

CASE REPORT

Severe symptomatic hypomagnesaemia

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Abstract

Magnesium is an essential mineral for the human body and plays an important role in a variety of enzymatic processes. Disturbance of the plasma magnesium concentration can cause a range of cerebral, cardiac and muscular symptoms. We describe the case of a 69-year-old woman who presented to the Emergency Department because of a range of signs and symptoms, including confusion and disorientation. Laboratory examination revealed major electrolyte disturbances, in particular severe hypomagnesaemia.

In this case report we elaborate on the causes and consequences of hypomagnesaemia.

Introduction

Magnesium is an essential mineral for the human body. It plays an important role in many enzymatic processes, such as in the production of energy, and in DNA and protein synthesis. In addition, magnesium is of importance in nerve conduction and ion transport. It is predominantly present in bone and muscle tissue and only for a small percentage in the extracellular space.¹⁻³ Magnesium homeostasis is regulated by intestinal absorption and renal excretion.^{1,2}

Disruption of the equilibrium can be associated with a wide range of signs and symptoms. Mild hypomagnesaemia (< 0.7 mmol/l) is accompanied by mild symptoms such as apathy, nausea and vomiting. Severe hypomagnesaemia (< 0.5 mmol/l) may cause cerebral, cardiac and neuromuscular symptoms, such as a variety of cardiac arrhythmias, tetany, and even seizures.

Hypomagnesaemia can have a number of causes such as renal or gastrointestinal losses. In the past, a relation between the use of proton pump inhibitors (PPI) and hypomagnesaemia was described. In this article, the consequences of hypomagnesaemia, based on a case description, are illustrated.

Case

A 69-year-old woman presented to the Emergency Department (ED) because of headaches and dizziness, developing a few hours previously. The patient had recently been evaluated in the cardiology department because of a short episode of loss of consciousness in combination with complaints of fatigue for a longer period of time. Additional investigation by electrocardiography showed QT prolongation and negative T waves in all leads. However, cardiac catheterisation showed intact coronary arteries. During the following few days the QT interval normalised spontaneously, and the patient was discharged home. Her other medical history revealed a reconstruction of the anal sphincter and construction of a temporary colostomy because of a major postpartum injury of the rectovaginal septum approximately 30 years earlier. Furthermore, she had twice undergone a correction of ruptured scar tissue. Three years before admission a grade C/D oesophagitis based on a sliding hiatus hernia was detected and satisfactorily treated with a PPI. At presentation the patient's sole medication was pantoprazole 40 mg once a day.

As well as the headache and dizziness, she was now complaining of malaise and fatigue and, in addition, she was confused and disorientated in time, place and person. During a few days prior to admission she had had a decreased oral intake, in addition to diarrhoea for a few months. No other medical problems were present at the time of presentation.

On physical examination, the patient was restless and apparently in pain. Her blood pressure was 100/75 mmHg, with a pulse of 120 beats/min. The oxygen saturation was 97% at room air. She had a normal respiratory rate (16x/min) and no fever (37.1 °C). On auscultation prolonged expiration was heard with otherwise normal breathing sounds. The heart sounds were normal as well, without murmurs. Examination of the abdomen showed signs of several surgical procedures, and sparse peristalsis, but no other abnormalities.

Laboratory investigations (*table 1*) showed some electrolyte disturbances with severe hypomagnesaemia and hypocalcaemia, but also normokalaemia and a normal sodium concentration. Additional investigation by ECG again showed sinus tachycardia, prolonged QT intervals and negative T waves in all leads (*figure 1*). A chest X-ray showed no abnormalities.

The patient was initially admitted to the Internal Medicine ward. At that moment the plasma magnesium concentration was not yet known. Shortly after admission, the patient developed seizures with respiratory depression. Circulatory arrest occurred and basic life support (BLS) was immediately started. Upon arrival of the resuscitation team a sinus tachycardia was seen with cardiac output. However, respiration remained insufficient causing the need for intubation and artificial ventilation. In addition, at the time of the seizure, 4 g of magnesium sulphate was administered intravenously. Immediately thereafter, spontaneous and adequate respiration re-emerged. The patient was then transferred to the intensive care unit (ICU) where magnesium, calcium, and potassium were intravenously supplied as well.

