A new tubular disorder with hypokalaemic metabolic alkalosis, severe hypermagnesuric hypomagnesaemia, hypercalciuria and cardiomyopathy

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Introduction

Renal tubular magnesium loss in association with a defect in tubular chloride reabsorption has been reported in Bartter’s and Gitelman’s syndromes. Clinically, both syndromes are characterized by hypokalaemic metabolic alkalosis, renal salt wasting, hyperreninaemic hyperaldosteronism and altered renal prostaglandin metabolism [1]. In Bartter’s syndrome, hypomagnesaemia occurs in ~20% of patients, but is usually mild. Hypercalciuria may also occur. In Gitelman’s syndrome, hypomagnesaemia due to renal loss is the cardinal finding. However, hypercalciuria is pathognomonic for this syndrome and used in the differential diagnosis between the two disorders. Both syndromes are considered to be autosomally recessively inherited.

We report a novel Bartter-like phenotype in a father–daughter pair. This seemingly autosomally dominantly inherited disease is characterized by hypokalaemic metabolic alkalosis secondary to renal chloride loss and severe hypomagnesaemia due to renal magnesium loss. In contrast to Gitelman’s syndrome, these patients showed marked hypercalciuria. Both patients developed dilating cardiomyopathy, which was fatal in the father and required heart transplantation in the daughter.

Case

Patient 1

The early course of this patient, the father, has been described previously in detail [2]. Briefly, he presented at the age of 6 years with tetanic convulsions, hypokalaemic metabolic alkalosis, hypocalcaemia and nephrocalcinosis. Potassium and calcium supplementation were given, but had no effect on blood chemistry. At the age of 14 he developed arthritic pains. Serum magnesium was determined for the first time and found to be 0.24 mmol/l (normal: 0.60–0.90 mmol/l). The patient was studied extensively. Hypokalaemic metabolic alkalosis, hyperaldosteronism, normotension, hypomagnesaemia, hypermagnesuria, hypercalciuria and hyperplasia of the juxtaglomerular apparatus were found. He was given MgCl2, Mg(OH)2 and KCl supplementation, which resulted in cessation of subjective symptoms and improvement, but not normalization of blood chemistry. Subsequently, he became non-compliant and was lost from follow-up. He died a sudden cardiac death due to arrhythmia at the age of 31 years. At autopsy, dilating cardiomyopathy with calcium crystal deposits was found. Additional deposits were present in the lungs, liver and, especially, in the kidneys, where bilateral nephrocalcinosis was found.

The parents of the patient were from different parts of Finland and consanguinity is unlikely. Blood chemistry was normal in the first-degree relatives.

Patient 2

Patient 2 is the daughter of patient 1 and a non-consanguinous healthy mother. She presented initially at the age of 4 years with carpopedal spasms provoked by a concurrent infection. In the initial work-up, normotension, hypokalaemic metabolic alkalosis,
hypomagnesaemia, hypermagnesuria, hypocalcaemia and hypercalciuria were found. She was started on Mg(OH)₂, CaCO₃ and KCl substitution. These had only minor effect on blood chemistry, and no effect on subsequent numerous episodes of carpopedal and perioral spasms, which usually took place during a concurrent viral infection. Infrequently, tetania presented as generalized convulsions. During prolonged symptoms and convulsions, she was treated with intravenous MgCl₂ infusions. This lead to cessation of symptoms, but blood chemistry was usually unaltered with serum magnesium in the range of 0.30–0.45 mmol/l.

