Magnesium disorders: clinical experience and review of the literature

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Introduction

Magnesium (Mg^{++}) is the most abudant living cation in prokaryotic and mammalian cells, with a total cellular concentration of 15-25 mM (1, 2). In the cytosol the majority of magnesium is bound to ATP, other phosphonucleotides and enzymes. It constitutes an essential structural element for membranes and ribosomes and a cofactor for ATP in the catalitic pocket of many enzymes. In spite of the biological abundance and importance of Mg^{++}, a significant lack of information regarding both physiological and pathological aspects is still present. Hovewer, in the past decade major advances have been made in the understanding of Mg^{++} homeostasis (3, 4).
Specific receptors leading to Mg^{++} influx inside the cells have been identified; still less well carachterized are the efflux mechanisms. The main site of Mg^{++} absorption from the gut is the small intestine; minor quantities are absorbed at the colon level (5). In both sites, cellular (active, saturable transport) and paracellular (passive, not saturable transport) fluxes are present (6). The saturable absorption of Mg^{++} is low with respect to the total.
Almost 95% of filtered Mg^{++} is reabsorbed before excretion (7): 15-20% in the proximal convoluted tubule by a passive paracellular process, 70% in the tick ascending limb of Henle's loop also by a passive paracellular mechanism (with a regulatory role of paracellin-1 present in the thight junctions). 5-10% is reabsorbed at the level of distal convoluted tubule by an active, transcellular mechanism that constitutes the main site of regulation (8); 3-5% of filtered Mg^{++} is then excreted in the urine.
A significant contribution to the understanding of Mg^{++} homeostasis in recent years comes from the analysis of phenotypes of patients with rare disorders of Mg^{++} metabolism (9, 10). The first example was the identification of mutations of gene CLDN16, coding for synthesis of paracellin-1 in '*familial hypomagnesemia with hypercalciuria and nephrocalcinosis*' (FHHNC) (11).
A 'trafficking mutation' in the gamma subunit of Na-K ATPase causes the '*isolated dominant hypomagnesemia*' (IDH) (12), associated with renal magnesium loss.
A frequent disorder of renal metabolism of Mg^{++} is represented by '*Gitelman variant of Bartter syndrome*' (GS), associated to mutations of the Na^{+}-Cl^{-} cotransporter at the distal convolute tubule level. Beside hypokalemia and metabolic alcalosis, hypomagnesemia and hypocalciuria represent carachteristic hallmarks (13, 14).
The most recent and remarkable example of clinical contribution to the understanding of epithelial transport of magnesium is the carachterization of TRPM6 mutations in the sindrome of '*primitive hypomagnesemia with secondary hypocalcemia*', that led to the identification of the principal component of intestinal Mg^{++} absorption, the TRPM6 channel (15).

Case report

Patient's anamnesis

A 69 years old man was referred to the endocrinologist for chronic severe hypocalcemia. The patient's father died for Parkinson's disease at the age of 81, his mother died at the age of 103. His brother and two son were reported in good health.
He had ernia of the jatus for a long time, mild essential hypertension for the past 15 years, well controlled by a beta-blocker, a recent prostatectomy for benign hypertrophy; hyperomocisteinemia was diagnosed few years before.
He reported a state of well being until six years before the visit, when progressive asthenia, a slow decrease in intellectual function and occasional palpitations occurred.
Four years ago he had two episodes of generalized seizures; therapy with carbamazepine was started thereafter. After these episodes, a more rapid decrease in general condition, associated to unintentional tremor and toracic algias led to several hospitalizations, with diagnosis of arterial hypertension and reactive depression following the seizures. The only significant finding had been moderate hypocalcemia (7.8-7.5 mg/dl); no other evaluation of electrolyte and bone parameters had been done. Supplementation with 0.25 ug of calcitriol and 1 gr of calcium carbonate was initiated, with no significant effect on circulating calcium levels. Two years before, during an hospitalization at a Cardiology Unit for the evaluation of cardiac angina, severe hypomagnesiemia was detected (0.2 mg/dl, n.v. 1.6-2.4); i.v. magnesium infusion was disposed, and the patients was discharged. No specific cause was found for seizures, and cardiovascular or pulmonary diseases were excluded.

