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Review

Understanding the association of neurocysticercosis and mesial temporal lobe epilepsy and its impact on the surgical treatment of patients with drug-resistant epilepsy

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ABSTRACT

Mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) is one of the most common types of focal epilepsies. This is an epileptic syndrome commonly associated with treatment-resistant seizures, being also the most prevalent form of drug-resistant epilepsy which is treated surgically in most epilepsy surgery centers. Neurocysticercosis (NCC) is one of the most common parasitic infections of the central nervous system, and one of the most common etiological agents of focal epilepsy, affecting millions of patients worldwide. Recently, researchers reported a curious association between MTLE-HS with NCC, but this association remains poorly understood. Some argue that calcified NCC lesions in MTLE-HS patients is only a coincidental finding, since both disorders are prevalent worldwide. However, others suppose there might exist a pathogenic relationship between both disorders and some even suspect that NCC, by acting as an initial precipitating injury (IPI), might cause hippocampal damage and, eventually, MTLE-HS. In this review, we discuss the various reports that examine this association, and suggest possible explanations for why calcified NCC lesions are also observed in patients with MTLE-HS. We also propose mechanisms by which NCC could lead to MTLE-HS. Finally, we discuss the implications of NCC for the treatment of pharmacologically-resistant focal epilepsies in patients with calcified NCC or in patients with MTLE-HS and calcified NCC lesions. We believe that investigations in the relationship between NCC and MTLE-HS might offer further insights into how NCC may trigger epilepsy, and into how MTLE-HS originates. Moreover, observations in patients with drug-resistant epilepsy with both NCC and hippocampal sclerosis may not only aid in the understanding and treatment of patients with MTLE-HS, but also of patients with other forms of dual pathologies aside from NCC. This article is part of a Special Issue titled Neurocysticercosis and Epilepsy.

1. Introduction

Mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) is one of the most common types of focal epilepsies [1–6]. This is an epileptic syndrome commonly associated with drug-refractory seizures, being also the most common type of drug-resistant epilepsy that is treated surgically in most epilepsy surgery centers [4–10]. The pathogenesis of MTLE-HS is still not completely elucidated, although the most accepted theory is that some patients with unknown biological predispositions suffer hippocampal damage because of diverse events that are severe enough to cause cellular hippocampal death. Afterwards, the remaining viable cells reorganize, leading to hippocampal remodeling and eventually to mesial temporal epilepsy [11–22]. Analysis of the final stage of hippocampal remodeling in patients with epilepsy reveals typical patterns, known as hippocampal sclerosis [11–22]. This first acute event, most commonly occurring in early life, is known as the initial precipitating injury (IPI) [11–15]. Several forms of IPI have been described as triggering events for MTLE-HS. Among these are prolonged febrile seizures, *status epilepticus*, neonatal hypoxemic lesions, head trauma, and some forms of central nervous system infection [11–22].

Neurocysticercosis (NCC) is one of the most common parasitic infection of the central nervous system, affecting millions of patients worldwide [23–28]. The main symptoms of NCC are seizures and because of its prevalence, NCC has been considered one of the major causes of epilepsy in several world regions [23–32]. NCC is endemic in countries of South and Central America, Africa, and Asia, regions holding the largest

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proportion of the human population in the planet, and, therefore, accounting for an elevated number of patients with epilepsy worldwide. In fact, the patients living in developing countries might account for as much as 3/4 of all patients with epilepsy [23–32]. Neurocysticercosis can also be observed in developed countries, and might occur in these countries also as a result of traveling and immigration [33–42]. While studying epilepsy in patients with focal epilepsy and a single calcified NCC (cNCC) lesion, Sakamoto et al., observed three patients with MTLE-HS and cNCC in the same epileptogenic zone [43]. Histological examinations of temporal lobectomies performed as treatment for refractory epilepsy revealed typical MTLE-HS histological findings. The authors concluded that NCC could cause MTLE-HS during an acute insult, or that MTLE-HS arose as a consequence of repeated seizures triggered by cysticercosis [43]. After these first observations, and during the last twenty years, many other studies have reported the curious association between NCC and MTLE-HS. However authors have interpreted this association in different ways. In this article, we chronologically and critically review these studies and further explore plausible mechanisms explaining how NCC could lead to MTLE-HS. Finally, we discuss the surgical treatment of patients with refractory epilepsy in the context of MTLE-HS associated with NCC.

2. Review methodology

We searched online US National Library of Medicine National Institutes of Health PubMed using the terms [(cysticercosis OR neuro- cysticercosis) AND (temporal lobe epilepsy OR hippocampal sclerosis OR hippocampus)]. Using this strategy, we retrieved 57 articles published from 1960 to September 2016. Additionally, we searched American Epilepsy Society Abstracts online, from 2000 to 2016, using the word 'neurocysticercosis' for additional information. This survey resulted in 19 additional studies. All the information obtained by using these strategies and regarding the specific association between NCC and MTLE-HS was considered in the present review. All relevant articles cited by these authors were carefully reviewed and when pertinent for the present work were included in this review.

