

The relative frequency of hypomagnesemia in outpatients with chronic airflow limitation treated at a referral center in the north of the state of Paraná, Brazil*

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ABSTRACT

Objective: To determine the relative frequency of hypomagnesemia among patients with chronic airflow limitation treated as outpatients at a referral center in the northern part of the state of Paraná between 2000 and 2001, as well as to determine whether hypomagnesemia correlates with hypoxia, with other electrolyte disturbances and with the severity of airflow limitation. **Methods:** This was a descriptive study of the relative frequency of hypomagnesemia in 72 patients with chronic airflow limitation. All of the patients were submitted to blood tests to determine serum levels of magnesium and other electrolytes, as well as to staging of the underlying disease. **Results:** The prevalence of hypomagnesemia was 27.8%. The mean age was 65 ± 9.9 years, and there was a predominance of males. The mean forced expiratory volume in one second was 1.31 ± 0.52 L. Most of the patients (68.1%) were found to be in the advanced stages of the disease. Hypomagnesemia was not found to correlate with other electrolyte disturbances, hypoxemia or disease stage. **Conclusion:** The high frequency of patients in the advanced stages is likely attributable to the fact that the outpatient facility is a referral center for the region. Further studies should be conducted in order to determine the probable causes of this high prevalence of hypomagnesemia.

Keywords: Magnesium/blood; Pulmonary ventilation; Pulmonary disease, chronic obstructive; Respiratory insufficiency

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Submitted: 26 March 2005. Accepted, after review: 26 October 2005.

INTRODUCTION

Magnesium (Mg) is the fourth most abundant ion in the body and the second most abundant intracellular cation.⁽¹⁾ It is important to several stages of cellular metabolism, such as energy production through activation of the ATPase transporting enzymes, and directly influences tonus, muscle contraction, and cardiac excitability.⁽²⁾ There is no consensus in the literature regarding the normal serum Mg concentration, and, since it is mostly located within cells, serum Mg levels in isolation may not reflect the total amount of this ion in the body.⁽²⁻⁴⁾

Hypomagnesemia is the electrolyte disturbance most commonly found in hospitalized patients presenting chronic diseases such as cerebral vascular accident, ischemic heart disease, arterial hypertension, diabetes mellitus, atherosclerotic disease, and bronchial asthma.⁽⁵⁾ In these diseases, hypomagnesemia is usually concomitant with other disorders such as hypokalemia, hypophosphatemia, hyponatremia, and hypocalcemia.^(1,6-7)

The exacerbation of the respiratory failure in cases of chronic airflow limitation (CAL) can be triggered by infection, cardiovascular decompensation, pneumothorax, or pulmonary thromboembolism. Hypoxemia, which occurs in these situations, is reported to induce depletion of intracellular Mg ions.⁽⁸⁾ Since the Mg ion is involved in muscle contraction and in the maintenance of muscle tonus, a reduction in Mg ion levels in patients with CAL might represent one more factor that is detrimental to respiratory function or to the recovery of such function, since low levels of Mg induce muscle fatigue.

Therefore, the objective of the present study was to determine the relative frequency of hypomagnesemia among patients with CAL, as well as to determine whether Mg ion depletion is associated with hypoxia, with other electrolyte disturbances, and with the severity of airflow limitation.

METHODS

The present study was developed at the Pulmonology Clinic of the Hospital das Clínicas da Universidade Estadual de Londrina (HC/UEL, Londrina State University Hospital das Clínicas), which is an integral part of the Northern Paraná Regional University Hospital and serves the entire state of Paraná, together with the southern regions of the states of Mato Grosso

do Sul and São Paulo, as well as neighboring countries.

The objective of the present study was to carry out a cross-sectional study, using a convenience sample, with the aim of determining the prevalence of hypomagnesemia among patients with CAL. The frequency of this disorder among the general population is estimated to be 10%. Our hypothesis is that, in patients with CAL, the prevalence is twice as high. Therefore, using an alpha of 0.05% and a sampling error of 0.10%, the sample size calculated was 61 patients.

