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Erythrocytosis in a Patient with Type 1 Diabetes Mellitus and Concomitant Gitelman's Syndrome

Tip 1 Diabetes Mellitusu Olan Bir Hastada Eritrositoz ve Gitelman Sendromu

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Abstract

Gitelman's syndrome (GS) is characterized by hypokalemia, hypomagnesaemia, hypocalciuria, metabolic alkalosis, and neurological symptoms. The association of GS with type 1 diabetes is rare, described only in a few case reports. We report a patient with an unusual combination of GS and type 1 diabetes mellitus with erythrocytosis. A 26-year-old male with GS and type 1 diabetes, who was on intensive insulin therapy with poor compliance, presented with the complaint of headache. On physical examination, his blood pressure was 120/70 mmHg and there was no neurological deficit or proximal muscle weakness. He had no previous medical history of obstructive sleep apnea, heart or lung disease. He had negative smoking history. His laboratory tests revealed erythrocytosis with a hemoglobin level of 18.9 g/dL (13.6-17.2 g/dL) and a hematocrit level of 54.8% (39.5-50.3%). Cranial magnetic resonance imaging was normal. He had no evidence of hypovolemia. Hematological workout excluded polycythemia vera and chronic myeloid neoplasm. A bone marrow aspiration revealed a hypercellular marrow with increased erythroid precursors, megakaryocytes and granulocytes. The reticulin stain grade was zero. There was no iron accumulation with iron stain. There was no radiologic evidence of any kind of erythropoietin-producing tumors. His echocardiography was normal. Serum insulin-like growth factor-1 levels and endogenous androgens were within normal limits. After 2 therapeutic phlebotomies, his symptoms improved and his hemoglobin was 16.1 mg/dL. Our patient, besides having GS and type 1 diabetes, was complicated with idiopathic erythrocytosis, all having deleterious effects on hemodynamic status of the patient.

Keywords: Type 1 diabetes mellitus, Gitelman's syndrome, erythrocytosis

Öz

Gitelman sendromu (GS) hipomagnezemi, hipokalsiüri, metabolik alkaloz ve nörolojik semptomlarla karakterize tip 1 diabetes mellitus birlikteliği çok nadir olan bir tablodur. Biz, nadir görülen GS ve tip 1 diabetes mellitus ile eritrositozlu bir olguyu sunduk. Olgumuz 26 yaşında tip 1 diyabet ve GS tanılarıyla takip edilen ve yoğun insulin tedavisi kullanmasına rağmen tedavi uyumu iyi olmayan bir erkek hastaydı. Baş ağrısı yakınması olan hastanın kan basıncı 120/70 mmHg olarak ölçüldü. Herhangi bir nörolojik defisit ve proksimal kas güçsüzlüğü saptanmadı. Daha öncesine ait uyku apnesi, kalp ya da akciğer hastalığı öyküsü yoktu. Sigara kullanmayan hastanın laboratuvar tetkiklerinde eritrositoz mevcuttu. Hastanın hemoglobin düzeyi 18,9 g/dL (13,6-17,2 g/dL) ve hematokriti %54,8 (%39,5-50,3) olarak saptandı. Kraniyal manyetik rezonansı normal olarak rapor edildi. Hipovolemiye ait kanıt yoktu. Yapılan hematoloji tetkikleriyle polistemiya vera ve kronik miyeloid neoplazi dışlandı. Kemik iliği aspirasyonunda artmış eritroid prekürsörler, megakaryositer ve granülositer seri ile hipersellüler kemik iliği saptandı. Retikülin boyama ile derecesi sıfır saptandı. Demir boyası ile demir birikimi izlenmedi. Eritropoetin üreten tümörlerin herhangi bir çeşidine ait radyolojik bulgu görülmedi, ekokardiyografisi normaldi. Serum insülin benzeri büyüme faktörü düzeyi-1 ve endojen androjenleri normal sınırlardaydı. İki kez terapötik flebotomi yapıldıktan sonra semptomları geriledi ve hemoglobin 16,1 mg/dL olarak saptandı. Hastamız GS ve tip 1 diyabet olması yanında, hemodinamik özellikleri üzerine tüm zarar verici etkileriyle idiyopatik eritrositozla komplikeydi.

