

CLINICAL VIGNETTE

Calcium Pyrophosphate Deposition Disease in Gitelman Syndrome

Joyce Celino Aquino, BA and Yaqoot Khan, DO

Introduction

Gitelman syndrome is a primary renal tubular disorder characterized by the abnormalities of hypokalemia, hypomagnesemia, and hypocalciuria.¹ Additionally, the occurrence of chondrocalcinosis in patients with Gitelman syndrome has been reported as an example of hypomagnesemia-associated calcium pyrophosphate deposition disease (CPPD).² We describe a patient who presented with a knee effusion with subsequent findings of CPPD in the setting of Gitelman syndrome.

Case Report

A 35-year-old male with prediabetes, vitiligo, and mild psoriasis presented to rheumatology with a painful and swollen right knee for one week.

His review of systems was otherwise negative for involvement of other joints, constitutional symptoms, infections, injury, or systemic issues.

The patient recalled that, about five years ago, he had the same knee aspirated and was told of the possibility of gout, but was ultimately unsure. On physical examination, he was afebrile, noted to have a large right knee effusion with significant pain and warmth but minimal erythema. The rest of the musculoskeletal examination was normal. Pertinent negative findings included lack of tophi and the absence of pitting on his nail beds.

The valuation included right knee aspiration and 80 mL of yellow serosanguinous fluid was removed and sent for additional testing.

The aspirated fluid had a White cell count of 25,620 with negative gram stain and eventually negative cultures. It showed intracellular and extracellular calcium pyrophosphate crystals. There was no evidence of a systemic infection with a normal white cell count and differential, uric acid level was low at 4.5, creatinine and creatinine clearance were both normal. Incidentally, chemistries included potassium of 2.8 Meq/L and magnesium of 1.1 meq/L.

Upon further questioning he acknowledged recent non-compliance with potassium and magnesium supplementation as prescribed by his nephrologist. He was treated with an intra-articular steroid injection with resolution of the symptoms. His

hypokalemia and hypomagnesemia were both aggressively replaced.

Discussion

Gitelman syndrome is an inherited salt-losing tubulopathy characterized by hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis. First described in 1966,³ it is an autosomal recessive disease, specifically caused by inactivating mutations in the SCL12A3 gene, which encodes for the thiazide-sensitive sodium chloride cotransporter, the NCC channel.⁴ The co-existence of hypokalemia, hypomagnesemia, and hypocalciuria represent the biological hallmark of Gitelman syndrome.

Gitelman syndrome has a wide spectrum of musculoskeletal manifestations, with joint pain being one of the more prominent features. Other symptoms include salt craving, fatigue, dizziness, paresthesias, muscle weakness, muscle cramps, non-specific aches and pains, and associated CPPD arthropathy. Diagnosis of Gitelman syndrome is based on the combination of the aforementioned laboratory abnormalities including hypokalemia, hypomagnesemia, hypocalciuria, and metabolic alkalosis, as well as presence of mutations of the SCL12A3 gene.

Calcium pyrophosphate crystals are responsible for calcium pyrophosphate deposition disease (CPPD). CPPD occurs exclusively in articular tissues and is the most common cause of cartilage calcification in the affected joints.⁵ In our case, CPPD was the presenting manifestation of Gitelman syndrome.

The main function of the renal tubules is the control of reabsorption and secretion of electrolytes in order to correctly maintain homeostasis, with numerous proteins being involved in this function. Any impairment that compromises their correct function will cause, to some degree, a dysregulation of homeostasis, thus giving rise to different clinical manifestations, including tubulopathies such as Gitelman syndrome.

Magnesium is an essential element for the homeostasis of electrolytes. The reabsorption of Mg²⁺ ions in the renal tubules depends on proper function of a thiazide-sensitive sodium chloride cotransporter, the NCC channel, which is encoded by the SLC12A3 gene and exclusively located in the cells of the distal convoluted tubule. In tubulopathies such as Gitelman

syndrome, alteration in this transport mechanism causes a loss of electrolytes that interrupts the global reabsorption process, resulting in alterations of renal physiology.⁶ Hypomagnesemia seems to have a key role in CPPD, cartilage calcifications by increasing formation and reducing the solubility of the calcium pyrophosphate crystals. Furthermore, Mg²⁺ is a cofactor of the group of pyrophosphatases. A decrease in magnesium concentration causes a dysfunction of these proteins, which consequently increase the levels of pyrophosphate. Inorganic pyrophosphate binds to Ca²⁺ ions, resulting in crystal formation. These crystals are deposited over time and can eventually cause chondrocalcinosis and CPPD.

In conclusion, Gitelman syndrome is an autosomal recessive tubulopathy characterized by the co-existence of hypokalemia, hypomagnesemia, and hypocalciuria as well as the presence of a mutation in the SLC12A3 gene, which encodes for a thiazide-sensitive sodium chloride transporter. This combination of factors causes dysregulation of electrolyte homeostasis in the body, giving rise to tubulopathies such as Gitelman syndrome and, subsequently, CPPD. Treatment of Gitelman syndrome with oral magnesium may result in cessation of chondrocalcinosis flares and possible regression of CPPD.^{1,2}

More research and clinical analysis of the homeostatic pathways may identify additional beneficial therapies for Gitelman syndrome and CPPD.

REFERENCES

1. **Hisakawa N, Yasuoka N, Itoh H, Takao T, Jinnouchi C, Nishiya K, Hashimoto K.** A case of Gitelman's syndrome with chondrocalcinosis. *Endocr J.* 1998 Apr;45(2):261-7. doi: 10.1507/endocrj.45.261. PMID: 9700481.
2. **Punzi L, Calò L, Schiavon F, Pianon M, Rosada M, Todesco S.** Chondrocalcinosis is a feature of Gitelman's variant of Bartter's syndrome. A new look at the hypomagnesemia associated with calcium pyrophosphate dihydrate crystal deposition disease. *Rev Rhum Engl Ed.* 1998 Oct;65(10):571-4. PMID: 9809361.
3. **Gitelman HJ, Graham JB, Welt LG.** A new familial disorder characterized by hypokalemia and hypomagnesemia. *Trans Assoc Am Physicians.* 1966;79:221-35. PMID: 5929460.
4. **Cipolletta E, Di Matteo A, Filippucci E, Grassi W.** Calcium Pyrophosphate Deposition Disease in a Patient with Familial Hypokalemia-Hypomagnesemia (Gitelman's-Syndrome): A Case Report - CPPD in Gitelman's syndrome. *Ultraschall Med.* 2020 Dec;41(6):695-697. doi: 10.1055/a-0990-9960. Epub 2019 Aug 21. PMID: 31434112.
5. **Favero M, Calò LA, Schiavon F, Punzi L.** Miscellaneous non-inflammatory musculoskeletal conditions. Bartter's and Gitelman's diseases. *Best Pract Res Clin Rheumatol.* 2011 Oct;25(5):637-48. doi: 10.1016/j.berh.2011.10.013. PMID: 22142744.
6. **Nuñez-Gonzalez L, Carrera N, Garcia-Gonzalez MA.** Molecular Basis, Diagnostic Challenges and Therapeutic

Approaches of Bartter and Gitelman Syndromes: A Primer for Clinicians. *Int J Mol Sci.* 2021 Oct 22;22(21):11414. doi: 10.3390/ijms222111414. PMID: 34768847; PMCID: PMC8584233.