CASE REPORT

Gitelman's Syndrome (Familial hypokalemia-hypomagnesemia)

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Abstract

Gitelman's syndrome (GS) is a heritable renal disorder characterized by hypomagnesemia, hypokalemia and hypocalciuria, and is distinct from Bartter's syndrome (BS). As compared to those with BS, patients with GS present at an older age, and they have a milder clinical picture, normal or slightly decreased concentrating urine ability, reduced urinary excretion of calcium, and permanently decreased serum magnesium level. GS is caused by defective NaCl transport in the distal convoluted tubule, and is linked to the gene encoding the thiazide sensitive Na-Cl-cotransporter located on chromosome 16q. Patients with BS, on the other hand, have mutations in the transporters in the thick ascending loop of Henle (NKCC2, ROMK, and C1C-Kb). Treatment of GS consists of magnesium salt replacement. Long term prognosis in terms of maintaining growth, preserving renal function and life expectancy is excellent. *Hippokratia 2007; 11 (3): 150-153*

Key words: *hypomagnesemia, hypokalemia, Bartter's syndrome, Gitelman syndrome*

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The term Bartter's syndrome (BS) was used in the past to describe a spectrum of inherited renal tubular disorders with hypokalemic alkalosis, and similar clinical and biochemical features[1,2]. We now recognize two distinct clinical and genetic syndromes of hypokalemic alkalosis: BS and Gitelman's syndrome (GS)[3,4]. GS is a heritable renal disorder characterized by hypomagnesemia, hypokalemia and hypocalciuria linked to the gene encoding the thiazide sensitive Na-Cl-cotransporter located on chromosome 16q[3,5,6]. This report reviews GS, presents an affected 24-year-old man and emphasizes clinic, laboratory, molecular and genetic characteristics of the disease.

Table 1. *Biochemical data*

Parameter	Value	Normal range
Serum		
Creatinine mg/dl	3,4	05-1.3
Urea mg/dl	134	10-50
Sodium mEq/l	120	135-145
Potassium mEq/l	1,5	3.5-5
Chloride mEq/l	69.8	95-105
Ionized calcium mmol/l	1.21	1.15-1.35
Magnesium mg/dl	1,3	1.6-2.4
Bicarbonate mEq/l	30	24-26
PH	7.4	7.35-7.45
Renin pg/ml	25	1.31-4.95
Aldosterone pg/ml	120	4-31
Urine		
Sodium mEq/24 hr	400	100-250
Potassium mEq/24 hr	150	25-100
Calcium mg/24 hr	55	75-300
Calcium/creatinine mg/mg		0.03-0.25
Chloride mEq/24 hr	300	100-250
Magnesium mg/24 hr	150	70-120

An indicative Gitelman's syndrome case report

A 24-year-old male with diffuse muscle pain, weakness, leg cramps, vomiting and malaise of three weeks duration was admitted to our hospital. There was no history of fever, diarrhea, rash or abdominal pain. He reported having frequency of micturition, but no other urinary tract symptoms. He had no history of medication usage including diuretics. His perinatal history included a normal delivery at 40 weeks gestation, with normal prenatal history, and a birth weight of 3 kg. The family history was otherwise negative.

Physical examination at the time of admission revealed a height of 165 cm, weight 60 kg and blood pressure 90/60 mmHg. He exhibited clinical evidence of severe dehydration and peripheral muscle weakness.

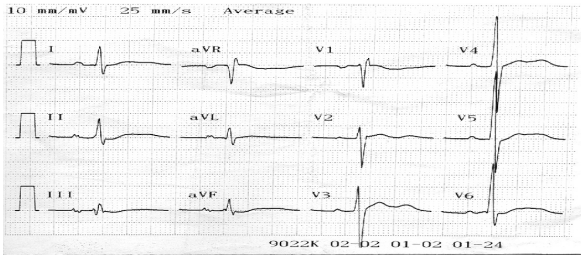

Figure: *Electrocardiogram showing normal sinus rhythm, with frequency 104/min, first grade block, incomplete right bundle branch block and wave T negativisation*

Renal ultrasound was normal; there was no evidence of nephrocalcinosis. During his hospital stay he developed hypokalemic myopathy with a serum CPK of 2099 iu/L and LDH 1252 iu/L and initially, he was treated with potassium supplements, and spironolacton which corrected his serum potassium level to 3.0-3.2 mmol/L.

After the first week the patient normalized renal function, CPK and LDH and 2 weeks later hypokalemia, hyponatremia, hypomagnezemia, hypochloremia were normalized too. Subsequently, he was exclusively treated with magnesium and potassium supplements and amiloride. Molecular genetic studies were not performed.

