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Environmental air pollution is an aggravating event for sudden unexpected death in epilepsy

Exposição ambiental à poluição do ar é um evento agravante para a ocorrência de morte súbita nas epilepsias

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ABSTRACT

It is extremely difficult to estimate the occurrence of sudden unexpected death in epilepsy (SUDEP). On the other hand, discovering and carefully evaluating new risk factors that may contribute to the onset of cardiovascular abnormalities in people with refractory epilepsy may prevent fatal events in these individuals. In this context, we should not ignore that urban air pollution is a leading problem for environmental health and is able to cause serious cardiovascular dysfunctions that culminate in sudden death. In this regard, we aimed to determine whether environmental exposure to air pollution is an aggravating event for SUDEP.

Keywords: air pollution, epilepsy, heart, omega-3, sudden death.

RESUMO

É extremamente difícil estimar a ocorrência de morte súbita em epilepsia (SUDEP). Por outro lado, detectar e avaliar cuidadosamente novos factores de risco que podem contribuir para o aparecimento de alterações cardiovasculares em pessoas com epilepsia refratária poderá ser capaz de impedir a ocorrência de eventos fatais nestes indivíduos. Neste contexto, não devemos negligenciar hoje que a poluição do ar nas grandes cidades é um problema para a saúde ambiental, podendo causar graves disfunções cardiovasculares, que culminam em morte súbita. Neste sentido, propusemos nesse trabalho que a exposição ambiental a poluição do ar é um evento agravante para a ocorrência de SUDEP.

Palavras-chave: coração, epilepsia, morte súbita, ômega-3, poluição do ar.

Epilepsy is the most common serious neurological condition that has no geographic, social, or racial boundaries; it occurs in men and women and affects people of all ages, although it more frequently affects young people in the first two decades of life and people over the age of 60 years[1,2]. It is a chronic disease, and several factors negatively impact the quality of life in people with epilepsy[1]. Thus, there is general agreement that stigma and exclusion are common features of epilepsy in developed countries and in developing countries[1,3]. Epilepsy furthermore often has profound physical, psychological, and social consequences since seizures may cause misunderstanding, fear, secrecy, stigmatization, and social isolation[1,3]. Despite all aforementioned features, the notion persists that epilepsy is a benign condition in which individuals only have seizures. Thus, it is pertinent to mention that epilepsy is a malignant condition that has a high rate of premature death, compared to the death rate in the general population[4–6]. By this reasoning, sudden unexpected death in epilepsy (SUDEP) is probably the most common cause of epilepsy-related deaths[4,5,7]. The term SUDEP is used when sudden death occurs in an otherwise reasonably healthy person with epilepsy and the autopsy examination does not reveal a toxicological or anatomical cause of death[4,8]. ***Sudden unexpected death in epilepsy*** is epidemiologically responsible for 7.5% to 17% of all deaths in people with epilepsy and has an incidence between 1:500 and 1:1000 patient-years among adults[9]. There is a significant body of literature suggesting the risk factors for SUDEP are the presence of or experiencing numerous generalized tonic-clonic seizures (GTCS), nocturnal seizures, young age at epilepsy onset, longer duration of

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epilepsy, dementia, absence of cerebrovascular disease, asthma, male gender, symptomatic etiology of epilepsy, and alcohol abuse[4,10–14].

Several predisposing and initiating factors may coexist and contribute to SUDEP; however, the exact causal mechanisms are poorly understood. Experimental and clinical studies suggest that major autonomic dysfunction (i.e. respiratory and cardiovascular abnormalities during and after seizures) seems to have a major role in SUDEP[4,15–17]. According to the mechanisms already proposed, it is well reported that the final events that may lead to SUDEP are a postictal central nervous system shutdown with pronounced EEG suppression, ictal or postictal apnea, and ictal cardiac arrhythmia[4,16–18].

It is unfortunately extremely difficult to estimate SUDEP. On the other hand, discovering and carefully evaluating new risk factors that may contribute to the onset of cardiovascular abnormalities in people with refractory epilepsy may prevent fatal events in these individuals. In this context, we should not ignore that urban air pollution is nowadays a leading problem for environmental health; it is able to cause serious cardiovascular dysfunctions that culminate in sudden death[19,20]. In this regard, would it be plausible to associate environmental exposure to air pollution as an aggravating event for SUDEP? Because of the information mentioned so far, it would be appropriate to consider that the answer to this question is true.

Our planet is being endangered by a capitalist society in which social injustice is based on a thorough environmental injustice. In this regard, the presence of solid or liquid particles in the air, which is called particulate matter (PM), has grown exponentially in modern capitalist societies. The big cities are areas that produce large quantities of PM that originate in traffic and from buildings and industries located on the perimeters of the cities. Thus, several epidemiologic studies have demonstrated that even low levels of exposure to air pollution contribute to the onset and aggravation of cardiovascular diseases, thereby increasing the rates of morbidity and mortality[20]. For that purpose, nine years ago the American Heart Association published its first scientific statement regarding PM air pollution and cardiovascular disease[21]. The purpose of this statement was to provide healthcare professionals and regulatory agencies with a comprehensive review of the literature linking PM air pollution exposure with cardiovascular morbidity and mortality[21]. In the final section, the experts unanimously concluded that exposure to PM air pollution contributes to acute cardiovascular morbidity and mortality, and is therefore able to reduce life expectancy by a few years[21]. After this first scientific statement, several studies were conducted focusing on the cardiovascular changes that occur with exposure to PM air pollution. In this way, some interesting results should be presented to demonstrate the importance of the topic posted in this paper. For example, the American Cancer Society (ACS), as part of the Cancer Prevention II study, demonstrated an increased risk for death by ischemic heart disease associated with longterm exposure to elevated levels of fine particles of less than 2.5 μm ($PM_{2.5}$) (in aerodynamic diameter)[22]. Ischemic cardiac events accounted for the largest relative risk (RR, 1.18; 95%CI 1.14-1.23) and absolute risk for mortality per 10 $\mu g/m^3$ elevation in $PM_{2.5}$[22]. The ACS study also found that deaths because of arrhythmias, heart failure, and cardiac arrest (RR, 1.13; 95%CI 1.05-1.21 per 10 $\mu g/m^3$) were also associated with prolonged exposure to $PM_{2.5}$[22]. Other studies have shown that exposure to elevated $PM_{2.5}$ levels resulting from vehicular traffic in urban areas may exacerbate the risk of myocardial infarction in susceptible people[23–25]. In a United States Medicare study, Dominic[26] and colleagues reported that short-term exposure to $PM_{2.5}$ increases the risk of hospital admissions for cardiovascular and respiratory diseases. They furthermore showed that a 10-$\mu g/m^3$ reduction in $PM_{2.5}$ would reduce the number of annual hospitalizations for heart failure in 204 urban counties by 1,523 cases per year[26].

