CASE REPORT

Hypocalcaemia and hyponatraemia masquerading the diagnosis of Gitelman syndrome

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SUMMARY

Gitelman syndrome is the most common renal tubulopathy, recently exhibiting a dramatic rise of incidence in Asia.

A 50-year-old woman presented with vomiting, fatigue and quadriparesis. Physical examination revealed a positive Trousseau sign, hypotonia and areflexia. Suspecting hypocalcaemia, she was given intravenous 10% calcium gluconate (10 mL administered slowly over 10 min) but her manifestations persisted. An exhaustive laboratory work up revealed the diagnosis of Gitelman syndrome.

The peculiarity of this case however, is entailed in its coexistence with hypocalcaemia and hyponatraemia. In addition, the age of primary presentation being 50 years further culminates its atypicality.

Multiple electrolyte imbalances were corrected by oral and intravenous supplementation and a high sodium-potassium diet was advocated. Administration of spironolactone imposed a pitfall in the management of our patient due to exacerbation of pre-existing hyponatraemia.

On follow-up, her electrolyte profile was stable and corresponding symptoms were alleviated.

BACKGROUND

With an estimated prevalence of up to 10 40 000,^{1 2 3} Gitelman syndrome or familial hypokalaemia-hypomagnesaemia, is the most commonly inherited renal tubular disorder and its incidence is steadily increasing in Asia. It is an autosomal recessive salt-losing tubulopathy involving mutations in the gene SLC12A3. This gene encodes thiazide-sensitive NaCl cotransporters in the apical membrane of the distal convoluted tubule. The condition typically manifests as hypokalaemic metabolic alkalosis in combination with substantial hypomagnesaemia and hypocalciuria.³

Patients are usually normocalcaemic or slightly hypercalcaemic as a result of hypocalciuria, however hypocalcaemia is extremely rare.⁴ Despite life-long salt wasting, patients usually have normal sodium levels and hyponatraemia is also an uncommon manifestation in these patients.⁴

Herein, we report the first case of Gitelman syndrome in medical literature with both hypocalcaemia and hyponatraemia. Given that most patients present in their adolescence or early adulthood, the age of presentation being 50 years is another unique feature of this case.⁵

Taking these factors into account, we emphasise the diagnostic challenges, treatment hurdles and precautionary measures to be considered for the optimal management of such patients.

Although Gitelman syndrome has been an established entity since 1966,⁶ the enigma surrounding this condition baffles our understanding of its widespread clinical spectra, ranging from asymptomatic individuals to others incurring unusual manifestations such as that seen in our case. A solid understanding is essential to expand the horizon for further research.

CASE PRESENTATION

A 50-year-old woman presented with recurrent vomiting over a period of 1 month alongside abdominal pain and fatigue. This was followed by progressive weakness in all four limbs, myalgia and cramping, as well as slurring of speech.

There was no history of diarrhoea and she denied any laxative or diuretic use, explicit drug abuse or any alcohol intake. There was no history of any ayurvedic treatment. There was no history of polyuria or arthritis.

Regarding her family history, she has no siblings and her parents are non-consanguineous and healthy.

General examination was normal and BP was 150/70 mm Hg with no significant postural variation. Examination of the respiratory system, cardiovascular system and the abdomen were unremarkable. On examination of the nervous system, Chvostek's sign and Trousseau sign were positive (figure 1), hypotonia was present, all reflexes were lost and grade 1 power in all the four limbs was detected without any sensory impairment.

Higher mental function and examination of the cranial nerves were normal.

INVESTIGATIONS

In view of the clinical findings, the patient was given antiemetics and was treated with intravenous 10% calcium gluconate (10 mL administered slowly over 10 min). However, her condition remained poor with persistent carpopedal spasm and hypotonia.

Dyselectrolytaemia was suspected owing to prolonged vomiting and hence serum electrolyte levels and urinalysis investigations were carried out.

Biochemical investigations (table 1), revealed hypokalaemia, hypomagnesaemia, hyponatraemia and hypocalcaemia with an overall decrease in serum osmolality. Twentyfour hour urinalysis tests showed profound hypocalciuria.

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Figure 1 The patient exhibiting carpopedal spasm (Trousseau sign).

Arterial blood gas analysis revealed metabolic alkalosis with a pH of 7.55, HCO_3^- 29.7 and a base excess of +6.0.

Complete blood picture, erythrocyte sedimentation rate (ESR), liver function tests, C-reactive protein, antinuclear antibodies, random blood sugar, thyroid profile, parathyroid hormone (PTH) and cortisol levels were all within normal parameters.

The kidneys were unremarkable on ultrasound imaging.

ECG showed QT prolongation.

