Case Report

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Congenital hyperreninemic hypoaldosteronism: A case report

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Abstract

Congenital hypoaldosteronism is a rare autosomal recessive or dominant endocrinopathy with variable penetrance, secondary to primary defects in aldosterone synthesis that could lead to hypovolemia, hyponatremia, hyperkalemia, failure to thrive, microcephaly, seizures, neurodevelopmental delay, or hearing loss. We present the case of a Colombian patient with congenital hypoaldosteronism, who owns two variants in the *CPY11B2* gene, and a heterozygous pathogenic variant for nonclassical congenital adrenal hyperplasia. However, the patient missed follow-up and treatment for 6 years. At the age of 7 years, he resumed medical follow-up with laboratory findings of hyperreninemia and hypoaldosteronism, as well as clinical findings of strabismus, left mixed hyperacusis, and pathological short stature (−4.3 SD). Therefore, a trial of fludrocortisone therapy was started with subsequent improvement in renin levels, weight gain, and growth velocity. After 10 months of the start of the medication, he presented hypertension. There is no literature about the late treatment of this condition for pathological short stature.

Keywords

Growth, hypoaldosteronism, hyperreninemic, *CYP11B2*, fludrocortisone

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Introduction

Hypoaldosteronism is an endocrinopathy that may be secondary to inadequate stimulation of aldosterone secretion, primary defects in aldosterone synthesis, or aldosterone resistance.[1] Primary defects in aldosterone synthesis can lead to hyperreninemic hypoaldosteronism which results from impaired aldosterone synthase enzyme activity encoded by the *CPY11B2* gene, which is responsible for catalyzing the conversion of corticosterone to aldosterone by 18-hydroxylation and 18-methyl oxidation.[1] Deficiency of this enzyme can display two distinct biochemical modalities; aldosterone synthase deficiency type I (ASD I) and aldosterone synthase deficiency type II (ASD II). Both disorders show low aldosterone and high plasma renin levels. However, ASD I shows mildly decreased 18-hydroxycorticosterone levels resulting from altered 18-hydroxylation, whereas ASD II exhibits significantly elevated levels of this molecule, as it affects the oxidation of 18-hydroxycorticosterone to aldosterone.[2]

Clinical presentation of this entity includes water and electrolyte imbalances with variable degrees of hyponatremia, hyperkalemia, and metabolic acidosis, as well as dehydration and failure to thrive. Most patients debut

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Table 1. Initial inpatient laboratories.

Laboratories
Complete blood count: WBC 14,729, N 50%, L 38%, Hb 10.6 g/dL, Ht 32.3%, Plt 362.000
Urinalysis density 1005, pH 6.5
Venous blood gases: pH 7.37, PCO2 26, HCO3 15, EB −10
Cortisol 16 µg/dL, ACTH 10.63 pg/mL, DHEAS 4.3 µg/dL, androstenedione 0.28 ng/mL, 10 OH progesterone 1.58 ng/dL
Renin > 300 pg/mL, aldosterone 34.42 pg/mL
Sodium 122 meq/L, potassium 7.5 meq/L, chlorine 98 meq/L
Glycemia 107 mg/dL

Anthropometric data based on growth charts for the Colombian population.

with symptomatology usually before the age of 3 months, but generally after the fifth day of life.[1] Patients with congenital hypoaldosteronism require continuous mineralocorticoid replacement therapy with fludrocortisone and occasional oral sodium supplementation to improve symptoms and achieve catch-up growth.[1,2]

The following article presents the first case of a Colombian patient with congenital hypoaldosteronism who has two variants in the *CPY11B2* gene and a heterozygous pathogenic variant for nonclassical congenital adrenal hyperplasia, in whom follow-up was lost for 6 years and resumed at 7 years with pathological short stature, a prepubertal stage, where replacement with fludrocortisone was restarted.

Case presentation

One-month-old male patient, son of healthy parents (Table 1 initial inpatient laboratories), with a history of full-term delivery at 39 weeks, with low weight and short height at birth (weight 2400 g, −1.93 SD, height 48 cm, −0.41 SD), who presented to the emergency room with a 1-month history of postprandial emesis of food content, 5–6 times a day, being exclusively breastfed. Physical examination was relevant for severe acute malnutrition, with weight at −4.32 DS, height at −1.68 SD, and W/H at −5.36 SD, with normal external male genitalia. An ultrasound was performed, which ruled out congenital pyloric stenosis. The blood workup showed hydro electrolytic imbalance due to hyponatremia down to 122 meq/L and hyperkalemia up to 7.5 meq/L, with normal cortisol, androgen panel, and adrenocorticotropin hormone (ACTH) levels. He did not present renal impairment and had normal aldosterone levels (34.42 pg/mL) and elevated renin levels (>300 pg/mL). Hyperreninemic hypoaldosteronism was suspected. It was not possible to carry out a genetic study at that time, so it was decided to start a therapeutic trial with fludrocortisone at a dose of 0.1 mg, and with a progressive increase, up to 0.25 mg per day divided into two doses.

