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Case report

A case report of Gitelman syndrome resulting from two novel mutations in SLC12A3 gene

Wojciech Wolyniec[a,*], *Sonia Kaniuka- Jakubowska*[b], *Mato Nagel*[c], *Zuzanna Wolyniec*[d], *Lukasz Obolonczyk*[b], *Renata Swiatkowska-Stodulska*[b], *Krzysztof Sworczak*[b], *Marcin Renke*[a]

[a] *Department of Occupational and Internal Medicine, Institute of Maritime and Tropical Medicine, Medical University of Gdansk, Poland*
[b] *Department of Endocrinology and Internal Medicine, Medical University of Gdansk, Poland*
[c] *Center for Nephrology and Metabolic Disorders, Weisswasser, Germany*
[d] *Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk, Poland*

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ABSTRACT

Introduction: Hypokalaemia is a common clinical problem. A potential but commonly overlooked cause of hypokalaemia is Gitelman syndrome.

Material and methods: A 26-year-old man was admitted to the hospital due to syncope with general and muscular weakness and muscle cramps. The patient's history revealed previous recurrent syncope events associated to hypokalaemia with the lowest serum potassium value being 2.6 mmol/l. At admission, blood pressure was normal and no changes were found at physical examination. Laboratory tests showed mild hypokalaemia (3.0 mmol/l), hypomagnesaemia (1.36 mg/dl), hypocalciuria (< 40 mg/24 h), and metabolic alkalosis (HCO_3^- 29.7 mmol/l, BE 5.3 mmol/l).

Results: Further laboratory tests (FeK, TTKG) confirmed inappropriate kaliuresis. Conn's disease was excluded by hormonal and imaging assessments. Genetic testing was performed and two novel heterozygous mutations: c.35_36insA and c.1095+5G>A were found in transcript NM_000339.2 in SLC12A3 gene.

Conclusion: The patient was diagnosed with Gitelman syndrome and was treated with supplements of potassium and magnesium.

* *Corresponding author.*
E-mail address: wolyniecwojtek@gmail.com (W. Wolyniec).

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El caso del síndrome de Gitelman causado por dos nuevas mutaciones en el gen SLC12A3

Palabras clave:
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Diuréticos

RESUMEN

Introducción: La hipopotasemia es un problema clínico común. El síndrome de Gitelman es una posible causa de hipopotasemia a veces no reconocida.
Material y métodos: Un hombre de 26 años de edad ingresa en un hospital por causa de un síncope, debilidad generalizada y calambres musculares. La historia clínica del paciente reveló la incidencia del síncope con hipopotasemia recurrente con el valor más bajo de potasio en 2,6 mmol/l. En el ingreso, el paciente presentaba una presión arterial normal y la exploración física no reveló ninguna enfermedad. La evaluación del laboratorio demostró una hipopotasemia leve (K+ 3,0 mmol/l), hipomagnesemia (Mg 1,36 mg/dl), hipocalciuria (<40 mg/24 h) y alcalosis metabólica (HCO3- 29,7 mmol/l, exceso de base 5,3 mmol/l).
Resultados: Otras pruebas de laboratorio (FeK, TTKG) confirman una caliuresis inadecuada. La enfermedad de Conn fue excluida tras la evaluación hormonal y radiológica. Se realizaron las pruebas genéticas y 2 mutaciones heterocigóticas: c.35_36insA y c.1095+5G>A fueron encontradas en la transcripción NM_000339.2 del gen SLC12A3.
Conclusión: El paciente fue diagnosticado con el síndrome de Gitelman y fue tratado con suplementos de potasio y magnesio.

Introduction

Hypokalemia is a common clinical problem in endocrinologists' and nephrologists' practice. There are many obvious causes of hypokalemia such as diarrhea, vomiting or diuretics abuse. Other causes such as tubulopathies are rarely observed and their diagnosis is more challenging. There are many inherited and acquired tubulopathies causing hypokalemia, sometimes severe and life-threatening.[1]

A relatively common but overlooked cause of hypokalemia is Gitelman syndrome (GS).[2] It is a recessive salt-losing tubulopathy caused by the *SLC12A3* gene mutation. *SLC12A3* gene encodes the thiazide-sensitive transporter NCCT (sodium chloride co-transporter). NCCT is located in the distal convoluted tubular cells (DCC), which are responsible for 7–10% of electrolyte tubular absorption.[3]

The most severe laboratory abnormalities found in GS are hypokalemia and hypomagnesaemia caused by renal K^+ and Mg^{2+} wasting. Other typical changes are metabolic alkalosis, hypocalciuria and hyperreninemic hyperaldosteronism.[4] Mild to moderate hypophosphatemia is frequently observed.[5] Severe hypophosphatemia with severe hyponatremia was also reported.[6,7]

First symptoms of GS occur in children or young adults with normal growth and history of salt-craving behaviors (children eager to consume pickle or brine, salted cucumbers, oranges and lemons, children licking salt from potato crisps, etc.).[8] Clinical presentation varies among patients. Some are asymptomatic but others develop life-threatening complications. Males manifest a more severe phenotype than females.[8] The most common symptoms are muscular cramps and weakness, constipation, nocturia, polyuria, thirst, polydipsia, cardiac arrhythmias, paresthesias and increased salt appetite. Arterial hypotension is common and in many cases the most prominent symptom, however, in aging GS population hypertension can occur.[8] The correlation between biochemical abnormalities and symptoms is not strong.[9] GS does not interfere with children's moods and social relationships.[9,10] Otherwise symptoms are more common in adults and can have negative impact on their quality of life. Forty-five percent of GS patients consider their symptoms as a moderate to big problem.[11] Extreme exhaustion, muscular weakness, paresthesias, severe fatigue and hypotension are associated with mild to severe reduction in daily activities.[9]

Estimated prevalence of GS is 1:40,000[8] and the prevalence of heterozygous is at least 1% in the European population. More than 180 different mutations in *SLC12A3* have been described until now.[12]

Case report

A 26-year-old male was admitted to the hospital due to incidence of syncope, generalized and muscular weakness and muscle cramps. The patient's history revealed an episode of syncope with potassium level 3.16 mmol/l. In further follow up in outpatient assessment, recurrent incidence of hypokalemia (the lowest value 2.6 mmol/l) was observed. Blood pressure was normal 110/80, heart rate was 72 per minute; there was no changes in physical examination. Nor neurological findings, weight 74 kg, height 178 cm. On admission to hospital laboratory evaluation showed mild hypokalemia (K^+ 3.0 mmol/l), hypomagnesaemia (Mg^{2+} 1.36 mg/dl), hypocalciuria (<40 mg/24 h), and metabolic alkalosis (HCO_3^- 29.7 mmol/l, BE 5.3 mmol/l). Kidney function was good with eGFR > 60 ml/min. Imaging studies were unremarkable, so was the ECG.