# Adrenal hypoplasia congenita: a rare cause of primary adrenal insufficiency and hypogonadotropic hypogonadism

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## Abstract

Primary adrenal insufficiency is defined by the impaired synthesis of adrenocortical hormones due to an intrinsic disease of the adrenal cortex. Determining its etiology is crucial to allow adequate long-term management and genetic counseling. We report the case of a male adolescent that presented in the neonatal period with adrenal crisis and received replacement therapy for primary adrenal insufficiency. During follow-up, adrenal hypoplasia congenita (AHC) was suspected given his persistently raised adrenocorticotropic hormone levels, with markedly low 17-OH progesterone and androstenedione levels. DNA sequence analysis revealed a mutation in *NR0B1* gene (c.1292delG), confirming the diagnosis. Delayed puberty and persistent low levels of gonadotropins led to testosterone replacement therapy. X-linked AHC is a rare cause of primary adrenal insufficiency and hypogonadotropic hypogonadism, related to mutations in *NR0B1* gene. Despite its rarity, AHC should be considered in patients who present with primary adrenal failure, low levels of 17-OH progesterone and hypogonadotropic hypogonadism.

## Introduction

Primary adrenal insufficiency is defined by the impaired synthesis of adrenocortical hormones, secondary to an intrinsic disease of the adrenal cortex. This can occur either due to an enzymatic defect in steroid biosynthesis or to abnormal gland development.[1] It usually presents early in life with severe salt-wasting requiring urgent glucocorticoid and mineralocorticoid replacement.[2,3] Defining the etiology can be challenging but is crucial to allow identification of associated features and appropriate genetic counseling.[2]

## Case Report

An 18-day-old male newborn was admitted with vomiting and failure to thrive. He had a 13-year-old healthy sister and was born from non-consanguineous and healthy parents, after an uneventful pregnancy. Birth weight and length were adequate for gestational age. He showed severe signs of dehydration and malnutrition, generalized skin hyperpigmentation and normal genital development.

Biochemical measurements showed hyponatremia, hyperkalemia and metabolic acidosis. Hormonal evaluation revealed high levels of adrenocorticotropic hormone (ACTH) [2615 pg/mL; reference values (RV): 0-46 pg/mL], and mildly elevated plasma 17-OH progesterone (13.1 ng/mL; RV: 1-7 ng/mL) and androstenedione levels (4.6 ng/mL; RV: 0.6-3.1 ng/mL). Aldosterone was low (20.6 ng/dL; RV: 35-300 ng/dL), active renin high (1170 pg/mL; RV: 1.6-15 pg/mL) and serum cortisol was inadequately normal (11.1 μg/dL; RV: 4.3-23 μg/dL) given the stressful context. Primary adrenal insufficiency due to congenital adrenal hyperplasia (CAH) was suspected. Treatment with hydrocortisone, fludrocortisone and salt was initiated with good response. He was discharged home, maintaining follow-up care in our unit and treatment with good adherence. Throughout infancy he maintained adequate growth, normal development, with no major illnesses. However, his ACTH levels were persistently raised, and 17-OH progesterone and androstenedione markedly low (Table 1). Adrenal ultrasonography was normal. At the age of 6 years, these findings prompted further investigation to exclude an abnormal gland development, rather than a steroid biosynthesis defect as was first hypothesized. DNA sequence analysis revealed a hemizygous deletion mutation in *NR0B1* gene (c.1292delG), originating a non-functional DAX1 protein. The final diagnosis of congenital adrenal hypoplasia was then made. His mother was identified as a carrier of this mutation and his sister was found to be unaffected.

Delayed onset of puberty and consistently low levels of gonadotropins and testosterone (Table 2) were observed throughout his preadolescent and adolescent years. This led to the initiation of therapy with testosterone at the age of 14. He is currently 16 years old, has adequate growth and a A3P3G4 Tanner stage with prepubertal testes.

## Discussion

X-linked AHC is a rare disorder caused by genetic defects in the differentiation of adrenocortical cells. Its precise incidence is unknown but is estimated to be within 1:140,000 and 1:1,200,000 live births.[2] The development of the definitive zone of the adrenal cortex in the first trimester of gestation is impaired in AHC, compromising both cortisol and mineralocorticoid secretion.

