Clinical case

doi: http://dx.doi.org/10.22265/acnef.7.1.338

Magnesium depletion secondary to hypercalcemic nephropathy during pregnancy: Case report and literature review.

Depleción corporal de magnesio durante el embarazo por nefropatía hipercalcemica. Reporte de caso y revisión de la literatura

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Abstract

Serum magnesium is the «forgotten ion» in medical practice. Most of the times it is not taken into account in clinical studies, its alterations tend to be ignored and its therapeutic approach is not well defined. The symptomatology produced by hypomagnesemia is nonspecific and its diagnostic approach is complex. We present the case of a pregnant patient with symptomatic hypomagnesemia secondary to renal damage due to hypercalcemia.

Keywords: hyperparathyroidism, hypercalcemic nephropathy, nephrogenic diabetes insipidus, pregnancy, hypomagnesemia.

doi:http://dx.doi.org/10.22265/acnef.7.1.338

Resumen

El magnesio sérico es el "ion olvidado" en la práctica médica: la mayoría de veces no se tiene en cuenta en los estudios clínicos, sus alteraciones tienden a ser ignoradas y su aproximación terapéutica no está definida de forma adecuada. La sintomatología producto de la hipomagnesemia es inespecífica y su aproximación diagnostica es compleja. Se presenta el caso de una paciente con hipomagnesemia sintomática severa asociada a daño renal por hipercalcemia durante la gestación.

Palabras clave: hiperparatiroidismo, nefropatía hipercalcemica, diabetes insípida nefrogénica, embarazo, hipomagnesemia.

doi:http://dx.doi.org/10.22265/acnef.7.1.338

Citation: García Habeych JM, Pradilla Suárez LP, Castellanos Bueno R. Depleción corporal de magnesio durante el embarazo debido a nefropatía hipercalcemica: Reporte de caso y revisión de la literatura. Rev. Colomb. Nefrol. 2020;7(1):121-129. https://doi.org/10.22265/acnef.7.1.338

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Received: 14.06.19 • **Accepted:** 19.06.19 • **Published Online:** 8.02.19

http://dx.doi.org/10.22265/acnef.7.1.338

Introduction

Hypercalcemia is a frequent electrolyte disturbance that usually arises due to cancer or alterations in parathyroid hormone.[1,2] In acute or chronic presentations, it affects the renal concentrating ability, being a reversible cause of diabetes insípida.[2,3] Primary hyperparathyroidism is the third most frequent endocrine disorder in the general population.[4]

Magnesium, unlike calcium, can be considered as the «forgotten ion»; this is due to the infrequency with which alterations in its serum concentration are investigated in clinical practice[5] or to the number of articles published regarding the other electrolytes.[6] Hypomagnesemia is observed in 10% of hospitalized patients,[7] being often asymptomatic or with manifestations overshadowed by alterations of other electrolytes[7,8]; its main etiology are kidney losses associated with increased glomerular filtration, polyuria, decreased tubular absorption of magnesium and hypercalcemia.[7,9]

Below we present the case of a young pregnant woman who presented neuromuscular symptoms due to body depletion of magnesium secondary to hypercalcemic nephropathy due to primary hyperparathyroidism which required surgery and chronic oral magnesium oxide replacement, with which the correction of the symptoms and resolution of the electrolyte disorder were achieved.

Case presentation

A 24-year-old female patient, 27.4 weeks pregnant without prenatal controls at the time of admission, consulted for a process of tachycardia and chest pain of one month of evolution. The woman was assessed by the obstetrics service, where it was performed an electrocardiogram, which evidenced a sinus rhythm; the medical history, the physical examination and the tests did not suggest an infectious process, which is why a concept from internal medicine was requested.

As an obstetric antecedent, the patient stated that she had had two pregnancies that required cesarean section due to persistent tachycardia during pregnancy, although these episodes occurred suddenly and were self-limited during the last six years. The woman reported intermittent low back pain with a finding of left renal lithiasis of 5 mm in outpatient ultrasound scan, and a bowel habit every four days for four years despite the consumption of a high-fiber diet.

