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
Calcium (Ca) reabsorption that is responsible for the hypocalcemia [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].

### 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 | Superotemporal |
| Number of lesions                      | Multiple    | Multiple    | Single      | Multiple    | Single      | Multiple    | Multiple    | Multiple    |
| Color                                  | Yellow–white | Yellow–white | Single      | Single      | Single      | Single      | Yellow      | NA          |
| Elevation                              | Yes         | Yes         | NA          | NA          | NA          | NA          | Low         | Low         |
| Clinical features                      |             |             |             |             |             |             |             |             |
| Muscle weakness/pain                   | NA          | Present     | Absent      | Absent      | Present     | Absent      | Absent      | Absent      |
| Arthritis                              | Present     | NA          | Absent      | Absent      | Present     | Absent      | Absent      | Absent      |
| Blood pressure                         | NA          | NA          | NA          | NA          | NA          | NA          | Low         | Low         |
| Chondrocalcinosis                      | Present     | Present     | Absent      | Absent      | Present     | Absent      | Absent      | Absent      |
| Biochemical features                   |             |             |             |             |             |             |             |             |
| Metabolic alkalosis                    | Present     | Present     | Present     | Present     | Present     | Present     | Present     | Present     |
| Serum bicarbonate                     | Elevated    | Elevated    | Elevated    | Elevated    | Elevated    | Elevated    | Elevated    | Elevated    |
| Hypokalemia                            | Present     | Present     | Present     | Present     | Present     | Present     | Present     | Present     |
| Hypomagnesemia                         | Present     | Present     | Present     | Present     | Present     | Present     | Present     | Present     |
| Hypocalciuria                          | Present     | Present     | Present     | Present     | Present     | Present     | Present     | Present     |
| Hyperkalemia                           | Present     | Present     | Present     | Present     | Present     | Present     | Present     | Present     |
| Hypermagnesemia                        | Absent      | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      |
| Serum Ca                               | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      |
| Parathyroid hormone                    | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      |
| Hyperreninism                          | NA          | Present     | Absent      | Absent      | Present     | Absent      | Absent      | Absent      |
| Hyperaldosteronism                     | NA          | Present     | Absent      | Absent      | Present     | Absent      | Absent      | Absent      |
| Ophthalmic examination                 |             |             |             |             |             |             |             |             |
| Symptoms                               | None        | None        | None        | None        | None        | None        | None        | None        |
| Visual acuity                          | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      |
| Anterior chamber                       | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      | Normal      |
| Fundus examination                     | SCC         | SCC         | SCC         | SCC         | SCC         | SCC         | SCC         | SCC         |
| Ophthalmic imaging                     |             |             |             |             |             |             |             |             |
| Autofluorescence                       | NA          | SCC         | SCC         | SCC         | SCC         | SCC         | SCC         | SCC         |
| B-scan                                 | SCC         | NA          | SCC         | SCC         | SCC         | SCC         | SCC         | SCC         |
| Fluorescein angiography                 | RPE atrophy | Subretinal lesion | Subretinal lesion | Subretinal lesion | Subretinal lesion | Subretinal lesion | Subretinal lesion | Subretinal lesion |

SCC, sclerochoroidal calcification; NA, not available; F, female; RPE, retinal pigment epithelium.
caused by urinary K losses due to activation of the renin–angio-
tensin–aldosterone system. KCl supplements are preferred be-
cause 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 hypo-
aldosteronism results in K retention. Low-dose angiotensin con-
verting enzyme (ACE) inhibitors may be used to limit the
aldosterone-mediated electrolyte disturbances. Early diagnosis
of Bartter syndrome with genetic testing and subsequent treat-
ment is critical in infants and young children. Sustained hypo-
kalemia and hyperreninemia may result in kidney failure, but
the prognosis is generally good with early treatment of the elec-
trolyte 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 tem-
poral 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 dem-
onstrates ‘mountainlike’, ‘flat’, ‘rolling’, ‘rocky-rolling’ and ‘ta-
ble 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 neo-
vascular membrane [18].

Deposits are noted from about the age of 40 years, increase
in size and number with increasing years and are more com-
mon 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 accompa-
nies 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 loca-
tion 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 calcifi-
cation from retinal nevi, melanoma and tumors.

Other rare causes of sclerochoroidal calcification include un-
derlying systemic disorders such as hyperparathyroidism, pneu-
dohypoparathyroidism, 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 oste-
oma and intraocular lymphoma, which are all rare, and from

| 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.
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, metacarpophalangeal 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
### 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          | Irregularly pigmented | Yellow-orange     | Whitish             |
| Location                       | Superior or inferior arcade | Macular, or within the vascular arcades | Near the optic disc |                   |                     |
| Laterality Number              | Bilateral               | Unilateral or bilateral | Unilateral or bilateral | Single lesion, unilateral | Unilateral |
| Number                         | Single or multiple      | Single or multiple   | Single or multiple | Multiple or diffused | Multiple or diffused |
| B scan ultrasound              | Calcified               | Not calcified        | Not calcified      | Not calcified     | Not calcified       |
| CT scan                        | Calcified               | Not calcified        | Not calcified      | Calcified         | Not calcified       |
| Other retinal abnormalities    | Minimal, or choroidal   | Lymphocytes in vitreous | Calcified          | Calcified         | Secondary retinal detachment |
| Secondary retinal detachment   |                         |                      |                    |                   |                     |
| Risk factors                   | Age                     |                      | History of primary cancer |                   | Visceral or central nervous system lymphoma |
extracellular inorganic 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 for this review. This person provided signed informed consent.

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