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Depressive, inflammatory, and metabolic factors associated with cognitive impairment in patients with epilepsy☆

Josi Arend [a,d], Aline Kegler [a,b], Ana Letícia Fornari Caprara [a], Camila Almeida [a], Patricia Gabbi [a,d], Eduardo T. Pascotini [a,b], Lori Ane Vargas de Freitas [a], Cinara Miraglia [a], Taíse Leitemperger Bertazzo [a], Raphael Palma [a], Patrícia Arceno [a], Marta M.M.F. Duarte [d], Ana Flavia Furian [d], Mauro Schneider Oliveira [d], Luiz Fernando Freire Royes [b,c,d], Gary W. Mathern [e], Michele Rechia Fighera [a,b,c,d,*]

[a] Centro de Ciências da Saúde, Departamento de Neuropsiquiatria, Universidade Federal de Santa Maria, RS, Brazil
[b] Centro de Ciências Naturais e Exatas, Programa de Pós-graduação em Ciências Biológicas: Bioquímica Toxicológica, Universidade Federal de Santa Maria, RS, Brazil
[c] Centro de Educação Física e Desportos, Departamento de Métodos e Técnicas Desportivas, Laboratório de Bioquímica do Exercício (BIOEX), Universidade Federal de Santa Maria, RS, Brazil
[d] Centro de Ciências da Saúde, Programa de Pós-Graduação em Farmacologia, Universidade Federal de Santa Maria, RS, Brazil
[e] UCLA, School of Medicine, Los Angeles, CA, United States

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ABSTRACT

Purpose: The purpose of this study was to examine the cognitive function and depressive traits most frequently associated with the clinical assessment of patients with epilepsy and if these clinical parameters are linked to glycolipid levels and inflammatory and apoptotic markers.
Methods: Patients with epilepsy (n = 32) and healthy subjects (n = 41) were recruited to participate in this study. Neuropsychological evaluation was performed in both groups through a battery of cognitive tests. Inflammatory markers, apoptotic factors, and deoxyribonucleic acid (DNA) damage were measured in blood samples. Additionally, the metabolic markers total cholesterol (CHO), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), and glucose (GLU) levels were analyzed.
Results: Statistical analyses showed that patients with epilepsy presented decreased scores in memory, attention, language, and executive function tests compared with the control group. Analysis revealed that there was negative correlation in epilepsy for seizure duration vs. oral language ($R = -0.4484$, $p < 0.05$) and seizure duration vs. problem solving (executive functions) ($R = -0.3995$, $p < 0.05$). This was also observed when comparing depression with temporal–spatial orientation (TSO) ($R = -0.39$, $p < 0.05$). Furthermore, we observed a higher depression score in patients with epilepsy than in the healthy ones. Statistical analyses showed higher acetylcholinesterase (AChE) ($p < 0.05$), interleukin 1β (IL-1β, $p < 0.001$), and tumor necrosis factor-alpha (TNF-α) ($p < 0.001$) levels compared with those in the control group. Moreover, patients with epilepsy had significantly higher serum levels of caspase 3 (CASP 3) ($p < 0.001$) and Picogreen ($p < 0.001$) compared with the control subjects. Regarding the metabolic markers, higher glycolipid levels were observed in the patients with epilepsy (CHO < 0.05*, LDL < 0.0001*, TG < 0.05*, GLU $p < 0.05$). High-density lipoprotein levels were not significant. The patients with epilepsy had significant correlation when comparing total language with TNF-α ($R = -0.4$, $p < 0.05$), praxes with CASP 3 ($R = -0.52$, $p < 0.01$), total CHO with total language ($R = -0.48$, $p < 0.05$), TG with semantic memory ($R = -0.54$, $p < 0.05$), TG with prospective memory ($R = -0.2165$, $p < 0.02$), TG with total memory ($R = -0.53$, $p < 0.02$), and GLU with total attention ($R = -0.62$, $p < 0.002$).
Conclusion: This study supports the evidence of a distinct neuropsychological profile between patients with epilepsy and healthy subjects. Furthermore, our findings suggest that inflammatory pathway, glycolipid profile, and depressive factors may be associated with cognitive dysfunction in patients with epilepsy.

1. Introduction

Epilepsy is a clinical condition that involves recurrent epileptic seizures. Epileptic seizures cause episodic behavioral or perceptual disturbances because of excessive periodic and hypersynchronous electrical activity of neurons located predominantly in the cerebral cortex.

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* Corresponding author at: Centro de Ciências da Saúde, Departamento de Neuropsiquiatria, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS, Brazil.
E-mail address: mrfighera@yahoo.com.br (M.R. Fighera).

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These episodes can also occur because of the absence of toxic-metabolic conditions or fever [1]. The understanding of epilepsy involves the study of the possible cognitive functions affected and associated factors. Nevertheless, many studies have reported cognitive alterations despite still differing in several points [2].