In the initial assessment by internal medicine, the electrocardiogram confirmed sinus tachycardia associated with a short QT interval, and for this reason an electrolyte disorder was suspected. The laboratories confirmed hypercalcemia of 16.5 mg/dL (calcium corrected for albumin, reference value [RV] 8.2-10.4 mg/dL) and hypophosphatemia (Table 1 and Figure 1A). A study of hypercalcemia was started with a report of intact parathyroid hormone (iPTH) of 524 pg/mL (RV 16-46 pg/mL) and 24-hour urine calcium of 1066 mg with a urine volume of 7,085 mL, which configured the diagnosis of primary hyperparathyroidism. Treatment with intravenous crystalloids, prednisone, and furosemide was indicated due to the limitation for the use of bisphosphonates during pregnancy and the unavailability of calcitonin. The nephrology service proposed to perform hemodialysis to reduce the serum calcium levels and be able to control the polyuria and reduce the cardiovascular and fetal toxic effects, prior to the parathyroidectomy.

On the fifth day of hospital stay, the patient persisted with severely elevated calcium despite two hemodialysis sessions and pharmacological management (Figure 1A), therefore, a cervical surgical exploration procedure was performed, with a finding of a parathyroid mass dependent of the right lower lobe of the thyroid, requiring a right partial thyroidectomy with a subsequent pathology report of parathyroid adenoma. The surgical procedure had no maternal or fetal complications and allowed the discontinuation of hemodialysis and the withdrawal of pharmacological management for hypercalcemia. 24 hours after the procedure, an iPTH control test was performed, with a result of 7.63 pg/mL. On the sixth day of hospitalization, the woman presented abnormal uterine activity, associated with hypomagnesemia of 1.0 mg/dL (RV: 1.6-2.6 mg/dL), and the

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Table 1. Reference laboratories during hospitalizations.

Test		First hospitalization		Second hospitalization	
		Entry	Egress	Entry	Egress
Serum/Blood.	Sodium (135-145 mEq/L)	134	138	134	137
	Potassium (3,5-4,5 mEq/L)	4,2	4,2	3,8	4,1
	Calcium corrected for albumin (8.2-10.4 mg/dL)	15	9,3	8,8	10,5
	Magnesium 1.6-2.6 mg/dL)	0,7	2,8	1	2,4
	Creatinine (0.5-0.95 mg/dL)	0,8	0,8	0,7	0,6
	Urea nitrogen (8-23 mg/dL)	13,7	15	12,8	15,6
	Osmolality * (275-300 mOsm/kg)	276			
	iPTH (16-46 pg/mL)	524	7,6	57	60,4
	Vitamin D25 (>30 ng/mL)	27,6			
Urine.	Urinalysis	pH: 6.5; density: 1.015. Negative red blood cells, leukocytes. Calcium oxalate crystals.		pH: 6.5; density: 1.010. Negative red blood cells, leukocytes, proteins.	
	Osmolality ** (390-1093 mOsm/kg)	525		350	
	24-hour volume (600-1600 mL/24h)	7085	3720		
	24 hours calciuria (<250 mg/24 h)	1066	84,4		
	Spot urine calcium (mg/dL)	15	2,27		
	Spot urine creatinine (mg/dL)	16,3		35	
	Spot urine calcium/creatinine ratio(<0.2 mg/mg)	0,92			
	Spot urine magnesium (mg/dL)			20	
	FeMg (%)			37	

* Calculated serum osmolality: 2Na+(Glucose/18)+BUN/2.8.
** Calculated urine osmolality: (Urine density of the patient - 1000)*35.
iPTH: intact parathyroid hormo

obstetrics service indicated intravenous infusion of magnesium 2 g per hour for 24 hours. On the eighth day, hospital discharge was authorized with oral calcium and vitamin D supplementation.