We evaluated all of the patients with CAL, diagnosed according to the criteria established by the Brazilian Society of Pulmonology and Phthysiology,⁽⁹⁾ who were treated at the HC/UEL between January 1, 2000 and December 31, 2001, who presented pulmonary alterations (functional, radiological, or both), and who agreed to participate in the study.

We excluded all patients presenting conditions known to cause hypomagnesemia: using antibiotics, gastric acid inhibitors (H1-receptor blockers or proton pump inhibitors), thiazide diuretics, loop diuretics, digoxin or insulin; presenting left cardiac insufficiency confirmed through echocardiogram; having had gastrointestinal surgery or other major surgery; suffering from malnutrition or having been submitted to enteral or parenteral feeding within the preceding year; and having a history of chronic alcoholism.

The research protocol for each of the patients was completed by the researcher and the research team. The following data were recorded: demographic and epidemiological data; clinical history in search of signs associated with hypomagnesemia (apathy, depression, arrhythmias, hypertension, convulsions, tremors, and headaches); data from the cardiovascular and pulmonary physical examination; medications used within the past 30 days; and history of the last hospitalization.

After the research instrument had been completed, the treatments were optimized, and the patients returned within three weeks in order to undergo laboratory tests: blood workup, urea, creatinine, sodium, potassium, magnesium, phosphate, total proteins, protein fractions, and arterial blood gas analysis. Creatinine levels were determined in order to rule out renal disorders that might have been overlooked during the collection of histories. Albumin levels, as well as lymphocyte levels, were determined in order to rule out nutritional alterations in these

patients. All of the tests were carried out within the first month after the medical appointment, and in accordance with internationally accepted criteria. Electrolyte and blood gas levels were considered depressed when the values found were below the lower limit of the reference range.

Complete pulmonary function tests and chest X-rays were requested for patients who had not had such tests within the last six months, as well as for those who presented acute exacerbation of chronic bronchitis or who had been hospitalized within the last 60 days.

All of the ventilatory tests were carried out by a licensed professional working in the respiratory therapy sector of the HC/UEL. The techniques used to perform the exams, as well as the reference values, were in accordance with the recommendations of the American Thoracic Society.⁽¹⁰⁾ The functional tests were judged to present an obstructive pattern when the ratio between forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) was below 90% of predicted, being classified as: mild ($FEV_1 > 60\%$), moderate (FEV_1 between 41% and 59%) or severe obstructive ($FEV_1 = 40\%$), whether concomitant with a reduction in forced vital capacity or not.⁽⁹⁾

Chest X-rays were analyzed by the researcher in order to identify the following: hypodense, hyperdense, focal, or diffuse lesions; interstitial patterns; and signs of pulmonary hyperinflation. Only the patients with an $FEV_1 < 40\%$ or with intense dyspnea were submitted to arterial blood gas analysis. All of the reference values were in accordance with international criteria.

Data analysis was performed using the Epi Info program, version 6.01, developed by the Centers for Disease Control. Descriptive data are presented in tables. The Student's t-test was used to compare the means between two groups of variables. The chi-square test was used to compare categorical variables between two groups.

The study design was approved by the HC/UEL Ethics in Research Committee.

RESULTS

The sample studied comprised 72 patients. Of those, 43 (59.7%) were male, and the mean age was 65 ± 10 years. Table 1 shows the demographic and epidemiological variables.

TABLE 1

Epidemiological and demographic characteristics of the patients with chronic airflow limitation treated at the Londrina State University *Hospital das Clínicas* between 2000 and 2001

Variable	Characteristics	
	Number	%
Gender		
Male	43	59.7
Female	29	40.3
Race		
White	69	95.8
Non-White	3	4.6
Current smoking		
Present	17	23.6
Absent	55	76.4
Smoking habit		
Never smoked	13	23.6
Have smoked	42	76.4
Origin/residence		
Rural zone	1	1.4
Urban zone	71	98.6
Most common symptoms		
Dyspnea	59	81.9
Cough	10	13.9
Chest pain	3	4.2

In the physical examination, 62 patients (86.1%) presented alterations upon lung auscultation. All of the alterations were bilateral. The following were the most common predominant alterations: reduced breath sounds (50.7%); ronchi/rales (27.4%); and expiratory wheezing (21.7%). Most of the patients (63%) presented radiological signs of hyperinflation.