He had clinical and biochemical improvements. He presented no further episodes of emesis, with weight gain up to 50 g/day, and presented correction of the hydroelectrolytic disorder. He received supplementation without interruption for 1 year and then, due to severe socioeconomic difficulties, he lost follow-up and suspended management for approximately 6 years. He returned to the pediatric endocrinology clinic at the age of 7 years and 9 months, due to pathological short height and very low weight. He additionally had right strabismus and left mixed hearing loss. Paraclinical findings (Table 2), showed an inappropriately normal level of aldosterone for the level of hyperreninemia, without electrolyte alteration.

Table 2. Blood test when the patient returns to clinic.

Date	Laboratories	Normal range
April 9, 2017	Aldosterone: 2.28 ng/dL	3–35 ng/dL
	Renin: 149.2 ng/L	0.04–4.95 ng/L
	Sodium: 137.2 me/L	133–145 meq/L
	Potassium: 4.77 meq/L	3.5–5.0 meq/L
December 30, 2019	Aldosterone: 2.79 ng/dL	3–35 ng/dL
	Renin: 1312 ng/L	0.04–4.95 ng/L
	Sodium: 140 meq/L	133–145 meq/L
	Potassium: 4.82 meq/L	3.5–5.0 meq/L

Normal range were taken from Esoterix Labcorp.

Table 3. Molecular analysis.

1. Primary findings
- The patient is heterozygous for *CYP11B2* c.594A > C, p.(Glu198Asp), which is pathogenic
- The patient is heterozygous for *CYP11B2* c.395 + 1_395 + 2del, which is likely pathogenic
2. Additional findings
- The patient is heterozygous for CYP21A2 c844G > T, p(Val282Leu), which is pathogenic

Upon return to clinic, a genetic study was performed for *CYP11B2*, which shows two variants: (1) pathogenic for congenital hypoaldosteronism, and (2) possibly pathogenic for a heterozygous pathogenic variant for nonclassical congenital adrenal hyperplasia (Table 3). During the follow-up, he did not show electrolyte alterations (Table 4), however, he continued with slow growth velocity and poor weight gain.

In the review of the literature, there are few reported cases of congenital hypoaldosteronism, and to a lesser extent, we found none for patients with such prolonged loss of medical follow-up, as well as the results of late treatment on the growth pattern. Since the patient was prepubertal, with a bone age of 5 years (chronological 7 years 9 months), normotensive, with normal electrolytes and normal renal function, it was decided to start a new therapeutic trial with fludrocortisone at a dose of 0.2 mg per day divided into two doses. We carried out continuous monitoring of blood pressure, levels of electrolytes, and anthropometry.

Table 5 shows the improvement of the SD in weight and height when starting the medication. It is observed that an improvement in weight was achieved from −5.28 SD to

Table 4. Follow-up laboratories.

Age	Paraclinical findings	Dose of fludrocortisone
1 year 5 months	Na 139 meq/L K 4.23 meq/L	Without medication
4 years 6 months	Na 137.2 meq/L, K 4.77 mmol/L Urinary K 43 mmol/L	Without medication
7 years 10 months	Na 135.5 meq/L K 4.3 meq/L	Without medication
8 years 2 months	Na 141 meq/L K 5 meq/L	Without medication
8 years 10 months	Na 143 meq/L K 3.4 meq/L	0.1 mg every 12 h
9 years	Na 139 meq/L K 3.9 meq/L	0.1 mg every 24 h
9 years 5 months	Na 142 meq/L K 3.9 meq/L	0.1 mg every 12 h
9 years 8 months	Na 137 meq/L K 4.9 meq/L	Without medication
10 years 1 month	Na 140 meq/L K 4.8 meq/L	0.1 mg every 24 h
10 years 4 months	Na 144 meq/L K 4.5 meq/L	0.1 mg every 24 h

−3.34 SD in 10 months and an improvement in height from −4.32 SD to −4 SD in 8 months. Nevertheless, he presented hypertension, reaching the percentile 99 +5 in systolic and diastolic blood pressure, although the dose was decreased to 0.1 m/day, so medication was suspended (Table 5). Once the medication was stopped, growth velocity decreased from 6 to 2.88 cm/year.

