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Case Report

Bartter's syndrome type II due to a novel mutation in KCNJ1 gene presenting in adulthood as recurrent hypokalaemic periodic paralysis

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ABSTRACT

Bartter's syndrome affects salt reabsorption transporters in Henle's loop's thick ascending limb (TAL). Bartter's syndrome type II begins in antenatal/neonatal period with an autosomal recessive pattern of inheritance due to mutation in the KCNJ1 gene. Renal disorder begins early. It is a disorder which usually presents in infancy but not in adulthood. We report a case of late onset Bartter's syndrome type II due to a novel mutation in the KCNJ1 gene manifesting with bilateral medullary nephrocalcinosis and recurrent hypokalaemic periodic paralysis.

Keywords: Bartter's syndrome type II, KCNJ1 gene, Medullary nephrocalcinosis

INTRODUCTION

Bartter's syndrome is a renal tubular defect affecting salt reabsorption transporters in Henle's loop's TAL. It is rare, with a prevalence of 1 per million people.[1,2] It is clinically characterised by low-normal blood pressure, hypokalemia and metabolic alkalosis, increased renin and aldosterone levels. Hypercalciuria, polyuria and polydipsia are also seen.[3,4]

Bartter's syndrome type II results from renal outer medullary potassium (ROMK) channel defects due to mutations in the KCNJ1 gene. It begins in antenatal/neonatal period with an autosomal recessive inheritance. It presents with renal salt wasting, resulting in severe dehydration and delayed growth. It is a disorder which usually presents in infancy but not in adulthood.

We report a case of Bartter's syndrome type II due to a novel mutation manifesting in adulthood.

CASE REPORT

A 31-year-old gentleman presented with a history of bilateral upper and lower limbs weakness associated with tingling and numbness after taking a carbohydrate rich diet one-day prior. He was found to have hypokalemia with serum potassium-2.2 mEq/l. There was no history of loose stools, vomiting, laxative abuse or diuretic abuse. Patient had a similar history 5 years back, which was managed conservatively.

He is a product of a non-consanguineous marriage with an uneventful antenatal or neonatal history. He was born at full term through normal vaginal delivery. There is no history of strong thirst and polyuria in childhood. He is married and has a single child. There is a positive family history of end stage renal disease in his elder brother. His BMI was 21.6 kg/m^2. He was normotensive (124/82 mmHg) and non-diabetic.

Investigations showed normal serum creatinine (1.09 mg/dl), hypokalemia (3.1 mEq/l), hypocalcemia (8.8 mg/dl), hypophosphatemia (1.7 mg/dl), normal sodium (135 mEq/l). Venous blood gas analysis showed venous pH 7.34, HCO_3 29 mmol/L, pCO_2 55.3 mmHg, PO_2 34.3 mmHg).

Urine examination showed hypercalciuria (Table 1). The urinary potassium: creatinine ratio was <1.5. Serum

magnesium was 2.14 mg/dl (1.7-2.7), vitamin D was 26. HIV, hepatitis B, and hepatitis C serology was negative. Immunological workup was also normal. Serum thyroid profile was normal and anti TPO antibody titre-57.9 (Normal). ECG and chest-X ray were normal. USG abdomen showed bilateral medullary nephrocalcinosis (Figure 2 and 3). Patient had lithuria and stone analysis with Fourier transform infrared spectroscopy (FTIR) with ATR was done which showed calcium oxalate stones (Figure 1). In view of positive family history of ESRD in elder brother, and patient having bilateral medullary nephrocalcinosis, we advised for genetic analysis. After taking informed consent, next generation whole exome sequencing was performed. It showed homozygous missense mutation of KCNJ1 gene in exon 3, resulting in the substitution of leucine for proline at codon 91. {c.272C>T; p.Pro91Leu}. With this, diagnosis of Bartter's syndrome type II was made. Patient was started on spironolactone and potassium citrate.

Table 1: Spot and 24-hour urinary examination findings.

Parameters	Spot urine examination	24-hour urinary examination
Urine osmolality	309 mosm/kg (60-1200)	-
Urinary calcium	6.2 mg/dl (<300)	384 mg (<300)
Urinary potassium	69 mmol/l (11-164)	35 (25-125)
Urinary chloride	77 (10-250)	-
Urinary creatinine	67 (24-392)	1528 mg
Urinary protein	-	167 mg/day
Urinary potassium to creatinine ratio	1.03	0.02

Figure 1: Urinary stone (calcium oxalate).

