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**Case Report**

# A rare cause of salt wasting and failure to thrive in infancy: case of aldosterone synthase deficiency

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## ABSTRACT

Aldosterone synthase deficiency (ASD) is a rare autosomal recessive disorder caused by pathogenic variants in CYP11B2 that impair aldosterone biosynthesis. It presents with salt-wasting, hyponatremia, hyperkalaemia and failure to thrive in infancy and can be life-threatening if not recognized and treated. We report an infant with early-onset salt-wasting and a novel CYP11B2 variant. A 56-day-old female, presented with poor weight gain and dehydration. Laboratory investigations showed hyponatremia, severe hyperkalaemia, metabolic acidosis and mildly elevated 17-hydroxyprogesterone; cortisol and ACTH were normal. Plasma aldosterone was low (4.4 ng/dl) with low-normal renin activity (2.39 ng/ml/h). Clinical exome sequencing identified a homozygous c.542G>C (p. Arg181Pro) likely pathogenic variant in CYP11B2, consistent with aldosterone synthase deficiency. Acute management included intravenous fluids, sodium supplementation and anti-hyperkalemic measures. The child received empirical hydrocortisone initially and was started on fludrocortisone (200 µg/day) with oral sodium chloride supplementation. On follow-up the infant demonstrated appropriate weight gain and normal development. ASD should be considered in infants with salt-wasting and failure to thrive without virilization. Prompt recognition, acute electrolyte correction, and mineralocorticoid replacement lead to favourable short- and long-term outcomes. Genetic testing confirms the diagnosis and enables counselling for recurrence risk.

**Keywords:** Aldosterone synthase deficiency, CYP11B2, Salt wasting, Hyperkalemia, Hyponatremia, Failure to thrive, Congenital hypoaldosteronism

## INTRODUCTION

Aldosterone synthase deficiency (ASD) is a rare autosomal recessive disorder of adrenal steroidogenesis caused by pathogenic variants in the CYP11B2 gene, which encodes aldosterone synthase responsible for the final steps of aldosterone biosynthesis in the zona glomerulosa. The exact incidence is unknown, but ASD is considered extremely rare, with fewer than a hundred cases reported worldwide, predominantly from Europe and North America, with increasing recognition in Asian populations, including India. Clinically, ASD presents as isolated congenital primary hypoaldosteronism, most often in the neonatal period or early infancy. Affected infants typically manifest with salt-wasting symptoms such as vomiting, dehydration, hypotension, failure to thrive, and, in severe cases, hypovolemic shock. Biochemically, ASD is characterized by hyponatremia, hyperkalemia, and metabolic acidosis in the presence of normal cortisol and adrenocorticotropic hormone levels,

with absent genital ambiguity. Aldosterone levels are low or inappropriately normal, while plasma renin activity is usually elevated but may be variable in early infancy.[1,2] The clinical relevance of ASD lies in its diagnostic overlap with congenital adrenal hyperplasia, particularly 21-hydroxylase deficiency, leading to potential misdiagnosis and delayed treatment. ASD should be suspected in infants with early-onset salt-wasting without virilization and normal cortisol levels.[1] Genetic confirmation enables definitive diagnosis, guides management, and allows family counselling. We report this case to highlight the diagnostic challenges of ASD and to contribute to the limited Indian literature on this rare but treatable condition.

## CASE REPORT

A 56-day-old female infant was referred to our tertiary care center for evaluation of failure to thrive. The symptoms began at around one month of age, initially manifesting as poor weight gain noted at 30 days of life. The mother did not report difficulty in feeding or sucking at the breast.

The caregiver was advised structured bi-hourly feeds; however, over the subsequent 20 days, the infant demonstrated a 13% weight loss from birth weight. She did not have recurrent infections, loose stools, polyuria or suck-rest suck cycle. She was the second-born child to non- consanguineous parents, born at 39 weeks of gestation by normal vaginal delivery following an uneventful antenatal period, with a birth weight of 3100 g. Antenatal history was uneventful , and she was born by normal vaginal delivery with birth weight of 3100 gram is repeated twice. There was no history of abortions or previous sibling death. Developmentally, the infant had attained a social smile, appropriate for age. She was immunized as per the National immunization schedule (NIS). There was no significant past medical history.

On examination, the infant had features of moderate to severe dehydration, including poorly palpable peripheral pulses, sunken eyes, and absence of tears while crying. Vital signs revealed a heart rate of 160/min, respiratory rate of 48/min, blood pressure of 70/56 mm Hg, and a temperature of 98°F. Anthropometric measurements showed a weight of 2.98 kg (−4.07 SD) and a length of 54 cm (−1.51 SD). There was no pallor, icterus, cyanosis, edema, repeated cyanosis, lymphadenopathy, cushingoid features, neurocutaneous markers, rashes, or skin lesions. The infant had no syndromic facies. Systemic examination was unremarkable, with no hepatosplenomegaly, and the neurological examination was normal. The external genitalia were normal.

