Serum levels of magnesium in sudden cardiac deaths among people with schizophrenia: hit or miss?

Níveis séricos de magnésio em morte súbita entre pessoas com esquizofrenia: erro ou acerto?

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ABSTRACT

Schizophrenia is a devastating mental disorder, affecting cognitive, emotional, and behavioral conditions, ability to work, social functioning, family stability and self-esteem of the patient. People with schizophrenia show a two to three-fold increased risk to die prematurely than those without schizophrenia. Understanding the mechanisms behind sudden cardiac death in individuals with schizophrenia is a key to prevention. Although different mechanisms may be related, there are clear indications that cardiac abnormalities play a potential role. Some antipsychotics may be associated with cardiovascular adverse events, e.g., QT interval prolongation, metabolic dysfunction, blood pressure and heart rate alterations. Magnesium (Mg) abnormalities may lead to various morphological and functional dysfunctions of the heart and low levels of serum Mg are considered to be at high risk for sudden cardiac death. As low serum Mg is associated with detrimental effects on the heart and that antipsychotic-treated schizophrenia patients frequently affect the heart rate, possibly, these factors together must change the normal functioning of the heart and consequently being able to culminate in a catastrophic event.

Key words: schizophrenia, sudden death, magnesium.

RESUMO

A esquizofrenia é uma doença mental que afeta as condições cognitivas, emocionais e comportamentais, a capacidade de trabalho, a estabilidade familiar e social e a auto-estima do paciente. Pessoas com esquizofrenia apresentam um risco de duas a três vezes maior de morrer prematuramente em relação às pessoas sem esquizofrenia. A compreensão dos mecanismos envolvidos na morte súbita em indivíduos com esquizofrenia é de suma importância para sua prevenção. Apesar de diferentes mecanismos associados à doença, evidências mostram que as anormalidades cardíacas desempenham papel importante neste contexto. Alguns antipsicóticos podem estar associados com eventos cardiovasculares adversos, como o prolongamento do intervalo QT, disfunção metabólica e alterações na pressão arterial e no ritmo cardíaco. Anormalidades do magnésio (Mg) podem levar a várias alterações morfológicas e funcionais do coração assim como a um alto risco para a morte súbita. Como baixos níveis séricos de Mg estão associados a efeitos nocivos ao coração e indivíduos com esquizofrenia tratados com antipsicóticos frequentemente apresentam alteração do ritmo cardíaco, possivelmente, estes fatores em conjunto podem alterar o funcionamento normal do coração e, consequentemente, culminar em um evento catastrófico.

Palavras-Chave: esquizofrenia, morte súbita, magnésio.

Schizophrenia is a devastating mental disorder, affecting cognitive, emotional, and behavioral conditions, ability to work, social functioning, family stability and self-esteem of the patient[1,2]. Furthermore, schizophrenia is a malignant condition which has a high rate of premature death compared with the general population. Thus, people with schizophrenia show a two to three-fold increased risk to die prematurely than those without schizophrenia and this excess of mortality is accounted for by a combination of factors, such as patients' life style, suicide (in particular in young male patients soon after diagnosis), premature development of cardiovascular disease, high prevalence of metabolic syndrome, carbohydrate

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Support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Instituto Nacional de Neurociência Translacional, Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG).

Conflict of interest: There is no conflict of interest to declare.

