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Update on Cysticercosis Epileptogenesis: the Role of the Hippocampus.

Permalink

https://escholarship.org/uc/item/3mj896vw

Journal

Current neurology and neuroscience reports, 16(1)

ISSN

1528-4042

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Publication Date

2016

DOI

10.1007/s11910-015-0601-x

Peer reviewed

INFECTION (J HALPERIN, SECTION EDITOR)

Update on Cysticercosis Epileptogenesis: the Role of the Hippocampus

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Abstract Neurocysticercosis (NCC) is the most common helminthic infection of the nervous system and a frequent cause of reactive seizures and epilepsy worldwide. In many cases, multiple episodes of focal seizures related to an identifiable parenchymal brain cyst (and likely attributable to local damage) continue for years after the cyst resolves. However, cases where seizure semiology, interictal EEG abnormalities, and parasites location do not correlate raise concerns about the causal relationship between NCC and either reactive seizures or epilepsy, as well as the epileptogenic potential of parasites. Neurosurgical series of patients with intractable epilepsy and cross-sectional population-based studies have shown a robust association between NCC and hippocampal sclerosis (HS), which might contribute to the above-referred inconsistencies. Current information does not allow to define whether in patients with NCC, HS could result from recurrent seizure activity from a local or distant focus or from chronic recurrent inflammation. In either case, HS may become the pathological substrate of subsequent mesial temporal lobe epilepsy (MTLE). Longitudinal clinical- and population-based cohort studies are needed to evaluate the causal relationship between NCC and HS and to characterize this association with the occurrence of MTLE. If a cause-and-effect relationship between NCC and HS is demonstrated, NCC patients could be assessed to examine neuronal mechanisms of hippocampal epileptogenesis in comparison with animal models, to identify biomarkers of hippocampal epileptogenesis, and to develop novel interventions to prevent epilepsy in NCC and perhaps in other forms of acquired epilepsy.

Keywords Cysticercosis · Neurocysticercosis · Hippocampus · Hippocampal sclerosis · Seizures · Epilepsy

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Neurocysticercosis Overview

The pork tapeworm *Taenia solium* may produce two different diseases, taeniasis (in humans only) and cysticercosis (in pigs or in humans). Taeniasis is the intestinal infection with the adult tapeworm, caused by ingestion of infected pork containing parasitic larvae (cysticerci), and is often a benign disease causing mild abdominal discomfort or no symptoms at all. Cysticercosis—resulting from the infection with the larval stage of *T. solium*—occurs when either pigs or humans get infected by eating the stools of a tapeworm carrier [1]. Ingestion of contaminated pork as the cause of human cysticercosis is a common misbelief, since the role of pigs is to perpetuate the infection cycle by causing human taeniasis, while human cysticercosis is mostly transmitted from person to person through non-hygienic handling of food or by direct contact with human feces. This explains the occurrence of autochthonous cases in regions where swine husbandry is adequate or nonexistent, as well as in countries where most of the population is vegetarian [2–4].

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Significant disease caused by cysticerci is often related to invasion of the central nervous system and its coverings, causing a condition called neurocysticercosis (NCC). The disease may be asymptomatic or may present with seizures, headaches, focal neurological deficits, increased intracranial pressure, or cognitive impairment; these manifestations may present alone or in combination, giving rise to complex and bizarre clinical syndromes that may result from inflammation, mass effect, blockage of the CSF transit, fibrosis, or vasculitis [5•, 6]. This clinical pleomorphism is mainly related to individual differences in the number and location of parasitic lesions within the nervous system (brain parenchyma, subarachnoid space, ventricular cavities, and spinal cord), as well as to the severity of the host's immune response against the parasite [5•].

The introduction of modern neuroimaging technology, together with improved immunodiagnostic tests, enhanced the diagnostic accuracy for NCC. However, both neuroimaging and serologic tests must be interpreted in the context of a given patient, to avoid overdiagnosis and misdiagnosis of NCC. Few neuroimaging findings are pathognomonic, and many serologic tests are faced with problems related to poor reliability. The only available systematization of diagnostic criteria [7] includes four categories of criteria (absolute, major, minor, and epidemiologic), allowing two degrees of diagnostic certainty (definitive and probable), according to the likelihood that NCC is present in a given patient (Table 1).

