Compound Heterozygous Loss of Allele Coding for KCNJ16 in an Adult Presenting as Recurrent Hypokalemic Periodic Paralysis with Metabolic Acidosis and Hypokalemia

Abstract

A 20-year-old male presented with fever and rapidly progressive muscle weakness. He had hypokalemia and metabolic acidosis, suggesting renal tubular acidosis (RTA). Further investigation revealed distal RTA with preserved acidification. A channelopathy was suspected. Whole exome sequencing identified a novel biallelic mutation in the KCNJ16 gene, which encodes the Kir5.1 protein. This is the first reported case of an Indian adult with biallelic KCNJ16 mutations presenting as pure renal phenotype without sensory neural hearing loss or cardiac manifestation.

Keywords: *Channelopathies, Hypokalemia, Periodic palsy, KCNJ16, Kir5.1*

Introduction

Inwardly rectifying potassium (Kir) channels are crucial for maintaining potassium balance, resting potential, and cellular excitability. The KCNJ16 gene encodes Kir5.1, a subunit that partners with Kir4.1 (encoded by KCNJ10) to form an inwardly rectifying potassium channel in the distal nephron. We describe a 20-year-old adult male carrying a loss-of-function mutation of this channel.

Case Report

A 20-year-old male presented with fever for 1 day, followed by weakness in lower limbs, which progressed to quadriplegia in 48 hours. There was no sensory or autonomic involvement.

He was lean built with a height of 176.1 cm and weight of 50.2 kg, and had hypopigmented patches in the lower limbs. The neurologic examination revealed grade zero power in all four extremities, with no sensory, cranial nerve, and autonomic involvement.

ECG showed sinus tachycardia with prominent U waves. The hemoglobin was 13.1g/dL, total leukocyte count 18,500 cells/mm^3 (90% polymorphs), creatinine 0.63g/dL, potassium 2.5meq/L, sodium 141meq/L, calcium 8.2meq/L, phosphorus 2.78g/dL, bicarbonate 13.2meq/L, and magnesium 1.2meq/L. Urinalysis showed pH 5.0, specific gravity 1.010 mOsm/kg, protein 11.1 mg/dL, and negative for blood, leukocyte esterase, and nitrites. Thyroid function was normal. The patient tested negative for ANA and E ANA profiles, HIV, HBsAg, anti-HCV, EBV, and CMV tests. The urine osmolality was 754 mOsm/kg, serum osmolality 301 mOsm/kg; urine electrolytes: sodium 96 meq/L, potassium 30.97 meq/L, and chloride 121 meq/L; FeHCO3 2% and 24-hour urine citrate 2.01 (0.6–4.81mmol/L). Magnetic resonance imaging (MRI) of the spine and brain was normal. Ultrasonography was normal, and pure tone audiometry showed no sensory neural hearing loss.

Our case showed preserved urinary acidification with preserved bicarbonate absorption and increased urine anion gap, suggesting incomplete distal renal tubular acidosis (dRTA). The patient was treated with intravenous (IV) potassium chloride, which completely reversed his weakness.

The patient was suspected of channelopathy due to incomplete distal RTA-like features. Whole exome sequencing identified a novel compound heterozygous 2-base pair deletion in exon 4 of the KCNJ16 gene, as shown in Table 1. The patient is on regular potassium citrate supplementation and had no exacerbation or periodic paralysis for the last 6 months of follow-up, maintaining potassium at 2.5–3.0 meq/L.

Discussion

We present the first reported case of an Indian adult harboring biallelic loss-of-function mutations in the KCNJ16 gene. This individual exhibited hypokalemia and metabolic acidosis, which were consistent with the findings in Kcnj16-deficient mice and case reports.[1,2]

Seven pathogenic variants of the KCJN16 mutation are described, with 10 (seven females and three males) patients reported, ours being the eleventh. All ten patients, including ours, had hypokalemic metabolic acidosis.[3,4]

Consanguinity was noted in three cases, and the age of onset ranged from 5 days to 26 years. Fever and gastroenteritis were observed as predisposing factors in four cases. Several genetic variants were identified, with *c.409C>T, p.R137C* and *c.526C>T, p.R176* being the most common. All individuals had hypokalemia and 10

Table 1: Gene transcript of the affected patient

Gene (Transcript)	Location	Variant	Zygosity	ACMG Classification
KCNJ16 (+) (ENST00000392671.6)	Exon 4	c.269_270del(p.Ser90CysfsTer15)	Likely compound Heterozygous	Likely pathogenic
KCNJ16 (+) (ENST00000392671.6)	Exon 4	c.404G>T (p.Gly135Val)		Uncertain significance¥

¥: Insilco prediction of this variant is damaging by polyphen-2 (Humdiv), SIFT, LRT and Mutation tester 2, ACMG: American college of medical genome and genetics

experienced acidosis. Sensorineural deafness was reported in eight cases, and renal salt wasting in seven. Other findings included hypomagnesemia, rhabdomyolysis, dyspnea, hypoparathyroidism, and brain edema.[4]

Metabolic alkalosis was seen in one patient harboring pT461 mutation in KCNJ16 gene. It was hypothesized that the gene also played a role in regulating the Kir4.1 channel.[3] Unlike severe pediatric encephalopathy cases, our adult case was benign, with hypokalemia-related periodic paralysis responsive to potassium and bicarbonate supplements.[4]

The KCNJ16 gene encodes Kir5.1, a subunit that partners with Kir4.1 (encoded by KCNJ10) to form an inwardly rectifying potassium channel in the distal nephron.[5] This Kir4.1/Kir5.1 complex regulates potassium conductance and exhibits high sensitivity to intracellular pH.

Loss-of-function mutations in KCNJ10 that code for Kir4.1 are associated with SeSAME/EAST syndrome, characterized by sensory neural hearing loss, epilepsy, ataxia, hypokalemia, and metabolic alkalosis.[5]

Kir5.1 is expressed in the thick ascending limb, descending convoluted tubules, and cortical collecting duct principal cells of the kidney.[6] Conversely, Kir5.1 knockout mice (Kir5.1−/−) exhibit stimulated distal convoluted tubule (DCT) function.[6]

Kir4.1 subunits form functional homomeric channels. However, their single-channel conductance is lower than the Kir4.1/Kir5.1 complex. KCNJ16 deletion leads to the formation of constitutively active, pH-insensitive basolateral Kir4.1 homomeric channels. This increased potassium conductance is predicted to enhance chloride excretion and stimulate Na+K+-ATPase and NCC activity, promoting overall salt reabsorption by the DCT.[6] Kir5.1 also maintains electrocochlear potential and contributes to potassium conductance in cardiac channels.

This case underscores the crucial role of Kir5.1, encoded by KCNJ16, in maintaining potassium balance and acid-base homeostasis in the kidneys. The compound heterozygous mutation in KCNJ16 led to a pure renal phenotype with recurrent hypokalemic periodic paralysis and metabolic acidosis, without the hearing or cardiac issues seen in other cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Conflicts of interest

There are no conflicts of interest.

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