Table 1. Laboratory data at presentation to the emergency department

	Patient A	Reference value
Haemoglobin (mmol/l)	7.2	7.5-10.0
Haematocrit (l/l)	0.34	0.35-0.45
C-reactive protein (mg/l)	20	< 10
Leukocytes (109/l)	14.2	4.0-10.0
Thrombocytes (109/l)	338	150-400
Urea (mmol/l)	4.1	2.9-7.5
Creatinine (μ mol/l)	67	50-90
Sodium (mmol/l)	140	135-145
Potassium (mmol/l)	3.6	3.5-5.0
Calcium (mmol/l)	1.49	2.20-2.65
Magnesium (mmol/l)	< 0.10	0.70-1.10
Phosphate (mmol/l)	1.34	0.90-1.50
Albumin (g/l)	32	31-46
25-OH vitamin D3 (nmol/l)	34	50-150
Parathormone (pmol/l)	4	1.0-7.0

Figure 1. ECG during presentation to the emergency department showing sinus tachycardia, prolonged QT intervals and negative T waves in all leads



The day after admission to the ICU, the plasma magnesium concentration had normalised (0.94 mmol/l) and the plasma calcium concentration had been partially corrected (1.66 mmol/l, with albumin 25 U/l). In the meantime, the clinical situation had greatly improved; the patient had become lucid and responsive. However, she was still hypotensive (81/33 mmHg) responding well to administration of additional crystalline intravenous fluids. The hypotension was assumed to be the consequence of dehydration and intravascular hypovolaemia due to severe and prolonged diarrhoea. The ECG showed a sinus rhythm with a prolonged QT interval and persistent negative T waves in all leads.

The results of a previously performed stool culture showed the growth of *Yersinia enterocolica* which was treated with ciproxin orally. The diarrhoea waned quickly.

After three days the patient was transferred to the cardiology ward in good clinical condition for analysis of the ECG abnormalities. Three days later, the ECG abnormalities spontaneously resolved: the QT interval normalised and the negative T waves disappeared. After another three days, the patient was again transferred to the internal ward for further treatment of the remaining electrolyte deficiencies. Finally, after a total of nine days, the patient could be discharged in good clinical condition.

Discussion

Magnesium plays a vital role in the human body, and is quantitatively the most important cation after potassium. Magnesium has several essential functions.^{1,2} It is mainly stored in bone and in intracellular compartments of muscle and connective tissue.¹⁻³ Magnesium homeostasis is regulated by intestinal absorption and renal excretion. Magnesium is present in chlorophyll-containing vegetables, grains, nuts, and dairy products in large concentrations.⁴ Absorption predominantly takes place in the small intestine, particularly in the jejunum and the ileum, and to a smaller extent in the colon. Absorption takes place by means of active transcellular transport through the TRPM-6 Mg channels and through passive transport as well.^{1-3,5} In the kidneys, 80% of the total plasma magnesium is filtered in the glomeruli, and more than 95% is reabsorbed in the tubuli.¹⁻³

The prevalence of hypomagnesaemia in the general population is high and is estimated to be between 2-15%. In the general hospital population, the estimated prevalence is even higher, up to 11%.⁶ Studies measuring the plasma magnesium concentration in patients presenting to the ED show that 2.5% have severe hypomagnesaemia (< 0.5 mmol/l).⁷ The incidence rises to as high as 60-65% in patients in an intensive care setting.^{1,2}

Hypomagnesaemia can have a variety of causes. Large renal magnesium losses caused by the use of medication (diuretics), acute tubular necrosis or tubulo-interstitial disease can be underlying problems. In addition there are extra-renal causes such as gastrointestinal loss or a low

intake of magnesium through the diet. Redistribution as a cause of hypomagnesaemia may result from, for example, pregnancy, or pancreatitis, and in addition, there may be an expansion of the extracellular volume by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyperthyroidism.^{1-3,9} Moreover, the use of PPI (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole) has been described as a cause of hypomagnesaemia in case reports and population studies.^{1,9-12} The best data originate from a large cohort of 11,490 patients admitted to the intensive care unit at a single centre.¹³ In this study, the relationship between PPI use and magnesium varied according to whether patients concurrently used diuretics. In patients taking diuretics, concurrent use of PPI was associated with lower adjusted serum magnesium. In addition, the prevalence of hypomagnesaemia (defined as a serum magnesium less than 0.66 mmol/l) was significantly higher in patients taking both drugs as compared with those who only used diuretics (15.6 vs. 11%). But in patients not taking diuretics, the use of PPI was not associated with the serum magnesium or the prevalence of hypomagnesaemia.