After 14 days of hospital discharge, the patient consulted again due to generalized muscle weakness, walking difficulty and facial paresthesias of four days of evolution. In the emergency service, the woman who was 30 weeks pregnant, presented normal vital signs, but bilateral palpebral ptosis and generalized hyperreflexia associated with positive Trousseau's sign at 90 seconds. A diagnostic impression of hypocalcemia due to the antecedent of partial thyroidectomy with resection of parathyroid adenoma was made and intravenous calcium replacement was started after obtaining samples for laboratory testing. The results ruled out hypocalcemia and evidenced a calcium corrected for albumin of 8.8 mg/dL and severe hypomagnesemia of 1.0 mg/dL, for this reason, a concept of the endocrinology service was requested, which indicated infusion with intravenous magnesium sulfate 1 g every hour (Table 1). A collection of magnesium in spontaneous urine

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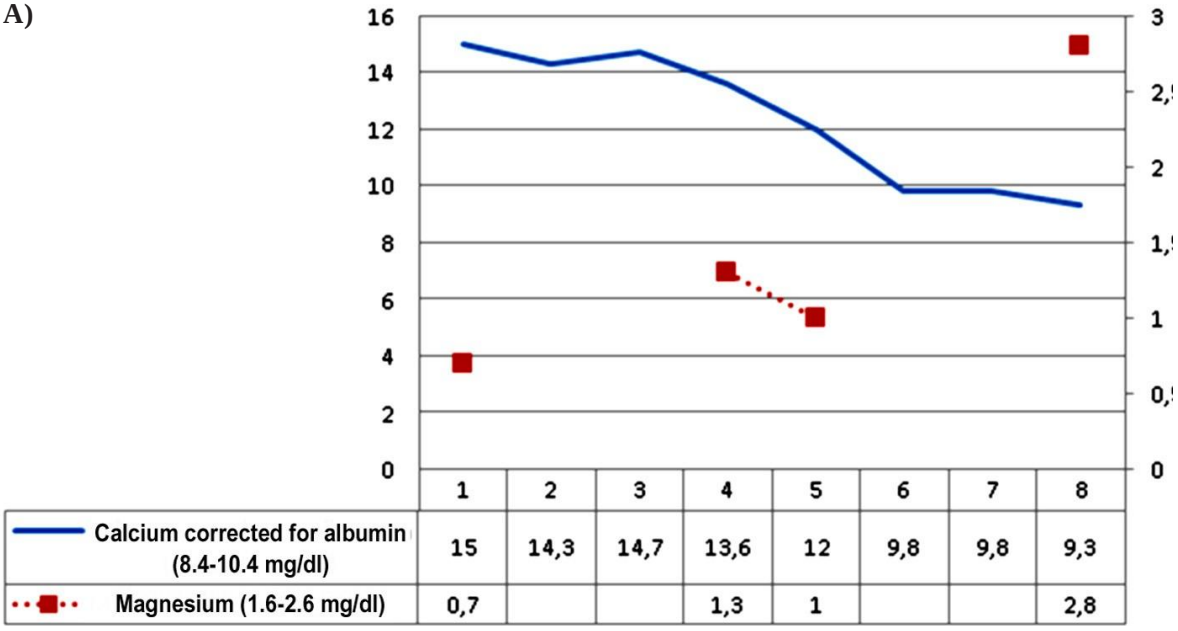
A)



B)