Diagnosis

The diagnosis of GS is made on the basis of clinical, biochemical and molecular findings. Disease-free intervals may be prolonged resulting in delay of diagnosis until adulthood. This condition was previously confused with BS; however, patients with GS have a milder clinical picture, absence of polyuria, normal or slightly decreased concentrating urine ability, reduced urinary excretion of calcium, permanently decreased serum magnesium level, and usually there is no history of maternal polyhydramnios or prematurity[3,4,7]. One third of patients with GS may have a short stature[5]. Chondrocalcinosis may also be seen[8]. Patients are frequently asymptomatic or suffer from carpopedal spasms especially during periods of fever or when extra magnesium is lost by vomiting or diarrhea. Paraesthesias, especially of the face, frequently occur. Some patients experience severe fatigue interfering with daily activities, while others never complain of tiredness[9-11].

Progression to renal insufficiency is extremely rare in GS. As yet, only one patient developed chronic renal disease and progressed eventually to end stage renal failure. Blood pressure in GS patients is lower than in the general population, indicating that even the modest salt wasting due to this disease reduces blood pressure. Heterozygous mutation carriers remain normotensive, but consume larger quantities of salt, pointing to a compensated defect[3,12-14]. Molecular DNA diagnostic studies are used to establish mutations of the gene encoding the thiazide-sensitive Na-Cl-cotransporter which is responsible for the syndrome.

Molecular genetics

Gitelman's syndrome is inherited as an autosomal recessive trait. An autosomal dominant inheritance in some families with GS, suggested by Bettinelli et al[2] was later dismissed by molecular genetic analysis showing that inheritance in these families was in fact pseudodominant[9,13]. In contrast to BS, GS is a molecularly homogeneous disorder caused by loss-of-function mutations in the SLC12A3 gene[9]. The SLC12A3 gene maps to chromosome region 16q13, consists of 26 exons, and encodes the renal thiazide-sensitive sodium chloride cotransporter (NCC), specifically expressed in the distal comvoluted tubule (DCT). NCC is a polypeptide which consists of 1021 amino acids. Its 2-D structure is predicted to contain 12 transmembrane domains and intracellular amino- and carboxy-terminal regions[3,13]. At present more than 100 different, putative loss-of-function mutations in the SLC12A3 gene have been identified in GS patients[3,15]. They include missense, non-sense, frame shift, and splice-site mutations and are scattered throughout the protein with a possible clustering of mutations in the carboxy-terminal tail. By functional expression studies and results of immunocytochemistry in Xenopus leavis oocytes, it was shown that most disease-causing NCC mutants are completely or partly impaired in their routing to the plasma membrane.

Pathophysiology

Normally, about 7 per cent of the filtered load of sodium chloride is reabsorbed in the DCT. The disruption of NaCl reabsorption in the DCT, resulting from loss-of-function mutations in NCC, can explain most, but not all, features of GS[16]. Impaired NaCl reabsorption in the DCT, increases sodium delivery in the collecting duct and results in mild volume reduction. The vascular volume reduction increases renin activity, angiotensin, and aldosterone levels[12]. Raised aldosterone levels increase electrogenic sodium reabsorption in the CCD via the epithelial sodium channel ENaC and maintain salt homeostasis at the expense of an increased secretion of potassium and hydrogen ions, and an attendant hypokalaemia with metabolic alkalosis.

The mechanisms of hypocalciuria and hypomagnesaemia in GS remain a matter of speculation. It has been suggested that mutations which inactivate NCC may cause hypocalciuria by the same mechanism as thiazides. According to this hypothesis, the reduced influx of NaCl in the DCT cells in combination with continued exit of intracellular chloride through basolateral chloride channels, causes hyperpolarization of the cell. This in turn increases calcium entry via apical calcium channels. The subsequent increase in intracellular calcium stimulates calcium efflux via the basolateral Na + /Ca 2+ exchanger and the Ca 2+ -ATPase. The lowered intracellular sodium concentration facilitates calcium exit via the basolateral Na + /Ca 2+ exchanger. Hypomagnesaemia has been attributed to the associated hypokalaemia, a hypothesis disputed by studies in NCC-knockout mice which developed severe hypocalciuria and hypomagnesaemia despite the absence of hypokalaemia or alkalosis. Renal defects in Ca 2+ and Mg 2+ reabsorption might thus be a consequence of functional and/or structural alterations in the DCT caused by loss of NCC activity, rather than secondary to systemic metabolic disturbances such as hypokalaemia or alkalosis. An alternative hypothesis is based on the possible existence of both an apical Mg 2+ channel and a basolateral Mg 2+ extrusion mechanism in DCT cells. These putative transporters could be affected by differences in NaCl homeostasis within these cells[12,15]. Affected patients have increased natri-

uretic and kaliuretic response to intravenous administration of furosemide, and blunted natriuretic response to thiazides, suggesting that the defect in sodium chloride reabsorption is in the distal tubule rather than in the ascending limb of the loop of Henle as is the case in BS. Unlike patients with BS, these patients exhibit blunted calciuric response to furosemide[14].

