Gitelman's syndrome in pregnancy: case report and review of the literature

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Abstract

Gitelman's syndrome (GS), a rare renal disorder, results in hypokalaemia, hypomagnesaemia, hypocalciuria and a metabolic alkalosis. It is unclear if an alteration in management is necessary or beneficial during pregnancy. A 32-year-old woman with GS was managed in her second pregnancy. Antenatally, the patient required 39 (principally day case) admissions to the hospital for intravenous (IV) therapy and received a cumulative total of 47 l of IV 0.9% saline solution, 47 doses of 20 mmol magnesium chloride and 46 doses of 80 mmol potassium chloride. She delivered a 2940-g female infant in excellent condition by caesarean section. We would suggest that close attention to maternal weight gain during pregnancy is an easily available clinical tool to assess adequacy of fluid and electrolyte repletion in this condition.

Keywords: Gitelman's syndrome; pregnancy

Introduction

Gitelman's syndrome (GS) is a rare autosomal recessive condition first described in 1966 [1,2]. Incidence varies with reports but is estimated at approximately 1.2 per million [3]. Mutation in the SLC12A3 gene on chromosome 16 (16q13) results in loss of function of the encoded thiazide-sensitive sodium chloride cotransporter in the distal convoluted tubule of the kidney, leading to sodium wasting and hypocalciuria. The consequent increased sodium delivery to the cortical collecting duct leads to increased sodium reabsorption by the epithelial sodium channel, counterbalanced by potassium (K⁺) loss ultimately resulting in hypokalaemia. Hypomagnesaemia occurs because of increased distal exchange of magnesium (Mg⁺) for sodium (Na⁺). Characteristic features include salt craving, tiredness and postural hypotension. GS in pregnancy has been associated with an increased risk of miscarriage, oligohydramnios and intrauterine growth restriction, as well as significant maternal morbidity due to difficulties in maintaining electrolyte balance [3–6].

Case report

A 32-year-old-woman with GS booked at 9 weeks gestation in her second pregnancy. The diagnosis had been established by the prior and repeated demonstration of an increased (>7.0 when serum [K⁺] <3.5 mmol/l) urinary transtubular gradient for potassium (TTKG), increased (>5% when serum [Mg⁺] <0.5 mmol/l) fractional excretion of Mg⁺ and hypocalciuria (24-h urinary calcium excretion <0.2 mmol/day on a normal diet), as opposed to those electrolyte excretory features which would favour a diagnosis of Bartter's syndrome. Genotype profiling had not been sought nor performed.

Her previous pregnancy had resulted in the birth of a female infant at 38 weeks gestation by emergency caesarean section for fetal distress. This pregnancy had been managed elsewhere and was notable for the fact that the patient had spent almost her entire gestation feeling dizzy and unwell as a hospital inpatient receiving repeated infusions of calcium and Mg⁺ salts.

Maintenance medications at booking included: Sando-K® tablets, a preparation containing potassium bicarbonate and potassium chloride, providing 48 mmol of K⁺ daily; Magnesium Verla® granules providing 40 mmol of Mg⁺ daily; spironolactone, which was replaced by amiloride 15 mg daily. These were continued throughout pregnancy.

The patient was seen fortnightly and was monitored for the presence or absence of postural hypotension and weight gain as well as assessment of serum [Na⁺], [creatinine], [Mg⁺] and [K⁺]. Urinary TTKG and FEMg were measured every 4 weeks to assess changes in urinary wasting of these electrolytes.

In the year preceding this pregnancy, the patient had received a cumulative total of approximately 4–6 l intravenous (IV) 0.9% saline solution over 12 months. Clinical observation had revealed a tendency for increasing tiredness, peripheral dysaesthesia, palpitation and dizziness to occur approximately every 3–4 months and typically when serum [Mg⁺] was <0.4 mmol/l and serum [K⁺] was <3.0 mmol/l. The administered fluid (usually 1–2 l, with supplemental...
**Table 1.** Maternal weight, BP, blood and urine [electrolytes] with derived indices; pre, during and post pregnancy

