Journal of the Postgraduate Institute of Medicine 2022; 9(2): E183 1-4
http://doi.org/10.4038/jpgim.8367

Case Report

An elderly patient with Graves' disease presenting with hypercalcemia and Gitelman syndrome – a diagnostic challenge

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Key words: **Graves' disease, hypercalcemia, Gitelman syndrome**

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Received: 14 Dec 2021, accepted revised version: 09 Jul 2022, Published: 24 Aug 2022
Competing Interests: Authors have declared that no competing interests exist

Introduction

Graves' disease is known to be associated with hypercalcemia and, rarely, Gitelman syndrome. The occurrence of both conditions in the same patient has not been reported. The presence of hypercalciuria secondary to hypercalcemia gives rise to a clinical picture similar to Bartter's syndrome at the onset and makes the diagnosis challenging.

Case presentation

A 76-year-old female with type 2 diabetes mellitus and hypertension presented with a history of loose stools of 1 months duration. She complained of passing small amounts of semisolid stools 5 to 6 times a day. She had lost 5 kg during the last 2 months despite a good appetite. She complained of increased fatigue and difficulty in getting up from the seated position in the last 2 weeks. She did not have a history of recent worsening of hypertension or treatment with diuretics. Her physical examination revealed sweaty palms and tachycardia. There were no features of a Graves' ophthalmopathy or thyroid enlargement or tenderness. Rest of her examination was normal.

Her investigations revealed marked hypokalemia, hypercalcemia, hypomagnesemia and metabolic alkalosis. The rest of her investigations were planned to evaluate the cause of these metabolic derangements. Her urinary investigations revealed marked hyperkaluria which was persistent after correcting serum magnesium. Although her urinary calcium excretion was initially high, it became normal subsequently and was thought be secondary to hypercalcemia. Her plasma aldosterone level and plasma renin activity after

replacing Losartan with Prazocin and correcting serum potassium were normal excluding primary hyperaldosteronism.

Her serum phosphate level and vitamin D level were normal while serum parathyroid hormone level (PTH) was markedly suppressed indicating a non PTH driven cause of hypercalcemia. Further investigations revealed an elevated free T4 level and suppressed TSH. TSH receptor antibodies were highly positive with a titer of 14.0 U/l (0.0-2.0 U/l). USS of neck showed a diffuse enlargement and increased vascularity of the thyroid gland. Radionuclide uptake scan showed diffusely increased radioiodine uptake confirming the diagnosis of Graves' disease.

The CECT chest, abdomen and pelvis, colonoscopy and serum protein electrophoresis, done as a part of the evaluation to exclude a malignant cause for hypercalcemia, were normal.

She was commenced on carbimazole 20 mg bd and oral potassium replacement. After 3 months of treatment her serum free T4 level came back to the normal range along with serum calcium, serum magnesium and urinary calcium. Patient exhibited mild metabolic alkalosis and marked urinary potassium loss even at 3 months. At one year, she was euthyroid without medications and all her electrolyte abnormalities reversed back to normal, further confirming that the underlying mechanism accounted for the electrolyte abnormalities.

Results of her investigations are summarized in Table 1.

Table 1: Summary of investigations

Investigation	**Result**
Full blood count	WBC – 8.3×10^3/ µL, N- 54.8%, L - 35.3%, Hb 11.7g/dL, plt 228× 10^3/ µL
Serum creatinine	92 µmol/dL
Serum sodium	138 mmol/dL
Serum potassium	2.4 mmol/dl
Serum ionized calcium	1.41mmol/l (1.12-1.32)
Serum phosphate	1.2 mmol/l (0.8-1.5)
Serum magnesium	0.48 mmol/L (0.8 – 1.1)
Serum PTH level	4.8 pg/ml (14 -72)
Serum Vitamin D level	32 ng/ml (30 – 100)
Arterial blood gas	pH 7.48, pCO2 47 mmHg, pO2 85 mmHg, HCO3 35 mmol/dL
Urinary spot sodium	28 mmol/L
Urinary spot potassium	37 momol/L
Urinary calcium creatinine ratio	0.45 to 0.011 mol/mol (0.1 – 0.4)
Trans tubular potassium gradient	16.35 (<3)

Urinary fractional excretion of magnesium	31.76% (>2%)
Serum renin	3.2 ng/ml/hr (0.6- 4.18)
Serum aldosterone	22 ng/dL (3.47 – 27.5)
TSH	0.002 mIU/L.
fT4	4.56 ng/dl (0.89-1.76)
Iodine up take scan	Diffused Increased uptake

Discussion

The constellation of biochemical abnormalities in this patient offer a certain diagnostic challenge. In the first place, the patient had evidence of Graves' disease which is typically a disease of young females although it is known to occur in elderly [1].