Table 2. *Comparison between Bartter and Gitelman Syndromes*

Signs	Bartter	Gitelman	Our patient
Growth retardation	+	±	±
Polyuria	+		
Tetany		+	+
Hypokalemic alkalosis	+	+	+
Hypomagnesaemia		+	+
Hypocalcaemia		+	+
Elevated urinary prostaglandins	+	-	-
Chondrocalcinosis	-	+	-
Renal defect	Thick ascending loop of Henle	Distal convoluted tubule	
Inheritance	Autosomal Recessive C1C-Kb, NKCC2, ROMK	Autosomal Recessive Mutation TSC	

Discussion

In 1962, Bartter et al described two patients with hypokalemia, metabolic alkalosis, hyperaldosteronism with normal blood pressure, decreased pressor responsiveness to infused angiotensin II, and hyperplasia of the juxtaglomerular apparatus[17]. Following that, various conditions of hypokalemic alkalosis were included under this syndrome. We now recognize two different clinical and genetic Bartter-like syndromes, BS and GS[15,18,19]. Both are inherited as autosomal recessive, but each represents a distinct clinical and molecular entity. BS usually has its onset during infancy or childhood and is associated with polyuria and growth retardation. The fundamental defect in this syndrome is an abnormality of chloride transport in the thick ascending limb of the loop of Henle. Deletions or mutations of the gene encoding a renal chloride channel (C1C-Kb), which is situated at the distal nephron segments have been identified[20,21]. Defects have also been identified either at the gene encoding the renal bumetanide-sensitive Na-K-2Cl cotransporter (NKCC2)[21,22] or the gene encoding an ATP-sensitive inwardly rectifying K channel (ROMK)[23].

A neonatal form of BS, referred to as hyperprostaglandin E2 syndrome, has also been described[24,25]. This is a life threatening condition often beginning in utero with fetal polyuria leading to polyhydramnios and premature delivery. The neonatal form of BS appears to differ from BS by its severity and early onset, but there seems to be no justification to consider this as a separate entity from BS[19]. In 1966, Gitelman et al described three adult patients with intermittent episodes of muscle weakness and tetany, hypokalemia and hypomagnesemia, but with no polyuria or growth retardation[26]. The incidence of GS is unknown, but it is thought to be more common than BS[4] that occurs with an incidence of 1-2 per million[27]. Mutations appear to be common, since the vast majority of patients studied have no history of consanguinity and are heterozygotes and different allelic mutations occur on the two alleles[3]. The SLC12A3 gene, located in 16q13 and containing 26 exons, encodes the renal thiazide-sensitive Na-Cl-cotransporter that is predominantly located within the distal convoluted tubule. BS and GS are distinct entities, clinically and genetically. An accurate diagnosis is necessary because of its impact on the treatment and prognosis of these two syndromes. The classification of "Bartter-like syndromes" into BS and GS appears to be adequate until the underlying defect is more clearly defined.

Treatment and prognosis

Most patients with GS remain untreated. The observation that chondrocalcinosis is due to magnesium deficiency, argues clearly in favour of magnesium supplementation[8]. Normalization of serum magnesium is, however, difficult to achieve since high doses of magnesium cause diarrhoea[28]. The bioavailability of magnesium varies according to the preparations. Magnesium oxide and magnesium sulfate have a significantly lower bioavailability than magnesium-chloride, magnesium lactate and magnesium aspartate[9]. All magnesium salts have been used, but $MgCl_2$ is preferred because it compensates for urinary Cl loss[15]. Each ml of the 5% solution contains 0.5 mEq or 6 mg of Mg++. The total dose is individualized and given at 6 to 8 hour intervals. Potassium and prostaglandin inhibitors are usually not needed, although some patients may require potassium salts and/or anti-aldosterone medications such as amiloride or spironolactone to correct and maintain the serum potassium level[6]. Growth hormone therapy may improve growth rate and restore the serum magnesium levels in short children with GS, particularly those resistant to conventional therapy[29]. We recommend the combination of amiloride with KCl but amiloride should be started with caution in order to avoid hypotension. In general, the long-term prognosis of GS is excellent.

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