Clinical presentation

On physical examination the patient appeared pale and suffering, with fine unintentional tremors; he complained of extreme weakness both physical and psichic. Routine biochemical tests resulted in the normal range, as well as cardiac evaluation by ECG, Holter dynamic ECG recording and echocardiography.
An evaluation of the patient's ematic and urinary electrolyte metabolism after 3-days interruption of vitamin D and calcium supplementation (while on carbamazepine therapy) is showed in Table I.
Severe hypomagnesemia with hypomagnesiuria and secondary hypocalcemia was detected; no secondary causes of magnesium deficiency were found.

Therapy

The patient started supplementation with magnesium p.o. (magnesium pidolate, 4 gr/day) and low doses of calcitriol and calcium. Tremors decreased after the intake of 2 gr. of magnesium and were no more evident by the third day after initiation of therapy; at the end of the first week a dramatic improvement of asthenia and depression was evident.
Serum and urine levels of magnesium progressively increased, without returning to normal levels after one year of therapy. At two and ten months the concentrations of magnesemia were 0.8 an 1.1 mg/dl and those of magnesiuria 10 and 37 mg/dl respectively. Serum calcium levels increased to 9.0 mg/dl, and PTH to 6 pM.

Patient's family analysis

Evaluation of the patient's family showed normal serum magnesium levels in the brother (2 mg/dl). On the contrary, both sons have hypomagnesemia with controlled values for the youngest (26 years old) of 1.6 mg/dl, and for the oldest (37 years old) of 1.3 mg/dl. Circulating total and ionized calcium levels were in the low-normal range. They were not available for further exams or follow-up.

Diagnostic conclusions

A diagnosis of late-onset, chronic, severe hypomagnesemia with secondary hypoparathyroidism/hypocalcemia, and hypomagnesiuria was made. The absence of increased urinary excretion of magnesium excluded a renal primary cause of hypomagnesemia. The apparent presence of the same – milder – alteration in the two sons suggest an hereditary disorder. The previous considerations and the response to treatment suggest a similarity with the sindrome of Hypomagnesemia with secondary Hypocalcemia (HSH, OMIM 602014, 607009).

Discussion

HSH is a recessive disorder manifesting in early infancy with generalized seizures or other symptoms of increased neuromuscolar excitability like tetany. Severe hypomagnesemia (levels < 1.0 mg/dl) is associated to tachiarytmias, alterations of mental status, delirium, stroke. It represents the only known Mg^{++} disorder with hypomagnesiuria: hypocalcemia is always present, in the absence of clear deficits of vitamin D. It was first described in 1967 (16) in a neonate, son of consanguineous parents. In 1970 Vainsel et al (17) described a 5-months old infant with convulsions and persistent tetany, associated to hypomagnesemia and hypocalcemia; vitamin D supplementation was able to correct hypocalcemia but not to improve the clinical manifestations of the disease. Autopsy showed calcinosis of the myocardium, kidneys, cerebral arteries. Two brother of the infant had died with similar symptoms, and three out of other four brothers had seizures.

Table I - Blood and urine parameters of the patient after 3 days withdrawal of calcitriol and calcium supplementation.

	Value	n.v.
Serum magnesium	0.31-0.43	1.8-2.5 mg/dl
Erythrocyte magnesium	3.7	4.7-6.5 mg/dl
Serum calcium	7.5	8.8-10.4 mg/dl
Serum phosphorus	2.9	2.5-4.5 mg/dl
Serum PTH	1.4	1.8-7.6 pM
25-OH vitamin D	20	30-50 ng/dl
1,25-OH vitamin D	20.3	19-70 pg/ml
Serum bone alkaline phosphatase	19	8-22 U/l
Urine magnesium	<0.4	75-125 mg/die
Urine calcium	86	100-300 mg/die