3. Insights from first reports on neurocysticercosis and temporal lobe epilepsy

Although studies regarding NCC and temporal lobe epilepsy can be found in the medical literature since the latter half of the XX century, few specific studies of temporal lobe epilepsy caused by NCC have been reported in this time period. With rare exceptions, these initial reports have no sufficient details to allow further speculations about the pathophysiology of epilepsy. For example, in 1963, Davies and Morgenstern reported an interesting case of a male patient who developed temporal lobe epilepsy, alterations in sexual behavior, and psychiatric abnormalities after neurocysticercosis [44]. It is possible that this patient was suffering from mesial temporal lobe epilepsy, considering he had episodes of epigastric sensations that resemble the epigastric aura commonly observed in patients with MTLE-HS. In spite of initial reports, a more consistent interest in studying specific associations between neurocysticercosis and temporal lobe epilepsy is relatively new. In 1998, Chun-Kee et al. reported a case of pharmacologically-refractory epilepsy caused by a solitary intrahippocampal calcified cysticercus [45]. The patient had no history of febrile seizures or other forms of IPI. The patient underwent standard temporal lobectomy with good seizure control. Histological examination revealed a degenerated cysticercus and scolex surrounded by hippocampal tissue, and neuronal loss and gliosis in the fascia dentate and corpora amylacea, most of which are findings of hippocampal sclerosis. In the same year, Garg et al., reported neuroimaging findings in patients from India with refractory epilepsy [46]. Curiously, even in cysticercosis-endemic areas, NCC lesions *per se* were considered a rare cause of refractory focal epilepsy. Even so, these authors reported that, in their cohort, the main lesion observed in the in the patients with refractory epilepsy was NCC [46]. In this study, few patients underwent an MRI and, therefore, it is possible that many of those patients could have had refractory epilepsy due to cerebral pathologies other than cNCC, such as hippocampal sclerosis or focal dysplasia. This report is important because it shows that in India, neuroimaging findings of cNCC can also be common in patients with refractory epilepsy, even as a coincidental finding, due to the high prevalence of cNCC in the population.

4. Discrepancy of early neuroimaging studies and electrophysiological findings in neurocysticercosis associated with epilepsy

Some studies have been designed to evaluate the relationship between the localization of cNCC lesions and epileptogenic zone utilizing neuroimaging techniques and interictal EEG findings. Neuroimaging in these studies relied mostly on CT scans, but interesting findings about the association of clinical and EEG activity from the site of cNCC might give additional clues for explaining epileptogenesis in MTLE-HS. Murthy et al. evaluated 97 patients with epilepsy associated with a single cNCC lesion, including clinical, neuroimaging, and electrophysiological findings [47]. In this cohort, lesion localization based on clinical and interictal EEG findings was congruent with the localization of cNNC in only 25 (26%) patients. Singh et al. studied 40 patients and observed that congruent electroclinical and cNCC CT-scan findings occurred in only 22 (55%) patients [48]. Kowacs et al. studied 47 patients with cNCC in diverse topographies, but most patients presented clinical findings and interictal EEG abnormalities consistent with temporal lobe epilepsy [49]. In all these studies, the authors attributed electroclinical–neuroimaging discordance to dual pathology or to seizure spread along anatomical pathways, a finding that perhaps suggests possible electrogenic mechanisms involved in secondary epileptogenesis in NCC-associated epilepsy. If this holds true, then cNCC would be an interesting natural model for epilepsy, and could be used to study secondary epileptogenesis in humans. In fact, cNCC calcifications are punctate and single in many patients, allowing for a more localized identification of lesional zones and perhaps more precise seizure onset zones. More recently, Del Brutto et al., while analyzing the hypothesis that cNCC could lead to hippocampal damage and MTLE, suggested that NCC–hippocampal interactions could explain the early observations of discrepancies between neuroimaging and clinical–electrophysiological findings in patients with cNCC [50].

5. Early studies on neurocysticercosis and mesial temporal lobe epilepsy

During the nineties, many authors started to question more seriously if NCC could lead to MTLE-HS. Analyzing 120 patients with cNCC, Sakamoto et al. observed three patients with MTLE-HS and concomitant cNCC in the same lesional zone, suggesting that NCC could cause MTLE-HS during an acute insult, or as a consequence of repeated seizures triggered by the cysticercus [43]. Leite et al. compared clinical, neuroimaging, and electrophysiological data of 30 patients with isolated MTLE-HS with the same variables of 32 patients with MTLE-HS associated with cNCC that underwent temporal lobectomy as treatment for refractory TLE [51]. A history of IPI was present in 83.3% of patients with MTLE-HS alone, but only in 62.5% of patients with MTLE-HS associated with NCC [51]. Histological findings showed hippocampal sclerosis typical of patients with MTLE-HS in both groups, and no significant differences were found for fascia dentate Timm-staining and hippocampal cell densities between the two groups of patients. Surgical seizure control was similar between groups, with Engel I long-term outcome in 76.6% of patients with MTLE-HS alone and in 81.2% of patients with MTLE-HS and cNCC [51]. Based on these findings, the authors concluded that cNCC findings in MTLE-HS can be frequent, probably as a coincidental pathology, and not as having an etiological factor in the epileptogenesis of MTLE-HS. This study is important because it was one of the first studies

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