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Hypomagnesaemia in cystic fibrosis patients referred for lung transplant assessment ☆

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Abstract

Background: Hypomagnesaemia in patients with cystic fibrosis (CF) is underrecognized although the true incidence is unknown. Many patients are asymptomatic, although severe deficiency may be associated with muscle weakness, cramps and tetany. Hypomagnesaemia may be a risk factor for post-transplant complications including convulsions, which may be exacerbated by the use of calcineurin inhibitors. The aims of the present study were to describe serum magnesium levels and to investigate the relationship between magnesium levels and age, and renal function measurements in patients with CF referred to a transplant centre for lung transplant assessment.
Methods: We reviewed the data of all 106 CF patients referred for transplant assessment from January 1995 to December 2003. Demographic and biochemical data were recorded and the explanatory variables were subjected to univariate analysis and linear regression analysis.
Results: Mean serum magnesium level was 0.75 mmol/L (range 0.46–1.03, normal range 0.74–1.1). 57% of patients had hypomagnesaemia. Serum magnesium levels were not associated with age, serum creatinine or GFR.
Conclusions: Hypomagnesaemia is a common finding in patients with CF referred for lung transplant assessment. Serum magnesium levels should be monitored in all CF patients being referred for lung transplant irrespective of the results of other renal function tests.
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Keywords: Hypomagnesaemia; Cystic fibrosis; Lung transplant

1. Introduction

The prognosis for cystic fibrosis (CF) patients has improved significantly in recent years [1]. This has been achieved as a result of increased understanding of the disease, the establishment of specialised treatment centres and aggressive management of complications. New problems are emerging as the prognosis improves; some of these may be iatrogenic and related to the requirement for aggressive medical therapy. Hypomagnesaemia is increasingly recognised and appears to be mainly related to proximal renal tubular damage associated with the use of frequent and prolonged courses of high dose aminoglycoside antibiotics [2], although other factors including malnutrition, malabsorption, secondary hyperaldosteronism and diabetes mellitus may also be relevant.

The true incidence and the exact mechanism of hypomagnesaemia in CF are unknown. In this study we assess serum magnesium levels in patients with CF referred to a transplant centre for lung transplant assessment and investigate the relationship between these levels and age, serum creatinine and glomerular filtration rate (GFR).

2. Methods

The study was conducted in the regional cardio-thoracic transplant unit at Freeman Hospital, Newcastle upon Tyne, United Kingdom which is a major supraregional lung transplant centre for both adults and children. Patient information and

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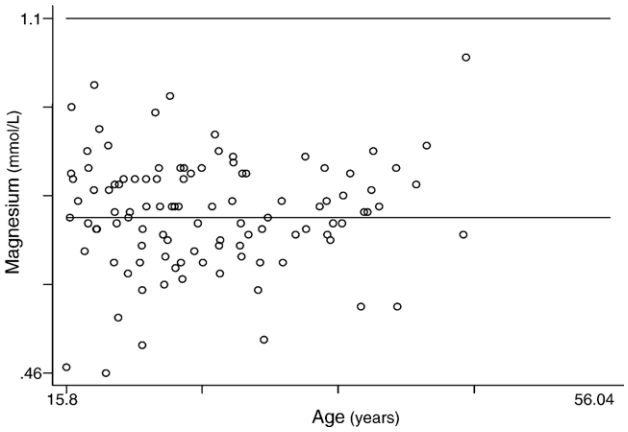

Fig. 1.

biochemical parameters were obtained from the lung transplant assessment database at Freeman Hospital.

We reviewed the data of all CF patients referred for lung transplant assessment from the transplant database from January 1995 to December 2003. Demographic and biochemical data included age, sex, serum magnesium levels, serum creatinine (in micromol/L) and GFR (creatinine clearance mL/min/1.73 m^2).

3. Statistical analysis

Univariate analysis and linear regression was used to describe associations between the explanatory variables (age, creatinine and GFR) and the outcome variable (magnesium).

