A Rare Case of Apparent Mineralocorticoid Excess Presenting as Endocrine Hypertension

Abstract

A 3-year-old boy presented with polyuria and polydipsia for 18 months, along with growth failure. He was born prematurely, at 34 weeks of gestation, with a low birth weight. On examination, the child was severely underweight and hypertensive. Clinical history and evaluation could not identify any secondary causes of hypertension. There was no significant family history. An endocrine workup was planned, considering hypokalemia and metabolic alkalosis. This demonstrated hyporeninemic hypoaldosteronism and raised the possibility of apparent mineralocorticoid excess (AME) and Liddle syndrome. Clinical exome sequence analysis of *HSD11B2* revealed a homozygous mutation in exon 5 (911A>G; p.His304Arg), which resulted in a missense mutation that confirmed the diagnosis of AME. A novel homozygous variant was found in the *HSD11B2* gene in a subject with early onset hypertension associated with hypokalemic metabolic alkalosis, establishing the diagnosis of AME.

Keywords: *Hypoaldosteronism, Low renin, Mineralocorticoid excess, Pediatric secondary hypertension*

Introduction

Endocrine causes of hypertension constitute a very small percentage of patients with secondary hypertension. Renal and renovascular causes are most common, constituting 34%–79% and 12%–13% respectively, whereas endocrine disorders account for only 0.5%–6% of causes of secondary hypertension.[1] The syndrome of apparent mineralocorticoid excess (AME) results from defective 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). This enzyme is predominantly expressed, together with the mineralocorticoid receptor (MR), in the renal distal tubules, collecting ducts in the distal colon, salivary glands, and placenta.[2] Firstly, as described in 1974 by Werder *et al*., biochemical abnormalities comprise suppressed plasma renin activity (PRA), undetectable serum aldosterone levels, hypokalemia, and hypertension.[3] Although AME is a congenital disease, it usually presents after infancy. It is not well documented whether laboratory aberrations and hypertension are already present in the period before clinical manifestations.[4] Early recognition and intervention are crucial to prevent long-term complications.

Case Report

The 3-year-old male born as a third child to a nonconsanguineous marriage presented with complaints of polyuria and polydipsia for 18 months and growth failure. He was born prematurely at 34 weeks of gestation with a low birth weight (1.8 kg) and was asymptomatic until 18 months of age. Perinatal history was uneventful. On examination, the child's weight (8.4 kg) and height (0.75 m) were both below the third centile. Pubertal development was age-appropriate, with a tanner sexual maturity rating of stage 1. However, his blood pressure was 140/100 mmHg (>95th+12 percentile). There was no significant difference between upper and lower limb blood pressure. There was no evidence of pallor, periorbital, or pedal edema, cushingoid features, neurocutaneous markers, rashes, or skin lesions. An abdominal bruit was not heard, and a fundus examination revealed no evidence of hypertensive retinopathy. Respiratory, cardiovascular, abdominal, and central nervous system examinations were unremarkable. Thus, the clinical diagnosis of early onset hypertension with failure to thrive was kept.

Investigations revealed metabolic alkalosis (venous blood gas pH 7.510, bicarbonate level 32.9 mEq/L) and hypokalemia (1.8 mEq/L) in the presence of normal serum sodium levels (142 mEq/L). The complete blood count and liver and renal function tests were within the normal limit. Routine microscopy of urine was normal. Raised urinary calcium creatinine ratio was 3 mg/mg (normal is <0.14 mg/mg), while an ultrasound of abdomen and pelvis revealed bilateral nephrocalcinosis. Renal doppler showed normal renal vasculature. Estimated glomerular filtration rate was of 145 mL/min/1.73 m^2. 2D echocardiography and ECG showed features of left ventricular hypertrophy that were attributed to prolonged systemic hypertension. The presence of hypokalemia and metabolic alkalosis suggested a hyperfunctioning mineralocorticoid axis. Thus, we decided to measure plasma aldosterone levels and plasma renin activity. Plasma renin activity was 0.63 ng/mL/h (normal 0.8–1.8 ng/mL/h), and aldosterone levels were 1.29 nmol/L (normal 0.29–0.83 nmol/L).

A high ratio of cortisol to cortisone metabolites was suggestive of a defect in the 11β hydroxysteroid dehydrogenase type 2 enzyme. Thus, the child had features of hyperaldosteronism in the presence of decreased aldosterone levels and a possibility of AME was kept, and a clinical exome was ordered. Sequence analysis of *HSD11B2* revealed a homozygous mutation in exon 5 (911A>G; p.His304Arg), which resulted in a missense mutation that confirmed the diagnosis of AME, and this is novel. Treatment was started with oral potassium supplements, mineralocorticoid antagonist (spironolactone), amlodipine, labetalol, and hydrochlorothiazide, which were added sequentially until the control of hypertension.