As noted, NCC is a pleomorphic disease that causes several neurological syndromes and pathological lesions. Therefore, characterization of the disease in terms of cysts' viability, degree of the host's immune response to the parasites, and location of the lesions is important for a rational therapy [8]. A first line of management should target the presenting symptoms and pathogenetic mechanisms involved in their occurrence. Therefore, proper institution of symptomatic therapy—antiepileptic drugs, analgesics, anti-inflammatory drugs, anti-edema agents, or surgery—should always be instituted before considering the use of currently available cysticidal drugs, albendazole, and praziquantel [5•, 8]. Cysticidal therapy is indicated in most cases of NCC and is effective to kill live parasitic cysts, although it may cause transient periods of symptom exacerbation due to peri-parasitic inflammation secondary to antigen liberation [5•].

Natural History of Parenchymal Brain Cysticerci

For a better understanding of the complex pathogenetic mechanisms involved in NCC-related epilepsy, it is necessary to review the involutive stages of parenchymal cysticerci. Soon after lodging into the brain parenchyma, most T. solium embryos evolve into viable cysticerci, which are in the so-called vesicular stage. These parasites elicit little or no inflammatory

Table 1 Diagnostic criteria for neurocysticercosis

Diagnostic criteria

Absolute criteria:
- Histologic demonstration of the parasite from biopsy of a brain or spinal cord lesion
- Evidence of cystic lesions showing the scolex on neuroimaging studies
- Direct visualization of subretinal parasites by fundoscopic examination

Major criteria:
- Evidence of lesions highly suggestive of neurocysticercosis on neuroimaging studies
- Positive serum immunoblot for the detection of anticysticercal antibodies
- Resolution of intracranial cystic lesions after therapy with albendazole or praziquantel
- Spontaneous resolution of small single enhancing lesions

Minor criteria:
- Evidence of lesions suggestive of neurocysticercosis on neuroimaging studies
- Presence of clinical manifestations suggestive of neurocysticercosis
- Positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens
- Evidence of cysticercosis outside the central nervous system

Epidemiologic criteria:
- Individuals coming from or living in an area where cysticercosis is endemic
- History of frequent travel to disease-endemic areas
- Evidence of a household contact with T. solium infection

Degrees of diagnostic certainty

Definitive diagnosis:
- Presence of one absolute criterion
- Presence of two major plus one minor or one epidemiologic criteria

Probable diagnosis:
- Presence of one major plus two minor criteria
- Presence of one major plus one minor and one epidemiologic criteria
- Presence of three minor plus one epidemiologic criteria

Adapted from Del Brutto OH et al. (2001)

changes in neighboring tissues and may remain in this stage for years or may enter—as the result of an immune attack from the host—into a process of degeneration that ends with their transformation into coarse mineralized nodules (calcified stage). From the vesicular to the calcified stage, cysticerci often go through intermediate stages of involution that are called colloidal and granular, respectively [9]. Colloidal cysticerci are surrounded by a thick collagen capsule and a mononuclear inflammatory reaction that includes the parasite itself; in addition, edema, astrocytic gliosis, microglial proliferation, neuronal degenerative changes, and perivascular cuffing of lymphocytes are commonly observed in the surrounding brain parenchyma. When parasites enter into the granular and calcified stages, the edema subsides but astrocytic changes may

become more severe, and epithelioid cells appear and coalesce to form multinucleated giant cells [10].

As mentioned, calcifications are the end result of most parenchymal brain cysticerci and may occur either spontaneously or after a therapeutic course with cysticidal drugs. Calcified cysticerci are erroneously perceived by clinicians as inert lesions. However, neuroimaging and histopathological studies have provided evidence that calcified cysticerci are not completely solid nodules but contain remnants of parasitic membranes [11, 12••]. Recurring inflammatory changes in the brain parenchyma around calcified cysts occur with some frequency causing seizures and some other clinical manifestations of NCC [13, 14]. These episodes of peri-calcification edema are attributed to periodic morphological changes related to mechanisms of remodeling (thus exposing the host immune system to trapped antigenic material), although it is unclear the role of seizures itself in causing or worsening perilesional brain edema.

