Late-Onset Bartter Syndrome Type II Due to a Homozygous Mutation in \( KCNJ1 \) Gene: A Case Report and Literature Review

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Patient: Male, 31-year-old
Final Diagnosis: Bartter syndrome
Symptoms: Weakness
Medication: —
Clinical Procedure: —
Specialty: Genetics • Nephrology

Objective: Unusual clinical course
Background: Bartter syndrome is a rare genetic disease characterized by hypokalemia, metabolic alkalosis, and hyperreninemic hyperaldosteronism. Five different subtypes have been described based on the genetic defect identified. Bartter syndrome type II is caused by homozygous or compound heterozygous loss-of-function mutations in the \( KCNJ1 \) gene encoding ROMK. This subtype is typically described as a severe antenatal form of the disease, often presenting with polyhydramnios before childbirth.

Case Report: Here, we describe the case of a 26-year-old man who presented with generalized body weakness and hypokalemia and was ultimately diagnosed with Bartter syndrome type II based on his clinical features coupled with the identification of a homozygous missense mutation in \( KCNJ1 \).

Conclusions: To the best of our knowledge, this is the fifth case of late-onset Bartter syndrome type II. Interestingly, the mutation identified in our patient has been previously described in patients with antenatal Bartter’s Syndrome. The late presentation in our patient suggests a surprising degree of phenotypic variability, even in patients carrying the identical disease-causing mutation.

MeSH Keywords: Bartter Syndrome • Hypokalemia • Mutation, Missense • Nephrocalcinosis • Potassium Channels, Inwardly Rectifying

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**Background**

Bartter syndrome is a rare condition with a prevalence of 1 in 1,000,000 [1]. It is characterized by polyuria and polydipsia, hypokalemia, metabolic alkalosis, and high renin and aldosterone levels.

Bartter syndrome results from gene mutations leading to impaired function of the transporters or channels responsible for sodium chloride reabsorption in the thick ascending part of the loop of Henle. Bartter syndrome type I is due to SLC12A1 (solute carrier family 12 member 1) gene mutation leading to malfunction of the sodium-potassium-2 chloride cotransporter (NKCC2). Bartter syndrome type II is due to KCNJ1 (potassium inwardly rectifying channel subfamily J member 1) gene mutation, which leads to malfunction of the renal outer medullary potassium channel (ROMK). In Bartter syndrome type III (classic Bartter syndrome), there is a mutation in the gene encoding chloride channel Kb (CLC-Kb).

Type IV A and B are antenatal types of Bartter syndrome. In both types, there are defects in the 2 chloride channels, Ka and Kb (CLC-Ka and CLC-Kb). Autosomal dominant hypocalcemia, which occurs due to a gain-of-function mutation in the gene encoding calcium-sensing receptor (CaSR), can lead to a phenotype similar to Bartter syndrome. In addition to the above types, transient antenatal Bartter syndrome can occur due to a mutation in MAGED2 (MAGE Family Member D) gene [2]. Type I, II, IVa, and IVb cause a severe antenatal form of Bartter syndrome, while type III usually has a late and less severe presentation.

It is uncommon for type II to present in adolescence or adult life. To the best of our knowledge, there are only 4 reported cases of late-onset type II Bartter syndrome [3–6]. Here, we report the case of a patient with adult presentation of Bartter syndrome type II. The genetic mutation in our patient was identical to the mutation found in patients with neonatal presentation [7], suggesting a surprising degree of phenotypic diversity.

**Case Report**

A 26-year-old Qatari man presented to the hospital in 2007 with generalized body weakness which began 4 days prior to admission. He noted that he had a similar episode of weakness in the past, and had been told he had low potassium, but he had not had this followed up. On review of systems, he revealed that he had had symptoms of thirst, polydipsia, polyuria, and fatigue since childhood. Information on his antenatal course was not available. There was no information about his childhood growth, but we assume it was normal considering his adult height. He denied taking any medications at home. His family history was notable in that he was a child of a consanguineous union. He had 8 siblings, none of whom had a similar condition. He was married with 3 healthy children.

His weight was 64 kg, height 160 cm, pulse 89/min, and blood pressure 118/71 mmHg. His examination was significant for bilateral lower-limb weakness, with 4/5 strength in the lower limbs. Babinski sign was negative bilaterally, and reflexes were intact. His exam was otherwise within normal limits.