Siblings were screened for growth failure and hypertension, but they were normal. Attendants were given genetic

counseling. On follow-up of 1 year, the child's blood pressure returned to normal and was between the 50th and 90th centiles, gaining height and weight. The child is currently on aldosterone antagonists, antihypertensives, and potassium supplements with good compliance.

Discussion

AME is rare, with fewer than 100 cases reported worldwide, but its presentation is dramatic. Usually, the patients are children with low birth weight, failure to thrive, short stature, and severe, often fatal, hypertension with hypokalemic metabolic alkalosis and muscle weakness. Hypokalemic nephropathy sometimes causes nephrocalcinosis, polycystic kidney disease, and nephrogenic diabetes insipidus, manifesting as thirst and polyuria. Renal insufficiency is also not rare. Severe hypertension causes left ventricular hypertrophy, cardiomegaly, and hypertensive retinopathy. The mortality rate is more than 10% due to stroke, cerebral hemorrhage, and infarction.[1] Stroke is one of the main causes of death for people with AME. In a series of 14 children with AME, 8 had neurologic symptoms at the time of diagnosis. Two of them (aged 5 and 14 years) showed signs of a cerebral infarct on MRI.[4] Apart from the kidney, 11 HSD2 and MCR expression is also found in human vascular cells and the brain. The inhibition of 11HSD2 induces endothelial dysfunction, which has been shown to have a deleterious effect on cerebral vasculature in rats.[5-7]

Dexamethasone is the treatment of choice. Doses ranging from 1.5 to 2 mg/day brought serum potassium levels to normal in 7–10 days in approximately 60% of cases by suppressing cortisol and progressively decreasing blood pressure.[1] Thiazide diuretics are indicated when hypercalciuria and/or nephrocalcinosis are present. Spironolactone, an MR antagonist, has been of variable benefit, presumably because very high doses are required to block the mineralocorticoid effects of cortisol on the MR. During the first year, there are high levels of plasma cortisol in comparison with cortisone, possibly due to the relative increase in activity of type 1 versus type 2 11βHSD. Type 1-11βHSD is primarily active in the liver and catalyzes the conversion from cortisone to cortisol.[8] An increase in type 1–11 HSD activity in the first year, along with hypo functioning of the type 2 isoform of the enzyme in the kidneys of patients with AME, contributes to an increasing imbalance of local glucocorticoids.[8]

This study concluded that a high index of suspicion should be kept for AME and other hyporeninemic hypoaldosteronism conditions in the case of early-onset hypertension.

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References

1. Koch C, Papadopoulou-Marketou N, Chrousos GP. Overview of endocrine hypertension. Endotext. 2020 Feb 4.
2. Palermo M, Quinkler M, Stewart PM. Apparent mineralocorticoid excess syndrome: An overview. Arq Bras Endocrinol Metabol 2004;48:687–96.
3. Werder E, Zachmann M, Vollmin JA, Veyrat R, Prader A. Unusual steroid excretion in a child with low renin hypertension. Res Steroids 1974;6:385–9.
4. Knops NB, Monnens LA, Lenders JW, Levtchenko EN. Apparent mineralocorticoid excess: Time of manifestation and complications despite treatment. Pediatrics 2011;127.6:e1610–4.
5. Dorrance AM, Rupp NC, Nogueira EF. Mineralocorticoid receptor activation causes cerebral vessel remodelling and exacerbates the damage caused by cerebral ischemia. Hypertension 2006;47:590–5.
6. Hatakeyama H, Inaba S, Miyamori I. 11β-Hydroxysteroid dehydrogenase in cultured human vascular cells: Possible role in the development of hypertension. Hypertension 1999;33: 1179–84.
7. Watzka M, Beyenburg S, Blümcke I, Elger CE, Bidlingmaier F, Stoffel-Wagner B. Expression of mineralocorticoid and glucocorticoid receptor mRNA in the human hippocampus. Neurosci Lett 2000;290:121–4.
8. Dube S, Slama MQ, Basu A, Rizza RA, Basu R. Glucocorticoid excess increases hepatic 11β-HSD-1 activity in humans: Implications in steroid-induced diabetes. J Clin Endocrinol Metab 2015;100:4155–62.

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