CASE REPORT

LIDDLE'S SYNDROME

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Hypertension in paediatric age group is commonly secondary to a known cause. It is crucial to identify the cause of hypertension and treat it before development of any associated complications to prevent morbidity and mortality. Paediatric Hypertension is one of the important clinical finding in a child with certain clinical syndrome. We are presenting a case of a 10 month old child presenting with hypertension and hypokalaemia, after excluding all identifiable causes and her positive response to therapy, that is amiloride, along with supportive biochemical data she was diagnosed as a case of monogenic type of hypertension known as Liddle's syndrome.

Keywords: Paediatric Hypertension; Liddle's Syndrome; Epithelial sodium channel (ENaC); Hypokalemia; Potassium sparing diuretics; Plasma Renin Activity (PRA)

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INTRODUCTION

The incidence of hypertension in paediatric population is as low as 1–5% and in majority of cases it is due to a secondary recognizable cause with renal being the most common cause.[1] However in some cases even after excluding the more obvious causes children with hypertension are strongly suspected of having secondary hypertension of unknown etiology.[2] Such group of children may have inherited form of hypertension due to monogenic mutations. These monogenic mutations can be inherited in autosomal dominant or autosomal recessive fashion.[2] Therefore these inherited aetiologies should be considered while managing persistent hypertension in a child.[2] In contrast to adult, it is not acceptable to treat a child with hypertension without prior essential investigations.[2]

One of the rare causes of monogenic hypertension is Liddle's syndrome stated in 1963 by Liddle *et al.*[3] Liddle's syndrome is a form of monogenic hypertension inherited in autosomal dominant fashion with early penetrance. It has been described in diverse backgrounds, including patients of Asians, Caucasians and African origin.[4] It is caused by a mutation in beta or gamma subunits of epithelial sodium channel (ENaC) leading to amplified activity of this channel which is independent of aldosterone activity. Therefore specific aldosterone antagonists like spironolactone have no impact on this monogenic cause of hypertension. Definitive diagnosis of the condition can be made only after genetic testing for identifying mutations in the ENaC, however in our case and in several others reported cases in literature; the diagnosis was made after exclusion of other causes and responsiveness to treatment.

Blood pressure control and correction of hypokalaemia can be achieved in these patients after treatment with ENaC blockers like amiloride or triamterene but this management has no influence on plasma aldosterone levels and only causes incomplete correction of plasma renin (PRA).[4] Liddle's syndrome is often referred to as 'pseudoaldosteronism' due to its typical presentation of hyperaldosteronism, i.e., hypokalaemia, hypertension and metabolic alkalosis but in absence of raised aldosterone levels.[5] Being a rare disorder, Liddle's syndrome can often be misdiagnosed and lead to uncontrolled hypertension followed by end point complications in the form of stroke, cardiac and renal complications and in some cases even death.[5] Prompt diagnosis and correctly tailored treatment can prevent these long period complications.[4]

CASE

Ten months old girl presented to our hospital with complains of polyuria, polydipsia for 5 months and fever for 4 months. Child had increase vomiting, abdominal distension and decreased responsiveness for the past 2 days. Child's Birth history was remarkable for antenatal oligohydramnios, born at full term with low birth weight (2 kg). Developmental history showed delayed achievement of motor milestones. Family history was not significant for early hypertension in paediatric age.

On examination, child was lethargic with some coarse facial features and elevated blood pressure in all four limbs of about 150/90. Rest of the general physical examination and systemic and genital examination was unremarkable. Height and weight was below 3rd centile as per WHO growth chart. Relevant laboratory workup was sent including baseline electrolytes, complete blood count. Echocardiography was performed to rule out cardiac cause. Thyroid profile was sent and came out to be normal. Electrolytes showed hypokalaemia, mild metabolic alkalosis and there was bilateral nephrocalcinosis in ultrasound kidney ureter bladder (KUB). Initially in management, replacement of

potassium was started and child was managed with working diagnosis of Barter's syndrome for which indomethacin and hydrochlorothiazide were started. Child's blood pressure in all four limbs remained high despite this treatment and amlodipine was added while hydralazine on per need basis was used. Child's renin level came out to be low so differential diagnosis of Liddle syndrome and congenital adrenal hyperplasia was considered.

