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ALDOSTERONE SYNTHASE DEFICIENCY FROM HOMOZYGOUS CYP11B2 MUTATION PRESENTING WITH SALT-WASTING CRISIS AND FAILURE TO THRIVE IN AN INFANT

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Abstract

Introduction: Aldosterone synthase deficiency (ASD) is a rare autosomal recessive disorder caused by pathogenic variants in the CYP11B2 gene, leading to impaired aldosterone synthesis and life-threatening salt-wasting. We present a case of an infant with failure to thrive, dehydration, and electrolyte imbalance, diagnosed through next-generation sequencing.

Material and Methods: mitted with persistent vomiting, constipation, and a10% weight loss. Laboratory evaluation showed severe hyponatremia (116 mmol/L), hyperkalemia (6.5 mmol/L), hypochloremia (87 mmol/L), and metabolic alkalosis. Differential diagnosis included gastrointestinal loss, renal salt-wasting, cystic fibrosis, celiac disease, and congenital adrenal hyperplasia. Normal 17-hydroxyprogesterone excluded classical CAH. Next-generation sequencing was performed.

Results: A homozygous pathogenic variant c.554C>T (p.Thr185Ile) in CYP11B2 confirmed ASD. Treatment with fludrocortisone and sodium supplementation resulted in rapid correction of electrolytes and improved growth. Follow-up at 3.5 years showed normal growth (14.5 kg, 103 cm), stable electrolytes, and normal development, with only mild transient hyponatremia during illness.

Conclusion: ASD should be considered in infants with vomiting, dehydration, and combined hyponatremia–hyperkalemia when CAH is excluded. Early diagnosis and mineralocorticoid therapy prevent complications and support normal development.

Key words: *aldosterone synthase deficiency; CYP11B2; infant; hyperkalemia; hyponatremia; fludrocortisone.*

Introduction

Aldosterone synthase deficiency (ASD) is a rare autosomal recessive disorder caused by pathogenic variants in the CYP11B2 gene, which encodes aldosterone synthase—the mitochondrial

enzyme responsible for the final steps of aldosterone synthesis (1). Aldosterone plays a crucial role in sodium and potassium regulation, extracellular fluid balance, and blood pressure homeostasis. Impaired synthesis leads to salt-wasting, dehydration, vomiting, failure to thrive, and potentially life-threatening electrolyte disturbances, most commonly hyponatremia and hyperkalemia (2).

Although ASD is extremely uncommon, with fewer than one hundred reported cases worldwide, its clinical presentation overlaps with more prevalent neonatal and infantile conditions such as congenital adrenal hyperplasia (CAH), renal tubular disorders, gastrointestinal salt loss, cystic fibrosis, and endocrinological abnormalities (3). Because CAH is often the first diagnostic consideration in infants presenting with hyponatremia and hyperkalemia, ASD may remain unrecognized until severe metabolic derangements occur or until genetic testing is performed (3,4). Early distinction between these disorders is essential, especially in critically ill infants with combined hyponatremia and hyperkalemia but normal cortisol and 17-hydroxyprogesterone levels.

ASD is classified into two biochemical subtypes: type I, characterized by defective conversion of corticosterone to aldosterone; and type II, characterized by partial enzymatic activity with insufficient aldosterone production (1,4). Both types may present in infancy with episodes of vomiting, dehydration, hypotension, and poor weight gain, often precipitated by physiological stress or decreased oral intake (5). Without timely recognition and appropriate mineralocorticoid replacement, affected infants are at risk for cardiovascular collapse, arrhythmias due to severe hyperkalemia, and significant long-term morbidity.

The availability of next-generation sequencing has substantially improved the ability to diagnose rare adrenal disorders such as ASD (4,5). This case report describes an infant with persistent salt-wasting, metabolic derangements, and growth failure, ultimately diagnosed with ASD following extensive clinical and genetic evaluation. The case emphasizes the importance of considering mineralocorticoid synthesis defects in infants presenting with unexplained hyponatremia and hyperkalemia, particularly when CAH has been excluded. We present a rare case of aldosterone synthase deficiency caused by a homozygous CYP11B2 mutation, presenting with severe salt-wasting crisis and failure to thrive.

Material and method

A 9-month-old male infant was admitted to the Pediatric Department at Acibadem Sistina Clinical Hospital due to persistent vomiting, constipation, reduced oral intake, and poor weight gain. He was born full-term with a birth weight of 4100 g, and was exclusively breastfed until 5 months of age, after which complementary feeding was introduced. The parents reported normal growth and feeding in the early months of life, with progressive onset of symptoms after transition to mixed nutrition. There was no history of fever, diarrhea, respiratory infection, or previous hospitalizations.

On admission, the infant appeared lethargic and clinically dehydrated. Vital signs were: heart rate 168/min, respiratory rate 42/min, blood pressure 75/45 mmHg, and capillary refill >3 seconds. Physical examination revealed dry mucous membranes, decreased skin turgor, mild hypotonia, and reduced subcutaneous fat tissue. His weight was below the 3rd percentile for age, with a documented weight loss of approximately 10% over several weeks.

