

Nephrocalcinosis as adult presentation of Bartter syndrome type II

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ABSTRACT

Bartter syndrome consists a group of rare autosomal-recessive renal tubulopathies characterised by renal salt wasting, hypokalaemic metabolic alkalosis, hypercalciuria and hyperreninaemic hyperaldosteronism. It is classified into five types. Mutations in the *KCNJ1* gene (classified as type II) usually cause the neonatal form of Bartter syndrome. We describe an adult patient with a homozygous *KCNJ1* mutation resulting in a remarkably mild phenotype of neonatal type Bartter syndrome.

KEYWORDS

Hypercalciuria, *KCNJ1* gene, renal salt wasting, renal tubulopathy

INTRODUCTION

Bartter syndrome is a rare renal salt-losing disorder presenting with hypokalaemic metabolic alkalosis, hyperreninaemic hyperaldosteronism accompanied by normal or low blood pressure. Bartter syndrome is divided into five types by the involved mutated gene. Type I is caused by mutations in the sodium-potassium-chloride co-transporter gene (*SLC12A1*). Type II is caused by loss of function in the inwardly rectifying potassium channel encoded by the *KCNJ1* gene.¹ Type I and II are also termed the neonatal Bartter syndrome because of their severe presentation in the neonatal period characterised by polyhydramnios leading to premature delivery, polyuria, dehydration, electrolyte disturbances, failure to thrive, elevated prostaglandin levels and nephrocalcinosis.² We present here the case of an adult man diagnosed with a late-onset Bartter type II due to a homozygous *KCNJ1* gene mutation, which has not been reported in the literature so far.

What was known on this topic?

Bartter syndrome is a rare renal disorder of salt losing tubulopathy. Mutations in five genes involved in salt absorption by the thick ascending limb of Henle have been identified in this syndrome (type I-V). Type II is also called the neonatal variant of Bartter syndrome because it presents with severe symptoms in the neonatal period.

What does this add?

We describe a mild phenotype of Bartter syndrome type II with a homozygous missense mutation in the *KCNJ1* gene. It suggests phenotypic variability in patients with *KCNJ1* mutations. Neonatal type Bartter syndrome may still be suspected in patients with a late-onset Bartter.

CASE REPORT

A 35-year-old man of Turkish origin consulted his general practitioner for lower back pain for two months. His medical history was unremarkable and he was not on any medication. Physical examination was unremarkable without dysmorphic features. He was normotensive. His general practitioner had already ordered an X-ray of the lumbar spine which showed extensive calcifications in both kidneys.

Laboratory findings were as follows: serum sodium 136 mmol/l, potassium 2.8 mmol/l, calcium 2.32 mmol/l (corrected for albumin), phosphate 0.65 mmol/l and creatinine 122 µmol/l (measured glomerular filtration rate using a 24-hour urine collection was 45 ml/min/1.73 m²).

Venous pH was 7.44 and the bicarbonate was 33 mmol/l. Aldosterone level was 1257 pmol/l (normal range 56-660 pmol/l) and renin level was 168 ng/l (normal range 3.5-28.5 ng/l). In a 24-hour urine collection, calcium excretion was slightly elevated (4.34 mmol/day). Excretion of sodium, potassium, phosphate, chloride and oxalate in the 24-hour urine was normal.

Our clinical diagnosis for this patient with nephrocalcinosis, hypokalaemia, metabolic alkalosis, hyperreninaemic hyperaldosteronism and a normal blood pressure was Bartter syndrome. DNA was isolated from peripheral blood. Molecular analysis of the *SLC12A1* gene (type I), the *KCNJ1* gene (type II), the *CLCNKB* gene (type III) and the *CASR* gene (type V) was performed. Bartter syndrome type IV is associated with sensorineural deafness. Type IV was therefore not tested because our patient did not have any hearing complaints. A homozygous missense mutation in the *KCNJ1* gene was identified. A cytosine to thymine mutation of the nucleotide 658 (c.658C>T) results in leucine being replaced by phenylalanine at amino acid 220 (p.(Leu220Phe)).

The patient was treated with oral supplementation of potassium and spironolactone. In the follow-up period, his serum potassium improved at a level of 3.2 mmol/l. His serum creatinine stabilised at the level of 140 µmol/l over the next year of follow-up. During the follow-up, the patient had an episode of back pain. The pain had a good response to butylscopolamine bromide. We considered the patient had a renal stone of calcium deposit penetrating into a calyx.

