On the relationship between neurocysticercosis and mesial temporal lobe epilepsy associated with hippocampal sclerosis: coincidence or a pathogenic relationship?

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Neurocysticercosis (NCC) and mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) are two common worldwide forms of focal epilepsy. In regions where NCC is endemic, both diseases can be observed in the same patient. There is recent and growing evidence suggesting that NCC might contribute to or even cause MTLE-HS. In this article, we review the literature regarding NCC and temporal lobe epilepsy, specifically addressing the relationship between NCC and MTLE-HS. In addition, we review some scenarios where NCC seems to emerge as a causative agent or contributor to the development of MTLE-HS in some patients. This association is important because it may have an impact on the evaluation and treatment of a sizable proportion of patients with epilepsy. Insights from these clinical observations might also contribute to the understanding of the neurobiology of both NCC and MTLE-HS. We hope that our review might shed some light on this interesting interplay between two of the most common worldwide conditions associated with human focal epilepsy.

Keywords: Neurocysticercosis, Epilepsy, Hippocampal sclerosis, Temporal lobe epilepsy, Initial precipitating injury

Introduction

Epilepsy is a common neurological disorder affecting at least 0.5% of the population in developed countries.¹ In developing countries, epilepsy is even more frequent and may account for about three-quarters of all affected patients in the world.^{2–4} In areas where neurocysticercosis (NCC) is not endemic, mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) is the most common form of human focal epilepsy.⁵ MTLE-HS is frequently resistant to pharmacological treatment and patients may reach seizure-free status only after surgical treatment.^{5,6} Although the pathogenic mechanisms of MTLE-HS development are not fully understood, evidence suggests that diverse forms of initial precipitating injury (IPI) might lead to hippocampal

damage followed by hippocampal cell loss, synaptic reorganization, and eventually to chronic temporal lobe epilepsy. Well-established types of IPI are head trauma, prolonged febrile seizures, and bacterial or viral central nervous system infections.^{7–10} In patients with MTLE-HS, it is not uncommon to observe other types of potentially epileptogenic lesions (temporal or extra-temporal). MTLE-HS has been observed to occur associated with other epileptogenic lesions such as cortical dysplasia, brain tumors, or vascular abnormalities.^{11–14}

NCC is the world's most common neurological infectious disease and is a common cause of focal epilepsy in regions where *Taenia solium* is endemic, including areas in Latin America, India, Asia, and Africa.^{15–19} It is estimated that millions of individuals worldwide are affected by the teniasis/cysticercosis complex.^{19,20} In developed countries, the disease is less common but still occurs in some areas.^{21–26}

NCC can cause neuropsychiatric symptoms, the most common being seizures occurring in 70–92% of

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patients.^{2,27–31} In endemic regions, it is not uncommon to observe patients with chronic calcified neurocysticercosis (cNCC) associated with MTLE-HS.^{32–35} Although the association between cNCC and MTLE-HS might be coincidental in many patients due to the elevated prevalence of both disorders in some populations, growing evidence suggests that NCC can be also involved in the pathogenesis of MTLE-HS. In this article, we review the literature regarding NCC and temporal lobe epilepsy, specifically addressing the relationship between NCC and MTLE-HS and some scenarios where NCC seems to emerge as an important causative agent of, or contributor to, the development of MTLE-HS. We hope that our review might shed some light on this interesting interplay between two of the most common conditions associated with human focal epilepsy.

Review Methodology

We searched PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) using the terms [(cysticercosis OR neurocysticercosis) AND temporal lobe epilepsy]. Using this strategy, we were able to retrieve 28 articles published from 1960 to 2011. Additionally, we searched American Epilepsy Society Abstracts online, all years (<http://www.aesnet.org/go/publications/aes-abstracts/abstract-search>) using the words ‘cysticercosis’ or ‘neurocysticercosis’ for additional information. This survey resulted in 13 additional studies. All the information obtained by using these strategies and regarding the specific association between NCC and MTLE-HS was used in the present review. All relevant articles cited by these authors were carefully reviewed and, when pertinent for the present investigation, were also included in the present review.

