

Late diagnosis of classic congenital adrenal hyperplasia: long-term consequences during adulthood

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Summary

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders related to enzyme deficiencies in the adrenal steroidogenesis pathway leading to impaired corticosteroid biosynthesis. Depending on the extension of enzyme defect, there may be variable severities of CAH – classic and non-classic. We report the case of a 37-year-old male patient with a previously unknown diagnosis of classic CAH referred to Endocrinology evaluation due to class III obesity and insulin resistance. A high diagnostic suspicion was raised at the first Endocrinology consultation after careful past medical history analysis especially related to the presence of bilateral adrenal myelolipomas and primary infertility. A genetic test confirmed the presence of a variant of the *CYP21A2* in homozygous with an enzymatic activity of 0–1%, corresponding to a classic and severe CAH form. Our case represents an unusually late definitive diagnose of classic CAH since the definition was established only during adulthood in the fourth decade of life. The missing diagnosis of classic 21 hydroxylase deficiency during infancy led to important morbidity, with a high impact on patients' quality of life.

Learning points:

- Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive enzyme disorders responsible for an impaired cortical adrenal hormonal synthesis.
- CAH may be divided into two major forms: classic and non-classic CAH.
- If untreated, CAH may be fatal or may be responsible for important multi-organ long-term consequences that can be undervalued during adulthood.
- Adrenal myelolipomas are associated with chronic exposure to high ACTH levels and continuous androgen hyperstimulation typically found in undertreated CAH patients.
- Testicular adrenal rest tumours (TART) and primary infertility can be the first manifestation of the disease during adulthood.

Background

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders related to enzyme deficiencies in the adrenal steroidogenesis pathway leading to impaired corticosteroid biosynthesis. Mutations of the steroid 21-hydroxylase gene (*CYP21A2*),

located at chromosome 6p21, are responsible for 95% of the congenital adrenal hyperplasia cases (1).

Depending on the extension of enzyme defect, there may be variable clinical severities of CAH. This entity can be classified in two distinct major forms: the classic form



– which includes two subforms: salt-losing and simple virilising – and the non-classic form that corresponds to a mild form of the disease.

The classic form is usually diagnosed at paediatric age, being the treatment essential to normal growth, development and survival during childhood. In the salt-wasting form, which corresponds to 75% of patients with classic CAH, enzyme activity is extremely low, which results in a deficiency of both aldosterone and cortisol. The clinical presentation includes an adrenal crisis in the first weeks after birth with vomiting, dehydration, hypoglycaemia and hypotension as well as pronounced hyperkalaemia and hyponatraemia. In the simple virilising form, a certain level of enzyme function is preserved (1–5%), so that aldosterone production is sufficient to prevent sodium loss and cortisol deficiency is not so pronounced. If untreated, girls may become significantly virilized leading to sexual ambiguity at birth and male patients may have a precocious pseudopuberty and growth acceleration (1).

The goal of maintenance of glucocorticoid and mineralocorticoid therapy in CAH is to replace deficient hormones and, at the same time, control the ACTH-driven adrenal androgens excess. Therefore, maintenance of glucocorticoid therapy controls the dysregulated HPA axis feedback in these patients (2). This is vital to achieve low levels of adrenocortical androgens preventing gland hyperplasia and appearance of benign tumours as adrenal myelolipomas as well as testicular adrenal rest tumours (TART) (3). TART development in undertreated male patients is a common finding, particularly in those with inadequate long-term hormonal control and are frequently responsible for male infertility during adulthood. These benign lesions correspond to ectopic adrenal tissue present during developing testes in response to high circulating ACTH levels and may lead to gonadal dysfunction and infertility (4).

Delayed diagnosis and suboptimal treatment may lead to important clinical consequences with impact in patient's survival and comorbidities during adulthood specially related to reproductive health.

We report the case of a male patient with previously unknown diagnosis of CAH referred to Endocrinology evaluation during adulthood.

Case presentation

We report the case of a 37-year-old male patient referred to an Endocrinology consultation in 2017 initially due to class III obesity and insulin resistance. After collecting his

past medical history, he had precocious development of secondary sexual characteristics at an early age (pubarche at 6 years old and facial hair at 11 years old) and short stature. He also had history of familiar consanguinity as his parents were first cousins.

