

A 48-year adult male with convulsion, collapses and generalized weakness – a rare presentation of Gitelman's Syndrome

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Abstract

Hypokalaemia is a common clinical condition, very often the cause of which can be determined by the patient's clinical history. Gitelman's syndrome is an inherited renal tubular disorder that must be considered in some cases of hypokalaemia. We present this case of a 48-year-old male patient admitted in our nephrology department for recurrent hypokalaemia. The patient had generalized seizure followed by unconsciousness, generalized weakness, fatigue, palpitation, orthostatic hypotension and polyuria for one month. Patient was on treatment for systemic hypertension with amlodipine and olmesartan.

On blood gas analysis, he had a metabolic alkalosis (pH 7.53; pCO₂ 40 mm Hg; HCO₃ 34.1mmol/l). Biochemical analysis revealed hyponatremia (105.8mmol/l), hypokalemia (2.07mmol/l), hypochloraemia (74.0mmol/l), hypomagnesaemia (1.10mmol/l) and hypocalcaemia (7.2 mg/dl). Serum creatinine (1.9 mg/dl) and blood urea (6.3mmol/l) were normal. Further investigations revealed hypocalciuria (0.5mmol/l; NR 2.5–7.5) and increased urinary excretion of sodium (210.0 mmol/l; NR 20–110), Potassium (35mmol/l) and chloride (220mmol/l; NR 55–125). Renal ultra-sonogram was normal. A diagnosis of Gitelman's syndrome was established. We started treatment with sodium chloride, potassium chloride and magnesium sulfate supplementation. Serum potassium was stabilized around 3mmol/l and the patient had significant clinical improvement. The aim of our article is to remind Gitelman's syndrome in the differential diagnosis of persistent hypokalemia and to highlight the need for further investigations in patients with recurrent hypokalaemic episodes.

This rare, inherited, autosomal recessive renal tubulopathy is associated with several genetic mutations in the thiazide-sensitive sodium chloride co-transporter and magnesium channels in the distal convoluted tubule. Patients with Gitelman's syndrome present during adolescence or adulthood as an inherited autosomal recessive traits with a wide range of clinical presentations from being asymptomatic to predominant muscular symptoms such as fatigue, weakness in association with hypocalciuria, hypomagnesemia with hypermagnesuria and normal prostaglandin production. Clinical suspicion should be raised in those with recurrent hypokalaemic paralysis with metabolic alkalosis associated with hypomagnesaemia.

Treatment of Gitelman's syndrome consists of long-term potassium and magnesium salt supplementation. In general, the long-term prognosis and life expectancy is excellent.

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Key words: Gitelman's syndrome; Bartter syndrome; Liddle's syndrome; metabolic alkalosis; thiazide sensitive sodium chloride co-transporter; distal convoluted tubule.

Background:

Hypokalaemia is a common electrolyte disturbance, particularly in hospitalized patients. In cases of chronic hypokalaemia, it usually results from unreplenished gastrointestinal or urinary losses. Gitelman's syndrome is an autosomal recessive salt-losing renal tubulopathy that causes hypokalaemia and metabolic alkalosis. They can present later in life for being asymptomatic or due to a missed diagnosis at a younger age. Herein, we present a case of Gitelman's syndrome in an adult male who had symptoms of recurrent hypokalaemia and unconsciousness.

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Case Representation:

A 48-year-old gentleman was admitted to our hospital with history of generalized convulsion followed by loss of consciousness and collapses one month back when he was admitted in a local hospital with the complaints of generalized weakness for several days. The patient had a feeling of extreme tiredness, fatigue, palpitation and vomiting, Patient was on treatment for hypertension with amlodipine, and olmesartan. Post prandial hyperglycemia was diagnosed during laboratory evaluation, which is controlled with dietary restriction. The patient had no history of diarrhoea, vomiting, laxative or diuretic abuse and alcohol intake. There was no history of exacerbation of weakness by exertion or after heavy carbohydrate meal. His growth and development was normal. One of his younger brothers was suffering from chronic kidney disease. No other family member had similar illness and there was no history of parental consanguinity. Physical examination at the time of admission revealed his vital signs were as follows: heart rate – 80/min, blood pressure - 130/80 mmHg, respiratory rate - 14 breaths/min and his BMI was 24 and oxygen saturation – 97% on air. There was neither neurological deficit nor proximal muscle weakness. Other systemic examination revealed to be normal.