Cysticercosis-related parenchymal brain calcifications are quite prevalent. In population-based studies using neuroimaging in cysticercosis-endemic areas, between 10 and 20 % of all villagers show one or more small, rounded calcified nodules in the brain parenchyma, which are rare in areas where NCC is not endemic [15, 16].

NCC, Seizures, and Epilepsy

Seizures occur in up to 80 % of symptomatic NCC cases and usually represent the primary or sole manifestation of the parenchymal form of the disease [18]. NCC is a leading cause of acquired epilepsy in most of the developing world and has been considered as the single most important disease explaining the excess fraction of epilepsy reported from these regions [19•]. It is not always possible, however, to distinguish reactive seizures caused by inflammatory changes, which can recur at long intervals, from epilepsy. Reactive seizures are symptomatic responses to transient brain insults, while epilepsy is a chronic condition indicating an enduring epileptogenic brain abnormality.

While it was initially believed that NCC-related seizures occur almost exclusively when parasites begin to degenerate, subsequent studies showed that parenchymal brain cysticerci in any of the above-described stages of involution may be associated with reactive seizures [5•]. However, pathogenetic mechanisms explaining the occurrence of reactive seizures differ according to the involutive stage of cysticerci. Viable cysticerci may induce reactive seizures due to compressive effects on the brain parenchyma or due to transient episodes of inflammation, or lead to persisting seizures if early established damage to the surrounding tissue is already set. Colloidal and granular cysticerci may induce reactive seizures as the result of the inflammatory reaction associated with the

attack of the host immune system to the parasites. On the other hand, with calcified cysticerci, the gliosis that develops around dead parasites, as well as late exposure of residual antigenic material to the brain parenchyma, could become an enduring epileptogenic lesion [20]. The presence of recurring inflammatory episodes and subsequent reactive seizure activity may cause permanent local or distant epileptogenic lesions that result in the occurrence of acquired epilepsy [21].

Patients frequently experience recurring episodes of focal seizures related to a specific parasitic lesion. Brain tissue around the parasite shows varying degrees of astrocytic reaction and neuronal damage [10], which become grossly evident after the cyst degenerates and enters the colloidal stage. It is often difficult to determine whether seizures originating from viable or degenerating parasites represent repeated episodes of reactive seizures rather than epilepsy. Unlike seizures occurring in patients with parasites in viable, colloidal, or granular stages, seizures occurring in the context of calcified cysticerci are much less likely to be reactive since the parasites have already left a gliotic scar in the brain parenchyma, although evidence of inflammation can be found in almost 50 % of these cases.

Seizures due to NCC may be generalized or focal [22]. Not infrequently, patients with NCC-associated epilepsy in endemic regions lack correlation between the location of the parasites, the semiology of seizures, and EEG findings, raising doubts on seizure causality and leading to hypothesize that in these cases, both conditions might merely occur by chance [23, 24]. While this is possible and might occur in a minority of cases, there is robust evidence favoring a causal relationship between NCC and seizures, including the higher prevalence of epilepsy in cysticercosis-endemic areas when compared with non-endemic regions areas [15–18, 19•] and the occurrence of focal inflammatory changes surrounding parenchymal brain cysticerci immediately after a seizure in about 50 % cases [25].

Hippocampal Sclerosis, Cysticercosis, and Epileptogenesis

Hippocampal sclerosis (HS) is the most common structural brain lesion associated with intractable epilepsy—particularly mesial temporal lobe epilepsy (MTLE)—worldwide [26]. Despite data compiled during the past decades from animal models and human studies, the causes of HS remain unknown. However, a sizable proportion of patients with HS and MTLE had an initial precipitating injury (perinatal trauma, recurrent febrile seizures, status epilepticus, traumatic brain injury), presumably leading to the development of neuronal loss in CA1 and CA3 hippocampal layers [27, 28, 29••]. In addition, some patients with HS and MTLE also have other potential brain lesions, such as focal dysplasia, located beyond the

hippocampus; in these cases, the term "dual pathology" has been used to define the occurrence of two distinct epileptogenic regions in the same individual, which may perpetuate the seizure disorder [29••].