The patient denied any hospitalization during neonatal and childhood periods or any other relevant hospital admissions since infancy.

There was a history of primary infertility diagnosed in 2007 investigated in another healthcare institution but with no aetiology defined. After careful review of his clinical record, he had documented azoospermia and advanced severe testicular atrophy in testicular biopsy. In spite of this histological finding, the patient was not referred to an Endocrinology consultation until 2017.

In 2015, the patient was referred to an Internal Medicine consultation due to severe obesity and cutaneous lesions. At that time, a diagnosis of leukocytoclastic vasculitis was established and therapy with prednisolone 20 mg once a day was started, with irregular compliance.

From this year, the patient presented frequent complains of low back pain and asthenia which motivated imaging investigation with abdominal CT revealing giant bilateral myelolipomas of the adrenal gland and a suspicious renal tumour mass. From the information available, the patient was proposed to right nephrectomy and adrenalectomy and histological findings revealed the presence of an ectopic adrenal cortical adenoma as well as a 3 cm adrenal myelolipoma in the right adrenal gland, excluding the malignancy nature of the kidney lesion first suspected.

At his first endocrinology clinic evaluation, the patient was on furosemide 40 mg/day (unknown indication), topiramate 25 mg/day and fluoxetine 20 mg/day (as appetite control strategy) and prednisolone 20 mg/day. Regarding prednisolone therapy, the patient admitted irregular compliance, only taking this drug during periods of skin lesions exacerbation.

Clinically, he complained about nausea without vomiting with several years of evolution, chronic asthenia, dizziness and lightheadedness and osteoarticular pain. In the preceding year, symptom exacerbation led to more than 20 emergency department visits and consequently several hospitalizations, without an etiologic definition. The patient also reported considerable weight gain during the past 7 years, without any significant lifestyle modification. Regarding sexual health, the patient, who is married for 20 years, revealed problems with erection, although with preserved sexual desire.