At the age of 9 years, she was supplemented with Mg(OH)₂, CaCO₃ and KCl (40 mmol/day each) with laboratory data still showing the original abnormalities, while serum parathyroid hormone concentration was normal (Table 1). Due to tendency to almost daily spasms, she was referred for nephrological consultation. A detailed investigation of kidney function was performed (Table 1). Clearance studies were performed as described previously [3]. Glomerular function was normal. A Bartter-like deficiency in distal nephron chloride reabsorption at the level of the thick ascending loop of Henle (TALH) was demonstrated. Urinary prostaglandin levels were increased. The patient was started on indomethacin (2.5 mg/kg/day) while electrolyte substitutions were continued. Subsequently, serum magnesium levels normalized and the patient became symptom-free. A repeated analysis of renal function showed that, as in Bartter’s syndrome, the underlying deficiency in chloride reabsorption remained unchanged (Table 1).

Also at the age of 9, dilating cardiomyopathy was diagnosed in chest X-ray and cardiac ultrasound examinations. The fractional shortening (FS) of the left ventricle was reduced (23%) and the patient was put on digitalis (125 µg x 1) and enalapril (5 mg x 1). At the age of 12 years, the cardiac function was satisfactory (FS 29%). Due to the side effects of the magnesium supplementation (loose stools and diarrhoea), the patient’s compliance with the medication was poor and she had repeated episodes of carpopedal spasms with occasional generalized seizures.

At the age of 16 years, digitalis was discontinued and replaced with carvedilol as an inotrope (6.25 mg b.i.d.). Cardiac catheterization revealed normal pulmonary pressure and coronary arteries. The left ventricle was enlarged and FS was 30%. Three months after the catheterization, the patient developed a clinically significant heart insufficiency. She presented with ischaemic stomach pains, pulmonary congestion and pericardial effusion. FS decreased to 21% and ejection fraction to 40%. Spironolactone and intravenous infusions of milrinone were added to the medication, but had no effect on cardiac function. Because of deteriorating heart function, the patient was listed for heart transplantation. A single simvastatin infusion showed mild myofibrosis but no calcification, necrosis or inflammation.

The patient is currently 18 years old and clinically well. In addition to immunosuppression (cyclosporin A, mycophenolate mofetil and methylprednisolone), her medication consists of indomethacin (1.1 mg/kg/day), Mg(OH)₂ (0.9 mmol/kg/day), KCl (0.3 mmol/kg/day), CaHPO₄ (0.13 mmol/kg/day), pravastatin, furosemide and atenolol. The patient has not received activated vitamin D treatment at any time during the course of her illness. Her cardiac function is normal with a FS of 37%. Renal function has deteriorated with Cr-EDTA clearance 30 ml/min/1.73 m² and serum creatinine 91 µmol/l. Serum magnesium levels have
remained quite stable in the low–low normal range (0.47–0.60 mmol/l) during the post-operative period while magnesium substitution has remained at the pre-transplantation level. Serum potassium, ionized calcium, bicarbonate and phosphate have been normal. Serum renin (6.2 µg/l/ h; normal: 2–5 µg/l/h) and aldosterone (2476 pmol/l; normal: 183–940 pmol/l) levels have remained elevated.

In other studies, renal ultrasound has not shown signs of nephrocalcinosis. Muscle biopsy was taken at the age of 11 years in order to study possible presence of mitochondrial diseases. Muscle histology and staining for cytochrome oxidase were normal and no lipid deposits were seen. Also, no deletions in the mitochondrial DNA were seen in Southern blot analysis and the activities of the mitochondrial respiratory chain enzymes were normal. DNA sequencing has not revealed mutations in genes, including the calcium-sensing receptor (CaSR), known to be affected in Gitelman’s and Bartter’s syndromes [4–8]. Growth retardation has not been documented at any time.