Regarding the clinical diagnosis of the underlying disease, 19 patients (26.5%) presented severe asthma, 40 (55.6%) presented chronic bronchitis, and 13 (18.1%) presented emphysema. Clinical staging of these patients based on disease severity revealed 23 patients (31.9%) to be in stage I (mild), 23 (31.9%) to be in stage II (moderate), and 26 (36.1%) to be in stage III (severe).

All of the patients presented an FEV_1/FVC ratio below 90% of predicted. The mean ratio was 65.3% of predicted, with a standard deviation of 18.2%. Twenty-two patients (30.6%) presented positive bronchodilator test results, which were characterized by a functional improvement of 12%, 200 mL, or both in FEV_1 after the use of 200 μ g of salbutamol spray (Table 2).

The electrolyte disturbance most commonly

TABLE 2

Spirometric characteristics of the patients with chronic airflow limitation treated at the Londrina State University *Hospital das Clínicas* between 2000 and 2001

Variable	Values	
	Number	%
Pre-BD FEV ₁ (Mean = 1.13 ± 0.52 L)		
% of predicted		
< 40	26	36.1
41 - 59	21	29.2
> 60	25	34.7
FVC (Mean = 2.07 ± 0.79 L)		
% of predicted		
< 40	7	9.7
41 - 59	11	15.3
> 60	55	75.0
BD response		
Positive	22	30.6
Negative	50	69.4

FEV₁: forced expiratory volume in one second;

BD: bronchodilator; FVC: forced vital capacity

found was hypocalcemia, being present in 37 patients (52.3%). Hypomagnesemia was found in 20 patients (27.8%). The mean serum level of Mg was 1.80 ± 0.18 mEq/L, which is close to the lower limit of the range of normality for this ion (1.8 to 2.2 mEq/L). Hypoxemia was observed in 50 patients (69.4%). Table 3 shows the electrolyte and arterial

TABLE 3

Electrolyte disturbances and blood gas changes found in the patients with chronic airflow limitation treated at the Londrina State University *Hospital das Clínicas* between 2000 and 2001

Variables	Values	
	Number	%
Electrolyte disturbances		
Hypocalcemia (Ca < 8.5 mg/dL)	37	52,3
Hypomagnesemia (Mg < 1.8 mEq/L)	15	27,8
Hypokalemia (K < 3.5 mEq/L)	3	4,2
Hyponatremia (Na < 135 mEq/L)	2	2,8
Blood gas changes		
Hypoxia (PaO ₂ < 80 mmHg)	50	69,4
Hypercapnia (PaCO ₂ > 45 mmHg)	19	26,4

Ca: calcium; Mg: magnesium; K: potassium; Na: sodium; PaO₂: arterial oxygen pressure; PaCO₂: arterial carbon dioxide tension

blood gas changes observed. Phosphate levels could not be analyzed due to the lack of reagents. Albumin levels were within the reference ranges in all of the patients.

None of the patients presented any sign or symptom that could be related to altered Mg levels.

In the univariate analysis, which was aimed at identifying possible associations with the Mg deficit, gender was the only parameter found to present a statistically significant difference. Ion levels were lower in male patients (p = 0.034). We found no association with electrolyte disturbances, arterial blood gas changes, or severity of the underlying disease.

DISCUSSION

The relative frequency of hypomagnesemia found in the present study was 27.8%, which is much higher than that reported in the medical literature.

