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ALDOSTERONE SYNTHASE DEFICIENCY: A CASE REPORT

Paediatrics

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ABSTRACT

Aldosterone synthase deficiency is a rare genetic disorder causing congenital hypoaldosteronism. We report a 6-month-old male infant presenting with failure to thrive and motor developmental delay.Investigations revealed severe hyponatremia,hyperkalemia,metabolic acidosis,normal cortisol and 17-hydroxyprogesterone levels.Notably, his low aldosterone level, low 18 hydroxycorticosterone level, and high plasma renin activity were suggestive of aldosterone synthase deficiency. Genetic analysis confirmed the diagnosis.Treatment with fludrocortisone replacement and sodium supplementation normalized electrolyte levels. On subsequent follow up, the infant demonstrated remarkable improvement with fludrocortisone maintenance therapy,exhibiting catch up weight gain and achieving age appropriate developmental milestones.

KEYWORDS

Aldosterone synthase, salt wasting, deficiency.

INTRODUCTION

Aldosterone Synthase Deficiency (ASD) is a rare autosomal recessive disorder characterized by impaired conversion of corticosterone to aldosterone, caused by genetic mutations in the CYP11B2 gene. Infants with aldosterone synthase deficiency may present with failure to thrive ,salt wasting and severe electrolyte abnormalities including hyponatremia, hyperkalemia, and metabolic acidosis.

Case Report

A 6 month old male infant presented with poor weight gain and delayed motor development. He was born at term out of a non consanguineous marriage , with a birth weight of 2.96 kg .His post natal period was uneventful.His weight gain was inadequate despite adequate breast feeding and complementary feeds.On examination the infant weighed 3.9 kg (< 3rd centile) and his length and head circumference were below 3rd centile. Baby had motor developmental delay in form of head lag and inability to roll over.The baby was irritable and moderately dehydrated.His blood pressure was at the lower limit of normal.He had no dysmorphic features or hyperpigmentation. His systemic examination was unremarkable and his external genitalia was normal.

Investigations revealed hyponatremia(115 mEq/ L), hyperkalemia (6.2 mEq/L) and metabolic acidosis(HCO3 12 mEq/L).Septic screen was negative.Echocardiogram,neurosonogram and ultrasound abdomen were normal. Serum creatinine,Blood sugar,Vitamin D and thyroid function tests were normal.

The Infant's plasma renin activity was markedly elevated and aldosterone level was low normal(3.86 ng/dl). 18 hydroxycorticosterone was low(18 ng/dL). S.Cortisol , 17 OHP , ACTH were normal. In view of hyperreninemic metabolic acidosis with hyperkalemia, salt wasting, and low aldosterone levels with normal cortisol, isolated aldosterone deficiency was suspected. Whole exome sequencing revealed homozygous missense variant in exon 3 of the CYP11B2 gene (chr8:g.142915099C>G; Depth: 67x) that results in the amino acid substitution of Proline for Arginine at codon 181 (p.Arg181Pro; ENST00000323110.2) The observed variant lies in the "Cytochrome P450" domain of the CYP11B2 protein (PF00067),confirming the diagnosis of ASD.

The infant was stabilized with fluid resuscitation ,sodium supplementation and IV hydrocortisone followed by Fludrocortisone maintenance therapy. He was discharged with a weight of 4.74kg and showed significant improvement in weight gain and neurodevelopmental milestones on follow up

DISCUSSION

Aldosterone synthase deficiency (ASD) is a genetic disorder characterized by isolated mineralocorticoid deficiency, with normal glucocorticoid and sex hormone levels. Aldosterone, a potent mineralocorticoid hormone, is synthesized from cholesterol in the zona glomerulosa of the adrenal cortex through a series of enzymatic reactions.

Aldosterone synthase (CYP11B2)[1] a cytochrome P450 enzyme found in the zona glomerulosa[2] of the adrenal cortex, catalyzes the conversion of deoxycorticosterone to corticostrrone, 18-hydroxycorticosterone, and finally aldosterone[3]. Mutations in the CYP11B2 gene[4], located on chromosome 8q22p, band q24.3[5], cause aldosterone synthase deficiency. Previously, aldosterone synthase was referred to as corticosterone 18 hydoxylase /18 methyloxidase(CMO 1/ CMO 11).