Discussion

The two patients represent a new phenotype of hypokalaemic metabolic alkalosis, hypercalciuria, hypomagnesaemia due to renal magnesium wasting and cardiomyopathy. Renal tubular magnesium loss in association with hypokalaemic metabolic alkalosis has been reported previously in Gitelman’s and Bartter’s syndromes. In Gitelman’s syndrome, which is caused by a defect in the distal tubular thiazide-sensitive Na–Cl co-transporter [4], hypomagnesaemia may be profound. However, the disease is characterized by the invariable presence of hypocalciuria [9], while in our patients hypercalciuria occurs. In addition, the abnormalities in Gitelman’s syndrome are responsive to treatment by MgCl2 substitution [1], which in our patients had little effect. In Bartter’s syndrome, hypokalaemic metabolic alkalosis may occur in combination with hypercalciuria and hypomagnesaemia. However, in this disease, hypokalaemia, not hypomagnesaemia, is the cardinal manifestation. Cardiomyopathy has not been reported in either Bartter’s or Gitelman’s syndromes. Moreover, both diseases are thought to be inherited in an autosomal recessive fashion, while the father–daughter presentation in our patients suggests autosomal dominant inheritance.

Functional studies in the daughter revealed a defect in the distal Cl– reabsorption at the level of the TALH. Although Cl– reabsorption was not specifically investigated in the father, the presence of hyperaldosteronism, hypokalaemic metabolic alkalosis and juxtaglomerular hyperplasia strongly support increased distal Cl– delivery. The favourable renal response to indomethacin in the daughter is also similar as that seen in Bartter’s syndrome [1]. It can be attributed to a decrease in glomerular filtration rate (GFR), decreased delivery from the proximal tubule (decreased lithium clearance) as well as inhibition of renal prostaglandin synthesis.

The renal pathophysiology in our patients is not clear. In Bartter’s syndrome, the defect in Cl– reabsorption is caused by direct or indirect inhibition of the TALH Na–K–2Cl co-transporter (NKCC2). Mutations in the genes coding for the transporter itself [5], for the rate-limiting apical outwardly rectifying K+ channel (ROMK) [6], the basolateral membrane Cl– channel (CLCNKB) [7] and the CaSR [8] have been demonstrated. It is thought that the hypermagnesuria in Bartter’s syndrome is secondary to the defect in NKCC2 function, which leads to an increase in negative ions in the tubular lumen. In our patients, mutational analysis has not yielded any positive results in these genes or in the thiazide-sensitive Na–Cl co-transporter gene affected in Gitelman’s syndrome, suggesting that a defect in another molecule may be responsible.

In the TALH, Mg2+ reabsorption occurs almost entirely by a passive paracellular pathway driven by a lumen positive electrical potential [10]. A genetic defect leading to a constant increase in the resistance of the paracellular pathway would decrease Mg2+ (and Ca2+) reabsorption. As ~60% of filtered Mg2+ is normally reabsorbed at this site, significant hypermagnesuria would ensue. Simultaneously, the more positive luminal potential would impair Cl– reabsorption and lead to the other renal manifestations of the phenotype. The decrease in divalent cation reabsorption might also be linked directly to intracellular mechanisms of NKCC2 inhibition. Such an association has been demonstrated for the extracellular CaSR, the activation of which leads to decreased NKCC2 function [8]. Although activating mutations in CaSR have been reported to be associated with a Bartter-like disorder with hypomagnesaemia and hypercalciuria, this particular phenotype is characterized by the presence of hypoparathyroidism since CaSR is expressed also in the parathyroid where it contributes to the regulation of hormone synthesis and excretion. In our patients, serum parathyroid levels were normal and DNA sequencing failed to identify activating mutations of the CaSR gene.

Mutations in the paracellin-1 gene cause a hereditary autosomally recessively inherited disease designated as familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC) [10]. While our patients presented with hypomagnesaemia, there are significant differences between them and FHHNC patients, both regarding renal and extrarenal manifestations. In FHHNC, serum calcium is normal and hypokalaemic metabolic alkalosis has not been reported. Further, cardiomyopathy has not been described in FHHNC while ocular manifestations (myopia, nystagmus and chorioretinitis) are commonly present in contrast to in our patients.

