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Neurocysticercosis and Epilepsy

Arturo Carpio

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1. Introduction

Neurocysticercosis (NCC) is a biological marker of poverty and underdevelopment [1]. The frequency of this brain parasitic disease is probably high worldwide, as well as epilepsy; however, little is known about the natural history of the infection in humans. Both, NCC and epilepsy, are an increasing burden on the welfare and economy of developing countries [2]. This is why knowledge of these diseases should be improved, in order to prevent them.

Acute symptomatic seizures are the most common clinical manifestation of NCC in those patients in whom a cysticercus is located in brain parenchyma [1-3]. Epilepsy attributable to NCC usually has a good prognosis in terms of seizure control and seizure remission [1,4]. Although some authors have suggested that anticysticercal treatment is associated with reduced seizure recurrence, there is no evidence that cysticidal treatment does more good than harm in addition to conventional antiepileptic treatment [2,5]. According to new information, the traditional view of the relationship between NCC and epilepsy [2,3] can be questioned. Nowadays, NCC is considered a comorbid component of epilepsy [6].

2. Epidemiology of neurocysticercosis and epilepsy

In developed countries, the age-adjusted incidence of epilepsy ranges from 24 to 53/100,000 [7]. In developing countries (DC) the incidence of epilepsy on the basis of two studies carried out in South America in the last decade, ranged from 114 to 190/100,000 [8]; considerably higher than that reported in industrialized countries. New studies carried out in the last few years confirm high incidence: A hospital-based study of children in Tunisia reported the incidence of first unprovoked seizures to be 102/100,000 [9]. A population-based study carried out among children in Kenya, reported the incidence of epilepsy (two or more two unprovoked seizures) to be 187/100,000 [10]. In a population-based study among all ages in Honduras, Central America [11], the incidence of patients with non-febrile seizures was 92.7/100,000. Because of the broader case-inclusion criteria and uncertainty

regarding age-specific distribution in these studies, there is no way to compare results from these incidence studies. Nonetheless, the incidence of epilepsy is probably higher in DC than in industrialized countries [7].

Reported prevalence of active epilepsy, based on methodology recommended by the International League Against Epilepsy (ILAE) Commission of Epidemiology and Prognosis [12] in DC, ranges from 3.9 to 15.7 per 1,000 person-years [13]. These differences, however, are due to different approaches used by the studies and differences regarding the definitions of active epilepsy: Limiting assessment to those studies that provide information for age-adjusted rates, the average age adjusted prevalence of active epilepsy is 8.5/1,000, which is similar to the developed countries. This prevalence is low given the high incidence of epilepsy in DC and may be due to the fact that mortality of people with epilepsy is higher in comparison with that of developed countries. While studies from developed countries show a consistent pattern suggesting that the onset of epilepsy occurs at both extremes of life [7]; on the other hand, incidence in DC is highest among young and middle-aged adults [13], perhaps as a manifestation of diseases prevalent in these age-groups. This includes conditions such as brain injury and infectious and parasitic diseases endemic in these countries.

Taenia solium infection is widely endemic in poor countries, both in highlands or tropical areas, in Central and South America, and non-Muslim populations of Asia and Africa [1]. Cysticercosis is considered an emerging infectious disease in some developed countries; persons who have never left the United States as well as visitors to disease-endemic regions are at risk [2]. Data on the frequency of NCC from endemic countries have been compiled from clinic-based patients or autopsied cadavers. NCC was found, for example, in 2.8%-3.6% of all autopsies in some hospitals [14]. However, such statistics can be misleading because differences in availability of medical services and lack of comprehensive and consistent reporting in most countries still confound attempts to compare incidence and prevalence among countries [15]. Most reports fail to provide even minimal information regarding diagnostic criteria and definitions; consequently, these data are definitely biased and hardly representative of the general population.

Immunoserologic assays, such as enzyme-linked immunoelectrotransfer blot assay (EITB) or enzyme-linked immunosorbent assay (ELISA), detect antibodies against *T. solium* or *cysticercus* [1]. Epidemiological surveys for human cysticercosis, using EITB as a marker of infection, report a seroprevalence from 8% to 12% in some regions of Latin American [16,17]. These assays are useful for identification of individuals who have had systemic contact with the parasite at some time. Seropositivity, however, does not necessarily mean an active systemic infection or central nervous system (CNS) involvement at any time [1,18]. Most seropositive individuals in these populations were asymptomatic. There are no prospective cohort studies providing information on the proportion of seropositive individuals that will develop seizures or other neurological symptoms. Some studies [17], but not all [19] have reported an association between seizures and seropositivity. Although a higher proportion of patients with epilepsy have been shown to be EITB positive when compared to those without epilepsy, the proportion of seropositivity in epileptic patients is similar to that reported in the general population in these same areas [17].