Anahtar kelimeler: Tip 1 diabetes mellitus, Gitelman sendromu, eritrositoz

Introduction

Gitelman's syndrome (GS) is an autosomal recessive salt-losing renal tubulopathy caused by a mutation in the genes encoding the sodium-chloride cotransporters and magnesium channels in the thiazide-sensitive segments of the distal convoluted tubule. GS presents by hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis, and neurological symptoms, such as muscle weakness (1). The association of GS and type 1 diabetes mellitus (DM) is rare, only described in a few case reports. Concomitant presence of GS and type 1 DM is a challenging situation for physicians as the treatment of hyperglycemia is complicated by hypokalemia (2). Furthermore, in case of diabetic ketoacidosis (DKA), management can be more difficult. Usually high doses of potassium chloride are needed to obtain normal serum potassium levels. If there is a treatment-resistant hypokalemia in a recent onset type 1 diabetic patient with DKA, one should consider the presence of associated tubulopathies (3). Both type 1 DM and

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GS affect the kidneys and, the primary site of erythropoietin (EPO) production is the kidney. Erthrocytosis may be due to primary or secondary causes (4).

Case Report

A 26-year-old male, who was diagnosed with GS in 2009, was hospitalized due to DKA two years after the diagnosis. Laboratory examination revealed hyperglycemia (glucose: 564 mg/dL), ketonuria, acidosis, and the followings: HbA1c: 8.8%, insulin: 2.42 (16-166), c-peptide: 0.6 (0.28-2). It was also found that the patient was negative for anti-GAD and anti-islet cell antibodies. Since then, he was on intensive insulin therapy. There were not significant changes in potassium levels after treatment, however, hematocrit (Htc) and hemoglobin (Hb) levels decreased slightly. Other hematological parameters were in the normal ranges. He had poor glycemic control and poor compliance. At his last visit, laboratory tests revealed erythrocytosis with a Hb level of 18.9 g/dL (13.6-17.2 g/dL) and a Htc level of 54.8% (39.5-50.3%). On physical examination, his blood pressure was 120/70 mmHg and heart rate was 70 beats per minute. There was no neurological deficit or proximal muscle weakness. Further laboratory investigations showed the following results: Serum glucose: 246 mg/dL (75-99 mg/dL), serum creatinine: 0.89 mg/dL (0.84-1.3 mg/dL), serum potassium: 2.62 mmol/L (3.5-5 mmol/L), serum sodium: 131 mmol/L (135-150 mmol/L), serum chloride: 92 mmol/L (96-110 mmol/L), serum magnesium 0.71 mg/dL (0.7-1.06 mg/dL), serum calcium: 9.66 mg/dL (8.8-10.6 mg/dL), and serum phosphate: 4.08 mg/dL (2.5-4.5 mg/dL). The urinary calcium level was subnormal at 30 mg/24 hour (100-300 mg/24 hour). Renin levels were elevated (592 pg/mL; normal range: 0.2-27.8 pg/mL), and also his aldosterone level was slightly elevated (525 pg/mL; normal range: 30-313 pg/mL). Glomerular filtration rate (GFR) was 109 mL/min (Cockcroft-Gault formula). His plasma renin activity was somewhat high, whereas the plasma aldosterone level was normal which suggested the clinical diagnosis of GS. He had no previous medical history of heart or lung disease. He had negative smoking history.

