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Gitelman syndrome and ectopic calcification in the retina and joints

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ABSTRACT

Gitelman syndrome is a rare inherited renal tubular disorder with features that resemble thiazide use, including a hypokalemic metabolic alkalosis, hypomagnesemia, hypocalciuria and a low or normal blood pressure, hyperreninemia and hyperaldosteronism. Treatment is primarily correction of the potassium and magnesium levels. The diagnosis is confirmed with genetic testing but Gitelman syndrome is often not suspected. However, the association with ectopic calcification in the retina, blood vessels and chondrocalcinosis in the joints is a useful pointer to this diagnosis. Bilateral symmetrical whitish deposits of calcium pyrophosphate are visible superotemporally on ophthalmoscopy and retinal photography but are actually located beneath the retina in the sclerochoroid. Optical coherence tomography is even more sensitive for their detection. These deposits increase in size with time, but the rate of progression slows with long-term correction of the hypomagnesemia. Calcification may be complicated by atrophy of the overlying retina and visual loss. The deposits often correlate with ectopic calcification in the aorta and coronary and cerebral vessels. Chondrocalcinosis occurs in the large joints such as the knees. Ectopic calcification in Gitelman syndrome indicates the need for more aggressive management of Mg levels. Calcification is much less common in Bartter syndrome, which itself is rarer and associated less often with hypomagnesemia.

Keywords: Bartter syndrome, chondrocalcinosis, Gitelman syndrome, hypertension

Gitelman syndrome (OMIM 263800) affects 1 in 40 000 individuals [1] and is an autosomal recessive inherited renal disease caused by mutations in the *SLC12A3* gene [2], which codes for the thiazide-sensitive sodium chloride symporter (NCC) in the distal convoluted tubule [2, 3].

Affected individuals typically present in late adolescence or adulthood and have a metabolic hypokalemic alkalosis, hypomagnesemia, hypocalciuria and low or normal blood pressure, hyperreninemia and hyperaldosteronism [4]. Metabolic features resemble those found with thiazide diuretics. Some individuals have only mild symptoms such as tiredness, but others have seizures, tetany, muscle weakness, paresthesia, arrhythmias and an impaired quality of life [5]. Hypertension is not uncommon in late disease.

Mutations in the *SLC12A3* gene result in salt wasting, volume contraction and stimulation of renin and aldosterone secretion. The volume reduction produces a compensatory increase in proximal sodium (Na) reabsorption and passive proximal

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Table 1. Clinical and biochemical features of eight reported cases of Gitelman syndrome with sclerochoroidal calcification (SCC)

Characteristics	Case 1 [18]	Case 2 [16]	Case 3 [17]	Case 4 [17]	Case 5 [17]	Case 6 [17]	Case 7 [19]	Case 8 [19]
Gender, age (years)	F, 49	F, 58	NA, 84	NA, 70	NA, 49	NA, 73	F, 50	F, 26
Features of SCC								
Laterality	Bilateral	Bilateral	Bilateral	Right side	Bilateral	Left side	Bilateral	Bilateral
Location	Superotemporal	Superotemporal	NA	NA	NA	NA	Superotemporal	Inferotemporal
Number of lesions	Multiple	Multiple	Single	Single	Multiple	Single	Multiple	Multiple
Color	Yellow–white	Yellow–white	NA	NA	NA	NA	Yellow	NA
Elevation	Yes	Yes					Mild	
Clinical features								
Muscle weakness/pain	NA	Present	Absent	Absent	Present	Absent		
Arthritis	Present	NA	Absent	Absent	Present	Absent		
Blood pressure	NA	NA	NA	NA	NA	NA	Low	Low
Chondrocalcinosis	Present	Present	Absent	Absent	Present	Absent	Present	Absent
Biochemical features								
Metabolic alkalosis	Present	Present	Present	Present	Present	Present		
Serum bicarbonate			Elevated	Elevated	Elevated	Elevated	Elevated	Elevated
Hypokalemia	Present	Present	Present	Present	Present	Present	Present	Present
Hypomagnesemia	Present	Present	Present	Present	Present	Present	Absent	Absent
Hypocalciuria	Present	Present	Present	Present	Present	Present	Present	Present
Hyperkaluria	Present	NA	Normal	Present	Absent	Present	Present	Present
Hypermagnesuria	Absent	NA	Present	Present	Present	Present	Present	Present
Serum Ca	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Parathyroid hormone	Normal	Normal						
Hyperreninism	NA		Present	NA	Absent	Absent		
Hyperaldosteronism	NA		Present	NA	Absent	Absent		
Ophthalmic examination								
Symptoms	None	None					None	None
Visual acuity	Normal	Normal						
Anterior chamber	Normal	Normal						
Fundus examination	SCC	SCC	SCC	SCC	SCC	SCC	SCC	SCC
Ophthalmic imaging								
Autofluorescence	NA	SCC						
B-scan	SCC	NA					SCC	SCC
Fluorescein angiography	RPE atrophy	Subretinal lesion					SCC	