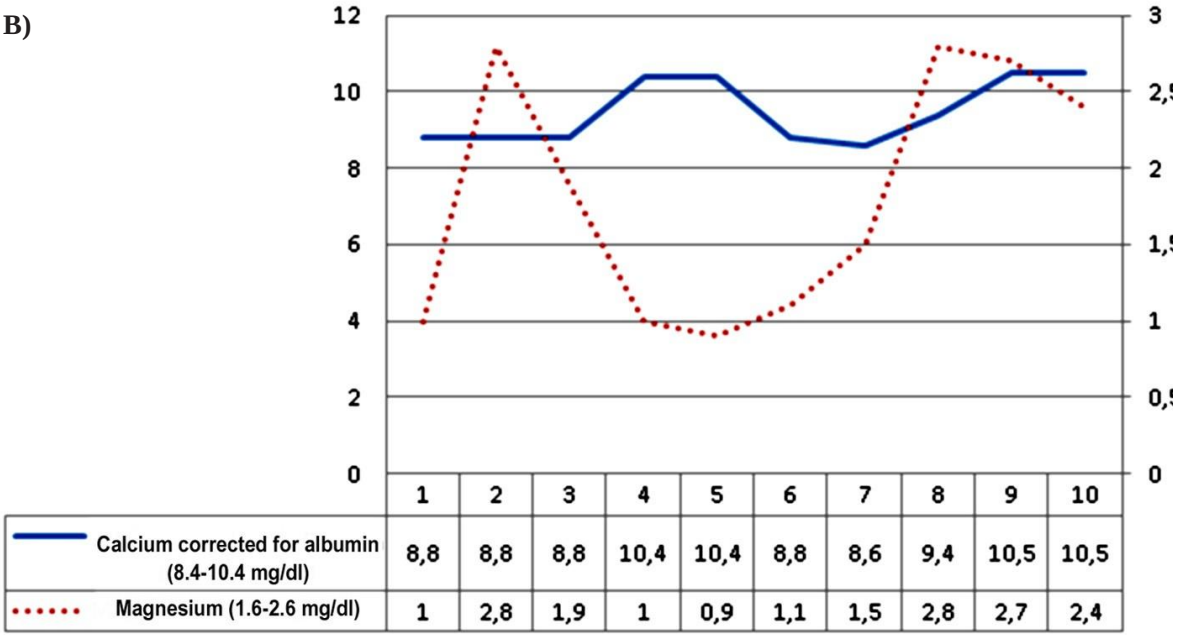


Figure 1. A) Electrolyte profile with calcium corrected for albumin and magnesium during the first hospitalization. **B)** Electrolyte profile with calcium corrected for albumin and magnesium during the second hospitalization. Source: Own elaboration

was made, which confirmed renal losses by a fractional excretion of magnesium (FeMg) of 37%.

The patient was admitted to the intensive care unit to be continuously monitored for the risk of ventilatory failure with an infusion of magnesium sulfate 24 g/day. On the second day of the new hospital stay, her serum magnesium levels were corrected (Figure 1B) with resolution of the palpebral ptosis, normalization of the osteotendinous

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reflexes and positive Trousseau's sign at 2:20 minutes.

After five days of intravenous supplementation of magnesium sulfate, the hypomagnesemia was corrected, and having a negative Trousseau's sign at five minutes, progressive withdrawal of the replacement was started, until leaving an infusion of magnesium sulfate of 6 g/day. Due to the dependence of magnesium supplementation, magnesium oxide was prescribed in one capsule of 50 mg of elemental magnesium orally per day (Figure 2), with which it was possible to achieve normal serum magnesium levels and absence of neurological symptoms on the tenth day of hospital stay, and the infusion was withdrawn. The patient was discharged from the hospital with oral supplementation of magnesium oxide, calcium carbonate, calcitriol and vitamin D25.