The mechanism by which PPI contributes to the development of hypomagnesaemia is not fully elucidated, but it is assumed to be related to a selective gastrointestinal malabsorption of magnesium, because of disturbance of active uptake through TRPM 6 magnesium channels.^{1,2,5} The patient described here had been using pantoprazole for a long time, but no diuretics. In the literature, a distinction is made between mild (0.5-0.7 mmol/l) and severe hypomagnesaemia (< 0.5 mmol/l). Usually, and to a certain extent, mild hypomagnesaemia is not accompanied by symptoms. However, occasionally mild symptoms as nausea, vomiting and apathy may occur. In contrast, severe hypomagnesaemia is usually accompanied by severe symptoms of cerebral, cardiac and neuromuscular nature, such as cardiac arrhythmias, tetany, and even seizures.^{1,2} In addition, severe hypomagnesaemia is often accompanied by other biochemical abnormalities, hypokalaemia, hypocalcaemia and / or metabolic acidosis.

Symptoms are divided into three groups: neuromuscular, cardiovascular and metabolic symptoms.

The neuromuscular symptoms include muscle weakness, apathy, paraesthesia, tetany, and vertical nystagmus. If combined with hypocalcaemia the Chvostek and Trousseau signs may be positive. ECG changes can develop due to a deficiency of intracellular magnesium and as a consequence of the dysfunction of the Na / K-ATPase pump, resulting in an intracellular potassium deficiency, which leads to a disruption of the resting potential and the repolarisation of myocardial cells. Hypomagnesaemia can consequently lead to a variety of atrial and ventricular arrhythmias.⁶

In the case we describe here, the plasma magnesium concentration was extremely low (< 0.10 mmol/l), which is very

rare in itself. Several factors may have added to this problem. The use of pantoprazole (however not in combination with diuretics) for a long period of time (three years) in combination with prolonged diarrhoea due to a *Yersinia* infection, or due to post-infectious lactose intolerance. In addition the colon resection she had undergone in the past could have added to the problem. Although the hypomagnesaemia in this case is probably due to problems on the 'absorption side', it should be stated that renal excretion of magnesium to exclude renal loss is not determined. In addition to hypomagnesaemia, also severe hypocalcaemia was present. The combination of the two disturbances is relatively common and is generally explained by inadequate parathyroid hormone secretion.⁵

One could argue that our patient initially should not have been admitted to the internal ward, but instead to the cardiology ward, because of the presence of a prolonged QT interval without diagnosis. However, the patient had recently undergone an extensive analysis at the cardiology department without a clear conclusion. The clinical signs and symptoms explained why admission to the internal ward was chosen.

Although protocols suggest treatment with 1 or 2 grams of magnesium sulphate intravenously, our patient was treated with 4 grams. Although we cannot explain this deviation from the protocol, the patient showed a swift recovery without apparent complications from the relatively high dose.

In summary, hypomagnesaemia is a highly prevalent problem. Its prevalence is underestimated due to the fact that it develops slowly, often has a long latency period (using proton pump inhibitors) and induces no or mild symptoms. Therefore, in patients with a combination of cardiac, cerebral and neurological symptoms, hypomagnesaemia should have a prominent position in the differential diagnosis. During prolonged use of PPI the plasma concentration of magnesium should be evaluated regularly. Because hypomagnesaemia is often accompanied by other electrolyte disturbances, those should be evaluated too. Conversely, one could defend the need for evaluating the plasma magnesium concentration in cases of hypokalaemia and/or hypocalcaemia is detected.

This case illustrates how a simple treatment such as suppletion of magnesium can result in marked and swift clinical improvement.

Conclusion

It is important to evaluate electrolyte concentrations, in particular the plasma calcium and magnesium concentrations in patients with unexplained symptoms of confusion, and/ or with unexplained ECG abnormalities, since adequate treatment can result in swift clinical improvement.

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