The mean age of the patients in the present study was 65 years, and there was predominance of males (60%) and Whites (95.8%). Studies that evaluated similar population samples in North America⁽¹¹⁾ and in Brazil⁽¹²⁾ found the same epidemiological characteristics. There was predominance of patients from urban zones (98.6%), which is logical based on the distribution of the population seeking treatment at the HC/UEL outpatient facility. Most of the patients were smokers (76.4%), which is a very common finding among patients with CAL.⁽¹¹⁻¹³⁾

Dyspnea (81.9%) was the predominant symptom, followed by cough (13.9%) and chest pain (4.2%). The predominance of dyspnea indicates that the population studied comprised more severe cases, since dyspnea principally occurs in individuals over the age of sixty and is related to the degree of disease severity.⁽¹³⁾ Some authors,⁽¹²⁾ studying a population sample consisting of individuals in a similar age group and presenting similar disease severity, also demonstrated that dyspnea was the most common symptom. The predominance of reduced breath sounds during the physical examination (observed in 50.7% of the cases evaluated in the present study) has also been found by other authors.⁽¹¹⁾ A high rate of wheezing (21.7% in the present study) was also described in another study, in which

18.5% of the patients studied had a history of bronchial asthma.

In the present study, the FEV₁/FVC ratio was below 90% in all of the patients, with a mean of 65.3% of predicted, and the mean postbronchodilator FEV₁ was 1.10 L, with a standard deviation of 0.49 L. Some authors,⁽¹²⁾ studying a similar sample, also demonstrated similar means. The only divergent spirometric value between the present study and the above-mentioned study was the number of positive bronchodilator test results. In the present study,⁽¹⁴⁾ 22 patients (30.60%) presented positive bronchodilator test results (200 mL or 12% of variation), compared with only 5.7% in the above-mentioned study. Despite this divergence regarding the positive response to the bronchodilator, all of the patients of the present study presented FEV₁ values below 70% after the bronchodilator test. In another study analyzing 22 patients with CAL, a mean FEV₁ of 0.9 L or 38% of predicted was also found. In a book on respiratory medicine, it was stated that up to 30% of patients with CAL present a positive bronchodilator response. These data can be compared because the present study used criteria for definition and diagnosis that were the same as those cited by the authors in their book.

We observed that most of the patients in the present study were classified as being in more severe stages (stages 2, 3, or 4). This occurred because the HC/UEL outpatient facility is a tertiary-care referral center. Therefore, the cases treated there are quite complex.

The following was the distribution of underlying diseases that caused the chronic airflow limitation: asthma (in 24.4%); chronic bronchitis (in 55.6%); and emphysema (in 18.1%). In a review article, the conclusion was that severe asthma looks like chronic bronchitis in most patients, and that it is difficult to make the differential diagnosis based on clinical data. Other authors also reported that 18.5% of the patients with chronic obstructive pulmonary disease have a history of asthma. We classified patients presenting chronic airflow limitation and postbronchodilator FEV₁ below normal as having severe asthma. Patients with severe asthma and patients with chronic bronchitis were predominant in this population sample (82%), and the remainder comprised patients with emphysema. In an article published in 2001, the same percentages were reported.⁽¹⁵⁾

In the analysis of Mg levels, potential confounding factors such as anemia, malnutrition, hypoproteinemia and alterations in renal function were ruled out through the use of complementary exams during the selection of patients. None of the patients presented lymphocyte counts, total protein levels, protein fraction levels, or creatinine levels that were not within the limits of normality.

There are few studies in the medical literature that report altered Mg levels in patients with CAL.⁽¹⁶⁾ Only two studies were found. In both, the prevalence of hypomagnesemia was 11%.⁽¹⁷⁾ However, the criteria used for the definition of CAL in these studies were different from those used in the present study. The criteria for inclusion and exclusion of patients were also different.

The high prevalence of hypomagnesemia found in the present study might be explained by the differences between patients with CAL and healthy individuals in terms of population characteristics, demographic profile, socioeconomic status, and eating habits, as well as by the treatment given to patients with CAL (based on high doses of xanthines and inhaled beta-agonists) and by the significant differences in body composition.⁽¹⁹⁻²⁰⁾