Laboratory investigations (Table 1) revealed a serum potassium level of 1.7 mmol/L. During his hospital stay, his urine potassium/creatinine ratio was 12.4 mmol/mmol, and a concurrent serum potassium was 2.8 mmol/L, suggesting renal potassium wasting as the source of the hypokalemia [3]. He was admitted to the hospital 6 months later for evaluation of acute pancreatitis, and his potassium was 1.6 mmol/L on admission. Other laboratory investigations done during that admission are also shown in Table 1. An ultrasound scan and computerized tomographic scan of the abdomen with contrast showed medullary nephrocalcinosis in both kidneys.

He was treated with intravenous potassium during the first admission and discharged on potassium supplementation. After the second admission, in which he presented with acute pancreatitis, he was discharged on spironolactone and potassium supplementation.

**Genetic analysis**

The clinical picture of recurrent hypokalemia with renal potassium wasting, elevated urine chloride, hyperreninemia, and hyperaldosteronemia, coupled with the demonstration of calcific foci in the kidney with medullary nephrocalcinosis, raised the suspicion of Bartter syndrome.

After obtaining informed consent, a blood sample was sent to the Yale University School of Medicine for genetic testing. The sample was sequenced using the forward KCNJ1 primer (Figure 1) and the reverse KCNJ1 primer. The sequencing using both primers showed a homozygous missense mutation in the KCNJ1 gene in which a cytosine nucleotide replaced a thymine nucleotide (c.658C>T), leading to a substitution of phenylalanine for leucine at codon 220 (L220F). This position is entirely conserved among species (Figure 2) and the reverse KCNJ1 primer. The sequencing using both primers showed a homozygous missense mutation in the KCNJ1 gene in which a cytosine nucleotide replaced a thymine nucleotide (c.658C>T), leading to a substitution of phenylalanine for leucine at codon 220 (L220F). This position is entirely conserved among species (Figure 2) and is highly conserved among paralogs (Figure 3), indicating that the position is important for functioning of this protein. Moreover, this mutation has been previously identified as a disease-causing mutation for Bartter’s syndrome. The patient’s parents and the siblings were not available for genetic analysis.

Based on the clinical picture and the genetic results, the patient was diagnosed with type II Bartter syndrome.
Follow-up

His potassium level has remained between 3.5 and 4 mmol/L on this treatment. In 2010, he developed gynecomastia and underwent liposuction. The spironolactone was discontinued, and his potassium level decreased to 3.0 mmol/L and eplerenone 50 mg once daily was started, with normalization of his serum potassium. He maintained his potassium in the following 2 years within the normal range on eplerenone 50 mg TID and potassium chloride supplementation. His serum creatinine has ranged between 110 and 143 umol/L.

After the first episode of acute pancreatitis, the patient had multiple subsequent episodes of acute pancreatitis over years of follow-up, for which extensive workup was unrevealing. He underwent empirical cholecystectomy, but he continued to have recurrent moderate-to-severe abdominal pain requiring tramadol use. During these episodes, the pancreatic enzymes were mildly elevated, although at other times they were normal. The possibility of early chronic pancreatitis or sphincter of Oddi dysfunction was considered.

Discussion

In summary, we present the case of a man who presented with recurrent episodes of severe hypokalemia after the age of 26 years. Work-up revealed urinary potassium wasting with

Table 1. Laboratory investigations.