4. Results

A total of 106 patients were referred for lung transplant assessment over an 8 year period. The median patient age was 24.5 years (range 15.8–56.0 years). 59 (56%) were male. Mean serum magnesium was 0.75±0.10 mmol/L (mean±SD, range 0.46–1.03 mmol/L). 60 (57%) patients were hypomagnesaemic (serum magnesium<0.74 mmol/L). Mean serum creatinine was 80.1±20.8 μmol/L (mean±SD, range 50–226 μmol/L) and GFR 125.5±40.2 (22–227) mL/min/1.73 m^2. There was no statistically significant relationship between serum magnesium levels and age (*P* value= 0.43, 95% confidence interval −0.015, 0.034, regression coefficient 0.001). Similarly, there was no statistically sig nificant relationship between serum magnesium and serum creatinine levels (*P* value=0.47, 95% confidence interval −0.001, 0.006, regression coefficient −0.0003) and GFR (*P* value=0.60, 95% confidence interval −0.004, 0.001, regres sion coefficient 0.001). Scatter plot of serum magnesium levels against age is depicted in Fig. 1.

5. Discussion

Hypomagnesaemia is a common finding in patients with CF referred for lung transplant assessment occurring in 57% of referrals. Serum magnesium levels were not associated with age, serum creatinine or GFR. This is consistent with renal physiology as a rising serum creatinine is a late marker of renal dysfunction associated with impairment in GFR.

Magnesium homeostasis is controlled primarily by renal mechanisms. The kidney filters the equivalent of 5% of the total magnesium body store each day, but proximal tubular resorption of 95% of filtered magnesium ordinarily maintains homeostasis [3].

For many years respiratory exacerbations of CF in childhood have been treated with intravenous aminoglycosides administered up to three times a day. Even though safe blood levels are defined for single courses of aminoglycoside, repeated administrations are usually required. Concern has been raised over the long term renal damage produced by multiple exposures to intravenous aminoglycosides [2,4−6]. It was not possible in this study to document the cumulative dose of aminoglycosides for each patient over the course of their disease, but most patients will have received multiple courses over many years. It is interesting that we did not find a statistical relationship between serum magnesium and age, as the progressive nature of CF is usually associated with increasingly aggressive medical therapy and hence higher cumulative doses of aminoglycosides as the patient ages.

High concentrations of aminoglycosides may accumulate within the kidney, and damage the proximal tubular cells, leading to prolonged tubular leak of magnesium. It is still unclear whether aminoglycosides administered via nebuliser produce adverse tubular effects. Although acute renal failure has been reported with use of nebulised tobramycin [7]. It is likely that the combination of intravenous and nebulised aminoglycosides will have cumulative adverse effects [8,9].

There are several other reasons why CF patients may be prone to hypomagnesaemia including CF related diabetes mellitus, secondary hyperaldosteronism [11] and malabsorption. In patients with diabetes mellitus, the diuresis induced by glycosuria results in increased urinary sodium and magnesium losses [10]. Malabsorption can cause hypomagnesaemia as this binds to fat and is lost in the stool and Booth et al. [12] reported that faecal fat excretion correlated with serum magnesium levels.

Calcineurin inhibitors such as cyclosporine A (CsA) and tacrolimus (FK506) are widely prescribed in transplant recipients and are known to produce hypomagnesaemia particularly with long term usage. The mechanism of this effect is still unclear. Kim et al. [13] demonstrated that in mice these immunosuppressants inhibit the hormone-stimulated magnesium uptake into the mouse distal convoluted tubule cells by inhibiting the mitogen-activated protein kinase pathway. Hypomagnesaemia is known to be a risk factor for neurological complications including seizures in lung transplant recipients, which may be exacerbated by the use of calcineurin inhibitors [14]. Hypomagnesaemia has also been reported as a cause of severe cardiac arrhythmias in the immediate postoperative period following renal transplant [15] and during liver transplant surgery [16].

Patients with normal magnesium levels pre-transplant may still have low levels post-transplant, so magnesium levels still need to be monitored post-transplant irrespective of pre-transplant levels. There is no evidence to support the use of routine oral magnesium supplementation in CF patients with hypomagnesaemia.

In conclusion, hypomagnesaemia is a common finding amongst patients with CF referred for lung transplant assessment. This finding appears to be independent of age and other parameters of renal function (creatinine and GFR). This supports the recommendation to measure magnesium levels in patients referred for lung transplant assessment, even if creatinine and GFR are normal. Further work is required to investigate the relationship between hypomagnesaemia and post operative morbidity in lung transplant patients.

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