



## A rare case of childhood hypertension with apparent mineralocorticoid excess syndrome

### Pediatrics

**N. Narsaria**

Associate Professor, Department of Pediatrics, GCRG Medical College, Banda, India

**Ashutosh Kumar Singh**

Associate Professor, Government Medical College, India

### KEYWORDS:

Hypertension is defined as average systolic blood pressure and/or diastolic blood pressure that are  $\geq 95$ th percentile for gender, age, and height on  $\geq 3$  occasions (1). Renal parenchymal disease and essential hypertension are the most important causes in  $<12$  and  $>12$  years, respectively (2). Hypertension with hypokalaemia and suppression of plasma renin activity is known as mineralocorticoid hypertension. The most common cause of mineralocorticoid hypertension is probably primary aldosteronism. Monogenic forms of low renin hypertension are apparent mineralocorticoid excess (AME), Liddle syndrome, steroid  $11\beta$ -hydroxylase ( $11\beta$ -OHD) and steroid  $17$ -hydroxylase ( $17$ -OHD) deficiencies, glucocorticoid-remediable hyperaldosteronism (familial hyperaldosteronism type I), familial hyperaldosteronism type II, and primary hyperaldosteronism (Conn's syndrome) (3). AME described by New et al. in 1977 in a Zuni girl, is a potentially fatal disorder that results in juvenile low-renin hypertension, hyporeninemia, hypoaldosteronemia, hypokalemic alkalosis, low birth weight, failure to thrive, poor growth and in many cases nephrocalcinosis (4). AME is caused by a deficiency of  $11\beta$ -hydroxysteroid dehydrogenase type 2 ( $11\beta$ -HSD2) owing to autosomal recessive mutations in the HSD11B2 gene (5). Left ventricular hypertrophy (LVH) is the most prominent clinical evidence of target-organ damage caused by hypertension in children and adolescents and has been reported in 34% to 38% of children and adolescents with mild, untreated BP elevation. Abnormalities of the retinal vasculature have been reported in adults with hypertension. Very few studies of retinal abnormalities have been conducted in children with hypertension (1).

We present an interesting case of AME, one of the rare causes of monogenic low renin hypertension with evidence of end organ damage in the form of LVH and retinopathy that is uncommon in children.

### Case report

A 6 year old male child reported for routine check-up with a diagnosis of familial hypokalemic periodic paralysis. He belongs to Muslim community and a product of non consanguineous marriage with birth weight of 2.6 kg. The child received antitubercular treatment at one year of age for possible abdominal tuberculosis with some surgical intervention. For 3 months he remained asymptomatic when he developed sudden onset pure motor type quadriplegia. Low serum potassium levels with lowest value of 1.6mmol/l and ECG changes (ST segment depression and T-wave inversion) were documented following which child was discharged on oral potassium supplementation. There are no blood pressure recordings in any of the available papers. In the following episode, child had less severe forms of weakness at intervals of 6-12 months which was relieved by increasing the dose of potassium supplements. There were no further hospitalization and potassium levels documented in between the paralytic attacks were consistently low.

The child had history of occasional headache, nausea, polydipsia and polyuria. There was no history of blurring of vision, ptosis, sweating, palpitation, tremors, weight loss, urinary tract infection or hematuria. Family history of hypertension or young onset stroke was absent. There was history of two elder sibling deaths at 2 hours and 3 years of age, respectively and the exact causes were not known. However, the male child who died at 3 years of age, had history of one episode of quadriplegia 2 months prior to death that improved spontaneously within 24 hours. On examination, anthropometry showed weight of 16

kg (3rd centile) and height of 111cm (3-10th centile). The heart rate was 88/min and all peripheral pulses were equal with no radio femoral delay. Blood pressure recorded was 170/100 mm Hg in the upper limb and 180/104 mm Hg in the lower limb. There was no goitre, purplish striae, abdominal mass, renal artery bruit or stigmata of neurofibromatosis or tuberous sclerosis. Genitals showed no ambiguity or pigmentation with prepubertal SMR and testicular volume of 2ml bilaterally. Rest of the systemic examination was normal.