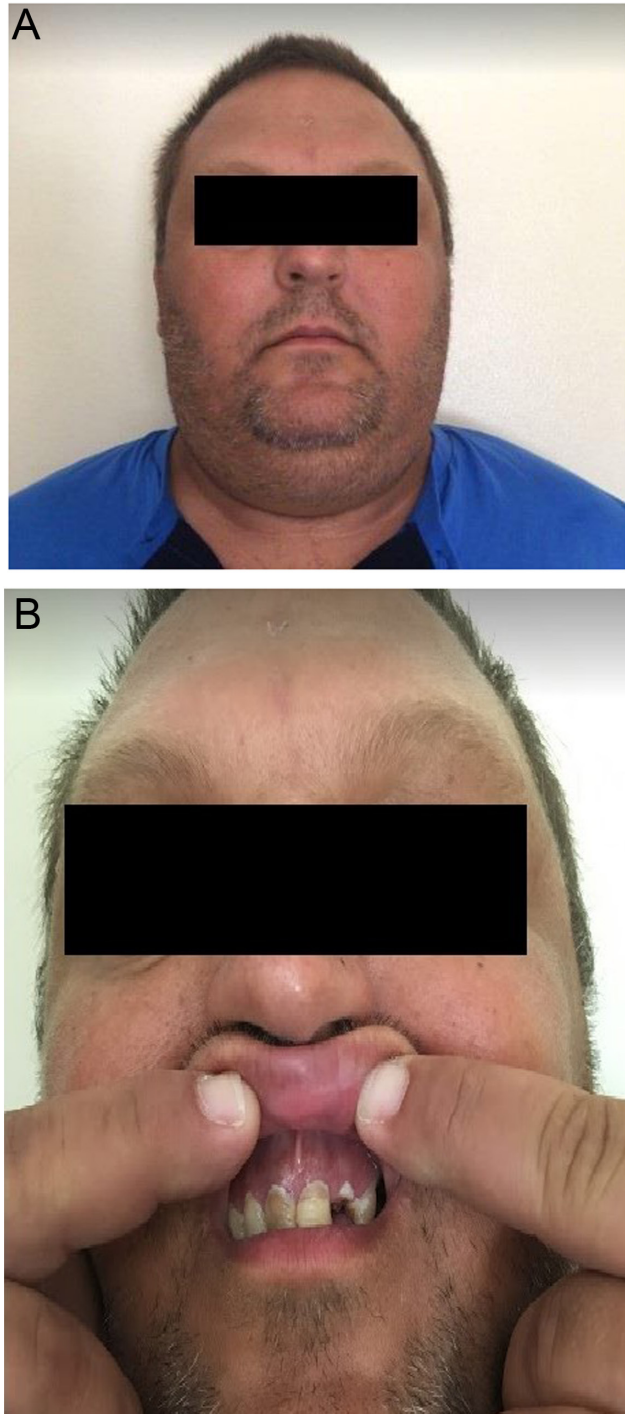


Figure 1
Mucocutaneous hyperpigmentation at first evaluation: face (A) and oral mucosa (B).

On physical examination, we highlight cervical and axillary acanthosis, mucocutaneous hyperpigmentation (Fig. 1A and B), centripetal obesity with a BMI of 46.8 Kg/m² (weight 125.8 Kg; height 165 cm), blood pressure of 111/60 mmHg and retractable, small, hard

and nodular testicles (10–15 cm³ volume) and 6 cm length penis with scarce pubic hair.

Investigation

For careful evaluation of the patient due the necessity of prednisolone therapy suspension, the patient was admitted to the Endocrinology Department ward.

Baseline biochemical and hormonal evaluation showed increased levels of 17-OHP: 57 ng/mL (NR: 0.6–3.4), renin: 181 uU/mL (NR: 7–76) and ACTH: 1351 pg/mL (NR: 9–52), and low levels of cortisol: 1.7 µg/dL (NR: 5–25). The serum ions were within normal range. Additionally, the hormonal workup also revealed low levels of LH, FSH and testosterone (Table 1) raising the suspicion of CAH diagnosis and subsequent hypogonadotropic hypogonadism.

An abdominal CT was performed, identifying signs of right nephrectomy and right adrenalectomy and a thickened left adrenal gland with larger dimension than usual with heterogeneous enhancement. Moreover, a 28 mm myelolipoma and two other nodular lesions were also found in the left adrenal gland, simultaneously (Fig. 2).

A dual energy X-ray absorptiometry scan (DXA) and a pituitary MRI were also performed and both imaging studies had no relevant alterations.

According to findings during genital evaluation, a testicular and scrotal ultrasound was performed and revealed reduced dimensions of both testes (left testis: 33 × 16 × 20 mm and right testis: 29 × 17 × 24 mm) and a 12 mm hypoechogenic nodular formation in the left testis (Fig. 3). These ultrasound findings associated with a negative measurement of βhCG and α-fetoprotein

Table 1 Baseline blood workup at first visit.

Investigation	Result	Normal range
17-OHP (ng/mL)	57	0.6–3.4
DHEA-SO ₄ (ug/mL)	0.5	0.8–5.6
Androstenedione (ug/mL)	4.5	0.6–3.7
Renin (uU/mL)	181	7–76
Aldosterone (pg/mL)	82.9	40–310
ACTH (pg/mL)	1351	9–52
Cortisol (µg/dL)	1.7	5–25
FSH (mUI/mL)	0.5	<15
LH (mUI/mL)	<0.1	<9
Total testosterone (ng/mL)	0.7	2.7–11
Estradiol (pg/mL)	40	6–44
Sodium (mmol/L)	138	135–145
Potassium (mmol/L)	4.5	3.5–4.5

17-OHP, 17-hydroxyprogesterone; DHEA-SO₄, DHEA sulphate. Abnormal values are in bold.