<table>
<thead>
<tr>
<th></th>
<th>Pre-pregnancy</th>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal weight (kg)</td>
<td>67.0</td>
<td>65.0</td>
<td>66.8</td>
<td>67.7</td>
<td>61.4</td>
</tr>
<tr>
<td>Maternal BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>104/70</td>
<td>104/64</td>
<td>124/78</td>
<td>90/60</td>
<td>100/70</td>
</tr>
<tr>
<td>Erect</td>
<td>116/72</td>
<td>116/60</td>
<td>118/70</td>
<td>80/40</td>
<td>108/67</td>
</tr>
<tr>
<td>Urinary creatinine (μmol/l)</td>
<td>3522</td>
<td>1326</td>
<td>5953</td>
<td>8307</td>
<td>2421</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/kg)</td>
<td>404</td>
<td>147</td>
<td>493</td>
<td>637</td>
<td>303</td>
</tr>
<tr>
<td>Urinary [K+] (mmol/l)</td>
<td>3.11</td>
<td>1.24</td>
<td>4.31</td>
<td>4.37</td>
<td>2.48</td>
</tr>
<tr>
<td>Urinary [K+] (mmol/l)</td>
<td>100</td>
<td>30</td>
<td>119</td>
<td>84</td>
<td>36</td>
</tr>
<tr>
<td>Serum [K+] (mmol/l)</td>
<td>4.0</td>
<td>3.1</td>
<td>2.6</td>
<td>2.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Serum [Mg+] (mmol/l)</td>
<td>0.67</td>
<td>0.61</td>
<td>0.47</td>
<td>0.53</td>
<td>0.66</td>
</tr>
<tr>
<td>Serum osmolality (mOsm/kg)</td>
<td>295</td>
<td>278</td>
<td>273</td>
<td>277</td>
<td>291</td>
</tr>
<tr>
<td>Serum [creatinine] (µmol/l)</td>
<td>68</td>
<td>64</td>
<td>49</td>
<td>52</td>
<td>65</td>
</tr>
<tr>
<td>TTKG</td>
<td>18.25</td>
<td>18.3</td>
<td>25.34</td>
<td>13.05</td>
<td>10.48</td>
</tr>
<tr>
<td>FEMg (%)</td>
<td>12.8</td>
<td>14.0</td>
<td>10.8</td>
<td>7.4</td>
<td>14.4</td>
</tr>
</tbody>
</table>

Mg$^2+$ of 20 mmol and K$^+$ of 80 mmol) led to rapid improvement in symptoms with an increase in serum cation levels. Clinical and biochemical improvement tended to be sustained for a further 3–4 months before the recurrence of symptoms.

Antenatally, despite ongoing aggressive oral electrolyte supplementation, the patient required 39 admissions to the hospital for IV therapy. The majority of these were as day cases. This was in response to symptoms and signs of extracellular fluid (ECF) volume depletion and postural hypotension. Episodic severe fatigue was a prominent symptom. Although hypokalemia and hypomagnesemia also occurred, these were not especially severe and were not associated with cardiac dysrhythmias or changes in the QT interval on electrocardiographic tracing. These symptoms were very similar to those which had been observed at much greater intervals prior to pregnancy. However, the witnessed improvement in symptoms was not sustained and, eventually, a policy of elective fluid administration at weekly and, subsequently, bi-weekly intervals was implemented. This stabilized the symptom fluctuation. Characteristic features of depression (early morning wakening, tearfulness, hopelessness) were not expressed.

During pregnancy and for the first week postpartum, the patient received a cumulative total of 47 l of IV 0.9% saline solution. Integrated with these infusions were 47 doses of 20 mmol magnesium chloride and 46 doses of 80 mmol potassium chloride. The variations in TTKG, FEMg, electrolytes, maternal weight and blood pressure (BP) pre-pregnancy, during pregnancy and postpartum are illustrated in Table 1.

Labor was induced at 38 weeks gestation following the development of oligohydramnios. She delivered a 2940-g infant in excellent condition by caesarean section for failure to progress in the first stage. Postnatal course was uncomplicated. In the subsequent year, the symptom pattern and requirement for fluid and electrolyte supplementation reverted to the pattern that had been seen in the year before pregnancy.

**Comment**

Based on a booking visit body mass index of 26, the patient was estimated to gain approximately 15 kg over the course of her pregnancy [7]. The difference in pre-pregnancy and third trimester weight in our patient was only 0.7 kg. This is most likely explained by the characteristic salt wasting seen in GS with attendant inability to maintain ECF volume. The serial TTKG and FEMg measurements clearly demonstrate the inappropriate K$^+$ and Mg$^+$ wasting characteristic of GS throughout all stages of pregnancy, although they fail to show an incremental relationship as pregnancy progressed. We postulate that the deterioration in her symptoms during pregnancy, manifested by her increased requirements for more frequent IV fluid and electrolyte repletion, therefore more likely represents an absolute extracellular volume depletion (or, rather, an inability to achieve the normal extracellular volume expansion seen in normal pregnancy) rather than worsening potassium or magnesium deficiency.