This condition is caused by mutations in *NR0B1* gene, encoding the DAX-1 protein, which plays a significant role in adrenal and gonadal development. *NR0B1* gene is located in the short arm of X chromosome and is expressed in the adrenal cortex, gonads, hypothalamus and pituitary gland.[4] Most mutations and large deletions lead to severe neonatal abnormalities, whereas some missense mutations or single deletions become apparent only in adulthood.[5] Clinical presentation is highly variable regarding the age of onset and the severity of adrenal failure, and even identical mutations may be associated with different phenotypes.[6-9] Most affected individuals tend to present with acute adrenal crisis in the first weeks of life. Few patients, however, have residual mineralocorticoid and glucocorticoid activity, and adrenal failure may not be evident until they reach childhood or adulthood.[5] Cases of isolated mineralocorticoid deficiency have also been described.[10]

Patients who present early in life with failure to thrive, vomiting, salt-wasting and skin hyperpigmentation have a clinical picture indistinguishable from the one observed in 21-hydroxylase deficiency, a fairly more common disorder. Therefore, AHC might be overlooked in this setting and patients misdiagnosed with CAH.[11,12] However, a prominent feature of AHC

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**Table 1. Patient's hormonal profile throughout the first 5 years of follow-up.**

| | Reference values | Age, years | | | | |
|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 |
| Adrenocorticotropic hormone, pg/mL | 0-46 | 271 | 1639 | 18.9 | - | 803 |
| 17(OH) progesterone, ng/mL | 0.3-2 | 0.06 | 0.15 | 0.04 | 0.02 | 0.02 |
| Androstenedione, ng/mL | 0.6-3.1 | 0.02 | 0.02 | 0.08 | 0.12 | 0.2 |
| Cortisol, μg/dL | 4.3-23 | - | 0.3 | 0.6 | - | 0.2 |

**Table 2. Patient's gonadotropins and testosterone measurements throughout preadolescence and adolescence, prior to testosterone replacement therapy.**

| | Reference values | Age, years | | | |
|---|---|---|---|---|---|
| | | 11 | 12 | 13 | 14 |
| Testosterone, ng/dL | - | <10 | <10 | <10 | <10 |
| Luteinizing hormone, U/L | 0.1-6.0 | <0.07 | <0.07 | <0.07 | <0.07 |
| Follicle-stimulating hormone, U/L | 1.2-7.8 | 0.3 | 0.66 | 1.81 | 1.63 |

is that androgen secretion is also impaired, unlike what typically occurs in CAH.

In our case, the initial presentation with salt-wasting, markedly raised ACTH and good response to glucocorticoids and mineralocorticoids led to the misdiagnosis of CAH at first. It is interesting, however, to recognize that the initial levels of 17-OH progesterone were only mildly elevated, differing from the markedly raised levels that typically characterize CAH. It has been hypothesized that this phenomenon might be due to a disturbed steroid production in the neonate's persisting adrenal fetocortex.[11] Moreover, the persistently low levels of both 17-OH progesterone and androstenedione throughout the years were key to evoke the hypothesis of AHC, encouraging further investigation. It is fundamental to distinguish these two entities – CAH and AHC – given the differences that eventually arise in their clinical course and associated features. Considering the difficulties to achieve confirmation of AHC relying only on clinical grounds, it is of the uttermost importance to obtain a precise genetic diagnosis. This has significant implications regarding long-term management, identification of the carrier status of the women in the family, and early treatment of potentially affected offspring.

Boys with AHC may develop hypogonadotropic hypogonadism due to impaired gonadotropin synthesis and release. Delayed or arrested puberty becomes evident during adolescence. This may be a consequence of combined hypothalamic, pituitary and Sertoli cell defects.[3] Testosterone replacement is then needed to ensure normal development of secondary sexual characteristics, growth and bone mineralization. Infertility is also associated with AHC in adult males and it does not appear to respond to treatment with exogenous gonadotropin or pulsatile gonadotropin-releasing hormone. A case of central precocious puberty has also been reported, adding more questions to the underlying mechanisms that affect puberty in patients with *NR0B1* mutations.[13]

Our patient exhibited delayed puberty with hypogonadotropic hypogonadism. Attainment of secondary sexual characteristics would have been unlikely if testosterone replacement had not been started. Very few articles mention the long-term evolution of patients with AHC – our patient has now a 16 year long follow-up (10 years after diagnosis) and close monitoring proved crucial to anticipate pubertal derangements and to intervene accordingly.

## Conclusions

We report a rare cause of primary adrenal insufficiency. Mutations in *NRB01* gene should be sought in patients presenting with adrenal crisis, low levels of 17-OH progesterone and hypogonadotropic hypogonadism.

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