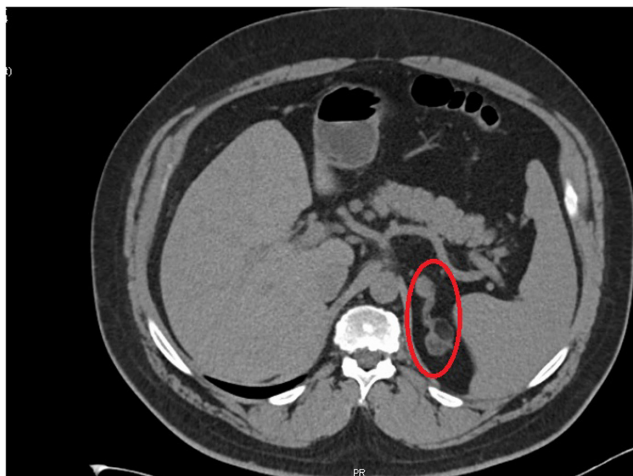


Figure 2
Abdominal CT scan showing an enlarged and thickened left adrenal gland with a 28 mm myelolipoma as consequence of prolonged undertreatment (red circle).

(Table 2), established the diagnosis of testicular adrenal rest tumour (TART) supported by a multidisciplinary team evaluation including Endocrinology, Urology and Radiology medical teams.

In order to obtain a definitive diagnosis, we performed genetic evaluation that confirmed the presence of a variant g.655C > G of the *CYP21A2* (In2G mutation) gene in homozygous (MLPA technique) (5).

Treatment

After in-patient comprehensive evaluation, he started replacement therapy with oral hydrocortisone (30

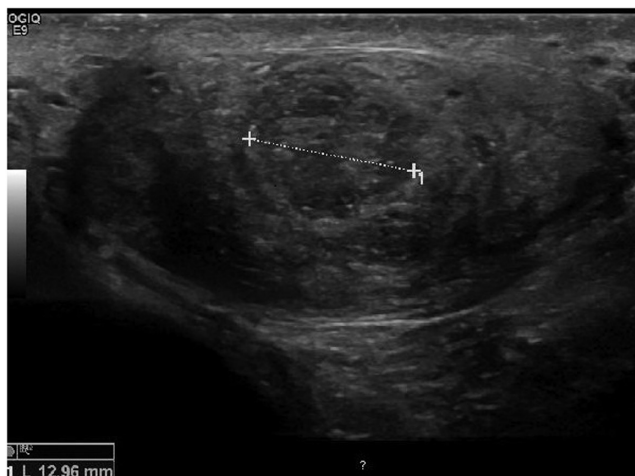


Figure 3
Scrotal and testicular ultrasound revealing a 12.9 mm hypoechoogenic nodular formation in the left testicular tissue.

Table 2 Biochemical markers for testicular cancer evaluation supporting the diagnose of Testicular Adrenal Rest Tumour (TART).

Investigation	Result	Normal range
α -fetoprotein (ng/mL)	1.1	<8.6
β hCG (mUI/mL)	<2.0	<5

mg/day), oral fludrocortisone (0.05 mg/day) and i.m. enanthate testosterone 250 mg every 3 weeks.

Furthermore, the patient initiated personalized medical nutrition therapy and a regular physical activity program.

Outcome and follow-up

The patient is symptom-free for the past 3 years and maintains regular follow-up with Endocrinology consultation. During each visit, a continuous educational strategy is implemented to maximize compliance to chronic therapy and minimize comorbidities. Besides, a recommendation on stress dosing and the importance of wearing a medical bracelet with the diagnosis is always reinforced.

Since the first evaluation, there was no need for any hospitalization due to adrenal crisis or any emergency department admission as was previously described during the last several years.

He also maintains regular follow-up with Urology clinics, once a year, performing bilateral scrotal ultrasound and clinical evaluation. After initiating regular replacement therapy with glucocorticoids, we noticed a near 30% volume reduction of TART lesion, with a current dimension of 8 mm.

Our patient was also referred to bariatric surgery after optimized chronic replacement therapy.

Discussion

Our case represents an unusually late definitive diagnosis of classic CAH since the definition was established only during adulthood in the fourth decade of life.

Indeed, this form is typically diagnosed during infancy or early childhood with signs and symptoms of virilisation and precocious puberty or as an adrenal crisis during neonatal period.