Renal and cardiac studies were carried out due to hypertension. No abnormality in renal function was found, and he had a normal echocardiogram and 24-h holter.

Nowadays, the patient is with fludrocortisone 0.1 mg every 24 h, he has maintained normal blood pressure, with a growth velocity of 5.1 cm/year. The patient is still prepuberal with delay in bone age.

Discussion

Aldosterone is a mineralocorticoid that maintains electrolyte balance by increasing sodium reabsorption and potassium secretion in the collecting duct of the nephron.[2] It is synthesized in the zona glomerulosa of the cortex of the adrenal gland; thereby, dysfunction of the latter could lead to aldosterone deficiency. Hypoaldosteronism can be classified into three categories: defective stimulation of aldosterone secretion, primary defects in adrenal synthesis or secretion of aldosterone, and aldosterone resistance. Within the second category, hypoaldosteronism can result from all causes of primary adrenal insufficiency and primary hypoaldosteronism caused by ASD or as an acquired state secondary to infections, lesions, or autoimmune processes.[3–5]

ASD is a rare genetic disorder inherited in an autosomal dominant or recessive manner with mixed penetrance. This condition is caused by impaired aldosterone synthase enzyme activity encoded by the *CYP11B2* gene located on chromosome 8q24.3, leading to hyperreninemic hypoaldosteronism. As mentioned before, ASD is subdivided into two types according to 18-hydroxycorticosterone levels, being mildly decreased in ASD I and significantly elevated in ASD II.[1–4]

Clinical presentation includes frequent vomiting, dehydration, hypovolemia, electrolyte disturbances such as hyponatremia, hyperkalemia, metabolic acidosis, and failure to thrive.[1,3,6] These symptoms generally develop as early as 3 months of age, most commonly after the first 5 days of life.[1] The patient presented these symptoms within the first month of life, mainly emetic episodes. At the time of evaluation, he had severe acute malnutrition associated with hyponatremia and hyperkalemia. Some case reports also mention the presence of microcephaly, neurological alterations such as seizures or neurodevelopmental delay,[7] and hearing loss due to aldosterone receptors in the cochlea.[5] Our patient had no neurological symptoms; his main compromise was weight and height. However, at the time that he reconsulted at age 7, he did present left mixed hearing loss.

Biochemical findings include electrolyte disturbances such as hyponatremia and hyperkalemia, as well as low aldosterone levels combined with elevated renin and plasma renin activity (PRA),[8] as was found in this patient, for which the diagnostic suspicion was made from an early age.

Measurement of adrenal steroids is also important in the diagnosis of ASD, with elevated plasma levels of 11-deoxycorticosterone and corticosterone, and mildly decreased or significantly increased levels of 18-hydroxycorticosterone levels (ASD I and ASD II, respectively). These measurements are not available in our country, so it was not possible to perform them. Patients with this condition require mineralocorticoid replacement therapy and oral sodium supplementation with plasma renin follow-up.[1–4] Mineralocorticoid replacement was started in our patient and maintained within a year, with improved symptoms, resolution of electrolyte disturbances, and weight gain.[9]

Among several studies, research has demonstrated the effects of hormone replacement in the biochemical variables implicated in hyperreninemic hypoaldosteronism, as well as in clinical variables such as height and weight.[4] The Kayes-Wendover study includes five patients with clinical manifestations of hydro-saline crisis and failure to thrive associated with a marked elevation of PRA and low or inappropriately normal levels.[5] This study demonstrated how fludrocortisone replacement in a dose of 150 µg per day normalized electrolyte levels and PRA at the first months of life.[5] However, hormonal replacement dose is debatable, since studies as the Rubio-Cabezas' group propose up to 25 µg/kg/day, Dr. Sethupathi's group used a dose of 12 µg/kg/day while Dr. White's proposes schedules between 100 and 300 µg per day.[5,9–11] But all of them started the medication during the first months of life.

Table 5. Follow-up data of weight, height, and blood pressure with fludrocortisone.

