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Melya Pelin Kirik, Can Hüzmeli

The concomitance of Gitelman syndrome with nephrocalcinosis in a case followed-up for primary biliary cirrhosis

Hatay Training And Research Hospital, Hatay, Turkey

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Abstract. *Gitelman syndrome is a rare autosomal recessive renal tubular disease characterized by hypokalemia, metabolic alkalosis, and hypocalciuria. The syndrome develops as a result of various mutations in the SLC12A3 gene. This manuscript aims to highlight the association of Gitelman Syndrome with nephrocalcinosis in a 48-year-old female patient who presented with pain and cramps in the lower limbs.*

Keywords: *Gitelman syndrome, primary biliary cirrhosis, nephrocalcinosis, hypokalemia.*

Conflict of interest. The authors declare no conflict of interest.

Correspondence should be addressed to Melya Pelin Kirik: melyapelin@hotmail.com

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Меля Пелін Кирік, Кан Хюзмелі

Поєднання синдрому Гітельмана з нефрокальцинозом у пацієнтки з первинним біліарним цирозом

Хатайська навчальна та дослідницька лікарня, Хатай, Туреччина

Резюме. *Синдром Гітельмана - це рідкісне аутосомно-рецесивне захворювання ниркових канальців, яке характеризується гіпокаліємією, метаболічним алкалозом і гіпокальціурією. Синдром розвивається внаслідок мутації гена SLC12A3. У цій роботі описано випадок асоціації синдрому Гітельмана з нефрокальцинозом у 48-річної жінки, яка звернулася із скаргами на біль та судоми в нижніх кінцівках.*

Ключові слова: *синдром Гітельмана, первинний біліарний цироз, нефрокальциноз, гіпокаліємія.*

Introduction. Gitelman Syndrome (GS) is an autosomal recessive renal tubulopathy characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria [1]. Dysfunction of the co-transporter develops with the mutation in the SLC12A3 gene encoding the thiazide-sensitive sodium chloride cotransporter in Gitelman syndrome. Approximately 500 different mutations on the SLC12A3 gene have been associated with Gitelman syndrome. The cases may be asymptomatic. Clinical symptoms may be mild such as mild fatigue, nocturia, muscle weakness, or muscle cramps, or these symptoms may be severe such as tetany, paralysis, rhabdomyolysis, and fatal arrhythmia [3].

The main function of the renal tubules is to control the reabsorption and secretion of electrolytes in order to maintain homeostasis. Bartter syndrome (BS) and GS are monogenic diseases belonging to the group of hereditary renal tubulopathies. Diagnostic findings of Gitelman and Bartter syndromes include hypokalemia, hypochloremic metabolic alkalosis, hyperreninism, and secondary hyperaldosteronism as a result of volume depletion, and activation of the renin-angiotensin-aldosterone system. The actual difference between Bartter and Gitelman syndromes is the hypocalciuria developed in the GS. The reason for that is the increase in calcium reabsorption in order to compensate for the loss of salt. Another relevant molecular feature is hypomagnesemia in the cases with GS. Hypomagnesemia is detected in GS; however, it is observed by 20% in BS. Hypomagnesemia also increases calcium reabsorption by stimulating the parathormone. However, this is not an exact differentiation between GS and BS [4].

Case report. A 48-year-old female patient who was followed up due to the diagnosis of primary biliary cirrhosis was referred to our outpatient clinic with increased serum creatinine and lower potassium level. The complaints included pain, cramps, and exhaustion in the lower limbs. There were primary biliary cirrhosis and psoriasis in medical history (she uses ursodeoxycholic acid and topical tacrolimus). She has a history of thalassemia carrier. Renal biopsy was suggested before upon renal function disorder; however, it was not performed. The physical exam revealed the following: blood pressure was 100/70 mmHg, pulse was 76/min, respiration count was 18/min; other examination findings were normal. No retinopathy or uveitis was detected in the eye consultation.

The laboratory analysis revealed the following: potassium 2.83mmol/L (3.5-5.5 mEq/L); sodium 136mmol/L (132-146 mEq/L); chlorine 102mmol/L (99-109 mEq/L); magnesium 2.05mg/dl (1.3- 2.7 mEq/L); serum creatinine 1.5mg/dl (0.5-0.9 mg/dL); calcium 9.52mg/dL (8.5-10.0); and phosphorus 3.08mg/dl (2.4-5.1). Aldesteron 450 pg/ml (30-160) and renin 40 ng/dL (4-31) were detected higher; parathormone and vitamin D were normal. Blood gas analysis revealed the following: pH 7.46 (7.35-7.45), HCO3 29mEq/L, PCO2 42mmHg; the findings were assessed as metabolic alkalosis.