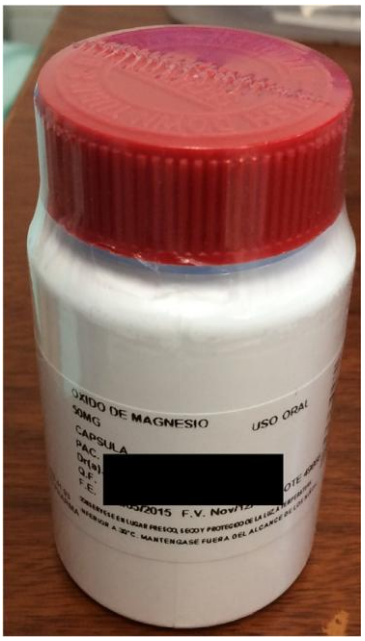

Figure 2. Presentation of Magnesium Oxide. Photograph of the bottle indicated for outpatient oral magnesium supplementation. Source: Original photograph of the author.

Discussion

Calcium and magnesium are essential minerals for multiple physiological processes in humans[9,10] and their serum concentrations are a poor reflection of the body deposits: only 0.1% of calcium and 1% of the total magnesium are present in the extracellular fluid.[9] Physiological changes associated with pregnancy, such as renal hyperfiltration and dilution of serum albumin, can affect the interpretation of the measurement of these electrolytes in serum[4,11]; in addition, due to their nonspecificity, the symptoms resulting from the alteration of the body concentration can be overshadowed or confused.[4,10,11] It is also important to mention that the clinical practice guidelines do not require the evaluation of serum calcium during pregnancy[4] and physicians rarely request the measurement of serum magnesium during the study of patients.[5]

Primary hyperparathyroidism has a prevalence between 0.4% and 1.4% in the general population, but in the case of pregnant patients the incidence is unknown, with less than 200 cases reported.[4] The detection and correction of hypercalcemia during pregnancy are of utmost importance, since it can cause maternal mortality of up to 30% associated with neonatal complications.[4,11,12] Due to the limitation of pharmacological options for treatment, in the present case the use of hemodialysis prior to partial parathyroidectomy was necessary; it was also interesting the renal involvement manifested by polyuria syndrome with preserved urine osmolality (Table 1).

Diabetes insipidus during pregnancy has a prevalence of 4 cases per 100,000 pregnancies.[13] In the case of nephrogenic diabetes insipidus, the ability to produce hypertonic urine is usually preserved, despite the alteration in the maximum urine concentrating ability[14]; it is usually acquired and its etiologies include hypercalcemia,[13,14] which both in acute and chronic elevations can alter the expression of aquaporins in the collecting tubule and in the Na-K-2Cl (NKCC2) pump in the thick ascending limb of the loop of Henle.[2,3] Neurogenic diabetes insipidus is reversible with the correction of serum calcium levels, however, it has not been described in the literature how long it may take the normalization of renal tubular functions.

The hypomagnesemia was documented since the first admission to the hospital (Table 1), but only until

