INTRODUCTION

Gitelman's syndrome, a variant of Bartter's syndrome, is primarily a renal tubular disorder characterized by hypokalemic metabolic alkalosis, hypomagnesemia, hypocalciuria with normocalcemia and hyperreninemic hyperaldosteronism with normal blood pressure. It is an autosomal recessive disorder caused by defective sodium chloride transport in the distal convoluted tubule and linked to the gene encoding the thiazide-sensitive sodium chloride cotransporter (NCCT) located on chromosome 16q. Sodium chloride wasting and hypovolemia stimulates the renin – angiotensin – aldosterone system resulting in an increase in sodium reabsorption and excretion of hydrogen and potassium ions (latter via activation of Na⁺/K⁺ ATPase pump) leading to hypokalemic metabolic alkalosis. The resultant low intracellular sodium increases calcium re-absorption through the distal convoluted tubule via Na⁺/Ca²⁺ exchanger causing hypocalciuria. The net negative transepithelial potential for Na⁺/Mg²⁺ exchanger is responsible for magnesium loss, which stimulates parathyroid hormone release, further enhancing calcium re-absorption. Associated hypokalemia, metabolic alkalosis and low renal magnesium threshold are the factors resulting in hypermagnesuria.¹

In contrast to the Bartter's syndrome, Gitelman's syndrome presents at an older age with milder clinical manifestations and hypocalciuria with hypomagnesemia being consistent features. Although, recent advances in molecular genetics may make it possible to both diagnose and differentiate these disorders, the phenotypes sometimes overlap. Patients with Gitelman's syndrome are either asymptomatic or present with muscle cramps, fatigue, muscle weakness, carpopedal spasms/tetany and/or paralysis related to hypokalemia and hypomagnesemia. Another outcome seen in these patients is chondrocalcinosis occurring secondary to hypomagnesemia and might be due to an increase in urinary calcium re-absorption with a positive calcium balance.² In children, growth retardation is usually absent, but occasionally may present evidence of growth hormone deficiency that improves with recombinant growth hormone therapy.³

Treatment at present consists of amelioration of symptoms by correction of electrolyte abnormalities. Although some patients require no treatment, the majority needs life-long magnesium supplementation. Continuous magnesium therapy not only corrects hypomagnesemia but also treats hypokalemia, acid-base imbalance and hypocalciuria.

One such case is reported here in which the observation of an electrolyte abnormality (hypophosphatemia) is highlighted that is not a usual feature of this entity.

CASE REPORT

A 14-year-old adolescent girl experienced a long-term history of transient episodes of tetanic spasms of hands and feet and difficulty in walking for 5 years. There was no history of vomiting or gastrointestinal disease and abuse of diuretics or laxatives was denied. She was delivered full-term to consanguineous parents with unremarkable family history.

Physical examination at the time of admission revealed a height of 141 cm (< 5th percentile), weight of 33.5 kg (< 5th percentile) and blood pressure of 110/60 mmHg. She exhibited tetany and genu valgum with rest of the general and systemic examinations being within normal limits.

The results of laboratory work-up are shown in Table I with outstanding findings being severe hypokalemia...
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Table I: Biochemical parameters of the patient at admission.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>Plasma magnesium</td>
<td>1.0 mg/dl</td>
<td>1.9-2.5 mg/dl</td>
</tr>
<tr>
<td>Plasma potassium</td>
<td>1.8 mmol/L</td>
<td>3.5-5.0 mmol/L</td>
</tr>
<tr>
<td>Plasma calcium</td>
<td>6.9 mg/dl</td>
<td>8.5-10.5 mg/dl</td>
</tr>
<tr>
<td>Plasma phosphate</td>
<td>1.2 mg/dl</td>
<td>2.7-4.8 mg/dl</td>
</tr>
<tr>
<td>Plasma bicarbonate</td>
<td>35.0 mmol/L</td>
<td>22-28 mmol/L</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.533</td>
<td>7.34-7.45</td>
</tr>
<tr>
<td>Urinary calcium</td>
<td>46 mg/24 hours</td>
<td>4 mg/kg/24 hours</td>
</tr>
<tr>
<td>Plasma renin</td>
<td>33.35 ng/ml/hour</td>
<td>0.5-2.3 ng/ml/hour</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>16.63 ng/ml</td>
<td>&gt; 20 ng/ml</td>
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(K⁺=1.8 mmol/L), metabolic alkalosis (pH=7.533; HCO₃⁻=35.0 mmol/L) and hypomagnesemia (Mg²⁺=1.0 mg/dl) with hypocalciuria (24 hours urinary Ca²⁺=46 mg) in addition to hypophosphatemia (PO₄=1.2 mg/dl). The renal ultrasound did not show any evidence of nephrocalcinosis. The electrocardiogram showed evidence of hypokalemia in the form of flat T-waves and prominent U-waves, while the radiographs of knees revealed ricketic changes.