| Laboratory investigations         | First admission | Second admission | During follow-up | Normal values |
|----------------------------------|----------------|-----------------|-----------------|---------------|
| Serum creatinine                 | 96 umol/L      | 106 umol/L      |                 | 62–124 umol/L |
| Serum urea nitrogen              | 9.3 mmol/L     | 9.5 mmol/L      |                 | 1.7–8.3 mmol/L|
| Serum potassium                  | 1.7 mmol/L     | 1.6 mmol/L      |                 | 3.6–5.1 mmol/L|
| Serum bicarbonate                | 30 mmol/L      | 23 mmol/L       |                 | 22–29 mmol/L  |
| Serum sodium                     | 134 mmol/L     | 135 mmol/L      |                 | 135–145 mmol/L|
| Serum chloride                   | 92 mmol/L      | 92 mmol/L       |                 | 96–110 mmol/L |
| Serum glucose                    | 5.13 mmol/L    | 8.47 mmol/L     |                 | 3.3–5.1 mmol/L|
| Serum calcium                    | 2.12 mmol/L    |                 |                 | 2.1–2.6 mmol/L|
| Serum phosphorus                 | 0.95 mmol/L    |                 |                 | 0.87–1.45 mmol/L|
| Serum parathyroid hormone        |                | 101 pg/ml       |                 | 15–65 pg/ml   |
| Vitamin D                        | 8 ng/ml        | 7 ng/ml         |                 | 20–50 ng/ml   |
| Serum lipase                     | 11826 U/L      |                 |                 | 13–60 U/L     |
| Serum aldosterone                | 1880 pmol/L    |                 |                 | 80–860 pmol/L |
| Renin activity                   | 7.64 ng/ml/hr  |                 |                 | 0.5–4.2 ng/ml/hr |
| Urine potassium creatinine ratio | 12.4 mmol/mmol | 8.09 mmol/mmol  |                 |               |
| Urine creatinine                 | 1.61 mmol/L    |                 |                 |               |
| Urine urea                       | 30.1 mmol/L    |                 |                 |               |
| Urine sodium                     | 76 mmol/L      | 70 mmol/L       |                 |               |
| Urine chloride                   | 83 mmol/L      | 71 mmol/L       |                 |               |
| Urine osmolarity                 | 274 mOsmol/KG   | 223 mOsmol/KG   |                 |               |
| Urine magnesium                  | 0.79 mmol/L    |                 |                 |               |
| 24-hour urine creatinine         |                | 9.1 mmol/24h    |                 |               |
| 24-hour urine potassium          |                | 50 mmol/24h     |                 |               |
| 24-hour urine calcium            |                | 3.5 mmol/24h    |                 |               |

Table 1 shows the laboratory investigations done during the 2 hospital admissions.
nephrocalcinosis, and the patient was diagnosed with Bartter syndrome type II based on the presence of a homozygous mutation in \(\text{KCNJ1}\) gene encoding the ROMK channel.

The impaired reabsorption of sodium chloride in this part of the nephron leads to increased secretion of potassium and hydrogen, resulting in hypokalemia and metabolic alkalosis.

**Figure 1.** Sanger sequencing electropherograms. Figure 1 illustrates the Sanger sequencing electropherograms of the PCR fragments using the forward \(\text{KCNJ1}\) primer for the patient (A) and the wild-type control (B). The mutant, TTT (Phenylalanine: F), and the wild-type residues, CTT (Leucine: C) are circled.

**Figure 2.** Conservation of \(\text{KCNJ1}\) L218 among homologs. Figure 2 illustrates the complete preservation of the leucine amino acid (L218) among homologs through Zebrafish (D. rerio).

The ROMK channel is necessary for the process of sodium chloride reabsorption in the ascending part of the loop of Henle [5].
The adult presentation of our patient is unusual for type II Bartter syndrome. Typically, infants diagnosed with type II have a history of polyhydramnios and premature delivery, and they present with failure to thrive, polyuria, and dehydration [6]. Unlike children with the other forms of Bartter syndrome, they have transient hyperkalemia and metabolic acidosis in the early postnatal life [7]. Finer et al. demonstrated in a case-series of 12 infants with type II Bartter syndrome that, after this period of transient hyperkalemia, the patients had normal serum potassium during their childhood, which could be the case in our patient. Similar to type I, nephrocalcinosis is a common finding in Bartter syndrome type II [6].

Our patient had hypokalemia, metabolic alkalosis, and normal blood pressure; hence, urine chloride testing was warranted to narrow the differential diagnosis. Since the urine chloride level was high, the possibilities were a renal tubular genetic defect (e.g., Bartter syndrome and Gitelman syndrome) or diuretic intake, which was denied by the patient. In addition, in multiple visits, the patient had a high potassium/creatinine ratio with concurrent hypokalemia, suggesting renal potassium wasting. Genetic testing was then performed, which revealed the diagnosis of Bartter syndrome type II.

In our literature review, we found only 4 case reports of patients with late presentation of Bartter syndrome type II; 3 of them presented in adult life. These 4 cases had several findings in common. Similar to our case, renal imaging in all the cases revealed nephrocalcinosis. In addition, all cases had hyperreninemic hyperaldosteronism, which is a common finding in all types of Bartter syndrome. Hypercalciuria is an inconsistent finding in these cases, with marked hypercalciuria in some, but normal calcium excretion in others (Table 2). The absence of hypercalciuria is curious in our patient, but likely reflects hypovitaminosis D (Table 1) and resultant decreased intestinal calcium absorption [4].