In an infant with failure to thrive and dehydration despite adequate feeding, salt-wasting endocrine disorders were the primary consideration. Salt-wasting congenital adrenal hyperplasia was considered but was less likely due to the absence of virilization, hyperpigmentation, or features of cortisol deficiency. Isolated mineralocorticoid defects, particularly aldosterone synthase deficiency, were favoured given normal external genitalia and lack of systemic illness. Pseudo hypoaldosteronism was considered but was less likely in the absence of recurrent infections, polyuria, or urinary tract anomalies. Renal tubular disorders, gastrointestinal malabsorption, infections, and inborn errors of metabolism were considered unlikely due to the absence of supportive clinical features.

**Table 1: Baseline investigations of the child.**

| Parameters | Values | Normal |
|---|---|---|
| **Haemoglobin** | 11.3 g/dl | 10-7-17.1 g/dl |
| **Total leucocyte count** | 29,000 cells/mm$^3$ | 5000-21000 cells/mm$^3$ |
| **Platelet count** | 4 lakh/mm$^3$ | 1.5-4.5 lakh/mm$^3$ |
| **C-reactive protein** | 1 mg/l | <6 mg/l |
| **PT** | 12.7 S | 12-16 S |
| **INR** | 0.99 | 0.88-1.5 |
| **APTT** | 31.2 | 26-36 |
| **Serum creatinine** | 0.3 mg/dl | 0.2-0.4 mg/dl |
| **ALT** | 140 u/l | <60 u/l |
| **Serum sodium** | 125 mEq/l | 132-142 mEq/l |
| **Serum potassium** | 7.4 mEq/l | 3.7-5.9 mEq/l |
| **Ionized calcium** | 1.24 mEq/l | 1.12-1.32 mEq/l |
| **Serum phosphorus** | 5.4 mg/dl | 3.7-6.4 mg/dl |
| **Bicarbonate** | 16 mEq/l | 22-29 mEq/l |
| **Blood culture** | No growth after 5 days of incubation | |
| **Serum cortisol** | 21 mcg/dl | 5-23 mcg/dl |
| **ACTH** | 8.88 pg/ml | 7.2-63.3 pg/ml |
| **Free T4** | 1.47 ng/dl | 0.8-2 ng/dl |
| **TSH** | 1.34 mIU/ml | 0.72-11 mIU/ml |
| **17 hydroxyprogesterone level** | 7.9 ng/ml | <2 ng/ml |
| **Plasma aldosterone levels** | 4.4 | 5-90 ng/dl |
| **Plasma renin activity** | 2.39 | 2.35-37 ng/ml/h |
| **18 hydroxy corticosterone** | 20 ng/dl | 5-220 ng/dl |

### *Management and outcome*

Baseline investigations showed hemoglobin of 11.3 g/dl, total leukocyte count of 29,000/mm$^3$, and platelet count of $4\times10^5$/mm$^3$. The increase in the leucocyte count was

probably due to the underlying dehydration. C-reactive protein was 1 mg/l. Coagulation profile was within normal limits (PT 12.7 s, INR 0.99, APTT 31.2 s). Serum creatinine was 0.3 mg/dl. Liver enzymes revealed elevated alanine aminotransferase (140 U/l). Electrolyte analysis demonstrated hyponatremia (125 mEq/l), hyperkalaemia (7.4 mEq/l), hypercalcemia (corrected calcium 12.4 mg/dl), with serum phosphorus 5.4 mg/dl and venous blood gas showed metabolic acidosis with bicarbonate 16 mEq/l with normal anion gap. Blood culture showed no growth after 5 days of incubation. Endocrine evaluation revealed serum cortisol 21 µg/dl, ACTH 8.88 pg/ml, and free T4 1.47 ng/dl. Abdominal ultrasound demonstrated normal adrenals and normal mullerian structures. ECG changes such as widened QRS complex and absent p waves were noted.

Given these findings, a primary disorder of mineralocorticoid deficiency was suspected. Differential diagnoses considered were congenital hypoaldosteronism, pseudo-hypoaldosteronism, and type IV renal tubular acidosis. Serum cortisol levels were normal 21 mcg/dl (5-23 mcg/dl). Plasma aldosterone was suppressed at 4.4 ng/dl (normal 5-90 ng/dl), and plasma renin activity was low at 2.39 ng/ml/h (normal range 2.4–37 ng/ml/h). The 17-hydroxyprogesterone level was mildly elevated at 7.9 ng/dl and adrenocorticotropin hormone (ACTH) levels were normal. Clinical exome sequencing revealed a homozygous variant (c.542G>C/ p. Arg181Pro) in exon 3 of the CYPIIB2 gene which was classified as likely pathogenic. Parental analysis for the variant is pending.