The treatment offered during hospital stay was magnesium, potassium and calcium supplementation along with vitamin D and phosphate therapy, latter in the form of Joulie's solution. The problems encountered during treatment were diarrhea due to phosphate therapy given in divided doses 5 times-a-day and secondly, severe hypotension following intravenous administration of magnesium. The electrolyte imbalance was corrected when she was discharged on this medication, the serum potassium level being 3.9 mmol/L, arterial blood gases showing a pH of 7.401 with bicarbonate concentration of 25.3 mmol/L, plasma magnesium level of 2.1 mg/dl, and spot urinary calcium and creatinine ratio being 0.25. Serum phosphate level improved with treatment although remained below the normal range, that is, 2.5 mg/dl. She is on regular follow-up with good compliance and no complaints.

### DISCUSSION

Gitelman's syndrome is an autosomal recessive renal tubular disorder resulting from loss-of-function mutations in the SLC12A3 gene encoding the thiazide – sensitive NaCl cotransporter located on chromosome 16q13. It is more common in adolescent age group with an incidence of 1-2 per million. Gitelman et al. first described three adult patients with intermittent episodes of muscle weakness and tetany, hypokalemia and hypomagnesemia without complaints of polyuria or growth retardation. This patient displayed the typical features of Gitelman’s syndrome, moreover, she developed hypophosphatemia. This has also been seen in another case reported by Katopodis et al. who stated it to be mainly due to inappropriate phosphaturia evidenced by increased FEPO₄³⁻ (>20%) and decreased TmPO₄³⁻/GFR (< 0.87 mmol/L). Various mechanisms have been held responsible for increased phosphate excretion in urine, coexistent hypomagnesemia being considered the main factor as was demonstrated experimentally by Ginn and Shanbour in magnesium-deficient rats. Other causes of phosphaturia are associated metabolic alkalosis (probably due to inhibition of phosphate re-absorption in the renal tubules as a result of competition between the bicarbonate ion and phosphate molecule in the tubular fluid), hypokalemia (the pathophysiology being unclear), and renal vasodilatation induced by prostaglandins leading to a decrease in filtration fraction, increased peritubular hydrostatic pressure and phosphaturia. Hypomagnesemia-induced hypocalcemia was also detected in the case as was observed in a study by Pantanetti et al. who reported impaired parathormone responsiveness to peripheral stimuli determined by hypomagnesemia leading to severe hypocalcemia.

The disease-free intervals in Gitelman's syndrome may be prolonged, and in many cases, diagnosis is made during adult life. It is not as infrequent as reflected in the literature because in the past, it has been confused with Bartter’s syndrome from which it is distinguished by a milder clinical picture, absence of polyuria with a normal/slightly decreased concentrating ability and the outstanding universal biochemical findings of both hypomagnesemia and hypocalciuria, thus allowing an easy differentiation from other hypokalemic syndromes as well. Hypokalemia and metabolic alkalosis are usually present but not necessary to establish the diagnosis of Gitelman's syndrome. Renal histology may be normal or show hyperplasia/hypertrophy of juxtaglomerular apparatus in both these conditions, while recent advances in molecular DNA diagnostic studies are used to establish mutations of the gene encoding the NCCT responsible for Gitelman’s syndrome. An accurate diagnosis is essential because of its impact on the treatment and prognosis of these two syndromes.

The long-term prognosis in terms of renal function and maintaining growth appears to be excellent for Gitelman’s syndrome, but sometimes life-long magnesium supplementation remains necessary to reduce the risk of tetanic episodes. Some patients do not respond well to magnesium therapy due to poor absorption and high urinary excretion of magnesium. Normalization of levels may be difficult to achieve despite high doses resulting in diarrhea. Occasionally, these patients may require additional administration of potassium salts or antialdosterone drugs (spironolactone and amiloride) to correct hypokalemia. High dose indomethacin may be indicated in exceptional cases with growth retardation and bad tolerance to magnesium supplementation. Cyclo-oxygenase–2 inhibitors (Rofecoxib) have also been successfully used in cases with growth retardation and bad tolerance to magnesium supplementation.
Gitelman’s syndrome. The exact fate of this entity is yet unknown because of underdiagnosis.

REFERENCES