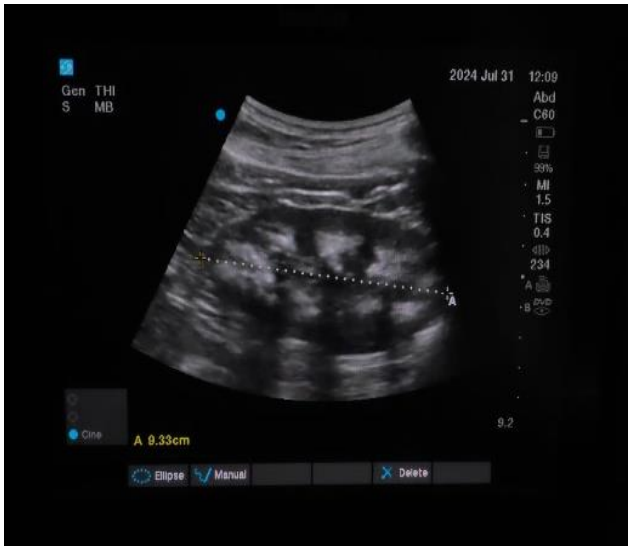

Figure 2: USG image of right kidney, normal size (9.33 cm) with medullary nephrocalcinosis.

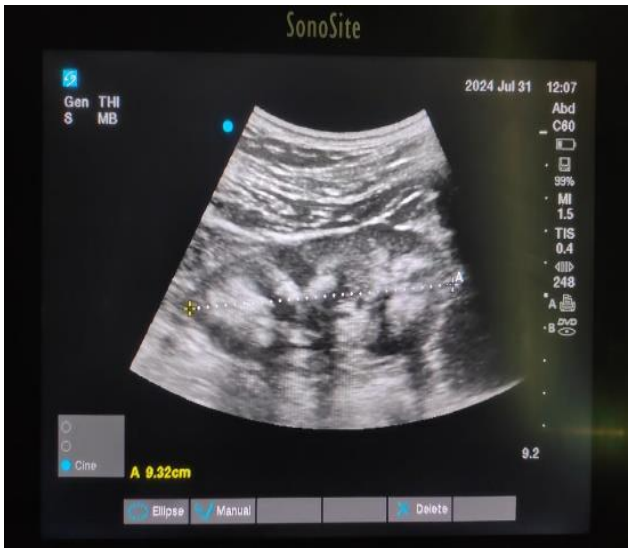

Figure 3: USG image of left kidney, normal size (9.32 cm) with medullary nephrocalcinosis.

DISCUSSION

We present a case of recurrent episodes of quadriparesis in a man onset at 26 years of age with hypokalaemia. Workup revealed increased urinary calcium and medullary nephrocalcinosis. During follow-up, he had lithuria (calcium oxalate stones). A novel mutation was detected in genetic analysis. Based on clinical findings and genetic analysis, we diagnosed Bartter's syndrome type II. Onset in adulthood is unusual in our case.

KCNJ1 gene is located on long arm of chromosome 11 and consists of five exons.[5] It is commonly seen in the neonates with severe clinical features. More than 70 missense/ nonsense mutations have been described in the KCNJ1 gene in literature.[6] These mutations which substitute conserved amino acid residues, commonly in

the coding exons 2 and 5.[6,7] In this case, a homozygous missense KCNJ1 gene mutation in the codon 91 of exon 3 was found which is not seen in earlier reported cases.

Some studies confirmed that Bartter's syndrome type II can present as in adulthood.[1,5,8,9] Similar to our case, Huang et al and Gollasch et al found mild clinical manifestations of Bartter's syndrome type II (hypokalaemia and mild hypercalciuria) with nephrocalcinosis. Inhibition of renin-angiotensin-aldosterone system (RAAS) may improve hypokalaemia as reported in previous case reports.[8] Hence, we started our patient on spironolactone.

Our patient initially presented with nephrocalcinosis and hypercalciuria. He later passed calcium oxalate stones in his urine. Bartter's syndrome patients commonly develop nephrocalcinosis due to their hypercalciuria. The literature search found that all previously reported cases had nephrocalcinosis.[1,8-10]

Gitleman syndrome is a vital differential. Both are genotypically distinct but have many clinical similarities. However, our patient had normal serum magnesium and hypercalciuria, which is commonly seen in Bartter's syndrome. Genetic analysis is fundamental for differential diagnosis between these entities.

CONCLUSION

From our case, we suggest that mutations in KCNJ1 should be considered even in adult patients who present with bilateral medullary nephrocalcinosis and recurrent hypokalaemic periodic paralysis even if the biochemical analysis do not reveal any specific renal salt wasting channelopathies. Genetic testing is necessary to establish the diagnosis.

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