Investigations:

On blood gas analysis, he had a metabolic alkalosis (pH 7.53; pCO₂ 40 mm Hg; HCO₃ 34.1mmol/l). Biochemical analysis revealed hyponatremia (105.8mmol/l), hypokalemia (2.07mmol/l), hypochloreaemia (74.0mmol/l), hypomagnesaemia (1.10mmol/l) and hypocalcaemia (7.2mg/dl). Serum creatinine (1.9mg/dl) and blood urea (6.3mmol/l) were normal. Further investigations revealed hypocalciuria (0.5mmol/l; NR 2.5–7.5) and increased urinary excretion of sodium (210.0mmol/l; NR 20–110) and chloride (220 mmol/l; NR 55–125). Estimated glomerular filtrate rate (MDRD) was 115 ml/min/1.73 m². His blood glucose, thyroid function, serum cortisol and lipid profile were within

the normal limits. Electrocardiogram showed normal sinus rhythm and a heart rate of 74/min. Renal and adrenal ultrasonogram and CT scan revealed normal kidneys and MRI of brain revealed normal.

Based on the association of hypomagnesaemia, hypokalaemia, metabolic alkalosis and hypocalciuria the diagnosis of Gitelman's syndrome was established.

Treatment:

The patient was treated with I.V and oral supplementation of potassium and magnesium along with normal saline and oral Sodium Chloride during hospital period. Serum potassium and magnesium levels improved gradually up to normal and the patient improved symptomatically. He was advised to maintain a high-magnesium, high-sodium and high-potassium diet. He was discharged with advice to continue oral potassium and magnesium supplementation. The patient remains symptom free and normokalemic after six months of follow up.

Outcome and Follow-up:

Two months later the patient was asymptomatic with serum potassium 3.4mmol/l and magnesium 1.10mmol/l. We encouraged to continue ion supplementation. He was followed up as an outpatient for six months.

Discussion:

Bartter's syndrome, Gitelman's syndrome and Liddle's syndrome are the three inherited renal tubulopathy that have now been recognized and occurs due to mutations in several renal tubular transport proteins, responsible for these syndromes.¹ In majority of the cases, there occurs inactivating mutations in the gene that encodes the thiazide-sensitive sodium-chloride transporter (NCC) present in the epithelial cells of the distal convoluted tubules (DCT) of the kidneys.² It causes hypomagnesaemia, hypocalciuria and secondary hyperaldosteronism that induce hypokalemia and metabolic alkalosis. Clinical manifestations that are produced are similar to the prolonged administration of thiazide type diuretics.³

Gitelman's syndrome patients have a diminished natriuretic response to thiazide, but an exacerbated natriuresis occurs after furosemide administration, indicating that the defect is located at the level of the distal renal tubule. The diagnosis may be confirmed by DNA mutation on analysis of the gene responsible for Gitelman's syndrome.^{4,5}

In our patient, diagnosis of Gitelman's syndrome was based on clinical findings and investigation reports like hypokalemic metabolic alkalosis, hypomagnesaemia and hypocalciuria. Renal biopsy is rarely necessary for confirmation of diagnosis and may show hyperplasia of the juxta glomerular apparatus and prominence of medullary interstitial cells, with variable degrees of interstitial fibrosis.⁶

Patients with Gitelman's syndrome do not have symptoms during early years of life. During infancy and preschool years, they may have some febrile seizures, a common presentation in this age group. In some cases Gitelman's syndrome is diagnosed by chance because of abnormal serum electrolytes measured for other reasons.⁷ Chronic vomiting is a common differential diagnosis for Gitelman's syndrome, which can be easily diagnosed by low urine chloride concentration.⁵

Rodriguez-Soriano *et al* first suggested that hypocalciuria may be useful in distinguishing the Gitelman's syndrome from classic Bartter's syndrome.⁸ The hypocalciuria of Gitelman's syndrome is due to the involvement of the distal convoluted tubule, where augmented calcium absorption occurs in association with reduced chloride absorption. But the increased urinary calcium excretion in patients with classic Bartter's syndrome occurs due to impaired reabsorption of calcium in the ascending limb of loop of Henle.⁹

Though blood pressure remains normal or low-normal in the general population with Gitelman's syndrome, interestingly, this case showed hypertension during middle age.