In the urine analysis, urine sodium was 99 mmol/L; urine potassium 36 mmol/L; urine chlorine 84 mmol/L; the anion gap of the urine was positive. The calcium excretion for 24 hours was 38 mg/day indicating hypocalciuria. The primary blood test results of the patient are presented in Table 1.

Melya Pelin Kırık
melyapelin@hotmail.com

Table 1

The primary blood test results of the patient

Markers	The date of the study		
	03.09.2021	27.12.2021	29.05.2023
Glucose (70-110 mg/dl)	96	101	86
Blood urea nitrogen (7-25 mg/dl)	22	18	19
Creatine (0.5-0.9 mg/dl)	1.5	1,2	1.1
Sodium (132-146 mmol/L)	136	139	139
Potassium (3.5-5.5 mmol/L)	2.83	3.8	3.6
Chlorine (mmol/L)	102	103	102
Magnesium (1.3- 2.7 mEq/L)	2.05	2.1	1.9
pH (7.35-7.45)	7.46	7.42	7.41
HCO3 (mmol/L)	29	26	25
PCO2 (mmHg)	42	40	40
Hemoglobin (12-16 gr/dl)	10	10.3	11.3
Hematocrit (% 35-46)	32.8	32.5	36
Thrombocyte count (150000-450000 mm^3)	295000	297000	27000
Mean corpuscular volume (80-96fL)	56	54	57

The renal ultrasound scan of the patient revealed that the kidneys are at normal location and dimensions bilaterally; diffuse parenchymal calcifications (nephrocalcinosis) were detected in both kidneys. Normal sinus rhythm and QT interval were detected in the electrocardiogram. The patient did not have any drug use such as diuretics and laxatives. Genetic analysis was also ordered. The Bartter-Gitelman gene panel was analyzed in genetic evaluation. The genetic analysis resulted in the detection of heterozygote NM_000339: c.1406C>T (p.Ala469Val) variant in the SLC12A3 gene.

The patient was diagnosed with GS according to those findings. A diet which is rich in potassium and sodium was recommended for the patient. Potassium and 25 mg of spironolactone treatment was started. Serum potassium level has returned to normal levels; complaints regressed. There was no additional problem in the follow-up of the patient. Her treatment continues in the same way. The patient's complaints of pain, cramps, and exhaustion in the lower limbs resolved and did not recur in the follow-ups. The patient is still under follow-up due to GS in our outpatient.

Discussion. Magnesium is a cofactor of the pyrophosphatase group, especially for alkaline phosphatase. A decrease in magnesium concentration causes organ dysfunction of these proteins, which in turn increases pyrophosphate levels. Inorganic pyrophosphate binds to Ca2+ ions by ionic interaction which results in crystal formation. These crystals accumulate over time and eventually cause chondrocalcinosis [5]. Ectopic calcification in the retina and joints may be observed in GS and BS; however, it is more common in GS due to lower magnesium levels [6]. Molecular genetic tests are not necessary for the diagnosis of GS [4].

Gitelman syndrome is characterized by hypocalciuria. Although urinary calcium excretion is decreased in patients, levels of serum calcium, phosphorus, vitamin D, and parathormone are expected to be normal. Our case presented hypocalciuria. A differential diagnosis of Bartter syndrome should be done. The higher prevalence of hypomagnesemia and hypocalciuria in GS is differential characteristics.

Nephrocalcinosis is a pathological condition that progresses with tubular calcified crystal deposits in the renal corticomedullary region. It is known that the deposits are hydroxyapatite crystals composed of calcium and phosphorus. Three common causes of medullary nephrocalcinosis are known as medullary sponge kidney, renal tubular acidosis, and hyperparathyroidism [7, 8]. Furthermore, BS is detected together with nephrocalcinosis [9]. Hypercalciuria and concomitant increase of urinary prostaglandin E2 and serum 1,25 dihydroxycholecalciferol levels are thought to be the pathophysiological elements of nephrocalcinosis detected in BS. A decrease in urinary calcium excretion may be observed by administration of indomethacin. However, it is unclear whether this improves the nephrocalcinosis [10]. Renal stones and calcinosis are not expected findings in Gitelman syndrome because of hypocalciuria. A case with kidney stones and proteinuria in GS was reported by Chen et al. in 2001 [11]. However, the association of nephrocalcinosis with GS is not available in the literature. Although renal tubular

acidosis is more common in primary biliary cirrhosis, metabolic acidosis was detected in the blood gas analysis of our patient.