Initial laboratory investigations showed severe electrolyte imbalance with serum sodium 116 mmol/L, potassium 6.5 mmol/L, chloride 87 mmol/L, and metabolic alkalosis (pH 7.51). Renal function tests were within normal limits for age. Blood glucose was normal. Stool examination showed no pathological findings. Abdominal ultrasound and chest radiograph revealed no abnormalities. Urine analysis demonstrated no glycosuria or proteinuria, while urine sodium was low, suggesting renal salt loss.

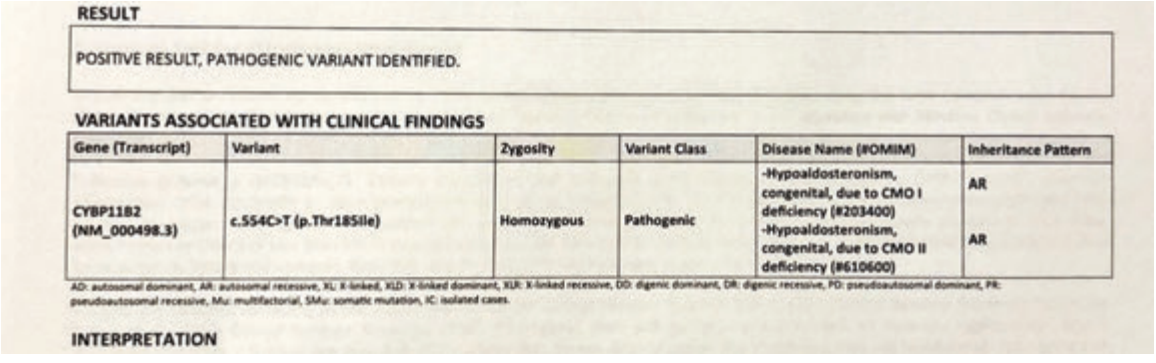
Given the clinical picture of dehydration, hyponatremia, and hyperkalemia, congenital adrenal hyperplasia (CAH) was initially suspected. However, serum 17-hydroxyprogesterone levels were normal, ruling out classical CAH. Differential diagnosis additionally included cystic fibrosis, celiac disease, metabolic disorders, and primary renal tubular dysfunction; all were excluded through targeted laboratory and imaging investigations.

Despite fluid resuscitation and partial correction of electrolytes, the etiology of the persistent salt-wasting remained unclear. Because the infant presented with hyponatremia, hyperkalemia, and metabolic alkalosis without elevation of adrenal androgens, a mineralocorticoid synthesis defect was suspected. Next-generation sequencing (NGS) using a targeted adrenal gene panel was performed.

Genetic analysis revealed a homozygous pathogenic variant c.554C>T (p.Thr185Ile) in the CYP11B2 gene, confirming the diagnosis of aldosterone synthase deficiency. Both parents were clinically healthy and declined carrier genetic testing.

Results

Following initial stabilization with intravenous fluids and careful correction of hyponatremia, the infant was started on fludrocortisone therapy (0.1 mg/day), accompanied by oral sodium supplementation adjusted to clinical response (2–4 mEq/kg/day). Within 48 hours, serum sodium levels began to rise, potassium decreased, and the clinical signs of dehydration improved. The child became more alert, with improved feeding and activity levels.



RESULT

POSITIVE RESULT, PATHOGENIC VARIANT IDENTIFIED.

VARIANTS ASSOCIATED WITH CLINICAL FINDINGS

Gene (Transcript)	Variant	Zygosity	Variant Class	Disease Name (#OMIM)	Inheritance Pattern
CYBP11B2 (NM_000498.3)	c.554C>T (p.Thr185Ile)	Homozygous	Pathogenic	-Hypoaldosteronism, congenital, due to CMO I deficiency (#203400) -Hypoaldosteronism, congenital, due to CMO II deficiency (#610600)	AR AR

AD: autosomal dominant, AR: autosomal recessive, XL: X-linked, XLD: X-linked dominant, XLR: X-linked recessive, DD: digenic dominant, DR: digenic recessive, PD: pseudoautosomal dominant, PR: pseudoautosomal recessive, Mu: multifactorial, SMu: somatic mutation, IC: isolated cases.

INTERPRETATION

By day 5 of hospitalization, laboratory values showed near-normalization of electrolytes, with sodium 130 mmol/L and potassium 4.8 mmol/L. Metabolic alkalosis resolved, and steady weight gain was recorded during hospitalization.

Genetic testing using next-generation sequencing identified the homozygous pathogenic variant c.554C>T (p.Thr185Ile) in the CYP11B2 gene, confirming the diagnosis of aldosterone

synthase deficiency.

Figure 1. *Next-generation sequencing (NGS) chromatogram demonstrating the homozygous c.554C>T (p.Thr185Ile) pathogenic variant in the CYP11B2 gene.*

Outpatient follow-up demonstrated sustained clinical improvement. Electrolytes remained stable with continued fludrocortisone therapy and sodium supplementation. Growth parameters progressively normalized.