Evidence Showing Increased Occurrence of NCC in MTLE-HS Patients

In areas where NCC is endemic, cNCC might be frequently observed in patients with MTLE-HS. Martinez *et al.* reported 11 cases of epilepsy surgery on NCC patients, some of them with hippocampal sclerosis.³⁶ Jorge *et al.* compared the clinical presentation and surgical outcome of patients with MTLE-HS with and without associated intracranial calcifications, but found no significant differences between these two groups.³⁷ In a more comprehensive study, Leite *et al.* observed that cNCC was found in 17.7% of the patients submitted to temporal lobectomy for the treatment of refractory epilepsy in MTLE-HS.³⁴ At that time, the authors concluded that cNCC observed in MTLE-HS patients was probably coincidental and did not influence the clinical or pathological profile or surgical outcome of patients with MTLE-HS if seizures were proved to emerge from mesial temporal structures.³⁴ The observation that clinical profile and post-surgical outcomes were similar for MTLE-HS

Figure 1 (A) Fluid attenuated inversion recovery (FLAIR) and (B) Inversion recovery magnetic resonance imaging (MRI) sequences in the coronal plane of a patient with mesial temporal lobe epilepsy associated with hippocampal sclerosis. The arrow shows a single calcified cysticercotic lesion in close relationship with the right hippocampus. Observe also right hippocampal atrophy, and structural and signal abnormality characteristic of hippocampal sclerosis. The patient had unilateral right mesial temporal lobe seizures and became seizure free after standard right temporal lobectomy.

and MTLE-HS associated with cNCC led to the conclusion that in endemic zones for NCC neuroradiological findings of cNCC in MTLE-HS would be probably coincidental due to the high prevalence of both pathologies and to the fact that NCC would not have any role in MTLE-HS genesis, clinical findings, or prognosis of MTLE-HS plus cNCC patients. However, later on, in a cohort of 178 patients submitted to surgery for treatment of MTLE-HS, neuroimaging findings of cNCC were observed in 71 patients (37.2%).³⁸ This prevalence was far higher than expected for our population, where cNCC is estimated to occur in 71.4/100 000 cases according to epidemiological data obtained from our Public Health System, in which NCC notification is compulsory.³⁹ This observation led us to evaluate a possible cause–effect relationship between cNCC and MTLE-HS. Similarly to the pathogenesis of MTLE-HS associated with other forms of neurological infection, NCC may eventually also lead to hippocampal damage and later to MTLE-HS in some patients (Fig. 1).

Evidence of a Pathophysiologic Relationship Between NCC and MTLE-HS

Anecdotal evidence suggested a possible pathophysiological association between NCC and MTLE-HS. Kobayashi *et al.* described neuroimaging evidence of MTLE-HS and non-refractory complex partial seizures after acute NCC in a previously healthy patient.³³ According to the authors, in this patient, hippocampal abnormality and MTLE-HS were perhaps due to the acute inflammatory response to cysticercosis associated with repeated partial seizures. Wichert-Ana *et al.* documented hippocampal sclerosis as the cause of refractory epilepsy in a patient with massive cNCC. The patient was rendered seizure-free after temporal lobectomy, in spite of massive cNCC

lesions. These authors suggested that NCC, similarly to other meningoencephalitic lesions, could act as an IPI leading to MTLE-HS and refractory epilepsy in that patient.³⁵ da Silva *et al.* described anatomopathological aspects of a patient with partial seizures due to NCC that evolved to refractory MTLE-HS.⁴⁰ Resected tissue analysis demonstrated cellular features of hippocampal malformation, including dysmorphic neurons and focal bilamination of the granular cell layer. The authors suggested that a developmental disorder of the hippocampus could eventually have led to a low seizure threshold for NCC-induced seizures, causing or contributing to the establishment of hippocampal sclerosis and refractory epilepsy. Later on, Singla *et al.* reported four patients who had neuroimaging evidence of active or inactive NCC, and who were later evaluated for refractory epilepsy due to MTLE-HS.⁴¹ The authors also agreed with the view that, despite a possible coincidence, seizures or inflammation provoked by NCC may also act as an IPI in some patients, leading to the development of MTLE-HS.⁴¹