SCC, sclerochoroidal calcification; NA, not available; F, female; RPE, retinal pigment epithelium.

calcium (Ca) reabsorption that is responsible for the hypocalciuria [6]. Cell membrane depolarization in hypokalemic cells contributes to reduced magnesium (Mg) reuptake, hypomagnesemia and hypokalemic metabolic alkalosis [7]. Molecular genetic testing is not required for the diagnosis of Gitelman disease, but is helpful, especially in its distinction from Bartter syndrome. The diagnosis of Gitelman syndrome is important because treatment is available in the form of a liberal dietary salt intake and Mg and potassium (K) supplementation, but lifelong monitoring of K and Mg levels is required [4, 8]. Secondary chondrocalcinosis of the joints may require symptomatic pain relief.

The clinical and metabolic features of Gitelman syndrome overlap with those found in some forms of Bartter syndrome and together these conditions represent a spectrum of clinical manifestations caused by defective chloride (Cl) reabsorption from genetic mutations acting at different locations in the nephron [9].

Bartter syndrome

Bartter syndrome is a much rarer recessively inherited disease affecting 1 in 1.2 million and characterized by a defect in the thick ascending limb of the loop of Henle [10, 11]. It also results in hypokalemic alkalosis, with low or normal blood pressure. Mg levels are often but not necessarily normal [12]. Mutations are found in *SLC12A1* (NKCC2) or *ROMK/KCNJ1* (neonatal form), *CLCNKB* (classic form), BSND (Bartter syndrome with sensorineural deafness) or CASR (autosomal dominant hypocalcemia) [13]. These genes code for the Na–K–Cl cotransporter, apical K channel or basolateral Cl channel. Mutations result in excess NaCl loss and defects in the ability to reabsorb electrolytes such as K and Ca.

Individuals with Bartter syndrome typically present in infancy or childhood with polyhydramnios, prematurity, polydipsia, polyuria, salt craving and growth retardation [14].

While both Bartter and Gitelman syndrome are associated with hypokalemic metabolic alkalosis, all individuals with Gitelman syndrome but only 20% of those with classic Bartter syndrome have hypomagnesemia. These diseases are usually differentiated by urinary calcium levels: in Gitelman syndrome, Ca excretion is low and Mg excretion is high, but in Bartter syndrome, Ca excretion is normal or high [8, 15]. Individuals with Bartter syndrome also have the elevated renin and aldosterone levels found in Gitelman syndrome. Increasingly Bartter syndrome is recognized in adults by genetic testing for variants in the Bartter genes.

Bartter syndrome is treated with K supplementation, prostaglandin synthetase inhibitors such as indomethacin and K-sparing diuretics including spironolactone [14]. Hypokalemia is

Table 2. Clinical and biochemical features of two reported cases of Bartter syndrome with sclerochoroidal calcifications

Characteristics	Case 1 [20]	Case 2 [21]
Gender, age (years)	M, 59	F, 42
Features of sclerochoroidal calcification		
Laterality	Bilateral	Bilateral
Location	Posterior pole	Superotemporal, superonasal
Number of SCCs	Multiple	Multiple
Color	White	Yellow–white
Elevation	Minimal	NA
Clinical features		
Disease duration (years)	18	26
Blood pressure	Normal	NA
Chondrocalcinosis in joints	NA	NA
Biochemical features		
Metabolic alkalosis	Present	Present
Hypokalemia	Present	Present
Hypomagnesemia	Present	Present
Hypercalciuria	Present	NA
Serum phosphate	Normal	NA
Serum calcium	Normal	Normal
Ophthalmic features		
Symptoms	None	None
Visual acuity	Normal	Normal
Anterior chamber	Normal	Normal
Fundus examination	Sclerochoroidal calcification	Sclerochoroidal calcification
Ophthalmic imaging		
OCT	NA	Sclerochoroidal calcification
B-scan	Sclerochoroidal calcification	Sclerochoroidal calcification

SCC, sclerochoroidal calcification; ST, superotemporal; SN, superonasal; OU, both eyes; NA, not available.

caused by urinary K losses due to activation of the renin–angiotensin–aldosterone system. KCl supplements are preferred because of the associated Cl deficiency. Spironolactone binds to the receptors at the aldosterone-dependent Na–K exchange site in the distal convoluted tubule and increases water excretion but retains K. Non-steroidal anti-inflammatory drugs decrease prostaglandin E2 synthesis, which otherwise causes the pressor response to angiotensin II. The resulting hyporeninemic hypoaldosteronism results in K retention. Low-dose angiotensin converting enzyme (ACE) inhibitors may be used to limit the aldosterone-mediated electrolyte disturbances. Early diagnosis of Bartter syndrome with genetic testing and subsequent treatment is critical in infants and young children. Sustained hypokalemia and hyperreninemia may result in kidney failure, but the prognosis is generally good with early treatment of the electrolyte disturbance.