At the most recent follow-up at 3 years and 6 months of age, the child showed appropriate growth (weight 14.5 kg, height 103 cm) and normal psychomotor development. Laboratory monitoring demonstrated low but stable aldosterone levels (3.75 ng/dL in February 2023; 6.55 ng/dL in October 2023). Occasional mild hyponatremia (Na 132 mmol/L) during intercurrent infections resolved without hospitalization.

No further episodes of dehydration, vomiting, or salt-wasting were recorded. The family received genetic counseling, although parental carrier testing was declined.

Discussion

Aldosterone synthase deficiency (ASD) is an uncommon but important cause of salt-wasting in infancy. Its rarity and overlapping clinical features with more prevalent endocrine and renal disorders frequently delay recognition and treatment (1). The typical biochemical profile—hyponatremia, hyperkalemia, dehydration, and metabolic derangements—often leads clinicians to initially suspect congenital adrenal hyperplasia (CAH), particularly 21-hydroxylase deficiency, which remains the most common etiology of life-threatening salt-wasting crises in infants (2,3). In the present case, normal 17-hydroxyprogesterone levels effectively excluded classical CAH, prompting further evaluation.

ASD results from pathogenic variants in the **CYP11B2** gene, which encodes aldosterone synthase, the enzyme responsible for the final steps of aldosterone biosynthesis (1,4). The homozygous c.554C>T (p.Thr185Ile) mutation identified in our patient has been previously described as a disease-causing variant associated with reduced enzymatic activity and impaired aldosterone production (5,6). Reduced aldosterone synthesis leads to renal sodium loss, volume depletion, and reduced potassium excretion, which collectively produce the characteristic biochemical abnormalities (7).

Clinical manifestations of ASD typically arise during the neonatal period or early infancy. Symptoms include vomiting, poor feeding, dehydration, hypotension, and failure to thrive, which can quickly progress to life-threatening crises if unrecognized (8,9). In many cases, symptoms are precipitated by physiological stress, reduced oral intake, or intercurrent illness. Our patient presented at nine months of age, later than typical for ASD, highlighting the variable and occasionally subtle onset of the disorder.

The diagnostic challenge lies in the clinical overlap with more frequent conditions. Besides CAH, differential diagnosis includes renal tubular disorders, pseudohypoaldosteronism, cystic fibrosis, and gastrointestinal salt loss (3,10). Normal renal function, absence of gastrointestinal symptoms, and low urine sodium in our case supported a renal salt-wasting state driven by

mineralocorticoid deficiency rather than tubular dysfunction. Routine hormonal testing cannot definitively distinguish isolated aldosterone deficiency; therefore, genetic confirmation is essential, especially when clinical suspicion is high and alternative etiologies have been excluded (11).

The widespread availability of next-generation sequencing (NGS) has significantly improved diagnostic accuracy for rare adrenal disorders, allowing early identification and precise classification of CYP11B2 variants (4,12). Early diagnosis is crucial, as prompt mineralocorticoid replacement prevents severe complications and supports normal growth and neurodevelopment.

Fludrocortisone remains the mainstay of therapy, acting as a synthetic mineralocorticoid that enhances sodium reabsorption and potassium excretion (13). Sodium supplementation is frequently required in infancy due to physiologically reduced renal responsiveness to mineralocorticoids (2). In our patient, combined therapy resulted in rapid correction of electrolytes, resolution of vomiting and dehydration, and subsequent catch-up growth.

Long-term outcomes in ASD are generally favorable when treatment is initiated early and electrolyte balance is maintained (8,14). Consistent with the literature, our patient demonstrated normal growth, stable electrolyte values, and no recurrent salt-wasting crises during follow-up. Mild hyponatremia during intercurrent infections is common and reflects increased physiological stress and transiently increased sodium requirements.

This case underscores the importance of considering ASD in infants with persistent hyponatremia and hyperkalemia, particularly when CAH has been excluded and no renal or gastrointestinal pathology is identified. Increased awareness among clinicians, combined with access to genetic testing, enables timely diagnosis and improves clinical outcomes.

Conclusion

Aldosterone synthase deficiency is a rare but clinically significant cause of salt-wasting in infancy. Because its presentation overlaps with more common endocrine, renal, and gastrointestinal disorders, the condition is frequently misinterpreted, leading to delayed diagnosis. Persistent hyponatremia and hyperkalemia in the absence of elevated adrenal androgens should raise suspicion for an isolated mineralocorticoid synthesis defect. Genetic confirmation using next-generation sequencing enables precise diagnosis and guides appropriate treatment. Early initiation of fludrocortisone therapy and sodium supplementation results in rapid clinical improvement and supports normal growth and development. This case highlights the importance of maintaining awareness of aldosterone synthase deficiency in infants with unexplained electrolyte disturbances and underscores the value of timely genetic evaluation in achieving favorable long-term outcomes.

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