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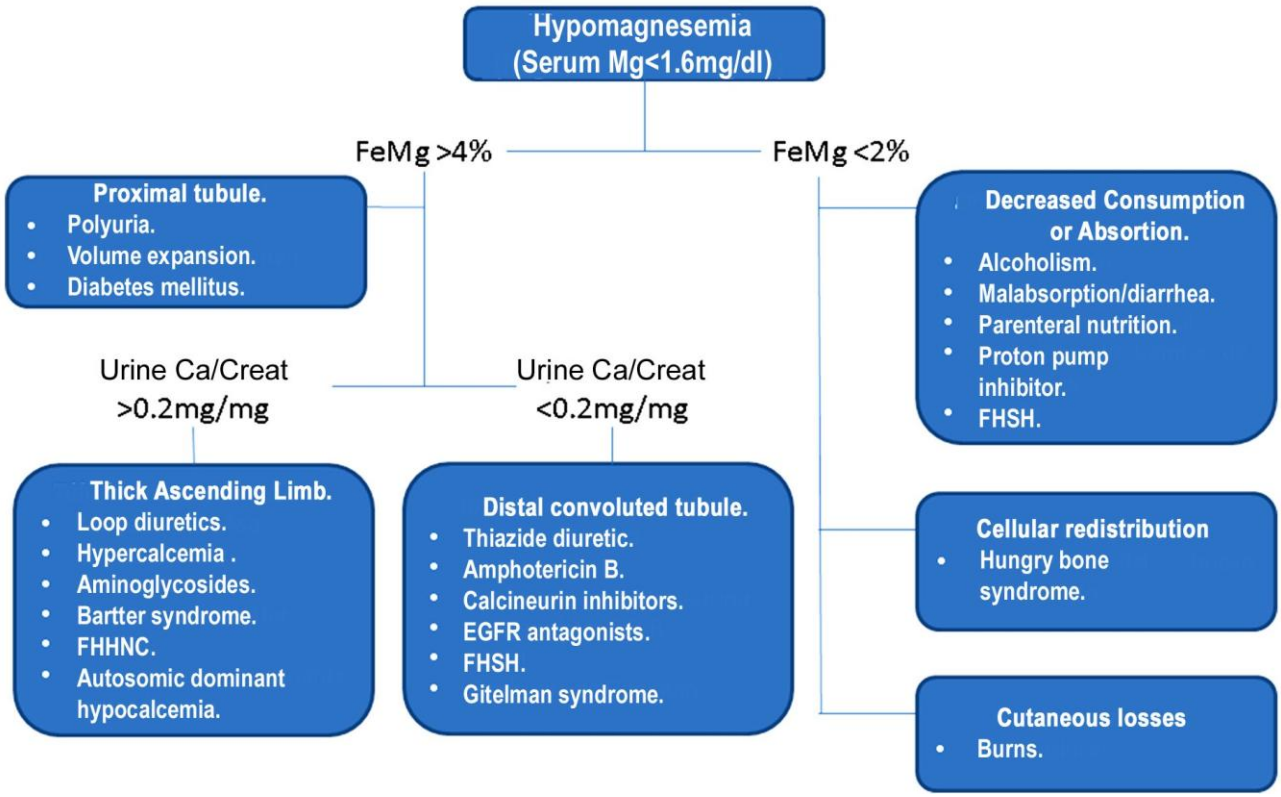
it was symptomatic it was considered a problem that required etiological diagnosis and treatment.

Magnesium is usually overlooked in clinical practice, as reported by Whang & Ryder,[5] who conducted, in an observational study, an active screening for the presence of hypomagnesemia in serum samples in which electrolyte alterations were investigated; of the 1,033 samples analyzed by the authors, only in 8.7% the treating physician requested serum magnesium levels, despite the fact that 53% of the total had hypomagnesemia.[5] Since other methods that evaluate the total body magnesium are only experimental, the magnesium levels are assessed by measuring of the total or ionized serum magnesium, being the total measurement the main method.[15]

The diagnostic approach to the patient with hypomagnesemia lies in differentiating intestinal absorption disorders from renal losses,[7,9] which can be performed by measuring the FeMg and the random urinary calcium/creatinine ratio.[6,8] (Figure 3) The reported patient had a FeMg >4%, a figure that in a subject with normal renal function indicates renal magnesium losses,[16] and a calcium/creatinine ratio in spontaneous urine >0.2mg/mg, indicating hypercalciuria and dysfunction of the thick ascending tubule of the Loop of Henle,[2,6,8,9,17] and a lesion secondary to hypercalcemic nephropathy.[2,3]

The symptoms of hypomagnesemia are mainly manifested when the values are <1.2 mg/dL[8,15] and are characterized by muscle weakness and excitability of the nervous system (Trousseau´s sign, Chevostek sign and tetany).[18] However, the manifestations can be overshadowed by those of other associated electrolyte disorders such as hypokalemia (10%), hyponatremia (6%) and hypocalcemia (Not reported).[5]



Mg: magnesium; FeMG: fractional excretion of magnesium; urine Ca/Creat: spot urine calcium/creatinine ratio; FHSH: familial hypomagnesemia with secondary hypocalcemia; FHHNC: familial hypomagnesemia with hypercalciuria and nephrocalcinosis; EGFR: epithelial growth factor receptor.