Going beyond a few case studies, da Gama *et al.* conducted a transverse study carefully designed to evaluate the relationship between hippocampal atrophy, cNCC, and seizure semiology in patients with partial epilepsy.³² The authors compared clinical, electrophysiological, and detailed neuroimaging of 89 consecutive patients, 63 of them with MTLE-HS and 26 of them with extratemporal epilepsy, exploring possible correlations between the epileptogenic zone, neuroimaging findings of cNCC, and hippocampal atrophy. In the cited study, the authors did not observe any relationship between the localization of cNCC (temporal or extratemporal) and seizure semiology and no impact of cNCC on MTLE-HS, considering coincidental cNCC in MTLE-HS patients. Later on, we carried out a cross-sectional study of 512 patients in which we examined the presence of cNCC and its relationship with various types of refractory epilepsy.⁴² We found that the frequency of cNCC was significantly higher in patients with MTLE-HS than in patients with any other types of refractory epileptogenic lesions.⁴² However, the presence of a relationship between cNCC and MTLE-HS does not mean that there is a causal relationship between NCC and MTLE-HS.⁴² A third variable or factor (the missing variable problem) could be responsible for this association. In other words, a possible alternative explanation would be that cysticercosis and hippocampal sclerosis could be both associated with a common third variable such as, for example, low socio-economic status and thus we could not establish a cause–effect relationship between NCC and MTLE-HS. At this point, we have three not mutually exclusive different scenarios regarding the co-occurrence of

cNCC and MTLE-HS. First, NCC may be directly involved in the development of hippocampal sclerosis and MTLE-HS. Second, patients with MTLE-HS and NCC might share some common biological susceptibility to both diseases, such as some immunological factors that might predispose to both conditions, and NCC and MTLE-HS would not be pathogenically related. Third, MTLE-HS and NCC might occur in the same population due to a common socio-economic background or other still missing variables. Of course, controlling for socio-economic status would help investigate this last hypothesis, but controlling retrospectively for socio-economic status three or four decades ago would be very difficult. However, in this venue, Oliveira *et al.* also studied 46 patients with MTLE-HS (33 patients) or idiopathic generalized epilepsy (13 patients) regarding the presence of cNCC. The authors observed that MTLE-HS patients had more seizures, received more antiepileptic drugs, were older, had a lower average age at onset of epilepsy, longer epilepsy duration, and lower socio-economic status and educational level. In line with our results, cNCC was found significantly more frequently in MTLE-HS patients than in patients with generalized idiopathic epilepsy.⁴³ Nevertheless, these authors also failed to establish a direct cause–effect relationship between NCC and MTLE-HS. More evidence to support possible pathophysiological mechanism for an association between MTLEH and NCC could be obtained by comparing possible similarities and differences existing between classical forms of MTLE-HS and MTLE-HS plus cNCC in large groups of patients. For this, we studied the demographic, clinical, and neuroimaging findings of patients with MTLE-HS plus NCC and compared them to those of patients with MTLE-HS without NCC in a retrospective cohort study of 191 patients with MTLE-HS.⁴⁴ That study confirmed our previous observations of radiological cNCC findings in a significant number of MTLE-HS patients (35.6%). Moreover, we observed that the radiological findings of cNCC in MTLE-HS patients occurred significantly and independently more often in women than in men, in patients without a classical history of an IPI before 5 years of age, and in patients who had bilateral temporal interictal spikes during a pre-surgical video-electroencephalogram.⁴⁴ That study was important because if the association between MTLE-HS and cNCC was only coincidental as a result of a high prevalence of both pathologies in the same region, no clinical or electrophysiological repercussions of NCC on MTLE-HS would exist.