DNA mutational analysis tests were not performed due to lack of resources and necessary expenditure for external testing.

DIFFERENTIAL DIAGNOSIS

Gitelman syndrome may not strike physicians as a definite diagnosis owing to its rarity and unspecific clinical picture. Hence, the incidental laboratory findings of hypokalaemic metabolic alkalosis aroused the suspicion of this diagnosis after having ruled out the more trivial causes of the same such as diarrhoea, laxative or diuretic abuse and alcohol intake.^{7,8}

The most common salt-losing renal tubulopathies presenting with hypokalaemic metabolic alkalosis are Gitelman syndrome, Bartter syndrome and Liddle's syndrome.⁹ Bartter syndrome, triggered by a NaK2Cl transporter defect, also exhibits hypocalcaemia mimicking that seen in our case. However, this is attributed to the presence of hypercalciuria,^{9,10} whereas our

patient showed hypocalciuria. The presence of hypercalciuria in Bartter syndrome may also induce nephrocalcinosis,¹⁰ which was absent in this case. Furthermore, the presence of hypomagnesaemia in our patient is in contrast to the normomagnesaemia typically encountered in Bartter syndrome. This grounded the likelihood of Gitelman syndrome, which is invariably associated with hypomagnesaemia.^{10,11} Liddle's syndrome, another renal tubulopathy resulting in hypokalaemic alkalosis, was also ruled out as it is characterised by normal calcium and magnesium homeostasis.¹²

Although genetic testing could not be done in our patient, it is advisable to do so in cases of strong phenotypic overlap between the various tubulopathies. This can be done through deletion/duplication analysis or by sequence analysis in the entire coding region of the SLC12A3 gene.¹³

The concurrence of hyponatraemia and hypocalcaemia along with a lack of DNA mutational evidence presented a diagnostic challenge by hindering the ground certainty of a renal tubulopathy. This necessitated the elimination of an array of various differentials.

Endocrine aetiology resulting in myalgia, fatigue and vomiting such as Addison's disease was also considered to rationalise the hyponatraemia in our patient. However, this was ruled out as a possibility due to the absence of metabolic acidosis and serum cortisol levels being normal.¹⁴ In view of the pronounced hypocalcaemia, hypoparathyroidism was initially contemplated but excluded given that the PTH level was normal. Thyrotoxic periodic paralysis, which also exhibits hypokalaemia and bouts of muscle paralysis, was eliminated as it usually presents with hyperthyroidism, its key differentiating factor, and does not exhibit alkalosis.¹⁵ Hypokalaemic periodic paralysis, an autosomal dominant condition, presents with intermittent attacks of weakness during periodic falls in potassium levels¹⁶ and was hence omitted since our patient's symptoms were continuous in nature.

Neurological aetiology such as Guillain-Barre syndrome (GBS) was considered as a possible differential given the presence of paralytic symptoms in conjunction with hyponatraemia, the most common reported dyselectrolytaemia in GBS.¹⁷ However, it is usually preceded by a respiratory or gastroenteric illness, and portrays a rapid onset of paresthesias and weakness.¹⁸

Our patient was ultimately diagnosed with Gitelman syndrome along with severe hyponatraemia and hypocalcaemia, two extremely rare concomitant findings. Moreover, most patients with Gitelman syndrome usually present with hypotension but our patient showed a systemic rise in blood pressure. This could be explained by secondary hyperaldosteronism or essential hypertension given the age of the patient.¹⁹

TREATMENT

Intravenous supplementation was initiated in order to improve the multiple electrolyte imbalances. The patient was initially started on intravenous 10% calcium gluconate (10 mL administered slowly over 10 min).

After confirmation of the diagnosis, the patient was administered intravenous 3% normal saline (15 mL/hour for 24 hours) and the sodium level stabilised to 126 mmol/L. Following this, she was given intravenous magnesium aspartate (250 mg, four times a day) and potassium chloride (600 mg, two times per day).

In addition, she was also advocated to maintain a high sodium (buttermilk, cheese, pickles, cured meat and fish, salted crackers) and potassium (kidney beans and chickpeas, pistachios, clams, bananas, sweet potatoes) diet.

