A rare cause of systemic hypertension in an African child: Answers

Patience Sigwadi* and Gertruida van Biljon

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Answers

1. The child presented with a hypertensive emergency and had accompanying hypokalemic metabolic alkalosis. Further investigation revealed low renin activity, low serum aldosterone level, and a normal steroid profile, which is suggestive of Liddle syndrome.

   Other conditions that present with hypertension, hypokalemia, and suppressed renin activity include the syndrome of apparent mineralocorticoid excess, hyperaldosteronism, glucocorticoid–remediable aldo-steronism (GRA), and congenital adrenal hyperpla-sia, which were all excluded for this patient.
2. Liddle syndrome is caused by hyperactivity of the amiloride-sensitive epithelial sodium channel (ENaC), which is highly selective for sodium. Increased Na^+ reabsorption in the distal convoluted tubules and cortical collecting duct results in plasma volume expansion, increased cardiac output, and hypertension.

   The patient tested heterozygous for the |3T594M mutation, which is associated with increased activity of ENaC and hypertension.
3. Treatment consists of drugs that directly inhibit ENaC such as amiloride and a salt-restricted diet.

Discussion

Liddle syndrome is a rare disorder that was first described in Alabama by Grant Liddle and his coworkers in 1963 [1]. It is an autosomal dominant disorder that causes early onset of hypertension associated with hypokalemic metabolic alka-losis, volume expansion, reduced plasma renin activity, and low aldosterone level [2]. It is caused by hyperactivity of the amiloride-sensitive epithelial sodium channel (ENaC).

ENaC is expressed in the distal connecting tubules and cortical collecting tubules of the nephron, where it stimulates reabsorption of sodium [3]. ENaC expression is regulated by mineralocorticoids and glucocorticoids.

ENaC consists of alpha (a), beta (|3) and gamma *(y)* subunits. The expression of all subunits leads to maximal channel activity, and the expression of the alpha subunit alone or combination of a|3 or *ocy* leads to moderate channel activity [3].

Several mutations in the subunits of ENaC channels have been identified as leading to either loss or gain of function of ENaC activity. Mutations described that increase the activity of ENaC include C618F and A663T in the C-terminal tail of *oc* subunit, and T594M mutation in the C-terminal tail of the |3 subunit [4, 5]. Schild in 1996 identified a proline-rich motif (PPPxY sequence), also called the PY motif, in the ENaC subunits as a target sequence for mutations causing channel activation in Liddle syndrome. Mutations of the PY motif lead to increased activity of ENaC, resulting in

P. Sigwadi (*)
Department of Pediatrics, 1 Military Hospital, Thaba Tshwane, University of Pretoria, Private Bag x323, Pretoria, Arcadia 0007, South Africa
e-mail: lusuno@mweb.co.za

P. Sigwadi : G. van Biljon
Department of Pediatrics, Steve Biko Academic Hospital, University of Pretoria, Private Bag x323, Pretoria, Arcadia 0007, South Africa

G. van Biljon
e-mail: ida.vanbiljon@up.ac.za

hypertension and hypokalemia [6]. ENaC is highly selective for sodium and the channel pore is blocked by the potassium sparing diuretic, amiloride [7]. Our patient is a South African black child who tested heterozygous for the βT594M mutation. The association of βT594M mutation and hypertension has been described mainly in studies of black adults from Ghana [8], South Africa [9], USA [10], and London [5]. On the contrary, Hollier et al. did not find any association of hypertension and βT594M mutation in their study among black people in Texas and Jamaica [11].

The differential diagnosis of severe hypertension and hypokalemia includes hyperaldosteronism, glucocorticoid–remediable aldosteronism (GRA), the syndrome of apparent mineralocorticoid excess (AME), congenital adrenal hyper-plasia (CAH), and Liddle syndrome. In a child with a strong family history of hypertension associated with hypokalemia, a monogenic form of hypertension should be strongly considered. Our patient did not have a family history of hypertension and was therefore considered unlikely to have a monogenic form of hypertension.

GRA is inherited as an autosomal dominant trait and is associated with early onset of hypertension. In GRA, there is abnormal production of aldosterone due to a chimera of the promoter of 11-beta-hydroxylase and the aldosterone synthetase gene. As a result of unequal crossing over between the two genes, aldosterone is expressed in the cortisol-producing zone of adrenal cortex under the regulation of adrenocorticotropic hormone (ACTH) [12]. High levels of mineralocorticoids upregulate sodium reabsorption and secretion of potassium.

The diagnosis of GRA is confirmed by demonstration of increased levels of 18-hydroxycortisol and 18-oxocortisol on a 24-h urine steroid chromatography, both of which have miner-alocorticoid activity. Increased levels of 18-hydroxycortisol and 18-oxocortisol are due to aberrant expression of aldoste-rone synthetase in the zona fasiculata where cortisol is a substrate. Treatment of GRA consists of glucocorticoids to suppress ACTH release. A mineralocorticoid antagonist alone or in combination with low-dose glucocorticoids is an alternative [12].

The syndrome of apparent mineralocorticoid excess is a rare autosomal recessive disorder due to an inactivating mutation of the 11β-hydroxysteroid dehydrogenase type 2 enzyme. This enzyme is responsible for conversion of cor-tisol, which has strong mineralocorticoid action, to cortisone which is less active. It is associated with low renin, low aldosterone hypertension, and hypokalemia. These patients respond to treatment with mineralocorticoid antagonists and ENaC blockers. Our patient did not respond to treatment with spironolactone.

There are different subtypes of CAH and not all of them are associated with hypertension. Defects in 11–beta-hydroxylase (CAH type IV) and 17α-hydroxylase (CAH type V) lead to excess production of 21-hydroxylated steroids, which activate mineralocorticoid receptors [13]. They are both autosomal recessive disorders. Treatment consists of glucocorticoid supplementation in CAH type IV and both glucocorticoids and sex hormone replacement in CAH type V.

We postulate that the cause of the severe hypertension in our African patient is associated with βT594M mutation, despite the negative family history of hypertension. More studies in children with early onset hypertension are necessary to investigate the association of βT594M mutation and hypertension.

Conclusions

In a child with severe hypertension, hypokalemic metabolic alkalosis, low renin activity, and low aldosterone levels, monogenic forms of hypertension should be considered once other secondary causes have been excluded.

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