Retinal calcification

Retinal, or more accurately, sclerochoroidal calcification is found in both Gitelman [16–19] and Bartter [20, 21] syndromes but occurs more often in Gitelman syndrome because it is more common and Mg levels are lower.

Sclerochoroidal calcification appears as solid yellow–white irregular multilobulated and moderately elevated subretinal lesions in the superotemporal mid-periphery between the temporal arcades and the equator (Tables 1 and 2 and Figure 1). The lesions are 4 mm wide (range 1–9) and up to 2 mm deep. They are located within the sclera and inner surface topography demonstrates 'mountainlike', 'flat', 'rolling', 'rocky-rolling' and 'table mountain' patterns. Lesions are bilateral and symmetrical in at least half the cases and sometimes multiple. These deposits comprise Ca and possibly calcium pyrophosphate. They may be accompanied by overlying retinal thinning and a choroidal neovascular membrane [18].

Deposits are noted from about the age of 40 years, increase in size and number with increasing years and are more common after the age of 70. The rate of progression is slower with long-term correction of the hypomagnesemia. Calcification may be complicated by atrophy of the overlying retina and visual loss. The deposits often correlate with ectopic calcification in the aorta, coronary and cerebral vessels. The deposits may also be associated with the hypertensive retinopathy that accompanies late-onset hypertension in Gitelman disease.

Vision is usually normal but is impaired when the overlying choroid, retinal pigment epithelium and other retinal tissues are damaged.

The deposits may be overlooked. They are usually evident on fundus examination or retinal photography, but their location may be just outside the normal range for retinal views. Ultrasound (B scans), optical coherence tomography (OCT, which resembles ultrasound but uses the reflection of light rather than sound to define the retinal layers and demonstrate surface topography) and orbital CT scans are all more sensitive [19]. OCT is also useful in distinguishing sclerochoroidal calcification from retinal nevi, melanoma and tumors.

Other rare causes of sclerochoroidal calcification include underlying systemic disorders such as hyperparathyroidism, pseudohypoparathyroidism, hypervitaminosis D and other causes of calcium pyrophosphate dehydrate deposition disease [22, 23]. Often no cause is found.

Sclerochoroidal calcification must also be distinguished from choroidal metastasis, choroidal melanoma, choroidal osteoma and intraocular lymphoma, which are all rare, and from