Regarding NCC, there is robust evidence showing that calcified parenchymal brain cysticerci and HS often co-exist in cysticercosis endemic areas, but to what extent this occurs just by chance has been a matter of debate [30••]. During the past two decades, anecdotal case reports and small case series have brought this association to the attention of the medical community by describing patients with intractable MTLE whose neuroimaging studies showed granular or calcified cysticerci located within the hippocampus or in the neighboring cerebral tissue [31–37]. In some of these cases, pathological examinations revealed hippocampal atrophy with neuronal loss in the CA1 layer and gliosis, as well as the presence of an intense inflammatory reaction in the cerebral tissue surrounding the calcified parasites [31, 33]. As a result, it was postulated that calcified cysticerci in the hippocampal region could be the trigger for the development of both seizures and late hippocampal atrophy that, in turn, perpetuates the seizure disorder.

There is also evidence supporting an association between HS and calcified NCC lesions (outside the involved hippocampal areas). Several publications from a single center in Brazil [38–42], likely representing a single cohort of patients, revealed a surprisingly high prevalence of NCC cases (more than 35 %) among patients with MTLE and HS undergoing surgery for intractable epilepsy. This, together with certain characteristics of these patients with NCC (more often women, having less often a history of an initial precipitating injury and showing more bilateral temporal spikes), led the authors to conclude that NCC might be causally related to MTLE with HS. Conclusions from this Brazilian group have been supported by studies from the Indian Subcontinent, showing that patients with NCC and HS have more often lesions located near the hippocampus than those with NCC alone and that history of febrile seizures (as an initial precipitating injury) was less often recalled in patients with NCC, HS, and MTLE than in those with HS and MTLS alone [43]. Moreover, a series reported an improved clinical outcome after surgical resection of both the calcified cysticercus and the hippocampus than when the parasites were left in the brain [44•]. This evidence contrasts with the results of two studies suggesting that calcified cysticerci are a fortuitous finding in patients with MTLE and HS; in these studies, there were no clinical or pathological differences between NCC and non-NCC patients with HS [45, 46].

Besides the above described studies, conducted in selected patients undergoing surgery for medically intractable epilepsy, two studies reported the association between NCC and HS at the population level. In a case-control study comparing the prevalence of NCC across patients with different forms of epilepsy and patients with headache (without a history of seizures), NCC was significantly more frequent in patients with
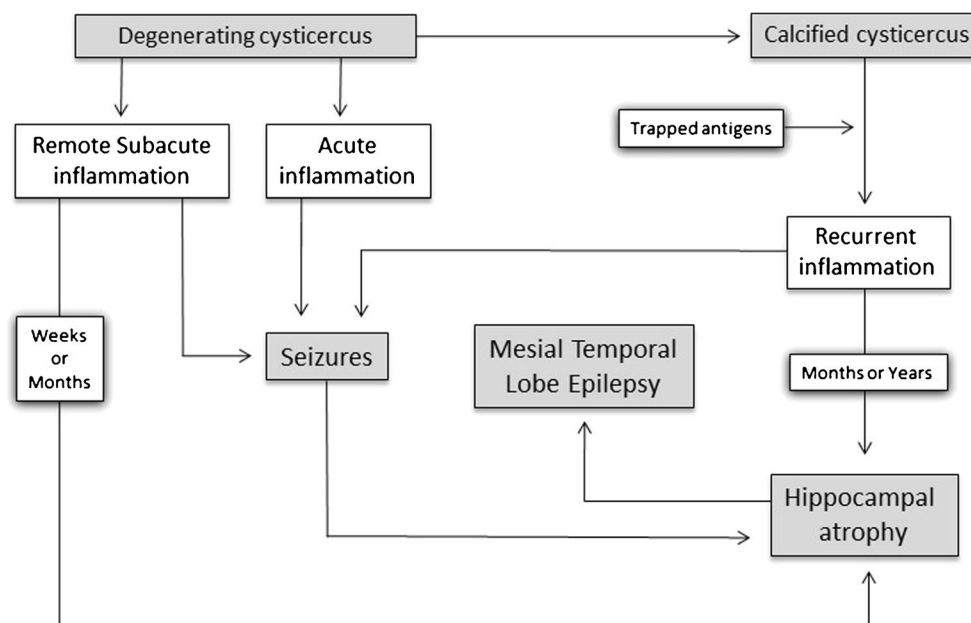
Fig. 1 Diagram showing the complex relationship between parenchymal brain cysticercosis, seizures, and hippocampal sclerosis. Seizures are frequent during cysticerci degeneration (colloidal and granular stages); in these cases, inflammation surrounding dying parasites is the most common mechanism causing acute reactive seizures. When parasites die (calcified stage), recurrent reactive seizures may result from bouts of inflammation related to exposure of the host immune system to parasitic remnants. Both, acute and recurrent reactive seizures, if repetitive, may cause hippocampal sclerosis which, in turn, could be the source of mesial temporal lobe epilepsy. In addition, degenerating as well as calcified cysticerci may directly induce hippocampal sclerosis by local or remote inflammation-mediated damage of hippocampal neurons causing chronic epilepsy