Received 22 May 2012; Received in final form 28 June 2012; Accepted 08 July 2012

and lipid metabolic disorders and, equally important but not so often mentioned, sudden cardiac death[2-6]. By definition, sudden cardiac death is a death from a cardiac cause within a short time (minutes to hours) after symptoms initially appear, often without warning[2,7]. In these lines, understanding the mechanisms behind sudden cardiac death in individuals with schizophrenia is a key to prevention. Probably, different mechanisms may be related in different cases; however, there are clear indications that cardiac abnormalities play a potential role[6,8]. In this regard, a number of considerations could be put forward to explain it. Firstly, it has been established that people with schizophrenia are at high risk for cardiovascular disease, and some antipsychotics may be associated with cardiovascular adverse events (e.g., QT interval prolongation), suggesting that this could lead to torsade the points or sudden death[6,8-10]. Second, the excellent review article by Ryan and Thakore[11] suggests that schizophrenia and/or antipsychotic agents are associated with metabolic dysfunction, including diabetes mellitus, increased triglyceride levels and weight gain, all of them known to be associated with increased cardiovascular risk[6,8,11,12]. Third, it also been demonstrated that antipsychotics frequently have effects on blood pressure and heart rate, among which orthostatic hypotension, with or without syncope, is relatively common[8,13,14]. Fourth, smoking is also considered an important risk factor for sudden cardiac death in schizophrenia patients[2] and the effects of smoking may be due to an increase in platelet adhesiveness and release of cathecholamines[2,15].

In face of these findings related above, the question arises as to whether sudden cardiac death in schizophrenia could be related to serum magnesium (Mg) levels? Before that, it is prudent to us clarify our point of view. Recently, our research group demonstrated a typical case of sudden unexpected death in epilepsy (SUDEP), the leading cause of mortality in people with epilepsy, highlights a possible biomarker that may have triggered a fatal cardiac event in this individual with epilepsy i.e., low levels of serum Mg[16,17]. Accordingly, this proposal became viable because it is well established in literature through experimental and clinical studies that Mg abnormalities may lead to various morphological and functional dysfunctions of the heart[18] and more than that, low levels of serum Mg are considered to be at high risk for sudden cardiac death[19,20]. In this context, this line of scientific thought could be considered important to individuals with schizophrenia? Probably, yes.

For several years, the relationship between serum levels of Mg in people with schizophrenia has been shown discreetly in the literature. For example, Alexander et al.[21], in 1978, studied serum Mg in drug-free and neuroleptic-treated schizophrenic patients. Although Mg was not significantly different in 31 unmedicated schizophrenic patients compared with normal controls, people with schizophrenia treated with pimozide and fluphenazine (a structurally different neuroleptic drug) showed significant decreased in the Mg levels when compared with their drug-free values[21]. The following year, the same group evaluated the relationship between serum Mg level and neuroleptic-induced extrapyramidal symptoms (EPS) in schizophrenic patients. In brief, they found that Mg value was significantly lower at the onset of neuroleptic-induced EPS than during the mean of an entire trial[22]. In parallel, Athanassenas et al.[23] studied serum Mg levels during neuroleptic treatment in a group of 29 chronic schizophrenic in patients who had previously remained drug free for at least 4 weeks. The authors demonstrated a significant Mg decrease in the whole group during treatment and the magnitude of the decreased was independent of the neuroleptic used, suggesting an interconnection between serum Mg changes and neuroleptic drug action[23]. Furthermore, Levine et al.[24] measured cerebrospinal fluid levels of Mg in acute schizophrenics *versus* schizophrenic patients in remission and clearly demonstrated that acute schizophrenics have significant lower levels of cerebrospinal fluid Mg.

To date, there are no reports in the literature on the relationship between low serum Mg and sudden cardiac death in schizophrenia. Thus, some considerations may be suggested on this new scientific approach. As low serum Mg is associated with detrimental effects on the heart and that antipsychotic-treated schizophrenia patients ***per se*** frequently affect the heart rate it is very plausible to believe that these factors together must change "twice" the normal functioning of the heart and thereby, being able to culminate in a catastrophic event. On the whole, evidence for this proposition at present is minimal; however, new considerations and future studies should be evaluated to establish with precision the significant of Mg dysfunction in schizophrenia field. In the mean time, caution with sudden cardiac death in schizophrenia continuous to be prudent and necessary.

ACKNOWLEDGMENTS

Wagner F. Gattaz, Director of the Laboratory of Neuroscience, Chairman of the Institute of Psychiatry and Full Professor at the Department of Psychiatry, Faculty of Medicine from Universidade de São Paulo.

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