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RESEARCH ARTICLE

NOVEL MUTATION IN THE CYP11B2 GENE IN AN INFANT WITH CONGENITAL HYPOALDOSTERONISM

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Abstract

We report a 4-monthboy infant withisolated congenital hypoaldosteronism due to a novel mutation in CYP11B2 gene who presented with, failure to thrive, profound hyponatremia, hyperkalemia and mild metabolic acidosis, which managed byintravenous saline, oral saline, resoniumandcaloriesformula. In infants with severe electrolyte disturbance,it is important to rule out CAH and consider other rare form of isolated hypoaldosteronism and pseudohypoaldosteronism, since prompt and appropriate treatment will correct the associated electrolytes abnormalities.

Introduction:-

In children, hypoaldosteronism can result from a deficiency of enzymes required for aldosterone synthesis, which may or may not be associated with concurrent abnormalities in cortisol and androgen production. Examples include genetic defects in aldosterone synthase (P450c11as, pure hypoaldosteronism) and P450c21 (21-hydroxylase, hypocortisolism with variable virilizing) [1, 2, 3].

Congenital isolated hypoaldosteronism is a rare inherited disorder that is transmit as an autosomal recessive trait. The clinical presentation is typical of aldosterone deficiency; affected infants have recurrent hypovolemia, salt wasting, and failure to thrive [2, 3]. The usual defect in this disorder is in the activity of the terminal enzyme in the aldosterone biosynthetic pathway, aldosterone synthase (CYP11B2) [4, 5]. Two types of aldosterone synthase defects can occur, reflecting its two enzymatic functions: CYP11B2 type I, characterized by impaired hydroxylation of corticosterone at the 18-carbon position; and CYP11B2 type II, characterized by impaired conversion of the 18-hydroxyl group to an aldehyde [4].

Aldosterone synthase type I deficiency would be expected to produce low plasma concentrations of products derived from corticosterone (18-hydroxycorticosterone and aldosterone) and low urinary excretion of their metabolites [6]; in contrast, aldosterone synthase type II deficiency should be associated with hypoaldosteronism but high plasma concentrations of 18-hydroxycorticosterone and increased urinary excretion of the major metabolite of 18-hydroxycorticosterone, tetrahydro-18-hydroxy,11-dehydrocorticosterone [6,7]. Thus, the ratio of plasma 18-hydroxycorticosterone to plasma aldosterone can be used to differentiate between the two disorders: <10 in type I; and >100 in type II [8].

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The CYP11B2 gene is located on chromosome 8q24.3 [9] and is the site of mutations causing both types I and type II aldosterone synthase deficiency. CYP11B2 is located adjacent to CYP11B1, which encodes P-450c11, the enzyme that converts deoxycortisol to cortisol.

Some patients with aldosterone synthase type I deficiency have a 5-nucleotide deletion in exon 1 leading to a frameshift and premature stop codon; as a result, they produce no functional aldosterone synthase [3, 10]. Other patients have a point mutation causing an R384P substitution; the arginine (R) is highly conserved and presumably important for enzyme activity [11]. An L461P and a nonsense E255X mutation have also been described [12, 13]. Twin boys with type I deficiency had simultaneous E198D and V386A mutations [14].

Patients with aldosterone synthase type II deficiency have one of two-point mutations resulting in R181W and V386A substitutions that do not affect 11-beta-hydroxylase activity, but reduce 18-hydroxylase activity and abolish 18-oxidase activity [3, 15]. A mutation that greatly reduces the activity of the enzyme in vitro is associated with normal aldosterone secretion [15]; thus, only the most severe enzyme deficiencies are manifest clinically.

A number of childrenwere reportedwith a similar presentation of familial hyperreninemic hypoaldosteronism have no mutation in CYP11B2 [5]. The genetic abnormality in these families is not known.

Patients present with signs and symptoms of mineralocorticoid deficiency during the first weeks of life with failure to thrive, hyponatremia, hyperkalemia, markedly elevated Plasma Renin Activity and low or inappropriately normal aldosterone levels [16].

Methods:-

This was retrospective review the medical records ofinfantadmitted to our hospital and seen by our pediatric specialist and consultant betweenAprilstoAugust 2016. All information was obtained from patient note and electronic medical record.

Case Report

4-month male infant with normal birth and pregnancy, birth weight 2.6kg, presented with failure to thrive, no diarrhea, and vomiting and normal stool. His feeding was satisfactory initially breast-feeding then weaned to formula. No family history of renal, endocrine or metabolic diseases the infant had no fever, urinary, cardiorespiratory symptoms or skin rash, neonatal screening was normal, the infant was active, thin, notcyanosed, clubbed or dysmorphic, systemic examination was normal except small capillary hemangioma in the shin with normal male genitlia.

His serum electrolytes revealed hyponatremia and hyperkalemia with normal anion gap mild metabolic acidosis, subsequently17OHP, cortisol and ACTH were normal renin very high and low normal aldosterone. The rest of investigations including urine culture were normal. As isolated hypoaldosteronism was cncidered, geneticstudy was requestedwhich revealed a genetic mutation of a homozygous deletion of entire CYP11B2 gene (deletion of 1-9exon) which was a new reported deletion, so genetic for parents was sended.

His serum sodium on admission was 117 mmol/L with a serum potassium 6.4 mmol/L, which started to correct with saline and oral salt, resonium and fludrocortisone was added his electrolytes (table 1) was normalized with these measures and remained normal on follow up, high calories milk was start, and he stared to gain weight (table2).

The infant developed many chocking episodes with cyanosis GERD was diagnosed and started on anti-reflux measures.

Table 1:- The Electrolytes.

Date	9/4	24/4	25/4	1/5	11/5	1/6
Na	117	127	128	136	134	132
K	6.4	5.9	5.9	6.7	5.7	5.1
CL		95	104	105	97	100
Urea			46			23
AG		11	12			9

CO2			23.3		20.4	23
creatinine	0.3					

Table 2:- Growth parameters.

Date	birth	2month	4month	5month	6month	7month	9month
Weight	2.6	2.7	3.2	4.4	5.1	5.2	7.0
Height	49		52			56	56.5
Head circum	33.5		38			41.5	42.5

Discussion:-

Isolated aldosterone deficiency results from loss of activityof aldosterone synthase encoded by the CYP11B2 gene. Different mutations in the CYP11B2 gene do not explain the two hormonal phenotypes in patients with CHH type I and type II [17, 18, 19]. Moreover, some patients with CHHdo not have mutations in their CYP11B2 gene [17]. The clinical and biochemical characteristics of the patient was consistent with the diagnosis of congenital hypoaldosteronism due to aldosterone synthase deficiency. Confirmation by Genetic study which showed homozygous mutations in the CYP 11 B2 gene by using second generation sequencing system, which showed deletion of the entire gene, which is novel mutation.

Conclusion:-

Isolated deficiency in aldosterone biosynthesis should be consider in newborn and infant with failure to thrive and salt wasting. Normal level of plasma aldosterone compared with elevated levels of plasma renin indicate impaired aldosterone biosynthesis and suggest this disorder. Recognition of its existence is important as fludrocortisone replacement therapy effectively normalize sodium balance and growth.

Declarations

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Ethical approval:

obtain from DHA

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