Our patient is hypertensive since 42 years of age. So, it is presumed that his raised blood pressure was due to essential hypertension in a sodium-losing state. This indicates that essential hypertension is genetically heterogeneous and multifactorial disease caused by genetic and environmental interactions.¹⁰ Many genes with significant differences in the polymorphisms have been reported to be responsible for essential hypertension.¹¹ The TSC gene has been identified as a candidate gene for essential hypertension.¹² However, this present case suggests that hypertension may be caused, and abnormality of all genes may not be necessarily required to cause the high blood pressure.¹³ Further studies are needed to confirm this concept.

This patient may also have secondary hypertension resulting from secondary hyperaldosteronism and prolonged intake of high salt and potassium containing diet.

Our patient also had hypermagnesuria. Magnesium is predominantly reabsorbed from the thick ascending limb of loop of Henle. So, it is suggested that involvement of thick ascending limb will promote magnesium wasting, which would not be expected from a tubular defect of distal convoluted tubule. These considerations suggest an additional tubular defect in the Gitelman's syndrome that may cause hypomagnesaemia and hypermagnesuria resulting from prompt magnesium wasting.⁹

Patients with Gitelman's syndrome should be treated with potassium and magnesium supplementation. There is no benefit of prostaglandin synthetase inhibitors in Gitelman's syndrome.⁶ But important therapeutic implications remain in the presence or absence of sodium wasting in these patients. Increased delivery of sodium to the distal tubules causes increased potassium excretion. In sodium wasting state or in patients with sodium supplementation in the diet, a large quantity of potassium supplementation and potassium sparing diuretics will be required to maintain the

normal plasma potassium level. But, small amounts of potassium supplementation with or without potassium sparing diuretics may be sufficient in the absence of sodium wasting.¹⁴

Differential Diagnosis:

Gitelman's syndrome should be considered as a differential diagnosis in all patients with hypokalaemic metabolic alkalosis where there is no obvious cause such as diarrhoea, vomiting, laxative and diuretic abuse or excess alcohol intake. Careful history and screening for urinary diuretics differentiate from diuretic abuse. Laxative abuse causes metabolic acidosis.

Similar biochemical picture can be found in certain endocrine disorders, for example, primary hyperaldosteronism, congenital adrenal hyperplasia and Cushing's syndrome, but usually associated with hypertension. Low serum magnesium, high cortisol and high aldosterone/ renin levels and response to spironolactone exclude these above-mentioned conditions from Gitelman's syndrome. Another condition thyrotoxic periodic paralysis, featured by attacks of muscle paralysis in the presence of hyperthyroidism to be borne in mind as a differential diagnosis in Gitelman's syndrome as hypokalaemia is usually present during attacks. Thyroid function test of our patient was within the normal limit, so thyrotoxic periodic paralysis was excluded.

Prognosis:

In general, the long-term prognosis and life expectancy in Gitelman's syndrome is excellent if treated early and adequately. However, there is a risk of cardiac arrhythmias in these patients due to severe hypokalaemia and hypomagnesaemia. So, detailed cardiac assessment and meticulous management is very important in Gitelman's syndrome patients and strenuous exercise and sporting activities should be discouraged, as this can trigger malignant arrhythmias. Muscular symptoms such as weakness and fatigue can interfere with physical activity and hence quality of life.

Conclusion:

There should be a high index of suspicion for hereditary renal tubular disorder in patients presenting with recurrent hypokalaemia especially when no obvious cause has been identified. Gitelman's syndrome can present also, later in life.

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