipose tissue and hematopoietic elements [14,16]. It is the second most prevalent adrenal incidentaloma, with adenomas being the most frequently identified16. The pathophysiological mechanisms of this condition are not fully elucidated, but there is evidence that chronic ACTH stimulation plays a fundamental role. ACTH stimulates the uptake of cholesterol, and blocking steroidogenesis favours fat accumulation and hematopoietic cell proliferation through metaplasia. Furthermore, infectious factors, necrosis, and chronic inflammation may also be related to tumour formation [14].

There are few reports in the literature of the association between CAH due to 17α-OHD and adrenal myelolipoma. Most cases have occurred in patients with poor adherence to treatment or inadequate control of ACTH levels, as observed in this report. Prolonged ACTH stimulation appears to be the determining factor in tumour formation [14,15,16].

The therapeutic management of CAH due to 17α-OHD aims to normalize ACTH secretion, and serum deoxycorticosterone and corticosterone levels, as well as to control SAH, correct hypokalemia, and induce the development of secondary sexual characteristics. This is achieved through the replacement of glucocorticoids and estrogens (i.e., when there are no contraindications to their use), as well as potassium correction and, when necessary, the use of mineralocorticoid action blockers. In this case, the hypertensive condition was exacerbated by the acute diffuse glomerulonephritis during myelolipoma treatment, which contraindicated the use of estrogens. Although acute diffuse glomerulonephritis and CAH due to 17α-OHD are unrelated, both affect kidney function.

In 46,XY individuals with poorly virilized or female genitalia, prophylactic gonadectomy is indicated due to the increased risk of gonadal malignancy [16].

This report highlights the importance of clinical suspicion of CAH due to 17α-OHD in the presence of clinical manifestations such as primary amenorrhea associated with hypertension and hypokalemia. Early diagnosis is essential for the institution of appropriate treatment and the prevention of comorbidities such as

osteoporosis, stroke, and the formation of adrenal tumours such as myelolipoma.

Adherence to continuous hormone therapy and frequent clinical follow-up is crucial for controlling the disease and preventing complications. Genetic testing is crucial for diagnostic confirmation, facilitating family genetic counseling, and conducting epidemiological studies.

Acknowledgement

None.

Conflict of Interest

None.

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