A venous blood gas done showed serum potassium-1.73 mmol/l, serum sodium-141.8 mmol/l, pH-7.526, Bicarbonate-35.9 mmol/l,  $\text{CO}_2$ -45.4, Base excess-9.0, urine chloride - 42.5 mEq/l ( $>20$  mEq/l suggestive of saline non responsive metabolic alkalosis) and random urine K+/creatinine ratio of 2.7 ( $>1.5$  suggestive of renal losses of potassium). So the child had hypokalemia with increased urinary loss of potassium, chloride resistant metabolic alkalosis and grade 2 hypertension. The possibilities at this stage considered were renovascular disease, apparent mineralocorticoid excess, Liddle Syndrome,  $11\beta$  OHD, glucocorticoid-remediable hyperaldosteronism, familial hyperaldosteronism type II and primary hyperaldosteronism. Further investigation showed blood urea of 13mg/dl and serum creatinine of 0.6mg/dl. Urine routine microscopy was normal. The spot urine  $\text{Ca}^{++}$ /creatinine ratio was 0.07 (Normal  $<0.2$ ). The bone age was normal. Ultrasound colour doppler showed normal flow in renal vessels. Basal cortisol and serum testosterone levels were 9.6  $\mu\text{g/dl}$  and  $<20\text{ng/dl}$  (prepubertal), respectively. Renin aldosterone assay done using radio Immunoassay method in mid morning after correction of potassium when patient was on prazosin and normal salt diet showed plasma renin activity (PRA) of  $<0.02$  ng/ml/hr ( $N=0.3-4.3$ ) and aldosterone level of  $<1.1$  ng/dl ( $N=4-31\text{ng/dl}$ ). Ultrasonography showed normal size kidney with bilateral increased cortical echogenicity with altered corticomedullary differentiation without nephrocalcinosis. Fundoscopy revealed grade-1 retinopathy with A-V crossing changes and arteriolar narrowing (Fig 1). ECG showed LVH and 2D- echocardiography showed concentric hypertrophy of left ventricle.

The child was put on antihypertensive medications in the form of prazosin (0.4mg/kg/day) and oral nifedipine (titrated up to 2mg/kg/day). The blood pressure recordings did not track down below 150/90 mm Hg. Then, the child was put on a trial with mineralocorticoid receptor antagonist spironolactone at dose of 2mg/kg/day with low sodium diet and the blood pressure normalised. Follow-up after one month showed normal blood pressure and normal serum potassium with resolving metabolic alkalosis.

### Discussion

In the present case, the initial possibilities considered were renovascular disease, AME, Liddle's Syndrome,  $11\beta$ -OHD, familial hyperaldosteronism type I, familial hyperaldosteronism type II and primary hyperaldosteronism. The presence of hyporeninemia, hypoaldosteronism excluded renovascular disease, glucocorticoid-remediable hyperaldosteronism, familial hyperaldosteronism type II and primary hyperaldosteronism. Normal serum cortisol, testosterone, bone age and genitalia excluded  $11\beta$ -OHD. The remaining causes left were apparent mineralocorticoid excess and Liddle's Syndrome. The distinction between Liddle's syndrome and AME was thus made therapeutically as the former is an autosomal dominant condition with

gain of functional mutation in the epithelial sodium channel with unresponsiveness to spironolactone whereas the latter is responsive as the mineralocorticoid receptor is equally sensitive to both aldosterone and cortisol (6).

The syndrome of AME, one of the causes of mineralocorticoid hypertension is rare, having been identified in only 30 patients worldwide in the past 20 years. AME is caused by autosomal recessive mutations in the HSD11B2 gene, which result in a deficiency of 11 $\beta$ -hydroxysteroid dehydrogenase type 2 (11 $\beta$ -HSD2). This enzyme converts cortisol to its inactive metabolite, cortisone. The deficiency allows mineralocorticoid receptors to be occupied by cortisol, because these receptors themselves have similar affinities for cortisol and aldosterone (7).

AME usually presents early in life. Long-term high blood pressure and metabolic defects start at an early age in children with severe AME. In others, AME may start later in life and cause less serious side effects. Symptoms can include poor growth in childhood, delayed puberty, muscle weakness, heart rate irregularity, polyuria and polydipsia. If left untreated, AME can cause serious damage to the eyes, kidneys, heart, and other organs. The biochemical marker of this disorder is an increased ratio of tetrahydrocortisol (THF) to tetrahydrocortisone (THE) in the urine. In one study, the ratio of THF + 5  $\alpha$  THF / THE ranged between 6.7 to 33, whereas the normal ratio is 1. Molecular genetic analysis is diagnostic (8).

The treatment of AME is primarily aimed at correcting hypokalemia and hypertension. Spironolactone, a mineralocorticoid receptor antagonist, is the accepted medication of choice. In addition to spironolactone, other medications can also be used, such as the K<sup>+</sup>-conserving diuretic amiloride, the adrenergic blocking agent atenolol and the ACE inhibitor enalapril. In some studies, dexamethasone has also been found to be useful but inadequate in effectively controlling the blood pressure (9). The follow-up studies of end-organ damage after 2–13 yr of treatment in six patients demonstrated significant improvement in all patients. This further demonstrates that proper treatment and meticulous compliance can control this disease (4). However, despite treatment, some individuals with AME still experience disease progression and even death within years of being diagnosed as AME. The usual frequency of attacks in children with familial hypokalemic paralysis is once a week and potassium supplements are required only during the attacks (10).

This case highlights how to approach a case of periodic paralysis due to hypokalemia and the importance of blood pressure measurement in children. Until the true prevalence of primary aldosteronism and monogenic forms of mineralocorticoid hypertension are defined, a high index of suspicion is needed in every hypertensive patient. If diagnosed earlier, the hypertensive end organ damage could be prevented thus offering a survival advantage to the child.

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