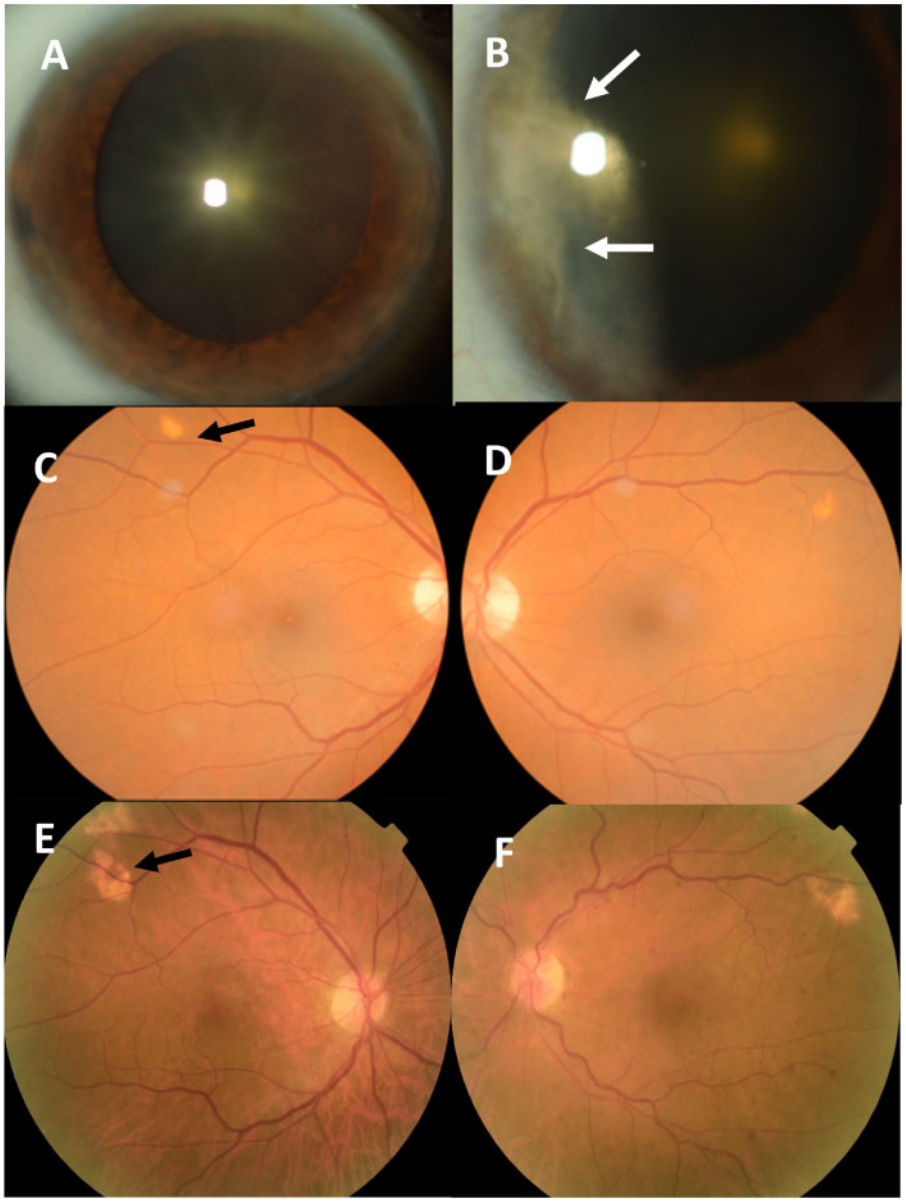

FIGURE 1: Ectopic calcification in a 74-year-old woman with Gitelman syndrome and poor Mg control. (**A** and **B**) Subepithelial opacities of the cornea (arrows). (**C** and **D**) Yellow deposits due to sclerochoroidal calcification in the superior temporal retina (arrow). (**E** and **F**) Enlarged deposits 9 years later (arrow). (**G**) Central retinal vein occlusion with dilated tortuous venules and hemorrhages (arrow) possibly due to late-onset hypertension. (**H** and **I**) OCT demonstrating choroidal deposits with 'mountain-like' features. (**J**) Ultrasound of the eye demonstrating a choroidal mass (arrow). (**K**) Right knee radiograph with calcified cartilage consistent with chondrocalcinosis (arrow).

other even less common conditions such as chorioretinitis, regressed retinoblastoma, retinal astrocytic hamartoma, choroidal hemangioma and eccentric macular degeneration (Table 3) [24].

Chondrocalcinosis

Chondrocalcinosis of the large joints, such as knee joints, wrists, metacarpophalyngeal joints, hips, shoulders and elbows, as well as ectopic calcification in the blood vessels is a feature of Gitelman syndrome [17]. Calcification affects the hyaline cartilage, fibrocartilage and other soft tissue structures, and where it affects joints is associated with arthritic pain [25]. Chondrocalcinosis also occurs in 20% of the normal elderly [25].

Calcium pyrophosphate dihydrate is deposited in the tissues ('pseudogout'), probably due to excess extracellular inorganic pyrophosphate [16, 18]. In individuals with hypophosphatasia, a deficiency of tissue nonspecific alkaline phosphatase increases extracellular inorganic pyrophosphate resulting in calcium pyrophosphate deposition [18]. Calcium pyrophosphate precipitates with low serum Mg levels, which reduces both pyrophosphate crystal solubility and alkaline phosphatase activity [7].

Mechanism underlying ectopic calcification

In Gitelman syndrome, the low Mg level is associated with reduced alkaline phosphatase activity, resulting in excess