Batter's syndrome and Gitelman's syndrome are closely related disorders due to renal tubular dysfunction which present with hypokalemia and metabolic alkalosis. Hypercalciuria is seen more in Batter's syndrome while hypomagnesemia is seen more in Gitelman's syndrome.

Hypokalemia, metabolic alkalosis without worsening of chronic hypertension raises the possibility of Gitelman's syndrome. This is further supported by the low serum magnesium level and renal magnesium wasting. To make the matters even more complicated, this patient had hypercalciuria at the onset resembling Batter's syndrome. However her hypercalciuria settled with normalization of serum calcium making the picture clearer during the follow up. Although hypomagnesemia leads to hypokalemia by inducing hyperkaluria by its effect on the ROMK type potassium channels in the distal convoluted tubules, correction of hypomagnesemia did not result in complete resolution of the hyperkaluria [2].

Hypokalemia in thyrotoxicosis is most commonly due to increased internalization of potassium. Gitelman's syndrome, as a cause of hypokalemia, is reported in autoimmune thyroid disease and, more commonly, in Graves' disease [3]. It has been identified that an inactivating mutation in the SLC12A3 gene, which encodes a thiazide-sensitive sodium chloride co transporter, is responsible for Gitelman's syndrome .It is postulated that some of the mutations of this gene are acquired later in life and seen in association with other autoimmune disorders [3].

Hypercalcemia is a known association of thyrotoxicosis, although severe symptomatic hypercalcemia is rare [4]. Hypercalcemia in thyrotoxicosis is believed to be due to increased bone turnover [5]. In this patient, hypercalciuria settled with the correction of serum calcium and thyroid function by her follow up at 3 months. This indicates that hypercalciuria was probably due to hypercalcemia and other direct effects of thyrotoxicosis. In thyrotoxicosis increased calcitriol metabolism and PTH suppression secondary to hypercalcemia are the probable mechanisms of hypercalciuria [6].

The presence of this constellation of biochemical abnormalities makes this case unique and reminds us to consider Grave's disease as a rare cause of hypercalcemia and Gitelman's syndrome.

References

1. Iitaka M. Graves' disease in the elderly. Nihon rinsho. Japanese journal of clinical medicine. 2006 Dec;64(12):2312-6.
2. Huang CL, Kuo E. Mechanism of hypokalemia in magnesium deficiency. Journal of the American Society of Nephrology. 2007 Oct 1;18(10):2649-52. https://doi.org/10.1681/ASN.2007070792
3. Zhou H, Liang X, Qing Y, Meng B, Zhou J, Huang S, Lu S, Huang Z, Yang H, Ma Y, Luo Z. Complicated Gitelman syndrome and autoimmune thyroid disease: a case report with a new homozygous mutation in the SLC12A3 gene and literature review. BMC endocrine disorders. 2018 Dec 1;18(1):82. https://doi.org/10.1186/s12902-018-0298-3
4. Daly JG, Greenwood RM, Himsworth RL. Serum calcium concentration in hyperthyroidism at diagnosis and after treatment. Clinical endocrinology. 1983 Sep;19(3):397-404. https://doi.org/10.1111/j.1365-2265.1983.tb00013.x
5. Daly JG, Greenwood RM, Himsworth RL. Serum calcium concentration in hyperthyroidism at diagnosis and after treatment. Clinical endocrinology. 1983 Sep;19(3):397-404. https://doi.org/10.1111/j.1365-2265.1983.tb00013.x
6. Douglas SR. Bone disease with hyperthyroidism and thyroid hormone therapy :Basow, ed. Up-to Date [database on the Internet]. Waltham (MA): UpToDate; 2020 [cited 18 May 2020]. Available from: http://www.uptodate.com