Aldosterone synthesis and secretion are primarily regulated by angiotensin II, extracellular potassium, and adrenocorticotropic hormone (ACTH). The renin-angiotensin system (RAS) [6] plays a crucial role in regulating aldosterone biosynthesis. Aldosterone acts on the aldosterone-sensitive distal nephron (ASDN), comprising the late distal convoluted tubule,and the collecting duct [7].

Aldosterone exerts its effects by increasing sodium reabsorption and potassium excretion in the renal system through activation of specific amiloride sensitive sodium channels(ENaC) and Na+/ K+ ATPase pump [8] Aldosterone deficiency leads to excessive sodium excretion and potassium retention .

Hypoaldosteronism is associated with either insufficient aldosterone production,secretion or unresponsiveness to aldosterone and can be isolated or with primary adrenal failure [9] .Isolated deficiencies of aldosterone biosynthesis are caused by inactivating mutations in the CYP11B2 gene [10] resulting in aldosterone synthase (CYP11B2) deficiency. ASD is subdivided into two types: aldosterone synthase deficiency type 1 (ASD 1) and type 2 (ASD 2). ASD1 is associated with a defect in the penultimate biochemical step of aldosterone biosynthesis, the 18-hydroxylation of corticosterone (B) to 18-hydroxycorticosterone (18-OHB),resulting in decreased 18-hydroxycorticosterone and aldosterone. ASD2 is caused by a defect in the final biochemical step of aldosterone biosynthesis, the 18-hydroxylation of 18-hydroxycorticosterone (18-OHB) to Aldosterone resulting in high 18-hydroxycorticosterone and low aldosterone levels[11]. The deficiency of aldosterone is much more severe in ASD 1. Congenital adrenal hyperplasia, adrenal hypoplasia congenita and pseudohypoaldosteronism may have similar clinical manifestations of aldosterone synthase deficiency.

ASD typically presents in infancy with symptoms such as vomiting, recurrent dehydration, salt wasting, and failure to thrive. In severe cases, symptoms may manifest in the neonatal period. Since cortisol synthesis remains intact,infants with ASD tend to be less severely ill compared to those with salt losing congenital adrenal hyperplasia.As affected children grow, symptoms tend to decrease in severity,and adults are often asymptomatic.However,stress and dehydration can

trigger symptoms in affected adults.Children with aldosterone synthase deficiency have normal external genitalia [12].

Electrolyte disturbances include variable degrees of hyponatremia, hyperkalemia, and metabolic acidosis. Additional investigations reveal elevated plasma renin activity, undetectable or low aldosterone levels, and normal or elevated cortisol levels. Mild uremia with a normal creatinine level reflects dehydration.Elevated plasma renin activity levels are more likely found in aldosterone synthase deficiency type 1 (ASD1) .Further evaluation involves multi-steroid analysis [13] measuring:11-deoxycorticosterone (DOC),Corticosterone,18-hydroxycorticosterone, 18-hydroxy-DOC and Aldosterone levels in plasma.Cortisol and 17-hydroxyprogesterone levels are typically normal in ASD. The diagnosis is confirmed by genetic analysis of the CYP11B2 gene.

Treatment of aldosterone synthase deficiency involves mineralocortcoid replacement with fludrocortisone (0.1-0.3 mg/day) [14] and Sodium supplementation.Hyponatremia should be corrected slowly to avoid central pontine myelinolysis .Regular monitoring of electrolytes and blood pressure is advised. Once plasma renin activity normalizes, sodium supplementation may be discontinued, but mineralocorticoid replacement is typically continued throughout childhood.If left untreated,this condition is life threatening; however,with adequate fludrocortisone replacement,the prognosis is favourable.

CONCLUSION

Aldosterone synthase deficiency is a rare cause of isolated aldosterone deficiency, which may not be detected by newborn screening using 17 OH Progesterone .Early diagnosis and timely intervention are critical in preventing long term complications and improving outcomes in patients with aldosterone synthase deficiency .Clinicians should suspect ASD in infants with failure to thrive,hyponatremia, and hyperkalemia.and consider multisteroid analysis and genetic evaluation to confirm the diagnosis.