The infant was managed with intravenous fluids, sodium supplementation, and anti-hyperkalemic measures including intravenous 10% calcium gluconate at 0.5 ml/kg over 10 minutes, insulin dextrose infusion and salbutamol nebulization during the acute presentation. She was managed initially with hydrocortisone at 25 mg/m2/day and fludrocortisone was initiated for mineralocorticoid replacement at 200 mcg/day. She also required oral sodium chloride supplementation (11 mEq/kg/day).

On outpatient follow-up, the infant demonstrated adequate weight gain and satisfactory growth. Normalization and stability of serum sodium, potassium, and bicarbonate levels at follow-up (serum sodium- 140 mEq/l and serum potassium- 4.1 mEq/l). The child showed gradual clinical improvement with stabilization of serum electrolytes. Once we received the genetic test reports, hydrocortisone was tapered and stopped. She is now 1 year old weighs 8.9 kg and has normal development and continues to be on oral fludrocortisone 200 mcg per day.

## DISCUSSION

Aldosterone is the principal mineralocorticoid regulating sodium balance, potassium excretion, and intravascular volume. Its secretion from the adrenal zona glomerulosa is primarily controlled by the renin–angiotensin system and serum potassium levels.[3] Aldosterone biosynthesis involves sequential enzymatic steps beginning with cholesterol and culminating in the action of aldosterone synthase (CYP11B2), a mitochondrial cytochrome P450 enzyme that uniquely catalyzes the final three reactions: 11β-hydroxylation of deoxycorticosterone to corticosterone, 18-hydroxylation to 18-hydroxycorticosterone, and subsequent oxidation to aldosterone.[3]

Mutations in CYP11B2 result in aldosterone synthase deficiency, a rare autosomal recessive disorder with an estimated prevalence of less than 1 per 100,000 population.[4] Affected infants typically present with salt-wasting, hyponatremia, hyperkalemia, and hypovolemia, with potential growth failure if untreated. In contrast, pathogenic variants in CYP11B1 give rise to steroid 11β-hydroxylase deficiency, a subtype of congenital adrenal hyperplasia characterized by excess adrenal androgen production and mineralocorticoid-induced hypertension. Given the risk of life-threatening electrolyte disturbances, prompt biochemical evaluation and molecular confirmation are essential to establish the diagnosis, guide therapy, and facilitate genetic counseling.[4] Deficiencies in aldosterone biosynthesis caused by inactivating mutations in the CYP11B2 gene are isolated and located on chromosome 8q24.[5,6] The p.Arg181Pro variant has been reported rarely in the literature and remains poorly characterized, thereby expanding the limited genotype–phenotype data available for CYP11B2 mutations.

Two distinct subtypes of ASD have been delineated according to the specific enzymatic defect within the aldosterone biosynthetic pathway and the resultant steroid profile. ASD type I is attributed to 18-hydroxylase deficiency, characterized biochemically by elevated corticosterone concentrations and reduced 18-hydroxycorticosterone levels. Conversely, ASD type II results from 18-oxidase deficiency and manifests with increased 18-hydroxycorticosterone. However, this subclassification does not hold significant clinical utility. Previously, aldosterone synthase was referred to as corticosterone 18 hydroxylase/ 18 methyloxidase (CMO 1 and 2).[7]

Isolated aldosterone synthase deficiency is a rare condition, leading to impaired aldosterone production. To date, more than forty distinct pathogenic variants of CYP11B2 have been identified, the majority of which are missense or nonsense mutations that significantly reduce enzyme activity. Clinical severity in ASD ranges from mild to severe, with the latter manifesting in early infancy as vomiting, dehydration, hypovolemia, and failure to thrive. Laboratory findings include hyponatremia, hyperkalemia, and metabolic acidosis. However, the absence of hyperkalemia does not rule out the diagnosis. Hormonal evaluation typically reveals elevated renin

levels, low or low-normal aldosterone, with normal ACTH and cortisol levels.[8] However, in our case, plasma renin activity (PRA) was low/normal. Although hyperreninemia is a hallmark of aldosterone synthase deficiency, Plasma renin activity (PRA) in neonates and young infants is physiologically elevated and highly variable. PRA measurements may be unreliable in the setting of dehydration, acute illness, prior fluid resuscitation, or sodium supplementation. Therefore, a low or low-normal PRA does not exclude aldosterone synthase deficiency in early infancy.[8]