The phenotype described in the present report is potentially fatal due to the development of dilating cardiomyopathy. It remains unclear whether the cardiac manifestation is secondary to the renal disease
or whether the heart itself is affected by a disorder in electrolyte transport. Cardiomyopathy is seen in both animal models of prolonged magnesium deficiency and in human malnutrition with magnesium deficiency [11]. Prolonged hypokalaemia may also promote cardiac dysfunction since potassium depletion has been reported to impair cardiac function in animals and healthy human volunteers [12], and lethal cardiomyopathy has been reported in a patient with profound hypokalaemia [13]. However, inherent defects in cardiac metabolism cannot be excluded. Their role is suggested by the fact that cardiomyopathy has not been described in Gitelman’s syndrome, despite similar degrees of hypomagnesaemia as in our patients. If a cardiac defect was responsible for the development of cardiomyopathy, the disease should not manifest in the transplanted organ.

In patient 2, renal glomerular function deteriorated markedly after heart transplantation with GFR decreasing to 30 ml/min/1.73 m² from pre-transplantation levels of >100 ml/min/1.73 m². Although this might be due to progression of her renal disease, it seems more likely that her cyclosporin A-based immunosuppression has resulted in drug-induced nephrotoxicity and glomerular dysfunction. In case of further progression, the use of less nephrotoxic immunosuppressive agents will have to be considered. In addition to effects on GFR, hypomagnesaemia secondary to renal tubular magnesium loss is one of the manifestations of cyclosporin nephrotoxicity. In our patient, this side effect did not seem to occur to a major degree as the patient’s need for magnesium substitution did not increase after transplantation and initiation of cyclosporin administration. However, since the patient’s requirement for magnesium substitution remained constant and could not be decreased despite the deterioration of GFR, cyclosporin may have promoted magnesium loss relative to GFR. As the patient has demonstrated improved compliance with medication (including magnesium substitution) after transplantation, exact comparison with her pre-transplantation status is difficult. The slightly higher serum magnesium concentrations obtained with magnesium substitution post-transplantation may reflect the improvement in compliance.

As discussed above, the phenotype demonstrated by our patients is not identical to any caused by currently known molecular defects. Phenotypically, hypocalcaemia, hypercalciuria, hypomagnesaemia, hypermagnesaemia and hypokalaemic metabolic alkalosis observed in our patients have all been reported to occur in patients with activating CaSR mutations [10]. Thus, while our patients are geno- and phenotypically novel with potentially fatal dilating cardiomyopathy, lack of activating CaSR mutations and normal serum parathyroid hormone concentration, it remains possible and attractive to postulate that our patients might still suffer from a genetic disorder affecting the CaSR signal transduction pathway.

Should the molecular abnormality reside at a point distal from the CaSR molecule itself, the CaSR would function normally in sensing serum calcium and, possibly, magnesium levels [8,10]. However, signalling from the receptor to intracellular effector molecules would be compromised, resulting in inadequate calcium conservation in the kidney leading to hypercalciuria and Bartter-type tubular dysfunction. As most cellular signal transduction pathways demonstrate tissue-specific differences, the intracellular events in the parathyroid gland might be sufficiently intact for the release of parathyroid hormone to occur at least in the low normal range observed in our patient. The current understanding of the intracellular CaSR signalling does not allow us to suggest any specific candidate molecule, but we intend to undertake further genetic studies in this respect as more information becomes available. However, the theory presented remains unproven and the actual molecular abnormality may reside in a completely separate pathway.

In conclusion, these patients demonstrate a novel Bartter-like phenotype in which massive renal magnesium loss is associated with milder signs of the classical Bartter’s syndrome. The disease is likely to be inherited in an autosomal dominant fashion, but genetics and molecular mechanisms of the entity remain unclear. However, a defect in Cl⁻ resorption in TALH is present. Response to magnesium substitution is poor and the side effects of substitution may lead to non-compliance. Cessation of tachypenic symptoms and partial normalization of laboratory data can be achieved with administration of indomethacin. Despite treatment, the patients may develop dilating cardiomyopathy with potentially fatal consequences.

Conflict of interest statement. None declared.

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