An interesting feature of our case is the phenotypic diversity that has been described for individuals homozygous for the L220F mutation. Both our patient and the patient reported by Huang et al. [3] had this mutation, and both presented as adults. In contrast, Walsh et al. described a patient homozygous for the identical mutation that presented before age 1 year [9]. Similarly, Vollmer et al. described a Turkish child, compound heterozygous for the L220F mutation, who presented as a neonate with typical Bartter’s type II symptoms [10]. Interestingly, in vitro studies in Xenopus found that the ROMK2 expressing the L220F mutation retained significant K conductance, but that the other mutation present in their patient, the A156V mutation, exerted a dominant negative effect on L220F [15]. Similarly, Srivastava et al. identified a patient with neonatal onset of Bartter’s syndrome type 2. They further demonstrated...
Table 2. Summary of previously reported similar cases.

| Author                  | Age | Sex | Clinical presentation                                                                 | Relevant investigations                                      | Type of mutation in KCNJ1 gene | DNA sequence change | Amino acid change | Treatment                                      |
|-------------------------|-----|-----|---------------------------------------------------------------------------------------|-------------------------------------------------------------|-------------------------------|--------------------|-------------------|------------------------------------------------|
| Huang et al., 2014 [3]  | 35  | Male| Incidental finding of nephrocalcinosis in lumbar spine X-ray done for low back pain | Potassium: 2.8 mmol/l                                      | A homozygous missense mutation | c.658C>T            | p.Leu220Phe       | Potassium supplementation and spironolactone |
| Gollasch et al., 2017 [4] | 43  | Female | Incidental finding of nephrocalcinosis in ultrasound done during pregnancy       | Potassium: 2.8 mmol/l                                      | A compound heterozygous missense mutation | c.197T>A (novel mutation) | p.Ile66Asn       | Potassium supplement and angiotensin-converting-enzyme inhibitors (ramipril) |
| Li et al., 2019 [5]     | 34  | Female| Weakness, persistent polyuria and polydipsia; weight and height were normal        | Potassium: 2.4 mmol/l                                      | A compound heterozygous missense mutation | c.701C>T            | p.The234Ile       | Potassium supplementation                          |
| Sharma et al., 2011 [6] | 8.5 | Female| Persistent polyuria and polydipsia; fifth percentile for weight and height          | Potassium: 2.5 mmol/l                                      | A novel compound heterozygous mutation                     | c.268G>T            | p.Gly90Trp        | Potassium supplementation and nonsteroidal anti-inflammatory drugs (NSAIDs) |
| Present case            | 26  | Male | Weakness, persistent polyuria and polydipsia; weight and height were normal        | Potassium: 1.7 mmol/l                                      | A homozygous missense mutation | c.658C>T            | p.Leu220Phe       | Potassium supplement and Aldosterone antagonists |

Table 2 shows 4 previously reported cases of late-onset Bartter syndrome type II.

that ROMK bearing L220F had significant K conductance, which was completely abolished when co-expressed with ROMK bearing S219R, perhaps explaining the neonatal presentation [16]. Thus, it seems likely that the L220F allele is a hypoactive allele that can produce a mild phenotype in the homozygous state, but whose activity can be further decreased in the presence of other mutant alleles. One can imagine that such partially functional channels might be amenable to direct therapy via the use of small-molecule correctors to correct folding defects, as has been done for diseases such as cystic fibrosis [17].

Our patient’s presentation is also notable for unexplained recurrent pancreatitis. ROMK is expressed in the pancreas [18,19], so we cannot exclude that the mutant ROMK may be playing a role in the disease process. We were unable to identify other case reports of pancreatitis in patients with Bartter syndrome, but we note that most such case reports highlight the cases of children. It will be of interest to determine if pancreatic phenotypes are noted if more older patients are reported.

Conclusions

Our case revealed that, in rare conditions, type II of Bartter syndrome can have an adult presentation, which is consistent with a few previous observations. L220F mutation in KCNJ1 gene is involved in the development of late presentation as well as neonatal presentation of type II Bartter syndrome. Further research is needed to study the possible relationship between type II Bartter syndrome and the unexplained recurrent pancreatitis.
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Data availability

The GenBank accession number is: GenBank: AK290797.1

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Conflict of interest

None.