Age	Weight (kg)	SD	Height (cm)	SD	Growth velocity	Arterial pressure Systolic blood pressure (SBP) Diastolic blood pressure (DBP)	Dose of fludrocortisone
7 years 2 months	13.7	(−) 5.45	102.0	(−) 4.34			
8 years 2 months	15.0	(−) 5.25	104.3	(−) 4.47	2.3 cm/year		
8 years 8 months						SBP P50 DBP P50	Medication started with 0.1 mg every 12 h
8 years 10 months	15.8	(−) 5.28	107.8	(−) 4.32		SBP P99, DBP P99 + 5	0.1 mg every 12 h
9 years 3 days	15.6	(−) 5.61	108.5	(−) 4.30	5.6 cm/year	SBP P99 + 5, DBP P99 + 5	Medication is decreased by 0.1 mg every 24 h
9 years 18 days						SBP P50, DBP P90	0.1 mg every 24 h
9 years 2 months						SBP P5, DBP P50	0.1 mg every 24 h
9 years 3 months						SBP P50, DBP P50	Medication is increased by 0.1 mg every 12 h
9 years 4 months	16.7	(−) 5.02	111.2	(−) 4.03	8.1 cm/year	SBP P5, DBP P50	0.1 mg every 12 h
9 years 6 months						SBP P99, DBP P99	0.1 mg every 12 h
9 years 7 months	16.5	(−) 5.37	112.0	(−) 4.0	6 cm/year	SBP P95, DBP P99	Medication is decreased by 0.1 mg every 24 h
9 years 7 months						SBP P99 + 5 DBP P99	Medication is suspended
9 years 9 months	20.0	(−) 3.34	112.0	(−) 4.12	2.88 cm/year	SBP P50, DBP P50	Without medication
10 years 2 days	18.0	(−) 4.64	113.2	(−) 4.05		SBP P5, DBP P5	Without medication
10 years 1 month							Medication is started with 0.1 mg every 24 h
10 years 2 months	19.8	(−) 3.75	114.5	(−) 3.92	6 cm/year	SBP P50, DBP P50	0.1 mg every 24 h
10 years 6 months	20	(−) 3.83	116.3	(−) 3.76	5.1 cm/year	SBP P5, DBP P5	0.1 mg every 24 h

Correspondingly, case reports such as Dr. Sethupathi's group show that hormone replacement is not the only determinant to normalize biochemical variables but also allows for adequate and continuous weight gain and improvement in developmental milestones at an early age.[2,9–11] Similar results were demonstrated by the study of Dr. H. Miao and collaborators, who present the case of a Chinese patient with congenital hypoaldosteronism in whom mineralocorticoid replacement started at 12 months of age at a dose of 75 µg per day; 5 months later, he recovered growth velocity.[2] On the other hand, a case report of Lages et al.,[6] involving a Portuguese patient with ASD type I in whom fludrocortisone replacement therapy was given at 54 days old at a dose of 75 µg per day, allowed weight and height recovery during a 6-year follow-up period. In the literature, there are few reported cases of congenital hypoaldosteronism, and to a lesser extent, we found none for patients with such prolonged loss of medical follow-up as our patient, as well as the results of late treatment on the growth pattern.

Fludrocortisone replacement therapy was initiated at a dose of 0.1 mg twice a day at the age of 7 years 9 months old when he returned to the clinic. After the first 2 months of therapy, the patient presented electrolyte balance, normal plasma renin levels, and improvement in growth velocity. Moreover, after 10 months of therapy, he achieved improvement in standard deviations of weight and height.

Current evidence demonstrates that early supplementation with fludrocortisone is necessary to resolve electrolyte disturbances and long-term growth recovery.[1–7,9–11] However, there is no consensus on the appropriate treatment dosage, nor the severity associated with discontinuing treatment and follow-up loss. Even though the literature presents different therapeutic regimens,[1–5,7,9,10] studies include diverse populations worldwide, excluding Latin American groups. Furthermore, there are no studies that evaluate fludrocortisone restart after missed follow-up in prepubertal patients.

Conclusion

ASD is a rare cause of hyperreninemic hypoaldosteronism and severe failure to thrive, mainly inherited in an autosomal recessive pattern. Fludrocortisone, started in early infancy, has shown to be an effective treatment to normalize height and weight in these patients, as well as electrolytes and renin levels. We described a patient with ASD without treatment up to 7 years of age who presented to the clinic with pathological short stature and extremely low weight. In the few reported cases in the literature for this entity, treatment was started within the first months of life and was given constantly. There are no reported cases of late treatment and outcome. A trial with fludrocortisone in our patient showed improvement in growth velocity and weight gain, but he presented arterial hypertension. Treatment for this patient has been challenging. There is no evidence of late therapy on final height outcomes, and it is unclear if it is worth it to expose the patient to arterial hypertension and its possible deleterious effects.

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Author contributions

P.D.V. and M.E.Y. wrote the article, designed the project, analyzed the data, and contributed to the discussion of the article; P.D.V. treated the patient, gathered the patient's information, and supervised the project and research. All authors have read and approved the article. All the authors have accepted responsibility for the entire content of this submitted article and approved the submission.

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Ethical approval

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Informed consent

Written informed consent was obtained from a legally authorized representative of the patient for their anonymized and approval information to be published in this article.

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