With the objective to advance one step further in the study of a possible cause–effect relationship between NCC and MTLE-HS, we investigated anatomical connections between cNCC and MTLE-HS.⁴⁵

Anatomical evidence would practically rule out co-occurrence of two different and unrelated diseases. For this purpose, we reviewed detailed data of 355 consecutive patients with unilateral MTLE-HS submitted to surgery.⁴⁵ Neuroimaging findings of cNCC were observed in 133 (37.46%) of those patients. NCC was significantly more common in women (66.4%) than in men (33.6%) ($P < 0.001$).⁴⁵ Fifty-seven patients presented a single lesion (42.85%) that was highly correlated with the side of MTLE-HS, suggesting an anatomical relationship between cNCC and MTLE-HS.⁴⁵ Since cNCC was anatomically related to the side of hippocampal sclerosis, we suggested that a possible mechanism would be that the cysticercus, by provoking repetitive seizures or status epilepticus, could lead to the development of MTLE-HS even if it is located outside the limbic circuits.⁴⁵ Another possible mechanism is that the cysticerci would lead to variable inflammatory responses and perhaps to hippocampal damage in patients with some still unknown genetic predisposition, similar to that reported in other forms of meningoencephalitis.⁴⁵ Because women are more prone to develop more severe forms of cNCC and more intense inflammatory reactions than men, our observation that significantly more women than men have MTLE-HS and cNCC agrees with the idea of inflammation-dependent hippocampal damage caused by NCC.^{45,46} This study is particularly important for two different reasons. First, an anatomical relationship between cNCC and MTLE-HS cannot be explained solely by demographic or socio-economic variables. Moreover, although both diseases might occur independently and co-occur in the same patient by chance, this certainly would not explain any anatomical correlation between them. Second, because we were able to observe this anatomical association by studying only 57 patients (those with MTLE-HS and a single cNCC lesion), it is possible that NCC might have a significant impact on MTLE-HS in some populations. If cNCC-causing MTLE-HS were a rare event, we would need a much larger number of patients to detect any anatomical associations. In line with our observations, Chen *et al.* also reported that cNCC occurs more frequently ipsilateral to MTLE-HS, agreeing with the view that NCC could cause MTLE-HS by repetitive focal seizures, interictal discharges, and/or focal inflammation.⁴⁷ They also concluded that the presence of this type of double pathology (MTLE-HS and cNCC) does not preclude temporal lobectomy.⁴⁷ Thus, at this point, there was growing evidence that NCC could lead to MTLE-HS in some patients. Therefore, the next step now is to examine possible mechanisms whereby NCC might lead to MTLE-HS and the impact of NCC on refractory epilepsy and surgical treatment of MTLE-HS and cNCC.

A Possible Mechanism Whereby NCC Might Lead to MTLE-HS

The presence of two different types of potentially epileptogenic lesions in the same patient has been observed frequently.^{11–14} In this venue, the presence of cNCC in MTLE-HS is a form of double pathology or dual pathology that might be common in regions where NCC is endemic. In these patients, cNCC might be observed to occur in MTLE-HS just by chance and that might be true for several patients. However, at least sometimes NCC seems to cause or contribute to the development of MTLE-HS. Based on previous studies and on what we already know about the genesis of MTLE-HS, we explore here some potential mechanisms of mesial temporal damage in NCC. Briefly, there is growing evidence that several forms of IPI might result in mesial temporal lobe damage, hippocampal sclerosis, and eventually MTLE-HS.^{7–10} In this scenario, very diverse forms of IPI can lead to a similar final form of hippocampal sclerosis and MTLE-HS.^{7–10} Most classical and well-studied forms of IPI include neonatal hypoxic insult, febrile seizures, status epilepticus, cranial trauma, and viral or bacterial infections of the central nervous system.^{7–10} Thus, NCC might be seen as one of the several possible forms of IPI that might lead to MTLE-HS. However, as is the case for other forms of IPIs, NCC has its own characteristics and particularities and it might lead to hippocampal damage or abnormalities by specific mechanisms that need to be further addressed. In our view, NCC could lead to hippocampal damage or dysfunction by at least two distinct and non-mutually exclusive mechanisms.⁴⁸ First, NCC can provoke repetitive interictal discharge, clinical or subclinical seizures, or eventually status epilepticus, damaging and kindling the hippocampus, eventually leading to MTLE-HS in some patients. Second, NCC can cause direct or indirect inflammatory-mediated hippocampal dysfunction or damage leading to hippocampal sclerosis and MTLE-HS. Of course, the two processes can agonistically overlap to cause MTLE-HS. In addition to these processes, less obvious forms of cysticercus-induced hippocampal dysfunction can also exist and perhaps need to be further explored as well.⁴⁸ In order to obtain the full picture, we propose a sequence of three stages suggesting how NCC can lead to MTLE-HS (Fig. 2). In the first stage, one or more active cysticerci might damage or cause dysfunction of mesial temporal lobe structures, mainly the hippocampus. The mechanisms of damage might be repetitive clinical or subclinical seizures or even status epilepticus.⁴⁸ Cysticerci might also cause damage by inflammatory-mediated mechanisms.⁴⁸ If the cysticercus is located inside the hippocampus, direct physical damage might also occur and the entire process might be more intense.⁴⁰ Moreover, based on animal models