Table 1 Biochemical investigations

Parameter	Value	Reference range
Serum		
Sodium	110.0 mmol/L	135–145
Potassium	1.4 mmol/L	3.5–5.5
Calcium	5.8 mg/dL	9–11
Chloride	56.6 mmol/L	95–105
Phosphorus	2.6 mg/dL	2.5–4.5
Magnesium	1.0 mg/dL	1.8–2.4
Creatine kinase	1680.0 U/L	20–200
Parathyroid hormone	5.1 pg/mL	4.7–114
25-hydroxy vitamin D	38.0 ng/mL	30–100
Osmolality	229.0 mmol/kg	275–295
Urine (24 hours)		
Volume	2500 mL	
Sodium	36.0 mEq/24 hours	40–220
Potassium	9.5 mEq/24 hours	25–125
Magnesium	138.0 mg/24 hours	70–130
Calcium	110.0 mg/24 hours	420–550
Chloride	225.0 mEq/24 hours	140–240
Calcium-to-creatinine ratio	<0.2	<0.14
Osmolality	140.0 mmol/kg	300–900

A complete cardiac work up was issued to screen for risk factors for cardiac arrhythmias and cardiac arrest; reports were unremarkable.

OUTCOME AND FOLLOW-UP

On a 2-week follow-up, the patient had a stable electrolyte profile and did not display any symptoms pertaining to the same.

Annual follow-up and evaluation by a nephrologist was recommended.

DISCUSSION

The amalgamation of these two very rare findings, namely hyponatraemia and hypocalcaemia, makes this a unique case of Gitelman syndrome and expands the horizon for further research.

Gitelman syndrome has rarely been reported with coincidental hyponatraemia, regardless of the life-long propensity for salt wasting.²⁰ An extensive review of literature revealed only three cases reported until now, being first reported by Schepkens *et al*²¹ in two patients in 2001. In light of these cases, the presence of hyponatraemia may be attributed to the multifaceted, intricate interplay between life-long tubular salt wasting, antidiuretic hormone hyper-secretion owing to extracellular volume depletion, and diminished diluting function of the distal tubules.²² When present, it induces symptoms such as headache, nausea and mental confusion. Seizures, coma and death may occur due to progressive, pronounced and untreated hyponatraemia.²³

Despite the presence of hypocalciuria that would substantiate hypocalcaemia in patients with Gitelman syndrome, our patient peculiarly exhibited hypocalcaemia. This elucidates the refractory carpopedal spasm and hypotonia despite the initial administration of calcium gluconate. This rare manifestation is most probably due to the presence of hypomagnesaemia. Magnesium is required for the synthesis and release of PTH hence deficiency results in inadequate PTH levels and resultant secondary hypocalcaemia.^{24 25} Pantanetti *et al*,²⁶ and Nakamura *et al*²⁷ described two patients with Gitelman syndrome in whom hypocalcaemia developed due to hypomagnesaemia. End organ resistance to PTH and vitamin D is another factor that may possibly substantiate the presence of hypocalcaemia in our patient.^{28 29} Hypocalcaemia exacerbates fatigue, irritability, muscle cramps, weakness and severe attacks of muscular spasms. Failure to treat the root pathology may incur marked hypocalcaemia, predisposing the patient to more sinister outcomes such as laryngospasm and cardiac arrhythmias.³⁰

The management of Gitelman syndrome should be highly individualised given its atypicality. The mainstay of treatment involves lifetime supplementation of oral potassium and magnesium. Magnesium correction should be a priority as it may potentiate hypokalaemia. Organic salts like aspartate and citrate should be preferred due to their higher bioavailability.

Potassium should be administered in the form of potassium chloride due to loss of chloride in the urine and metabolic alkalosis. Intravenous therapy is recommended in severe cases and when intolerant to oral drugs.^{7 31} In refractory cases, spironolactone, a potassium-sparing diuretic that proved to be efficacious in multiple other trials for Gitelman syndrome,^{7 32 33} can be administered. However, it was eluded in this particular case in order to avoid further exacerbation of the severe pre-existing hyponatraemia. This was an important precautionary measure to be instilled in the management of our patient. In addition to the aforementioned standards,^{7 31} our patient also required calcium and sodium correction.

Learning points

- The amalgamation of hyponatraemia and hypocalcaemia in conjunction with Gitelman syndrome, although rare, is nevertheless still plausible and potentially lethal when present. Therefore physicians should be aware that the recognition, early detection and management of this unusual unification, is crucial.
- Patients with renal tubulopathies mostly present in their adolescence and early adulthood. The primary presentation of our patient in the fifth decade of life should alert physicians to never neglect a renal tubulopathy as a differential in patients presenting with similar symptoms, regardless of their age.
- Hypocalcaemia and hyponatraemia are secondary manifestations that may potentially hinder the prompt diagnosis of the underlying tubulopathy. Hence, utmost precaution and an instrumental laboratory work up must be ensued to avoid wavering from the actual diagnosis.
- Appropriate and vigilant management should be swiftly entailed to avoid the more severe, life-threatening ramifications of these associated complications. The use of spironolactone, a drug that has been efficacious in multiple trials for Gitelman syndrome, should be deterred in the presence of hyponatraemia to prevent further exacerbation of pre-existing hyponatraemia.

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