There was no known consanguinity in the family. However, both parents were born in the same small village in Turkey. Parents and siblings were not available for genetic testing.

DISCUSSION

This report describes a patient with Bartter syndrome type II caused by a homogenous missense mutation in *KCNJ1*, with a first presentation in adulthood with nephrocalcinosis. To our knowledge, this is the first report to document this mild phenotype of Bartter syndrome type II caused by homozygous Leu220Phe mutation.

Loss-of-function mutations in *KCNJ1* are identified in Bartter syndrome type II.³ The *KCNJ1* gene encodes an ATP-sensitive inwardly rectifying potassium channel (ROMK). ROMK is expressed in the apical membrane of the thick ascending limb and cortical collecting duct.⁴ At the level of the thick ascending limb of the loop of Henle, 20% of filtered sodium and potassium by the glomeruli is reabsorbed.⁵ Impaired reabsorption will result in a large volume of urine with a high content of Na⁺, K⁺, Cl⁻ and

Ca²⁺ in the distal tubule. Na⁺-K⁺-2Cl⁻ co-transporter in the form of an electroneutral co-transport plays a crucial role in reabsorption of electrolytes in the thick ascending limb. Only 20% of the potassium ions is reabsorbed in the ascending limb, which will not provide the necessary amount of potassium ions for the Na⁺-K⁺-2Cl⁻ co-transporter for reabsorption of sodium. ROMK recycles reabsorbed potassium from the intracellular space back into the intraluminal space and thereby provides the amount of potassium ions necessary for Na⁺-K⁺-2Cl⁻ co-transporter. In the case of our patient with Bartter syndrome type II, malfunction of ROMK results in malfunction of Na⁺-K⁺-2Cl⁻ co-transporter, causing hypokalaemia, activated renin-aldosterone axis due to volume depletion, and metabolic alkalosis due to H⁺ loss.² Reabsorption of Ca²⁺ is a passive process coupled to Na⁺ reabsorption. Impaired Na⁺ reabsorption results in hypercalciuria and nephrocalcinosis. Calcium deposits in the kidney can be visualised by ultrasonography, abdominal X-ray or CT scan (figure 1).

The homozygous missense mutation Leu220Phe in our patient is located in a domain involved in ROMK regulation. This regulatory region contains a protein kinase C and a Mg²⁺-ATP-binding motif that have been shown to be important in the Mg²⁺-ATP regulation of ROMK.⁴ Mutations within this region may disrupt channel regulation and alter ROMK function. Functional studies of the mutation are required to show the altered ROMK function. The missense mutation Leu220Phe in the *KCNJ1* gene was described only once in a compound heterozygote setting in a neonate with severe manifestations of the syndrome.⁶ We report a remarkably mild phenotype of a patient who was homozygous for this missense mutation. This suggests a high degree of variability regarding severity of disease as shown in another report.⁷ Mutations

Figure 1. CT scan without contrast showed nephrocalcinosis in both kidneys



in the *KCNJ1* gene should thus be considered even beyond the neonatal period in patients who present with symptoms of renal salt wasting.

The main treatment for Bartter syndrome is replacement therapy. A large amount of potassium may be required. The addition of potassium-sparing diuretics or an aldosterone antagonist may improve hypokalaemia. Since prostaglandin levels are elevated in affected patients, cyclo-oxygenase inhibitors can be used. Indomethacin has been accepted as standard therapy in children. The use of indomethacin improves growth rate⁸ and early treatment in the neonatal period may decrease nephrocalcinosis.⁹ However, few data about the long-term outcome of patients with Bartter syndrome are available. Renal failure requiring dialysis is uncommon in Bartter syndrome. However, the oldest patient at the last follow-up was 18 years.^{10,11}

CONCLUSION

To our knowledge, we here describe for the first time an adult patient presenting with nephrocalcinosis, hypokalaemia, metabolic alkalosis, hyperreninaemic hyperaldosteronism and a normal blood pressure due to a homozygote mutation in the *KCNJ1* gene, coding for the ROMK channel, consistent with Bartter syndrome type II.

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