Figure 2 Sequence of three stages suggesting how neurocysticercosis (NCC) can lead to mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS). In Stage 1, there is active cysticercosis that generates seizures and might cause hippocampal damage or dysfunction (*). In Stage 2, cysticerci die and degenerate, possibly causing more hippocampal damage or dysfunction also by inflammatory mechanisms. In Stage 3, the cysticercus becomes slowly less active and calcified, but patients eventually develop mesial temporal lobe reorganization, seizures, and later on refractory MTLE-HS. Seizures originate in the cysticercus zone in Stages 1 and 2. In Stage 3, seizures might originate only from mesial temporal structures, causing difficulty in understanding a possible cause–effect relationship between NCC and MTLE-HS.

of cysticercosis, some authors have suggested that cysticerci could cause hippocampal abnormalities by other mechanism such as interference with gene expression, a question that remains to be explored for human NCC.^{49,50} In our view, it is possible that when patients in this stage are evaluated by neuroimaging and electrophysiology, cysticerci are active and neuroimaging shows no mesial temporal or hippocampal abnormalities (except if the cysticercus is located in mesial structures) and the electroencephalogram irritative zone might be more directly related to the anatomical localization of the cysticercus. In the second stage, when cysticerci die and are degenerating, seizures can be more frequent and intense, and inflammatory and immune-mediated mechanisms might become particularly important, although for a limited period of time. However, the combination of seizures and immune-mediated mechanism might be particularly relevant for hippocampal damage and later hippocampal reorganization. When patients are evaluated during this stage, neuroimaging and cerebrospinal fluid studies might reveal an intense immune-mediated process related to one or more cysticerci. In the third stage, the cysticercus or cysticerci slowly become calcified and mesial structures become reorganized. Seizures originating from the region containing cysticerci might enter into remission. On the other hand, concomitantly with the process of cysticercus calcification, damaged mesial temporal lobe structures and hippocampus reorganize

and patients eventually develop MTLE-HS and refractory MTLE-HS. When patients are observed during this stage, there is only cNCC and evidence of hippocampal sclerosis. Seizures, if present, especially if refractory, might originate only from mesial temporal lobe structures, mainly the hippocampus (Fig. 1). While computed tomography scans can easily observe cNCC, magnetic resonance imaging studies can show the hippocampal sclerosis or other mesial temporal abnormalities in detail and thus a combination of neuroimaging studies might be necessary for a better observation of the two pathologies. In this stage, a cause–effect relationship between NCC can be suggested, but not easily proved. Ideally, only a prospective study conducted on a large number of patients could reveal the full picture suggested here. However, for several reasons, this study would hardly be done. Nevertheless, we have lines of evidence that we can track and try to put together in order to understand this interesting, and perhaps frequent association.⁵¹ In spite of some initial evidence, much work needs to be done before we can understand the impact of NCC on the genesis of MTLE-HS. Thus, we believe that further studies will bring new evidence for a better treatment of these patients, providing new insights into the neurobiology of NCC, MTLE-HS, and into the occurrence of MTLE-HS plus cNCC.

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