In addition, other studies demonstrate an association of air pollution (fine PM and related pollutants) with the increased incidence of ventricular tachyarrhythmias (as recorded by implanted cardioverter defibrillators)[27–29]. From the data presented so far, although the mechanisms are not well understood, PM-induced cardiovascular abnormalities are believed to involve inflammation and oxidative stress initiated by the formation of reactive oxygen species (ROS) within affected cells[30,31].

After the presentation of these exciting results by the scientific community over these nine years, the American Heart Association published in 2010 an excellent updated scientific statement to provide a comprehensive review of the new evidence linking PM exposure with cardiovascular disease, with a specific focus on highlighting the clinical implications for researchers and healthcare providers[32]. In brief, the research team acknowledges that—although the existing evidence supports a direct causal relationship between exposure to elevated $PM_{2.5}$ levels and cardiovascular mortality – continued research is important in areas of controversy and uncertainty to further understand the full nature of this issue[32]. In this sense, the scientists encourage the examination of whether certain treatment modalities (such as supplementation with omega-3) will be associated with significant reduced cardiac stress that is caused by exposure to elevated $PM_{2.5}$ levels[32].

This dietary perspective began in 2008 with the elegant work by Romieu and colleagues, which was the first study to examine the effects of omega-3 on the biomarkers of the cellular response to the oxidative stress of air pollution[33]. In brief, they recruited residents from a nursing home in Mexico City who chronically exposed to particulates of 2.5 μg or

less in aerodynamic diameter and followed them for seven months. In a double-blind fashion, the authors randomly assigned the residents to receive either fish oil (containing the omega-3 polyunsaturated fatty acid [PUFA]) or soy oil. They afterwards measured the indoor $PM_{2.5}$ levels in the nursing home, and measured the biomarkers of the response to oxidative stimuli [copper/zinc (Cu/Zn) superoxide dismutase (SOD) activity, lipoperoxidation (LPO) products, and reduced glutathione (GSH) level], and they evaluated the impact of supplementation on plasma levels of these biomarkers[33]. They found that supplementation with either fish oil or soy oil was correlated with an increase of Cu/Zn SOD activity and an increase in GSH plasma levels, whereas exposure to indoor $PM_{2.5}$ levels was correlated with a decrease in Cu/Zn SOD activity and GSH plasma levels[33]. On the whole, the authors concluded that supplementation with either fish oil or soy oil was correlated with an increase of Cu/Zn SOD activity and an increase in GSH plasma levels, whereas exposure to indoor $PM_{2.5}$ levels was correlated with a decrease in Cu/Zn SOD activity and GSH plasma levels; this suggests that omega-3 PUFA intake could modulate oxidative response to $PM_{2.5}$ exposure[33].

These data inspired us as neuroscientists to develop the following question: would people with epilepsy around the world benefit from this therapeutic approach since they are also exposed to PM air pollution? The answer is twofold positive!

First, through experimental and clinical studies, our research group is quite convinced that omega-3 fatty acids are very important for the normal functioning of the brain and are useful in preventing and/or treating epilepsy[34–36]. Furthermore, these studies encourage researchers to seek a new possibility for use of omega-3 in epilepsy, based on their possible action in reducing SUDEP. In this sense, since omega-3 fatty acids ***per se*** have been shown to reduce cardiac arrhythmias and sudden cardiac deaths, it would be plausible to propose that supplementation with this polyunsaturated fatty acid in people with refractory seizures may reduce seizures and seizure-associated cardiac arrhythmias, and hence reduce SUDEP[37,38].

From all information in this new proposal, what is the best way to proceed forward? Most capitalist countries already have strict antipollution legislation that requires certain factories to have special equipment (filters, waste treatment, etc.) or to use less polluting processes. In these countries, there is also intense control on pollution caused by exhaust from automotive vehicles. These procedures achieve significant results, although they do not completely eliminate the problem of air pollution. A greater awareness of the population would be quite feasible. It would meanwhile be very important to assess carefully the precautionary recommendations described by leaders of the American Heart Association[32]. These researchers claim that, although some clinical recommendations have not been clinically tested or proven to reduce mortality, they are practical and feasible measures that may help to reduce exposure to air pollution and therefore potentially lower the associated cardiovascular risk[32]. Following this line of reasoning, epileptologists must keep in mind that air pollution is a serious problem for the general population, including for individuals with epilepsy. Therefore, it would be interesting to be knowledgeable of American Heart Association recommendations[32], to try to improve the quality of life of people with epilepsy around the world, and (most importantly) to decrease the risk of cardiovascular abnormalities and SUDEP in people with epilepsy who are at high risk for these outcomes.

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