Alterations in Mg levels are directly related to the ingestion, absorption and renal excretion of the ion.⁽²¹⁾ Patients who seek treatment at the HC/UEL outpatient clinic present a low socioeconomic status, and it is likely that their diet is based on animal fat and carbohydrates, which are more affordable but are also poor in Mg.⁽²²⁾ However, we did not study the eating habits of the patients. In addition, the very treatment used for this population is based on xanthines (aminophylline), short-acting inhaled beta-agonists (fenoterol and salbutamol), and systemic beta-agonists (salbutamol, parenteral and oral). These medications are distributed by the public health care system at no charge. There is some confusion regarding the role played by these medications in the genesis of electrolyte disturbances. Some studies have demonstrated that, rather than having a direct influence on Mg levels, systemic and inhaled beta-agonists, as well as aminophylline, indirectly affect those levels by working in combination with hypoxemia (when present) or by worsening a subjacent electrolyte disturbance.^(8,24) It has been shown⁽⁸⁾ that serum Mg levels suffer no alterations, expressed as mean values and on an individual basis, after the

inhalation of 200 µg of fenoterol. Others authors,⁽²⁴⁾ studying a group of patients with severe asthma and hypomagnesemia, demonstrated that neither the use of inhaled beta-agonist bronchodilators nor the use of aminophylline was associated in a statistically significant way with the genesis of hypomagnesemia, hypophosphatemia, or hypocalcemia.

Most authors agree that the influence of these medications on the genesis of alterations in Mg levels occurs in a dose-dependent way, and that the degree of their influence varies according to the route of administration and the duration of the treatment.⁽²⁵⁾ The principal electrolyte to suffer the influence of these medications is potassium, which, in turn, indirectly regulates Mg. Notable among the various explanations for the mechanism by which medications influence the genesis of hypomagnesemia is the decrease in serum levels of Mg caused by catecholamine-induced lipolysis concomitant with an increase in Mg sequestration by the adipocyte membranes.⁽²⁶⁾ The beta-adrenergic stimulation regulates plasma potassium and indirectly regulates plasma Mg, leading to the intracellular uptake of both ions, predominantly in the liver and in muscle cells.⁽⁸⁾

In the present study, the use of the medications mentioned can explain, in part but not totally, the high prevalence of hypomagnesemia. The patients who used medications strongly associated with this disorder were excluded during the selection. There are no specific intrinsic mechanisms of Mg regulation.⁽²⁷⁾ The renin-angiotensin system affects the metabolism of potassium and indirectly affects the metabolism of Mg. We found no relationship between hypomagnesemia and other electrolyte disturbances in the present study. Despite the high prevalence of hypocalcemia (52.3%) found in the present study, this value could not be attributed to hyperparathyroidism or malnutrition, since none of the patients studied presented either condition. The mechanisms postulated for hypocalcemia include irregular parathyroid secretion, end-organ resistance to parathyroid hormone, and resistance to Vitamin D.⁽²⁸⁾ However, hypomagnesemia can cause hypocalcemia.⁽²⁹⁾

Chronic respiratory insufficiency combined with hypoxemia has been described as a cause of Mg depletion and hypomagnesemia.⁽⁸⁾ However, we did not manage to confirm this association in the present study.

We speculated whether or not patients with chronic airflow limitations, and with hypomagnesemia, would benefit from total body Mg replacement so as to better maintain muscle potency and reduce cellular excitability that could lead to bronchial hyperreactivity. In the present study, we did not measure muscle strength. In addition, we could not determine whether the more severe cases of CAL (stages 3 and 4) were more closely related to hypomagnesemia than were the moderate cases (stages 1 and 2). There was no statistical difference when the clinical stages were individually compared with hypomagnesemia (chi-square = 5.8; p = not significant).

The only statistically significant association was the higher rate of Mg ion depletion among males, which can be explained by the influence of the use of hormones or hormone replacement by women.⁽⁵⁾ This finding was not duplicated in the literature.

Serum levels of Mg do not reflect total serum Mg concentration in the body, and this concentration can be underestimated. Patients with CAL depend on their respiratory muscles, and Mg is an important cofactor in muscle contraction.

The analysis and discussion of the results obtained in the present study allowed us to conclude that the frequency of hypomagnesemia in patients with chronic airflow limitation treated at the HC/UEL was 27.8%. In addition, there was no statistical relationship between higher stages of severity in patients with CAL and serum levels of Mg. Furthermore, the high frequency of patients in more advanced stages is likely attributable to the fact that the outpatient facility is a referral center for the region. Finally, Mg ion depletion was more common among males, and no other significant electrolyte disturbances were found to be associated with hypomagnesemia.

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