A continuous epileptogenic process can irreversibly damage the brain, causing persistent cognitive changes and global intellectual deficits [3]. Memory, attention, and language deficits are some of the most reported cognitive complaints in adult patients with epilepsy [4], while depression is the most frequent psychiatric comorbidity [5]. In addition to cognitive and psychiatric deficiencies, evidence suggests the involvement of the inflammatory pathway in the pathophysiology of epilepsies [6,7]. Cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin 1β (IL-1β), are produced during epileptic activity [7], thus contributing to neuronal death and apoptosis [8]. In addition to inflammation, metabolic markers also appear to be involved in cognitive impairment in epilepsies. Several inflammatory and metabolic parameters have shown to be associated with cognitive impairment and dementia in the general population [9]. In fact, studies have shown that changes in lifestyle and statin therapy reduce the atherosclerotic process and, consequently, vascular risk in patients with epilepsy [10–12]. Unfortunately, the association of these factors is rarely examined in relation to cognition in epilepsy and is generally viewed as potentially modifiable risk factors for cognitive impairment and dementia. Therefore, our objectives were to (1) evaluate the neurocognitive profile of patients with epilepsy compared with healthy subjects and its relation to depression scores, (2) investigate the neuropsychological status in patients with epilepsy and its association to inflammatory and apoptosis markers as well as glycolipid levels that have been related to abnormal cognitive function in the general population, and (3) correlate these markers with cognitive status in the participants with epilepsy.

2. Materials and methods

2.1. Study population

Seventy-three subjects were selected and divided into two groups: the group with epilepsy (n = 32) and the control group (n = 41). All patients and controls were evaluated using a questionnaire to determine clinical history. We prospectively recruited 32 patients diagnosed as having epilepsy from June 2013 to July 2015 at our institution. Forty-one healthy, sex-matched volunteers were included as healthy controls. Neurologists with experience in epilepsy revised the diagnostic criteria. Afterwards, the patients and healthy subjects received a protocol number as well as neuropsychological evaluation through a battery of cognitive tests. Blood samples were identified with the protocol number of each individual. Inflammatory markers, apoptotic factors, deoxyribonucleic acid (DNA) damage, IL-1β, TNF-α, acetylcholinesterase (AChE) activity, caspase 3 (CASP 3), and Picogreen (PG) were measured in the blood samples. Furthermore, the metabolic markers total cholesterol (CHO), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), and glucose (GLU) were also evaluated.

The local institutional review boards at the affiliated institutions of the authors approved the study protocol. Informed consent was obtained from all of the subjects and their legal surrogates. The work described was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Group with epilepsy

Among the 43 subjects with the disease, 32 (focal crises: n = 18 and generalized crises: n = 14) were selected through the following exclusion criteria: subjects under 12 years of age, history of autoimmune, liver, kidney, and inflammatory diseases, allergic response, immune deficiency disorders, diabetes, psychiatric illness, malignancy, severe cognitive impairment, or systemic or central nervous system (CNS) infection 2 weeks prior to sample collection. Two experienced neurologists [13] diagnosed the epilepsy according to the 2010 International League Against Epilepsy (ILAE) Classification. All patients were evaluated for seizure frequency and duration using seizure diaries [14]. Seizure types were confirmed through interviews with patients and their relatives as well as electroencephalographic (EEG) analysis and tomography or magnetic resonance imaging (MRI). Data on seizure frequency and status of seizure control with medication were also obtained.

Twenty-nine of the 32 participants had normal background on routine EEG without generalized waves in both hemispheres after light stimulus. Three participants exhibited bursts of polyspikes and waves after sleep deprivation in the right temporal zone. All participants were treated with standard antiepileptic drugs (AEDs). Two participants took sodium valproate (VPA) monotherapy; six took carbamazepine (CBZ) monotherapy; two took phenytoin (PNT) monotherapy; and two took phenobarbital (PNB) monotherapy. Twenty took more than one AED. Seizures in thirty patients were well-controlled except for two patients who were diagnosed as having refractory epilepsy. All patients with epilepsy had normal neurological examinations except for one who presented tetraparesis secondary to spinal cord lesion. Thirty-one patients had normal 1.5 T MRI imaging; one patient had right and left hippocampal sclerosis.

The Standard Progressive Matrices sets A–E [15] were used to evaluate the intellectual capacity of the patients and the control group. Those who presented values below 25 were excluded from the study.

2.3. Control group

For comparison, 41 healthy subjects were recruited, with respect to the mean age and sex of the group with epilepsy.

2.4. Neuropsychological profile

In order to evaluate memory, executive functions, and attention, a neuropsychological evaluation was performed in the group with epilepsy and the control group through a battery of cognitive tests [16–19]. Additionally, the Hamilton Rating Scale [20] was used to evaluate the diagnosis of depression in both groups. Neuropsychological tests and the Hamilton Rating Scale were performed at least 7 days from the last seizure attack.

2.5. Laboratory analyses

Samples were collected at least 7 days from the last seizure attack. After 12 h of overnight fasting, blood samples were collected by venipuncture using purple, green, and red top Vacutainer® (BD Diagnostics, Plymouth, UK) tubes with ethylenediaminetetraacetic acid (EDTA), heparin, or no anticoagulants, respectively. The specimens were routinely centrifuged within 1 h of collection for 15 min at 2500*g*. Aliquots of the serum samples and supernatant were saved and stored at −80 °C for subsequent laboratory analysis according to specific methods. Glucose levels were measured in plasma. Total CHO, LDL, HDL, and TGs were measured in serum. These samples were analyzed using standard enzymatic methods by Ortho-Clinical Diagnostics® reagents on the fully automated analyzer (Vitros 950® dry chemistry system; Johnson & Johnson, Rochester, NY, USA).

2.6. AChE enzyme determination

The enzyme AChE concentration was measured in serum by standard enzymatic methods using Ortho-Clinical Diagnostics® reagents in an automated analyzer (Vitros 950 ® dry chemistry system; Johnson & Johnson, Rochester, NY).