The outcome of GS in pregnancy appears favourable provided regular supplementation is used to relieve worsening maternal symptoms and close antenatal surveillance enables detection of growth restriction and oligohydramnios. Although the traditional focus in clinical practice has been on monitoring serum electrolytes, we would suggest that closer attention should be paid to maternal weight gain, or failure thereof, as an easily available clinical tool to assess adequacy of fluid and electrolyte repletion. Furthermore, it may be that the better target of therapy is the maintenance of ECF volume by saline infusion, rather than the more traditional potassium and magnesium repletion.

**Conflict of interest statement.** None declared.

**References**


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Renal failure due to combined cast nephropathy, amyloidosis and light-chain deposition disease

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Abstract

Renal dysfunction commonly occurs in multiple myeloma (MM) and is caused by deposition of abnormal light chain within various compartments of the kidney. Renal pathologic findings are diverse and include cast nephropathy (CN), amyloidosis and light-chain deposition disease (LCDD). We report a case of renal failure in a patient with MM caused by concurrent CN, amyloidosis and LCDD which has not been previously described.

Keywords: amyloidosis; light chain; myeloma; nephropathy

Background

Kidney disease is a common sequela of multiple myeloma (MM). The etiology of renal insufficiency in MM is heterogeneous and includes cast nephropathy (CN), amyloidosis and light-chain deposition disease (LCDD). Although most patients have only one pattern of renal pathology, up to two patterns occurring in the same patient has been described. CN and LCDD appear to be the most common combination [1], although amyloidosis with LCDD has been observed [2]. We report the case of a woman with MM and renal failure who had three concurrent pathologic findings on renal biopsy: CN, amyloidosis and LCDD.

Case Report

A 40-year-old woman with no previous medical history presented to an outside medical centre with hypertension and renal insufficiency. Serum protein electrophoresis showed an M-spike of 3.4 g/dL (34 g/L) and serum immuno fixation demonstrated a monoclonal IgG kappa. Urine protein electrophoresis revealed a monoclonal kappa plus IgG kappa fragment. Initial renal biopsy was consistent with acute tubular necrosis, CN and focal arterial amyloidosis. She was transferred to our institution. On admission, serum kappa free light chain (FLC) level was elevated at 1050 mg/dL (0.33–1.94 mg/dL) with a creatinine of 4.3 mg/dL (380 µmol/L). Bone marrow biopsy showed approximately 9% monoclonal kappa plasma cells with negative Congo red staining. Bone survey was negative for any lytic lesions or pathologic fractures. cDNA sequencing was performed on the bone marrow plasma cells. A dominant clone expressing kappa 1 immunoglobulin light chain with mutations in the L12 locus was identified, consistent with the circulating monoclonal kappa light chain (Figure 1). The patient was diagnosed with MM and treated with plasma exchange followed by dexamethasone and thalidomide. Five months after presentation, she underwent autologous stem cell transplantation. At the time of transplantation, her creatinine was 3.5 mg/dL (309 µmol/L) with a creatinine of 4.3 mg/dL (380 µmol/L). Bone marrow biopsy showed approximately 9% monoclonal kappa plasma cells with negative Congo red staining. Bone survey was negative for any lytic lesions or pathologic fractures. cDNA sequencing was performed on the bone marrow plasma cells. A dominant clone expressing kappa 1 immunoglobulin light chain with mutations in the L12 locus was identified, consistent with the circulating monoclonal kappa light chain (Figure 1). The patient was diagnosed with MM and treated with plasma exchange followed by dexamethasone and thalidomide. Five months after presentation, she underwent autologous stem cell transplantation. At the time of transplantation, her creatinine was 3.5 mg/dL (309 µmol/L) with a serum FLC of 33 mg/dL. She had 307 mg/24 h of proteinuria and a monoclonal kappa plus IgG kappa fragment on urine immuno fixation. Six months after transplantation, the patient's serum FLC level increased and her creatinine climbed to 4.4 mg/dL (389 µmol/L). To further evaluate her decline in renal function, a renal biopsy was performed. Renal biopsy showed no significant glomerular mesangial matrix expansion or inflammatory features. Several tubules contained periodic acid Schiff (PAS) negative cast material that had a fractured appearance and was asso-