Figure 3. Diagnostic flowchart for hypomagnesemia. Source: Own elaboration.

Although the initial presentation of the reported clinical case was the association of hypomagnesemia with hypercalcemia, which was not observed in two studies that analyzed the biochemical alterations along with serum magnesium disorders.[5,19] In the research conducted by Ahmad *et al.*,[1] the symptoms of hypomagnesemia appeared after the correction of the hypercalcemia, being associated with depression of the central nervous system. When trying to compare the clinical presentation of the patient, we found two case reports of women with hypomagnesemia and hypercalcemia secondary to hyperparathyroidism, but with hypokalemia and metabolic alkalosis due to Gitelman syndrome[20,21]; the reported patient did not present hypokalemic metabolic alkalosis (Table 1), in addition, neurological findings were not reported in these cases.

In the same way, it is important to highlight the association between serum magnesium levels and iPTH secretion, since extreme variations in the concentration of the former can dramatically affect the secretion of the latter,[22] being that chronic hypomagnesemia is associated with a reduction in the secretion of iPTH when developing functional hypoparathyroidism and hypocalcemia.[22]

Nevertheless, in the present case, despite the hypomagnesemia, the iPTH levels were elevated at the beginning due to the parathyroid adenoma and decreased after the parathyroidectomy (Table 1 and Figure 1A). In this way, its elevation with normal serum calcium levels was documented again in the second hospitalization and its rise with the correction of the magnesium deficiency. Due to the pregnancy status of the patient, it was not possible to perform a parathyroid gland scintigraphy to rule out whether she had more than one parathyroid adenoma, present in up to 1- 15% of cases of hyperparathyroidism.[23] The patient developed a tertiary hyperparathyroidism by generating a sustained response of secretion of iPTH despite the hypomagnesemia and the vitamin D25 deficiency (Table 1). Unfortunately, this doubt could not be clarified given that after pregnancy the woman did not continue with the medical controls.

The treatment of hypomagnesemia is complex, since, except for specific clinical indications (pre-eclampsia/eclampsia and cardiovascular surgery), there are no clinical studies that guide its correction.[15,24] The recommendation in symptomatic patients without ventricular arrhythmia is to administer 8-12 g of magnesium sulfate in the first 24 hours and continue at 4-6 g per day for three days until the body deficit is replaced.[24]

It should be highlighted that the presented patient required up to 24 g of magnesium sulfate per day and after six days of infusion, she presented decreases when it was discontinued. The intravenous magnesium reposition is slow to balance with the tissue deposits[8,24] and normal serum levels do not indicate a replenishment of the deposits,[24] which is why oral supplementation of magnesium salts is recommended in patients that are already asymptomatic. Although the literature refers multiple options in the market,[6,24] in the present case it was necessary to get a pharmaceutical laboratory that prepared the capsules of magnesium oxide to ensure the withdrawal of the intravenous supplementation.

Conclusion

Hypomagnesemia is a frequent electrolyte disorder, but ignored by physicians, that has significant systemic repercussions. Although there is no scientific evidence on its treatment, the adequate diagnostic approach allows a rapid correction and prevention of complications. In this sense, in this case we must highlight the presence of hypercalcemia due to hyperparathyroidism with damage of renal tubular function and hypercalcemic nephropathy that generated depletion of body magnesium which required oral supplementation to achieve hospital discharge.

Acknowledgments

None declared by the authors.

Conflict of interest

None declared by the authors.

http://dx.doi.org/10.22265/acnef.7.1.338

Contribution of the authors

The clinical case was initially treated by the internist José García Habeych, who during the clinical research requested a concept from the Endocrinology service, where doctors Lina Pradilla and Rafael Castellanos assisted to guide the etiological study.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

The authors declare that they have followed the protocols of their workplace on the publication of patient data.

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

Funding

None declared by the authors.

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