Approximately 75% of patients with classic CAH present with concurrent mineralocorticoid deficiency and impairment of aldosterone synthesis. In these cases, patients present, during first weeks of life, with vomiting,



hyponatraemia, hyperkalaemia and lethargy. In the simple virilising form, the clinical presentation includes early virilisation and accelerated growth velocity related to high serum androgen levels (1).

Distinctly, patients with non-classic form of CAH have a later onset and a milder presentation of the disease being usually diagnosed in late childhood or early adulthood. The symptoms related to this less severe form of disease are variable and may be progressive with age, ranging from asymptomatic individuals to patients with rapid early childhood growth, premature adrenarche, acne, hirsutism and impaired reproductive function (1).

The precocious puberty in CAH is related to the high androgen levels that promote progressive pubic hair development, rapid growth, and rapid bone age maturation, with short stature in adulthood (1, 2).

Adrenal myelolipomas are benign non-functioning tumours of the adrenal cortex composed of adrenal, adipose and myeloid components, accounting for up to 9% of adrenal incidentalomas. The prevalence of myelolipomas in CAH is 7.4% (6). Myelolipomas are usually easy to detect on the basis of their characteristic appearance on CT, where they appear as masses with the density of fat and most also with areas of higher attenuation due to the marrow elements (7). They are usually asymptomatic but can cause compressive symptoms as flank pain and abdominal discomfort due to mass effect. Numerous mechanisms have been proposed to explain the pathogenesis of adrenal myelolipomas in CAH context: the presence of embryonic bone marrow rests in adrenal tissue, adrenal embolization of bone marrow cells and metaplasia of adrenocortical cells. It is thought that these lesions are associated with chronic ACTH hyperstimulation, being described in situations of ACTH excess like in CAH (particularly late-diagnosed or poorly controlled patients), Cushing Disease and Nelson syndrome (6, 7). It has been postulated that these myelolipomas show an overexpression of the melanocortin 2 receptor (MC2R) and androgen receptors and these factors promote the development and growth of these adrenal lesions continuously (8).

In addition to this fact, undertreated CAH patients may present with TART, which corresponds to a nodular testicular lesion derived from ectopic adrenal tissue present during developing testes in response to high circulating ACTH levels. These lesions may lead to both testicular structure and spermatogenesis disorders and decreased testosterone production, as occurred with the patient of this case report (4).

Our patient also presented a documented hypogonadotropic hypogonadism and a history of

infertility with several years of follow-up with unknown origin. Hypothalamic-pituitary-gonadal axis is suppressed in this specific context by abnormally elevated adrenal androgen secretion observed in undertreated CAH patients. This, in turn, may result in a possible decrease in testicular volume and spermatogenesis, compromising fertility (9).

We recognize that cultural practices led to a devaluation of clinical symptoms during infancy and can explain part of the patient's lack of knowledge about his past medical history until adulthood. Nevertheless, in addition to the history of precocious puberty and consanguinity, high diagnostic suspicion was raised at the first Endocrinology consultation after careful investigation of past medical history especially related to the presence of bilateral adrenal myelolipomas and primary infertility.

Genetic analysis established the final diagnosis of classic simple virilisation due to 21-hydroxylase deficiency with an enzymatic activity of 0–1%. This genotype is congruent with the clinical manifestations of the patient, namely: precocious puberty, short stature, adrenal myelolipomas and adenomas and primary infertility.

Although it is a rare disease, CAH should be suspected in any male patient presenting with precocious puberty and a history of infertility. If it is diagnosed early and properly treated, life expectancy is similar to the general population and males' fertility may be re-established. However, when it is not diagnosed early and consequently undertreated for several years, this condition is associated with important morbidity, impacting patients' quality of life and future health.

The incorporation of the CAH screening in our neonatal universal screening programme should be considered shortly, to avoid situations like the one described in this case report.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article.



Author contribution statement

M A L and A S L wrote the case report. A S L was responsible for the case management. L B reviewed the manuscript. IP is the head of Endocrinology Department and supervised the patient follow-up. All the authors read and approved the final manuscript.

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Received in final form 31 March 2021

Accepted 8 April 2021