epilepsy than in controls and in patients with MTLE when compared to those with other types of epilepsy [47]. In a recent cross-sectional population-based study, conducted in a rural Ecuadorian village where NCC is endemic, calcified NCC was found to be significantly associated with hippocampal atrophy in community-dwelling older adults irrespective of whether they carried a diagnosis of epilepsy [48•].

In patients with parenchymal NCC, the relationship between seizures/epilepsy and HS seems to be bidirectional (Fig. 1). Acute or subacute inflammations associated with colloidal and granular cysticerci, as well as chronic recurrent inflammation related to calcified parasites, are triggers for recurrent reactive seizures that may cause HS, which, in turn, could be the pathological substrate for the subsequent development of MTLE. Parasites need not be located within limbic circuits, suggesting a remote deleterious effect of NCC-induced reactive seizures on hippocampal neurons. On the other hand, brain parasitic lesions may lead to an inflammation-mediated hippocampal damage associated or not with genetic susceptibility, not requiring recurrent seizures as a causative factor [49]. While the later pathway has not been demonstrated in humans, repeated endotoxin exposure and increased levels of pro-inflammatory cytokines correlate with hippocampal damage in mice independent of seizures [50].

Future Directions for Research

Despite a growing body of available evidence, the cause-and-effect relationship between NCC, HS, and MTLE is largely unknown. Longitudinal clinical- and population-based studies in cysticercosis-endemic areas, not solely based on epilepsy surgery center cohorts, are urgently needed to determine whether a causal relationship between calcified NCC and HS truly exists, to characterize this association with the occurrence of MTLE, and to determine whether neuroimaging features of HS in patients with NCC resemble those of classical HS [51]. These longitudinal studies would require both CT for proper recognition of calcified lesions and high-resolution MRI with voxel-based morphometry assessment of the regions of interest for categorization of subfield hippocampal atrophy, as well as careful clinical and EEG monitoring. Potential confounders such as genetic susceptibility, perinatal brain damage, history of initial precipitating injuries, and other co-morbidities should be documented.

If a cause-and-effect relationship between NCC and HS is demonstrated, NCC patients could be assessed to identify biomarkers and to examine neuronal mechanisms of hippocampal epileptogenesis in humans in comparison with animal models [52], which, with the exception of the ongoing Consequences of Prolonged Febrile Seizures in Childhood Study [53], have been scarcely investigated. Moreover, compared to

the existent traumatic brain injury model [54, 55], parenchymal brain calcified cysticerci have the advantage of being much more homogeneous and predictable in their structure and evolution than are traumatic brain lesions. Knowledge provided from these suggested cohort studies might also allow the development of novel interventions to prevent chronic epilepsy in NCC and perhaps in other forms of acquired epilepsy.

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