REFERENCES

1. Curnow KM, Tusie-Lunaf MT, Pascoe L, Natarajan R, Gu JL, Nadler JL, Whitef PC. The product of the CYP11B2 gene is required for aldosterone biosynthesis in the human adrenal cortex.Molecular Endocrinology. 1991;5(10):1513–1522. [PubMed]
2. Rainey WE. Adrenal zonation: Clues from 11β-hydroxylase and aldosterone synthase. Molecular and Cellular Endocrinology. 1999;151(1–2):151–160.[PubMed]
3. Clifford-Mobley,G. Rumsby, G.M. Woodward (Eds.), Aldosterone synthase deficiency, Disord. Steroidogenesis guide steroid profiling biochem. Diagn., Springer International Publishing, Cham (2019), pp. 93-101, 10.1007/978-3-319-96364-8_9
4. Kawamoto T, Mitsuuchi Y, Toda K, Yokoyama Y, Miyahara K, Miura S, Ohnishi T, Ichikawa Y, Nakao K, Imura H, Ulick S, Shizuta Y. Role of steroid 11β-hydroxylase and steroid 18-hydroxylase in the biosynthesis of glucocorticoids and mineralocorticoids in humans. Proceedings of the National Academy of Sciences of the United States of America. 1992;89(4):1458–1462. [PMC free article]
5. Kayes- Wandover KM, Tannin GM,Shulman D,Peled D,Jones KL,Karaviti L, White PC, Congenital hyperreninemic hypoaldosteronism unlinked to the aldosterone synthase (CYP11B2) gene. J clin.Endocrinol Metab 2001 Nov 86(11):5379-82
6. Tremblay, A., and LeHoux, J. G. (1993). Transcriptional activation of adrenocortical steroidogenic genes by high potassium or low sodium intake. FEBS Lett. 317, 211–215.
7. Reilly, R. F., and Ellison, D. H. (2000). Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy. Physiol. Rev. 80, 277–313. Doi: 10.1152/physrev.2000.80.1.277
8. Jorgensen PL. Structure, function and regulation of Na,K-ATPase in the kidney. Kidney International. 1986;29(1):10–20. [PubMed]
9. Vlachopapadopoulou E-A, Bonataki M. Diagnosis of Hypoaldosteronism in Infancy | IntechOpen n.d. https://www.intechopen.com/chapters/76423 (accessed July 31, 2023).
10. Portrat-Doyen S, Tourniaire J, Richard O, Mulatero P, Aupetit-Faisant B, Curnow KM, Pascoe L, Morel Y. Isolated aldosterone synthase deficiency caused by simultaneous E198D and V386A mutations in the CYP11B2 gene. J Clin Endocrinol Metab. 1998; 83:4156–4161. Doi: 10.1210/jcem.83.11.5258. [DOI] [PubMed] [Google Scholar]
11. K, McFarlane I, Nguyen HH, Curran S, Schwabe J, Halsall D, Bernhardts R, Wallace AM, Chatterjee VKK. A novel CYP11b2 gene mutation in an asian family with aldosterone synthase deficiency. Journal of Clinical Endocrinology and Metabolism. 2009;94(3):914–919
12. Klomchan T, Supornsilchai V, Wacharasindhu S, Shotelersuk V, Sahakitrungruang T. Novel CYP11B2 mutation causing aldosterone synthase (P450c11AS) deficiency. Eur J Pediatr. 2012;171:1559–1562. Doi: 10.1007/s00431-012-1792-7. [DOI] [PubMed] [Google Scholar]
13. Peter M, Partsch CJ, Sippell WG. Multisteroid analysis in children with terminal aldosterone biosynthesis defects. J Clin Endocrinol Metab 1995; 80: 1622-1627. Lee PD, Patterson BD, H
14. Root AW, Shulman DI. Clinical adrenal disorders. In: Pescovitz OH, Eugster EA, eds. Pediatric Endocrinology, Mechanisms, Manifestations, and Management. Philadelphia: Lippincott Williams & Wilkins; 2004:592-593.