Seventeen hydroxy-progesterone and aldosterone levels were sent. See table 1a and 1b.

Diagnosis of Liddle's syndrome was presumed in the presence of low rennin, normal 17-OHP and aldosterone levels. Patient was started on amiloride. She responded to amiloride therapy as shown in tables 2 and 3. On follow up potassium levels and B.P control became much better.

Table-1(a): Laboratory Investigations

Lab	Serum Electrolytes	Urinary Electrolytes
BUN mg/dl	5	
Creatinine mg/dl	0.4	6.0
Mg mmol/L	2.7	-
Calcium mmol/L	9.7	6
Na mmol/L	137	24
K mmol/L	2.0	13
Chloride mmol/l	96	44
Bicarbonate mmol/lit	24.9	
Osmolarity	311	129

Table-1(b): Laboratory Investigations

Renin	**<0.05 (2.8–39.9)ng/dl**
17-OHP	0.26 (0.03-0.90)ng/dl
Aldosterone	6.87 (1–16 in recumbent position)pmol/L

Table-2: Blood Pressure trend

Blood Pressure Trend	Day 1	Day 2	Day 3	Day 4	Day 5	Follow-up
Systolic/Diastolic mmHg	150/90	140/76	138/75	130/ 72	125/70	114/68

Table-3: Potassium level trend

Potassium level Trend	Day 1	Day 2	Day 3	Day 4	Day 5	Follow-up
Mmol/L	2	1.7	2.2	2.8	2.7	3.5

DISCUSSION

Liddle's syndrome, an infrequent cause of hypokalaemia hypertension, is featured by a renal tubular sodium channel defect causing excessive sodium absorption and associated potassium wasting.[6] It is caused by mutations of the epithelial sodium (Na^+) channel (ENaC) and analysis of the diseased pedigrees indicates an autosomal dominant inheritance. The identified mutations are heterozygotes of gain-of-function mutations. However, sporadic cases of Liddle's syndrome have been stated in the literature.[7] The ENaC in the distal nephron comprises of α, β and γ subunits that have similar structures. Mutations related with Liddle's syndrome are placed in either β or γ subunits and interrupt or shorten a conserved proline-rich sequence (i.e., PY motif), resulting in constitutive stimulation of the ENaC. Genetic testing will benefit to make precise diagnoses and formulate tailored management plans for specific mutation carriers.[5] Liddle's syndrome is caused by mutations in either beta or gamma subunit of the epithelial sodium channel (ENaC) that group in the cytoplasmic C-terminal regions of these subunits resulting in increased constitutive levels of ENaC activity. As this enhanced rate of sodium transport is autonomous of the action of alder stone, the specific aldosterone antagonists like spironolactone or epleronone, has no effect in these patients. Complete stabilization of blood pressure (BP) and hypokalaemia could be seen after treatment with inhibitors of the ENaC, like amiloride or triamterene, but these medicines has almost no influence on the plasma aldosterone level and causes only incomplete correction of plasma renin activity (PRA).[4] Liddle's syndrome patients are being underdiagnosed and facing severe complications at an early age. Wang *et al* results showed that Liddle's syndrome is an essential aetiology of hypertension in young people.[8] The hypertension in some families has been noted to be trivial and it shows increased variablility.[4] The related features include intrauterine growth retardation (IUGR), postnatal failure to thrive and renal concentrating defect, mainly due to chronic hypokalaemia; and occasionally hypercalciuria and nephrocalcinosis, the mechanism of which is not clear.[4] The diagnosis of Liddle's syndrome carries important consequences, especially when a late diagnosis is made or when it is not established by the physician. Also, we would like to point out the importance of genetic counselling, in addition to research regarding other family members, since it is a congenital disease. Renal, cardiovascular and growth squeal can be observed, although appropriate treatment usually causes significant improvement of clinical and laboratory conditions. Thus, the purpose of this case report is to mention the significance of a disease that, albeit rare, results in severe hypertension in children.[9] Prompt diagnosis and correctly tailored management plan should avoid the complications of long-term unpredictable or improperly managed hypertension. Genetic counselling is recommended if one of the parents is diseased in order to continue targeted surveillance of at-risk individuals at younger age.[10]

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