The disease is more frequent in males (1,8:1). A missed or delayed diagnosis, or the lack of compliance in treatment can led to death or permanent neurologic damage (18).
Secondary causes of moderate-severe hypomagnesemia include steathorrea and severe diarrhea as in Crohn's or Whipple's disease. At least fifty drugs have been involved in low circulating magnesium levels (19), but clinical effects are reported only for seventeen of these; furosemide and thiazides do not show any significant reduction in serum magnesium. Erytrocyte magnesium is reported to be low in severe depression and maniac disorders (20), and an increase of erythrocyte magnesium is probably involved in the mechanism of action of some psychotropic drugs, among which carbamazepine. Increased magnesium status positively correlates with enhancement of the clinical state.
The carachteristics of HSH patients led to the hypothesis of a primitive defect of intestinal absorption of Mg^{++} (21). In 1997 a genetic locus for HSH (HOMG1) was mapped on chromosome 9q22 (22, 23). TPRM6 was identified in the critical interval (15, 24); loss of function mutations of TRPM6 were therefore hypothesized as the cause of HSH.
TRPM6 belongs to the TRP (transient receptor potential) superfamily of protein forming ion channels expressed in a great number of cell types (review in 25). Several sub-families have been characterized so far, with wide differences even among members of the same family. TRPM6 is a member of the widely expressed 'melastatin-correlated' TRPM subfamily. More than 20 cation-related channels have been described, each with a definite role in a big variety of physiologic processes. TRPM6 is expressed along the small intestine and colon and in the apical membrane of renal distal collecting tubule. These studies confirmed previuos theories (9) on an additional pathogenetic role of renal dispersion of Mg^{++} in the clinical manifestations of HSH; indeed, i.v. Mg^{++} load in HSH patients leads to inadequate magnesium loss in spite of hypomagnesiemia (24).
Schlingmann et al. (26) reported 5 families (from Turkey, Sweden, Israel and Albania) with typical HSH, with seven different mutation of TRPM6. Walder et al. (24) described mutations of the gene in other seven families from Israel and Greece. In all cases symptoms were evident and severe in the first months of life.
There are no report in the literature on the evolution of the disease in surviving patients, except that of a 21 years old boy treated since 4 months (9): nocturnal enteral infusion of magnesium was necessary, due to chronic diarrhea with oral supplements, and latent tetany with reduced oral doses.
The observation that high dose magnesium intake p.o. in these patients does not allow a return to normal levels suggested the existence of two different and independent systems of intestinal transport. TRPM6 probably constitutes a moloecolar component of active transcellular transport of Mg^{++}; an increase in the intraluminal concentration leads to a partial compensation of the deficit of active transport, through the increase of passive, paracellular, transport.
The cause of hypocalcemia is not completely understood; in severe hypomagnesemia synthesis and/or secretion of PTH is decreased; indeed, PTH circulating levels are reported to be low in HSH patients (see Table I).
It has been also suggested a target organ resistance to PTH in chronic hypomagnesemia correlated to hypocalcemia (27), as

exogen PTH is not able to restore normocalcemia. Hypocalcemia improves in these patients only after supplementation with high doses of magnesium.

Conclusions

HSH represents the first human disorders attributable to a mutation of a 'channel-kinase', and the first disorder in which defects in magnesium absorption constitute the pathogenetic mechanism.
The recognition of the crucial role of TRPM6 for intestinal and renal Mg^{++} transport was driven by the clinical observation of patients affected by this rare disorder.
The clinical characteristics of the familiy described lead to the diagnosis of HSH; there are no reports of the disease in Italy.
The apparent progression of hypomagnesemia (as in the sons of the patients) and the delayed manifestation of severe symptoms have not been reported so far, thus suggesting different mutations with respect to those already identified.
Magnesium defects are largely unknown by clinicians and they are probably underestimated even in the emergengy settings, as is the case for the patient. The understanding of physiopathologic mechanisms of magnesium homeostasys should let to identification of different phenotypes and milder defects with possible higher frequence in the general population.

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