**Table 2: Summary of prior reports of aldosterone synthase deficiency in children.**

| Authors (references) | Age/sex | Clinical features | Key laboratory findings | Genetic findings | Outcome/ follow-up |
|---|---|---|---|---|---|
| **Wijaya et al, (2021)[3]** | 7-21 days, M/F (4) | Vomiting, diarrhoea, poor feeding | Hyponatremia, hyperkalaemia, ↑ renin, low/normal aldosterone | CYP11B2 variants: P.R374Q, P.L496FS, P.G435S, splice-site variants | Improved on fludrocortisone± sodium; some required long-term therapy |
| **Yupanqui et al, (2023)[11]** | 1 month, M | Vomiting | Hyponatremia, hyperkalaemia, ↑ renin, normal aldosterone | Two CYP11B2 variants (one pathogenic, one possibly pathogenic) | Initial good response; later short stature, lost to follow-up |
| **Rehman et al, (2023)[12]** | 15-17 months, M/F (2) | Failure to thrive, vomiting | Hyponatremia, hyperkalaemia, ↑ renin, low/normal aldosterone | Homozygous variants P.LEU464DUP, P.SER308PRO | Stable on fludrocortisone |
| **Lages et al, (2018)[13]** | 1 month, M | Vomiting, diarrhoea | Hyponatremia, hyperkalaemia, metabolic acidosis, markedly ↑ renin, normal aldosterone | Compound homozygous variants P.GLU198ASP, P.VAL386ALA | Improved after diagnosis and treatment |
| **Üstyol et al, (2016)[14]** | 2 months, M | Vomiting, failure to thrive | Hyponatremia, ↑ renin, low aldosterone; steroid profile consistent with ASD | Homozygous variants P.ILE263ASN, P.VAL386ALA | Not specified |
| **Sethupathi et al, (2007)[15]** | 4 months, F | Failure to thrive, seizures | Hyponatremia, hyperkalaemia, low aldosterone | Genetic testing not performed | Recurrent crises resolved with fludrocortisone |
| **Kamarajan et al, (2025)[16]** | Neonate | Vomiting, dehydration, failure to thrive | Hyponatremia, hyperkalaemia, ↑ renin, low aldosterone, normal cortisol/17-OHP | Novel homozygous deletion P.LYS175DEL | Good response to fludrocortisone |
| **Jessy et al, (2025)[17]** | 6 months, M | Poor weight gain, developmental delay | Hyponatremia, hyperkalaemia, metabolic acidosis, ↑ renin, low-normal aldosterone, low 18-OHB | Homozygous missense variant P.ARG181PRO | Stable on fludrocortisone |

Salt-wasting crises are clinically indistinguishable from those in other steroidogenic defects, particularly 21-hydroxylase deficiency. ASD presents in infancy with salt-wasting, dehydration, and failure to thrive, without virilization or cortisol deficiency. Laboratory findings include hyponatremia, hyperkalemia, metabolic acidosis, elevated plasma renin activity, and inappropriately low or normal aldosterone, with normal cortisol and 17-hydroxyprogesterone, distinguishing it from congenital adrenal hyperplasia (CAH). In CAH, 17-

hydroxyprogesterone or adrenal androgens are elevated, and cortisol deficiency is present. Pseudohypoaldosteronism is characterized by similar electrolyte abnormalities but markedly elevated aldosterone levels, reflecting renal mineralocorticoid resistance.

Accordingly, initial management typically includes hydrocortisone and fludrocortisone until steroid profiling confirms the diagnosis.[6,9] As clinical symptoms tend to lessen with age, affected adults are typically asymptomatic even without mineralocorticoid therapy. However, discontinuing mineralocorticoid treatment can result in postural hypotension and hyperkalemia, especially when triggered by stress factors such as dehydration or reduced salt intake in these adults.[6]

Neonatal screening for congenital adrenal hyperplasia, which also causes salt-wasting, typically involves measuring 17-hydroxyprogesterone levels. However, this approach may miss cases of aldosterone synthase deficiency, a condition that can go undetected until the patient experiences a salt-wasting crisis.

To mitigate this potentially life-threatening risk, a thorough hormonal evaluation followed by genetic testing for suspected cases is crucial. This comprehensive approach aids in proper clinical management and provides insight into the genetic implications.[10] Summary of prior case series and case reports on aldosterone synthase deficiency have been cited in Table 2.

## CONCLUSION

ASD is a rare cause of hyperreninemic hypoaldosteronism, with a genetic and molecular basis that is more diverse than previously understood. It should be considered in infants who do not show virilization but present with salt-wasting, as well as in adults experiencing stress-induced hyperkalaemia and having a history of childhood failure to thrive. Our case highlights the importance of identifying this condition, as it has a favourable long-term outlook when appropriate fludrocortisone replacement therapy is administered.

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