Further erythrocytosis workout revealed normal white blood and platelet counts and an EPO level of 23.4 mU/mL (3.7-31.5 mU/mL), as well as, a negative JAK2 V617F gene mutation. Thus, polycythemia vera was excluded. Bone marrow aspiration biopsy revealed a hypercellular marrow with increased erythroid precursors, megakaryocytes and granulocytes. The reticulin stain grade was zero (0/3 EUMNET 2007). There was no iron accumulation with iron stain. T(9;22) (q34;q11) was negative on real time polymerase chain reaction analysis which excluded chronic myeloid neoplasm. Biochemical, hormonal and hematological parameters of the patient are presented in Table 1. His chest radiograph and abdominal ultrasound were normal; there was no evidence of nephrocalcinosis or organomegaly. Computed tomography of the abdomen and pelvis were also normal. There was no radiological evidence of any kind of EPO-producing cancer, including hepatocellular, gastric or renal cell carcinoma. His echocardiography was normal. Hemoglobinopathies were excluded by normal electrophoresis. He had no obstructive sleep apnea or chronic obstructive pulmonary disease. His oxygen saturation level was 97.2% mm/Hg. Serum insulin-like growth factor-1 and endogenous androgen levels, which are possible etiologies for erythrocytosis, were normal. Activated renin-angiotensin system may cause secondary erythrocytosis, but neither renal artery stenosis nor renal mass were determined. After excluding all possible etiologies of secondary erythrocytosis, he was diagnosed as having idiopathic erythrocytosis. He had headache with a normal magnetic resonance imaging scan. After 2 sessions of therapeutic phlebotomies, his symptoms improved and his Hb level was 16.1 mg/dL. He was given a 100 mg of acetylsalicylic acid pill.

Discussion

GS presents with hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis, and neurological symptoms, such as muscle weakness. In our patient, the diagnosis was made based on laboratory and clinical findings. The association of GS with type 1 DM is rare, but it has been described in a few case reports. Concomitant presence of GS and type 1 DM complicated the treatment of glycaemia because of hypokalemia. Furthermore, in case of diabetic DKA, management can be more difficult. In a recent onset type 1 diabetic patient with treatment-resistant DKA, one should consider the presence of associated tubulopathies (3).

Table 1. Biochemical, hormonal and hematological parameters of the patient

Parameters	Patient	Reference range
Hemoglobin (g/dL)	18.9	13.6-17.2
Hematocrit (%)	54.8	39.5-50.3
Platellet (100 µL)	331	150-450
WBC (100 µL)	9.9	4.5-10.3
Glucose (mg/dL)	246	75-99
Creatinine (mg/dL)	0.89	0.84-1.3
Potassium (mmol/L)	2.62	3.5-5
Sodium (mmol/L)	131	135-150
Chloride (mmol/L)	92	96-110
Magnesium (mg/dL)	0.71	0.7-1.06
Calcium (mg/dL)	9.66	8.8-10.6
Phosphate (mg/dL)	4.08	2.5-4.5
Urinary calcium (mg/24 hour)	30	100-300
Renin (pg/mL)	592	0.2-27.8
Aldosterone (pg/mL)	525	30-313
GFR (mL/min)	109	90-137
EPO (mU/mL)	23.4	3.7-31.5
JAK2 V617F gene mutation	Negative	Negative
Reticulin stain	Zero (0/3)	0-3
T(9;22) (q34;q11)	Negative	Negative

GFR: Glomerular filtration rate, WBC: White blood cells, EPO: Erythropoietin, JAK2: Janus kinaz 2

The presence of erythroctytosis in a patient with GS has not been previously reported. Only in a study on phenotypic variability in GS by Lin et al. (5) one of the 5 patients was reported to have high Hb levels. They suggested that this finding may be due to a reduced plasma volume and a higher red blood cell mass because of the increased angiotensin II levels, as seen in renal transplantation associated with erythrocytosis and no further evaluation of the differential diagnosis of erythrocytosis was described as it was not the topic in that article. In a review about the presence of oxygen control system in the renal cortex for the release of erythropoietin, in the appendix of the paper, Halperin et al. (6) have described a young male with GS having an extremely high Hb concentration in blood. They deduced from quantitative analysis that he would have needed a 40 to 45% reduction in his plasma volume to explain his high Hb concentration without a rise in his red blood cell mass. Sochett et al. (7) have found that patients with type 1 DM had significantly higher GFR values than did control subjects and that they also had significantly higher filtration fractions.

