Indian Journal of Pediatrics (November 2022) 89(11):1158
https://doi.org/10.1007/s12098-022-04377-9

SCIENTIFIC LETTER

Mild Clinical Phenotype in an 8-Year-Old Boy with Pseudohypoaldosteronism Type 2E: A Diagnostic Challenge

Bobbity Deepthi[1] · Sriram Krishnamurthy[1] · Sudarsan Krishnasamy[1]

Received: 5 September 2022 / Accepted: 14 September 2022 / Published online: 27 September 2022

To the Editor: An 8-y-old boy was referred for evaluation of hypertension (detected incidentally). He had no seizures, altered sensorium, breathlessness, headache, vomiting, oliguria, or edema. There was no family history of hypertension or stroke. He had stage 2 hypertension (BP - 142/90 mm Hg), weight - 32 kg (+0.91 z), height - 134 cm (+0.61 z), and BMI - 17.8 (+0.82 z). Peripheral pulses were well felt, with no discrepancy in 4-limb BP. There were no neurocutaneous markers, Cushingoid facies, acne, or hirsutism. Hypertension was refractory to treatment with amlodipine, atenolol, and prazosin. Serum creatinine (0.45 mg/dL), sodium (135 mEq/L), potassium (4.5 mEq/L), chloride (105 mEq/L), albumin (4 g/dL), and bicarbonate (22.5 mEq/L) were normal. Urinalysis, kidney ultrasonogram, renovascular Doppler, CT-angiogram, and digital subtraction angiography (DSA) were normal. A dimercaptosuccinic acid (DMSA) scan showed no renal scars. An echocardiogram showed concentric left ventricular hypertrophy and grade 2 hypertensive retinopathy. Serum metanephrines and a metaiodobenzylguanidine (MIBG) scan were normal. Plasma renin activity (PRA) (0.3 ng/mL/h) and plasma aldosterone (PA) (5 ng/dL) were low (reference: PRA 0.9–6.6 ng/mL/h, PA 6.5–29.5 ng/dL). Next-generation sequencing revealed a heterozygous pathogenic deletion in the *CUL3* gene (exon 9) (c. 1329_1332 del; p. Asn443LysfsTer11), confirming pseudohypoaldosteronism (PHA) type 2E, an autosomal dominant disorder. Oral hydrochlorothiazide therapy led to control of hypertension.

PHA type 2 is characterized typically by hyperkalemia, metabolic acidosis, and hypertension [1]. Subtypes include PHA type 2A (gene not identified), type 2B (caused by *WNK4* mutations), type 2C (*WNK1*), type 2D (*KLHL3*), and type 2E (*CUL3* mutations) [2, 3]. PHA type 2E is considered the severest variant with early onset [2, 3]. While refractory hypertension with low PRA suggested monogenic hypertension in our patient, the atypical features (normokalemia without metabolic acidosis) posed a diagnostic challenge. Normokalemia has also been rarely reported in other forms of monogenic hypertension like Liddle syndrome, familial hyperaldosteronism type 1, PHA type 2B, and PHA type 2C; the mechanisms being unclear [2, 4]. Our case adds to the phenotypic heterogeneity of *CUL3* mutations and highlights the importance of a genetic diagnosis for initiating targeted therapy.

Declarations

Informed Consent Written informed consent for publication of the child's clinical details was obtained from the parents.

Conflict of Interest None.

References

1. Mabillard H, Sayer JA. The molecular genetics of Gordon syndrome. Genes (Basel). 2019;10:986.
2. Khandelwal P, Deinum J. Monogenic forms of low-renin hypertension: clinical and molecular insights. Pediatr Nephrol. 2022;37:1495–509.
3. Boyden LM, Choi M, Choate KA, et al. Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. Nature. 2012;482:98–102.
4. Litchfield WR, Coolidge C, Silva P, et al. Impaired potassium-stimulated aldosterone production: a possible explanation for normokalemic glucocorticoid-remediable aldosteronism. J Clin Endocrinol Metab. 1997;82:1507–10.

✉ Sriram Krishnamurthy
drsriramk@yahoo.com

[1] Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India