

## Serum Magnesium: A Clinical Biomarker for Sudden Unexpected Death in Epilepsy?

Vera C. Terra<sup>a</sup>, Marly de Albuquerque<sup>b</sup>, Carla A. Scorza<sup>b</sup>, Ricardo M. Arida<sup>c</sup>, Fulvio A. Scorza<sup>b</sup>

Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM) – São Paulo, Brasil

### ABSTRACT

**Introduction:** Epilepsy is one of the most common chronic neurological disorder in the world and has a higher mortality rate than would be expected in a healthy population. One of the most related category of death is sudden unexpected death in epilepsy (SUDEP). Many risk factors have been related to SUDEP, but the mechanisms involved in its genesis is still unknown. **Objective:** Here we describe one case of a patient with low serum magnesium levels that suffered of SUDEP. **Conclusion:** we discuss a possible cause-effect relation, suggesting that magnesium may be, in some cases, a biomarker of SUDEP.

**Keywords:** epilepsy, magnesium, sudden death.

### RESUMO

**Magnésio sérico: um biomarcador cerebral para morte súbita em epilepsia?**

**Introdução:** Epilepsia é uma das doenças neurológicas crônicas mais comuns, com uma elevada taxa de mortalidade quando comparada com a população saudável. Uma das principais causas de morte é a morte súbita em epilepsia (SUDEP). Muitos fatores de risco têm sido correlacionados com SUDEP, mas os mecanismos envolvidos na sua gênese são ainda desconhecidos. **Objetivos:** será descrito um caso de um paciente com nível sérico de magnésio baixo que sofreu SUDEP. **Conclusões:** discutiremos uma possível relação de causa-efeito, sugerindo que o magnésio pode ser, em alguns casos, um biomarcador de SUDEP.

**Unitermos:** epilepsia, magnésio, morte súbita.

### INTRODUCTION

Epilepsy is one of the most common chronic neurological disorder in the world and influences negatively the quality of people's life affected by this disease. Approximately 3 percent of the persons in the general population will have epilepsy at some point in their life.<sup>1</sup> Unfortunately, mortality rates are considerably higher in people with epilepsy than would be expected in a healthy population. Thus, most of the excess is due to underlying disease, but some is epilepsy related, including trauma, suicide, pneumonia,

*status epilepticus*, and sudden unexpected death in epilepsy (SUDEP), the most common epilepsy-related category of death.<sup>2,3</sup> Currently, SUDEP is responsible for 7.5% to 17% of all deaths in epilepsy and has an incidence among adults between 1:500 and 1:1,000 patient-years.<sup>4</sup> Some characteristics are shared by patients at highest risk for SUDEP, such as refractoriness of the epileptic condition, presence of generalized tonic-clonic seizures, polytherapy with antiepileptic drugs, young age, duration of the seizure disorder, early onset of epilepsy and winter temperatures.<sup>5,6</sup> The mechanisms of death in SUDEP remain unknown,

<sup>a</sup> Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Brasil.

<sup>b</sup> Disciplina de Neurologia Experimental, Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM), São Paulo, Brasil.

<sup>c</sup> Departamento de Fisiologia, Universidade Federal de São Paulo/Escola Paulista de Medicina (UNIFESP/EPM), São Paulo, Brasil.

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however, there are several evidences supporting that one of the most important domain of potential mechanism of SUDEP is cardiovascular.<sup>7</sup>

Actually, many biomarkers have been shown to predict cardiovascular mortality in the general population<sup>8</sup>; however, this perspective is rarely assessed in research on SUDEP. Accordingly, as previous and very recent studies in the Atherosclerosis Risk in Communities (ARIC) cohort have shown that low levels of serum magnesium (Mg) are considered to be at high risk for sudden cardiac death<sup>9,10</sup>, the present study aims to demonstrate a typical case of SUDEP and highlights a possible biomarker that may have triggered a fatal cardiac event in this individual with epilepsy: low levels of serum magnesium (Mg).

## CASE HISTORY

A 36-year-old male with normal neurodevelopment had two brief febrile seizures in the first year of life. At 11 years old patient started with complex partial seizures that consisted of conscious loss followed by oral automatisms with occasional tonic-clonic secondary generalization. MRI revealed left mesial temporal sclerosis and EEG showed left anterior temporal lobe discharges. Patient evolved with seizure refractoriness despite use of antiepileptic drugs in monotherapy and polytherapy. General biochemistry blood examination was normal, except for low levels of serum Mg: 0.64 mg/dl (normal range = 1.8 to 3.0 mg/dl). Unfortunately, one Saturday morning patient was found dead in bed after an uneventful day with his family. In general, patient was in a good state of health and post-mortem examination did not reveal any abnormality. In the vernacular of the world of epilepsy, the patient suffered what is called SUDEP.

## DISCUSSION

In this study we demonstrated a classic case of SUDEP probably associated with low levels of serum magnesium, which may be considered an interesting and promising biomarker for SUDEP. A number of arguments could be put forward to explain our proposal.

For over a decade there are significant evidence showing that Mg is able to suppress early ventricular arrhythmias and QT dispersion in patients with acute myocardial infarction.<sup>10,11</sup> Furthermore, it has been know that Mg deficiency results in progressive vasoconstriction of the coronary vessels leading to a marked reduction in oxygen and nutrient delivery to the cardiac myocytes.<sup>12</sup> Additionally, several experimental and clinical studies have suggested that Mg abnormalities may lead to various morphological and functional abnormalities of the heart, since Mg deficiency is able to induce elevation of intracellular

Ca<sup>2+</sup> concentrations, formation of proinflammatory agents, oxygen radicals, growth factors and changes in membrane permeability and transport processes in cardiac cells.<sup>12</sup> In parallel, there is a direct relationship between the decrease of Mg in myocardial tissue of individuals who died suddenly when compared with those dying of other causes.<sup>10,13</sup>

On the whole, although some studies have shown a relationship between serum Mg deficiency and refractory epilepsy in both children and adults,<sup>14,15</sup> our analysis is the first to demonstrate a possible significant risk of SUDEP in individuals with low levels of serum Mg. In this sense, we have to keep in mind that as Mg is a potential modulator of seizure activity (because of its ability to antagonize the excitatory calcium influx through the N-methyl-D-aspartate (NMDA) receptor),<sup>15,16</sup> its serum levels reduction in people with refractory epilepsy can increase the frequency of seizures in these individuals, which is currently considered the most important risk factor for occurrence of SUDEP.<sup>3,6</sup>

Despite some progress, SUDEP remains a significant clinical problem. Unfortunately, all the risk factors, the mechanisms, specific methods to prevent, and specific biomarkers for SUDEP are yet to be obtained. Furthermore, we are sure that randomized, controlled trials will be required to investigate with precision the relation of low levels of serum Mg in individuals that suffered of SUDEP; however, as the walk always begins with the first step, this is a specific line of research in the SUDEP field that should be carefully investigated.

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**Corresponding author:**

Fulvio A. Scorza  
Rua Botucatu, 862 – Edifício Leal Prado  
CEP 04023-900, São Paulo, SP, Brasil  
Phone: (+55-11)- 5549-2064 – Fax: (+55-11) 5573-9304  
E-mail: <address: scorza.nexp@epm.br>