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Neuroimaging observations linking neurocysticercosis and mesial temporal lobe epilepsy with hippocampal sclerosis

Marino M. Bianchin[a,b,*], Tonicarlo R. Velasco[a,c], Lauro Wichert-Ana[a,d], David Araújo Jr.[a,d], Veriano Alexandre Jr.[a,c], Francisco Scornavacca[a,b,c], Sara R. Escorsi-Rosset[a], Antonio Carlos dos Santos[a,d], Carlos G. Carlotti Jr.[a,e], Osvaldo M. Takayanagui[c], Américo C. Sakamoto[a,c]

[a] *Center for Epilepsy Surgery (CIREP), Hospital das Clínicas de Ribeirão Preto, Department of Neurology, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, SP, Brazil*
[b] *Basic Research and Advanced Investigations in Neurology (B.R.A.I.N.), Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil*
[c] *Department of Neurosciences and Behavior, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, SP, Brazil*
[d] *Department of Radiology, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, SP, Brazil*
[e] *Neurosurgery Division, Department of Surgery and Anatomy, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, SP, Brazil*

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ABSTRACT

Objective: To test if chronic calcificed neurocysticercosis (cNCC) and hippocampal sclerosis occur more often than by chance ipsilateral to the same brain hemisphere or brain region in mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) plus neurocysticercosis. This proof-of-concept would provide important evidence of a direct pathogenic relationship between neurocysticercosis and MTLE-HS.

Methods: A cohort of 290 consecutive MTLE-HS surgical patients was studied. A test of proportions was used to analyze if the proportion of patients with a single cNCC lesion matching the same brain hemisphere or region of hippocampal sclerosis was significantly greater than 50%, as expected by the chance.

Results: Neuroimaging findings of cNCC were observed in 112 (38.6%) of 290 MTLE-HS patients and a single cNCC lesion occurred in 58 (51.8%) of them. There were no differences in main basal clinical characteristics of MTLE-HS patients with single or multiple cNCC lesions. In patients with single cNCC lesions, the lesion matched the side in which hippocampal sclerosis was observed in 43 (74.1%) patients, a proportion significantly greater than that expected to occur by chance ($p = 0.008$). Neurocysticercosis in temporal lobe was ipsilateral to hippocampal sclerosis in 85.0% of patients and accounted mostly for this result.

Conclusions: This work is a proof-of-concept that the association of neurocysticercosis and MTLE-HS cannot be explained exclusively by patients sharing common biological or socio-economic predisposing variables. Instead, our results suggest the involvement of more direct pathogenic mechanisms like regional inflammation, repetitive seizures or both. Neurocysticercosis within temporal lobes was particularly related with ipsilateral hippocampal sclerosis in MTLE-HS, a finding adding new contributions for understanding MTLE-HS plus cNCC or perhaps to other forms of dual pathology in MTLE-HS.

* Corresponding author at: CIREP—Hospital das Clínicas de Ribeirão Preto, Campus Universitário—Bairro Monte Alegre, Ribeirão Preto, SP, 14048-900, Brazil. Tel.: +55 51 96 37 69 69.
E-mail addresses: mmbianchin@hotmail.com (M.M. Bianchin), tvelasco@fmrp.usp.br (T.R. Velasco), lwichert@gmail.com (L. Wichert-Ana), ddaraujo17@gmail.com (D. Araújo Jr.), alexandreveriano@gmail.com (V. Alexandre Jr.), francisco.scornavacca@gmail.com (F. Scornavacca), sararosset@gmail.com (S.R. Escorsi-Rosset), acsantos@fmrp.usp.br (A.C.d. Santos), carlotti@fmrp.usp.br (C.G. Carlotti Jr.), omtakay@fmrp.usp.br (O.M. Takayanagui), sakamoto@fmrp.usp.br (A.C. Sakamoto).

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1. Introduction

Mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) is one of the most common forms of human focal epilepsy (Engel, 2001; Tatum, 2012; Cendes et al., 2014). Causes of MTLE-HS are multifactorial and related with different forms of acute brain injury, generically denominated as the initial precipitating injury (IPI) (Mathern et al., 1995, 2002). Seizures or diverse types of brain insults would lead to hippocampal cell death, hippocampal circuit reorganization, and MTLE-HS. Among these injuries are status epilepticus, head trauma, prolonged febrile seizures, and different central nervous system infections or inflammatory-related processes (Mathern et al., 1995, 2002; Bando et al., 2011). Neurocysticercosis is a very common cause of worldwide cerebral infection and epilepsy (Nash and Garcia, 2011; Croker et al., 2012; Del Brutto, 2012; Singh et al., 2013; Cantey et al., 2014; Garcia et al., 2014). More recently, some authors have suggested that neurocysticercosis may act as an IPI, causing lesions, repetitive seizures or chronic neuroinflammation contributing or leading to MTLE-HS (Kobayashi et al., 2001; Wichert-Ana et al., 2004; Bianchin et al., 2006, 2010, 2012, 2014; Velasco et al., 2006; da Silva et al., 2006; Singla et al., 2007; Rathore et al., 2012; Oliveira et al., 2014).