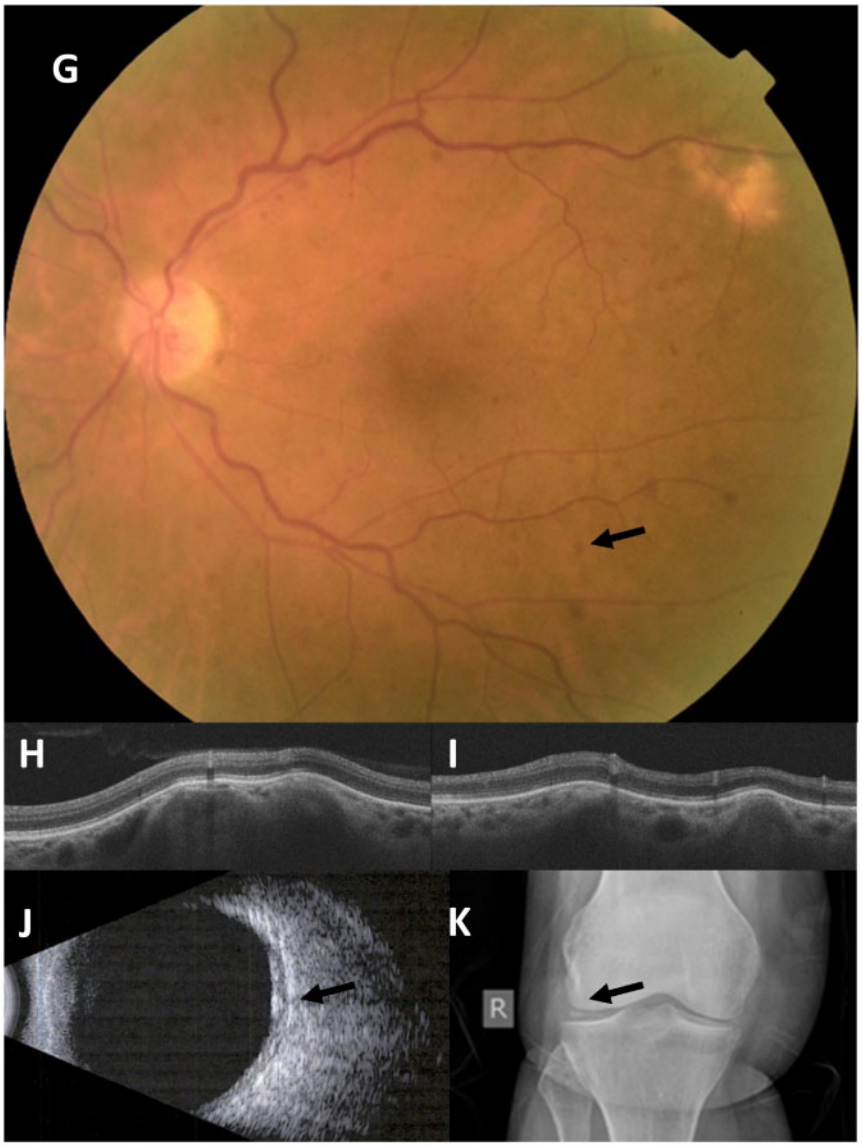

FIGURE 1: (Continued)

Table 3. Differential diagnosis for sclerochoroidal calcification [24]

Features	Choroidal calcification	Choroidal metastasis	Choroidal melanoma	Choroidal osteoma	Intraocular lymphoma
Age of onset	Elderly	Adults	Adults	Young adults	Adults
Colour	Yellow, white, orange	Homogeneous creamy-yellow	Irregularly pigmented	Yellow–orange	Whitish
Location	Superior or inferior arcade	Macular, or within the vascular arcades		Near the optic disc	
Laterality	Bilateral	Unilateral or bilateral	Unilateral or bilateral	Single lesion, unilateral	Unilateral
Number	Single or multiple	Single or multiple	Single or multiple		Multiple or diffused
B scan ultrasound	Calcified	Not calcified	Not calcified	Calcified	Not calcified
CT scan	Calcified	Not calcified	Not calcified	Calcified	Not calcified
Other retinal abnormalities	Minimal, or choroidal			neovascularization	Secondary retinal detachment
Secondary retinal detachment		Lymphocytes in vitreous			
Risk factors	Age	History of primary cancer			Visceral or central nervous system lymphoma

extracellular inorganic pyrophosphate and calcium pyrophosphate deposition. Low Mg levels are also associated with reduced calcium pyrophosphate solubility. Thus a low serum Mg results in calcium pyrophosphate formation in soft tissues and joints by inhibition of pyrophosphate hydrolysis and reduced crystal solubility.

In conclusion, ectopic calcification occurs in both Gitelman and Bartter syndrome, but is much more common in Gitelman syndrome. The finding of calcification in retinal photographs suggests the diagnosis of Gitelman syndrome. Metabolic and possibly genetic testing should be undertaken to confirm this diagnosis. This finding also suggests the need for better management of Mg levels.

PATIENT CONSENT

The authors would like to thank the patient whom they studied for this review. This person provided signed informed consent.

CONFLICT OF INTEREST STATEMENT

The authors have no financial or non financial conflicts of interest to declare. The results in this article have not been published previously in whole or part.

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