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Case Report
ABCC6 Missense Mutation

ABCC6 Missense Mutation and Severe Resistant Systemic Hypertension in a Child

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Pseudoxanthoma elasticum (PXE) is a rare multisystem disorder characterised by progressive calcification and fragmentation of elastic fibres. Recent genetic advances have identified the underlying defect in the ABCC6 gene on chromosome 16p13.1. Patients typically develop cutaneous, ocular, and cardiovascular manifestations, but there is considerable phenotypic variability. Skin changes are usually apparent in adulthood and rarely observed in childhood. Since the prognosis of PXE largely depends on the extent of extracutaneous organ involvement, early recognition, intervention, and lifestyle adjustments are important to reduce morbidity.

Keywords: Resistant Hypertension, Pseudoxanthoma elasticum, Primary hypertension

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Introduction

Primary hypertension is observed in older children (≥6 years) and is associated with overweight or obesity along with positive family history while secondary hypertension is more common in pediatric patients, with a prevalence of 75–85% [1]. Renal disorders and coarctation of the aorta are the most common causes of secondary hypertension [2].

Several factors have been identified as contributors to resistant hypertension namely poor patient adherence, physician inertia, inadequate doses, or inappropriate combinations of antihypertensive drugs [3].

Monogenic (Mendelian) HT which results from a pathogenic variant (mutation) in a single gene, even in the absence of environmental or other risk factors. These include two categories of disorders: a) diseases that cause HT directly by affecting the kidney (e.g., glucocorticoid-remediable aldosteronism) or rarely the blood vessels (e.g., PDE3A-related HT and brachydactyly syndrome). b) diseases that cause HT indirectly through other mechanisms (e.g., neurofibromatosis, tuberous sclerosis) [4].

Here we report a rare case of resistant hypertension where all common causes of hypertension according to age were ruled out, and further investigation like genetic study analysis reported adefect in the ABCC6 gene on chromosome 16p13.1that usually presents with cutaneous and ocular manifestations but in our case, it manifested as resistant hypertension.

Case Report

A five-year-old boy, second by birth order, born of third-degree consanguinity, was initially admitted 6 months back for an abscess over the scalp and was incidentally found to have severe hypertension (>95% centile for age) during a pre-anaesthetic checkup.

A significant family history was the death of the elder brother/sister at 3 months of age during admission for pneumonia which was also detected to have severe hypertension but no workup for hypertension was done during admission and no significant history of hypertension to parents and other close relatives.

Initial workup for secondary causes of severe hypertension [renal (USG abdomen and RFT), cardiac (2D ECHO) and adrenal (CAH profile)] was negative. The child was discharged against medical advice, on (Nifedipine and Dihydralazine), and was lost to follow-up for 4 months. He was then readmitted to us, with severe uncontrolled hypertension while on medications, but without signs of end-organ damage. On admission, the blood pressure was 140/90 mmHg (99th centile for age and height is 115/77 mm hg). Further workup with renal Doppler and CT abdomen for endocrine causes was negative. Meanwhile, the child was continued on Nifedipine, Dihydralazine, and Metoprolol (increased to maximum doses) followed by Chlorthalidone, after which the blood pressure remained below the 99th percentile.

As clinical examinations and extensive investigations did not lead to any possible diagnosis, rarer causes were thought of and genetic testing was done. Whole exome sequencing revealed a heterozygous missense variation in Exon 13 of the gene ABCC6 (NM_001171.6) (chr16:g.16282705T>C: Depth - 60X) [amino acid substitution Isoleucine to valine at 588 codon c.1762A>G (p.Ile588Val)].

Investigations	Reports
HB	10.7
TLC	11300
Platlets	358000
CRP	14.89
ESR	26
Sr. urea	20.97
Sr. creatinine	0.62
Na	136
K	4.6
Cl	104
Ca	10.23
P	2.6
Urine Proteins, sugars, RBC	Absent
Urine Na/K/Cl	165/48.4/130
ASO Titre	0.6(Negative)
Cortisol AM/PM	85.84/102.4 (Normal)
ANA	107AU/ml (Negative)
Renal Doppler	Normal renal doppler Mild enlarged left adrenal gland? adrenal hyperplasia
CT abdomen & pelvis (P+C)	Mild cardiomegaly, bilateral kidneys appear normal.

Discussion

Our case presented as resistant hypertension and an investigation workup did not find any cause for hypertension. So genetic study was done, which showed our patient had an ABCC6 missense mutation. Although the report showed uncertain significance to the current condition, isolated hypertension without other systemic manifestations was observed in the ABCC6 mutation.

The ABCC6 gene encodes the multidrug resistance protein 6, which plays a crucial role in vascular function and calcium homeostasis. This protein is found primarily in the liver and kidneys, with small amounts in other tissues such as the skin, stomach, blood vessels, and eyes [5].

ABCC6 gene mutations occur in the general population at an estimated prevalence of approximately 1% [6].

Diseases associated with ABCC6 mutations are Pseudoxanthoma elasticum (PXE) and generalised arterial calcification of infancy, caused by inactivating ABCC6 mutations, which are characterised by mineralization of cardiovascular, ocular, and dermal tissues. More than 200 ABCC6 gene mutations that cause PXE have been identified. PXE is an autosomal recessive connective tissue disorder characterised by skin, eye, and vascular involvement [7].

However, isolated severe hypertension is rare in ABCC6 mutations. It has also the potential for variable phenotypic expression even within the same genetic disorder.

The precise molecular and cellular mechanism linking deficient hepatic ABCC6 function to distal ectopic mineral deposition, including hypertension, is not yet fully understood [8].

Our patient's hypertension is under control with multiple antihypertensive drugs as of now. However, long-term follow-up will be crucial to monitor for the potential development of other PXE-related manifestations. Further studies are needed to elucidate the specific mechanisms by which ABCC6 mutations contribute to hypertension and explore potential targeted therapies. Early diagnosis and genetic counselling are crucial for appropriate management and future genetic risk assessment in these patients.

Conclusion

Genetic testing is crucial in resistant or atypical presentations of pediatric hypertension (especially with a positive family history) to find a rare genetic cause like ABCC6 mutations in our case for early diagnosis and appropriate management.

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