The frequency of neurocysticercosis is increased in patients with MTLE-HS. As neurocystercosis and MTLE-HS are two of the most common forms of human focal epilepsy, the coexistence of both disorders would be expected to occur by chance in several world regions in a great number of patients (Bianchin et al., 2006, 2010, 2012; Velasco et al., 2006). However, based on this aspect and in a few case reports and association studies, a possible cause-effect relationship between neurocysticercosis infection and MTLE-HS development has also been suggested by some authors. These studies failed to definitively prove that this association was, in fact, pathogenically-related because of the elevated frequency of occurring by chance, or because of missing variables common to both diseases, such as socio-economic status or immunological predisposition for both disorders (Leite et al., 2000; Bianchin et al., 2006, 2012; Velasco et al., 2006). However, evidences for a cause-effect relationship between neurocysticercosis and MTLE-HS have also been obtained from neuroimaging studies. Some authors, but not all, have empirically observed, but not adequately tested, that single cNCC lesions might occur more frequently in the same brain hemisphere of hippocampal sclerosis in MTLE-HS patients (da Gama et al., 2005; Bianchin et al., 2008, 2012, 2014; Chen et al., 2010; Rathore et al., 2013). The question of an ipsilateral association between neurocysticercosis and hippocampal sclerosis is particularly important because, if it is confirmed, it would be an important evidence to understand the association between NCC and hippocampal sclerosis, once it could hardly be explained by patients sharing common socio-economic or biological predisposition for two diverse and unrelated diseases. Instead, more direct pathological mechanisms for this association would need to be explored, leading neurocysticercosis to be contributor or even a causative agent of MTLE-HS in some patients. Thus, as far as we are concerned, this is an important question that has never been adequately tested, remains largely unsolved, and because of its potential implications, needs to be further investigated.

Here we present results of a simple study designed to evaluate the neuroimaging relationship between cNCC and hippocampal sclerosis in a cohort of MTLE-HS patients from a region where neurocysticercosis is endemic. More specifically, we test if cNCC and HS co-occurs more often than by the chance in the same brain hemisphere or brain regions in patients with unilateral MTLE-HS that also presents neurocysticercosis. In our view, the proof of this hypothesis would provide important evidence that neurocysticercosis might directly contribute or even cause MTLE-HS.

2. Methods

2.1. Patients

A cohort of 320 patients surgically treated for unilateral MTLE-HS at CIREP (Center for Epilepsy Surgery at Ribeirão Preto), from 1996 to 2003, was selected. Only patients with MTLE-HS alone or patients with MTLE-HS plus neuroimaging evidence of calcified neurocysticercosis were included. Patients with other forms of dual pathologies were excluded from the study. All patients included in this study had standard anterior and mesial temporal lobe resection for refractory MTLE-HS, as detailed bellow. All patients included in this study had anatomopathological confirmation of hippocampal sclerosis.

Two hundred and ninety patients met inclusion criteria, had all data available for revision and were included in this study. This frame time was chose because during this period all patients had CT-scan and MRI studies. More recently, patients are not submitted to CT-scans as a routine anymore. The possibility of having both neuroimaging exams, CT-scan and MRI studies for all patients helped us to understand the ipsilateral association between neurocysticercosis and MTLE-HS. Only patients with MTLE-HS plus cNCC were analyzed. The variables studied were gender, age at surgery, age at epilepsy onset (recurrent seizures), epilepsy duration, and CT-scan and MRI exams of all patients. For this study, patients were divided into two groups, according to the number of cNCC lesions: patients with unilateral MTLE-HS with a single cNCC lesion (MTLE-HS-single-cNCC group) and patients with unilateral MTLE-HS plus radiological evidence of two or more cNCC lesions (MTLE-HS-multiple-cNCC group). This research is in accordance with STROBE and The Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Research Ethics Committee of our institution.

2.2. Diagnosis of neurocysticercosis

Definitive neurocysticercosis was diagnosed if the following criteria were met (i) an absolute criterion, such as histological demonstration of the parasite or cystic lesions showing the scolex on CT or MRI; (ii) two major criteria, such as lesions highly suggestive of neurocysticercosis on neuroimaging studies, spontaneously resolving small single enhancing lesions, or resolution of intracranial cystic lesions after therapy with albendazole or praziquantel; or (iii) one major and two minor criteria, such as lesions compatible with neurocysticercosis on neuroimaging studies, clinical manifestations suggestive of neurocysticercosis, and positive CSF ELISA for the detection of anticysticercal antibodies, plus epidemiological evidence. According to the above criteria, the presence of solid, dense, supratentorial calcifications, 1–10 mm in diameter, in the absence of other illnesses should be considered to be highly suggestive of neurocysticercosis (Del Brutto et al., 2001; Terra-Bustamante et al., 2005; Velasco et al., 2006; Bianchin et al., 2013).

2.3. Neuroimaging

Neuroimaging included a CT-scan and MRI with special protocols for MTLE-HS. Based on MRI analysis, MTLE-HS was classified as unilateral or bilateral. Based on neuroradiologic findings, the patients were divided into two groups and compared: patients with MTLE-HS without radiological evidence of NCC (MTLE-only) and patients with MTLE plus radiological evidence of chronic NCC (MTLE-cNCC). Exams of patients with a single chronic calcified cNCC were carefully evaluated and the cerebral hemisphere of the cNCC lesions and side of hippocampal sclerosis were recorded for analysis.