The use of diuretics, inappropriate use of laxatives, and vomiting may be the cause of pseudoGS. The difference between primary GS and pseudoGS is the improvement when triggering factors were eliminated. Although GS is a genetically transmitted tubulopathy, acquired GS has also been rarely reported after kidney transplantation or due to autoimmune diseases [**12, 13**]. Our patient has not used any laxative or diuretic agents. Although the primary biliary cirrhosis which is an autoimmune disease reported in our case suggests acquired GS, molecular genetic evaluation was very useful for differentiation.

Conclusion: Consequently, renal tubular acidosis is primarily considered in a patient with primary biliary cirrhosis; however, the diagnosis may be different. The present case was the first for concomitance of Gitelman Syndrome and nephrocalcinosis.

Conflict of interest statement. The authors declare no conflict of interest.

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The authors' contribution.

Melya Pelin Kırık: collected the data of the case and manuscript writing;

Can Huzmeli: contributed to the writing of some parts of the case, and the final editing.

References

1. *Kurtz I.* Molecular pathogenesis of Bartter's and Gitelman's syndromes. Kidney Int. 1998;54: 1396-410. doi:10.1046/j.1523-1755.1998.00124.x.
2. *Mastroianni N, Bettinelli A, Bianchetti M, Colussi G, De Fusco M, Sereni F, et al.* Novel molecular variants of the Na-Cl cotransporter gene are responsible for Gitelman syndrome. [Інтернет]. American journal of human genetics. 1996;59(5):1019-26. Available from: https://pubmed.ncbi.nlm.nih.gov/8900229/. (Last accessed: 15.06.2023).
3. *Balavoine AS, Bataille P, Vanhille P, Azar R, Noël C, Asseman P, et al.* Phenotype–genotype correlation and follow-up in adult patients with hypokalaemia of renal origin suggesting Gitelman syndrome. European journal of endocrinology. 2011;165(4):665-673. doi: 10.1530/EJE-11-0224.
4. *Nuñez-Gonzalez L, Carrera N, Garcia-Gonzalez MA.* Molecular Basis, Diagnostic Challenges and Therapeutic Approaches of Bartter and Gitelman Syndromes: A Primer for Clinicians. International Journal of Molecular Sciences. 2021;22(21):11414. doi: 10.3390/ijms222111414.
5. *Iqbal Z, Sayer JA.* Chondrocalsinosis and Gitelman syndrome. QJM. 2016;109: 563–564. doi: 10.1093/qjmed/hcw045.
6. *Ham Y, Mack H, Colville D, Harraka P, Savige J.* Gitelman syndrome and ectopic calcification in the retina and joints. Clinical Kidney Journal. 2021;14(9): 2023-2028. doi:10.1093/ckj/sfab034.
7. *Riehl J, Schneider B, Bongartz D, Sieberth HG.* Medullary nephrocalcinosis: sonografic findings in adult patient. [Інтернет]. Bilgeung. 1995;62:18-22. Available from: https://pubmed.ncbi.nlm.nih.gov/7756819/. (Last accessed: 15.06.2023).
8. *Alon US.* Nephrocalcinosis. [Інтернет]. Curr Opin Pediatr. 1997;9:60-5. Available from: https://pubmed.ncbi.nlm.nih.gov/9204244/. (Last accessed: 15.06.2023).
9. *Garel L, Filiatrault D, Robitaille P.* Nephrocalcinosis in Bartter's syndrome. Pediatr Nephrol. 1988;2:316-317. doi:10.1007/BF00858685.
10. *Koşan CA.* Bartter syndrome case with nephrocalcinosis. Atatürk Üniversitesi Tıp Dergisi. 2001;033(2):57-59.
11. *Chen Q, Wang X, Min J, Wang L, Mou L.* Kidney stones and moderate proteinuria as the rare manifestations of Gitelman syndrome. BMC nephrology. 2021;22(1):1-6. doi: 10.1186/s12882-020-02211-y.
12. *Mount D, Sayegh MH, Singh AK.* Core concepts in the disorders of fluid, electrolytes, and acid-base balance. New York (NY): Springer, 2013. 377 s.
13. *Kim YK, Song HC, Kim YS, Choi EJ.* Acquired Gitelman Syndrome. Electrolyte Blood Press. 2009;7:5-8. doi:10.5049/EBP.2009.7.1.5.