Arterial hypotension is usually because of extracellular volume depletion which results from urinary water and electrolyte wasting. Patients with urinary electrolyte wasting have chronic hypovolemia and hence higher plasma Hb and total protein levels, arterial hypotension with a consequent renin angiotensin axis overstimulation (1). Yokoyama et al. (8) have described a patient on continuous ambulatory peritoneal dialysis who had erythrocytosis progressed along with exacerbation of the chronic severe hypotensive state. They hypothesized that circulatory insufficiency due to chronic severe hypotension may lead to the stimulation of the EPO production, due to a decreased oxygen supply to peripheral tissues and/or to the stimulation of the renin angiotensin system even in patients with end-stage renal failure. In our case there was no evidence of hypovolemia or proteinuria that might cause renin angiotensin axis overstimulation.

Lowering GFR by diminishing efferent renal artery vasoconstriction with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers can reduce the Hb concentration. These drugs are effective in treating post-transplantation erythrocytosis. They must be used carefully since there is a risk for inducing hemodynamic instability in patients with a low extracellular fluid volume (6). Since our patient had GS, type 1 DM and idiopathic erythrocytosis, all affecting the hemodynamic system, we started low-dose ACEI. Angiotensin converting enzyme inhibition may potentially have positive effects on all the three diseases but a careful follow-up of hemodynamic system is mandatory. GS and type 1 DM, especially in the presence of uncontrolled hyperglycemia, both affect the kidneys and, the primary site of EPO production is the kidneys. In our patient, EPO levels were within the normal levels and none of the other etiologies of erythrocytosis was found and the diagnosis of idiopathic erythrocytosis was made. In conclusion, our patient, besides having GS and type 1 DM, was complicated with idiopathic erythrocytosis, all having deleterious effects on hemodynamic status of the patient.

Ethics

Informed Consent: Consent form was filled out by all participants.
Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Müge Keskin, Neşe Ersöz Gülçelik, Cavit Çulha, Yalçın Aral, Design: Müge Keskin, Neşe Ersöz Gülçelik, Gönül Koç, Data Collection or Processing: Müge Keskin, Neşe Ersöz Gülçelik, Analysis or Interpretation: Müge Keskin, Neşe Ersöz Gülçelik, Literature Search: Müge Keskin, Neşe Ersöz Gülçelik, Ünsal Aydın, Writing: Müge Keskin, Neşe Ersöz Gülçelik, Müge Özcan.
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References

1. Graziani G, Fedeli C, Moroni L, Cosmai L, Badalamenti S, Ponticelli C. Gitelman syndrome: pathophysiological and clinical aspects. QJM 2010;103:741-748.
2. Zangeneh F, Chiang M, Zangeneh F. Pitfalls in the laboratory diagnosis of diabetic ketoasidosis in Gitelman's syndrome. Diabetes Care 2003;26:955.
3. Biagioni M, Marigliano M, Lannilli A, Cester A, Gatti S, D' Alba I, Tedeschi S, Syren ML, Cherubini V. Diabetic ketoacidosis complicated with previously unknown Gitelman syndrome in a Tunisian child. Diabetes Care 2011;34:107
4. Sheqwara J, Alkhatib Y, Dabak V, Kuriakose P. Idiopathic erythrocytosis in dialysis patients: a case report and literature review. Am J Nephrol 2013;37:333-338.
5. Lin SH, Cheng NL, Hsu YJ, Halperin ML. Intrafamilial phenotype variability in patients with Gitelman syndrome having the same mutations in their thiazide-sensitive sodium/chloride cotransporter. Am J Kidney Dis 2004;43;304-312.
6. Halperin ML, Cheema-Dhadli S, Lin SH, Kamel KS. Properties permitting the renal cortex to be the oxygen sensor for the release of erythropoietin: clinical implications. Clin J Am Soc Nephrol 2006;1:1049-1053.
7. Sochett EB, Cherney DZ, Curtis JR, Dekker MG, Scholey JW, Miller JA. J Am Soc Nephrol 2006;17:1703-1709.
8. Yokoyama K, Ogura Y, Matsushita Y, Takemoto F, Hara S, Yamada A, Kawaguchi Y, Hosoya T. Hypererythropoietinemia and hyperreninemia in a continuous ambulatory peritoneal dialysis patient with chronic severe hypotension. Clin Nephrol 1998;50:60-63.