3. Definitions of epileptic seizures, epilepsy and neurocysticercosis

In order to understand the relationship between epilepsy and NCC, it is crucial to promote consistency in definitions to enhance research studies, facilitate comparison between populations, provide data useful for detection, treatment, and prevention, and to promote effective health care for people with epilepsy and NCC [2].

The natural history of the cysticerci in the CNS is not entirely understood. Computed tomography (CT) and magnetic resonance imaging (MRI) have been useful in the study of the evolution of the cysticercus within the brain parenchyma [20]. Once the oncosphere has passed into the parenchyma, it grows and evolves through vesicular, colloidal, granular-nodular, and calcified phases [21]. In the vesicular phase the host tends to show immune tolerance, and in most cases there is no surrounding parenchymal reaction; the larva lives inside a translucent liquid-filled cystic structure surrounded by a thin membrane, where it can remain viable from a few months to several years [22]. The CT scan depicts circumscribed, rounded, hypodense areas, varying in size and number, without enhancement by contrast media [20]. With the MRI, the vesicular larva appears with a CSF-like intensity signal on all sequences, with no surrounding high signal on T2-weighted images. Both MRI and CT may show a high intensity, 2-3 mm. mural nodule, depicting the scolex, in the interior of some parenchymal vesicular cysts.

As the cyst degenerates, it goes through a transitional stage: the contrast enhanced CT scan shows an annular (colloidal phase) or nodular [nodular phase) enhancement surrounded by irregular perilesional edema [1,20,22]. In this stage, the fluid content gives slightly higher signal than CSF and is sometimes isodense with the parenchyma on MRI-T1 and/or proton density-weighted, and high signal on T2 images. The capsule shows higher signal than the adjacent brain with thick ring enhancement on T1 images, while on T2 images there is a low ring signal surrounded by high signal lesion, due mostly to edema. Although these pathological changes are responsible for clinical manifestations, usually seizures and headache, they may not cause symptoms at all. Finally, when the cyst dies it may disappear or become an inactive calcified nodule of homogenous high density on CT, or low intensity on proton-weighted MRI [1].

Based on the abovementioned concepts a classification based on the viability and location of the parasite in the CNS of the host has been proposed: active, when the parasite is alive; transitional, if it is in the degenerative phase; inactive, if there is evidence of its death [20]. Each viability category was subdivided into parenchymal and extraparenchymal forms. The viability criterion is very important, as it allows us to analyze the natural history of the parasite, and, according to the parasite's evolutionary stage, the production of physiopathological changes in the host's CNS. On the basis of this classification, it is possible to relate clinical manifestations and therapeutic procedures to each category of the proposed classification. For example, seizures are the main symptom in the transitional parenchymal form due to the brain inflammatory reaction, whereas cranial nerve abnormalities and intracranial hypertension syndromes are more frequent in the subarachnoid and intraventricular forms.

According to the definitions suggested by the International League Against Epilepsy's Epidemiology Commissions [6,12], epilepsy is defined as two or more unprovoked seizures occurring at least 24 hours apart. Unprovoked seizures may occur subsequent to a well-demonstrated antecedent condition, known to substantially increase the risk of epileptic seizures. New terminology and concepts proposed by the ILAE divide the causes of epilepsy into three broad categories: genetic, structural/metabolic, and unknown [23]. "The cause is considered structural/metabolic when a structural lesion (either static or progressive) or metabolic condition (e.g., inborn errors of metabolism) is present and is known to be associated with an increased risk of epilepsy." The cause is attributed to the condition that is most directly linked and proximate to the development of epilepsy, for example NCC, in the calcified phase.

An epileptic seizure is defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" [24]. Epileptic seizures, even if recurrent, are not always synonymous with epilepsy per se [6]. Provoked or acute symptomatic seizures are seizures which occur "in close temporal association with an acute systemic, metabolic, or toxic insult or in association with an acute central nervous system (CNS) insult (infection, stroke, cranial trauma, intracerebral hemorrhage, or acute alcohol intoxication or withdrawal)," [12,25]. Such seizures are often isolated epileptic events associated with acute conditions, but may recur if the acute condition recurs, as happens in the transitional or degenerative form of NCC, due to the underlying inflammatory process

The interval between the insult and the seizure—which is used to separate acute symptomatic from unprovoked seizures—may vary according to the underlying clinical condition [23,25]. In the NCC case, this interval lasts while the inflammation signs due to the transitional or degenerative cysts persist (six months on average). Nonetheless, if seizures occur in the presence of parasites in viable or calcified phase, they are unprovoked and, if recurrent, should be considered epilepsy [1-3].

Seizures associated with NCC may be categorized as either acute symptomatic or as remote symptomatic seizures. Individuals with cysticerci in the transitional form or degenerative phase develop acute symptomatic seizures due to the acute inflammatory response of the brain; on the other hand, a patient with seizures who has active, viable cysts and/or inactive, non-inflamed calcified parasites may be categorized as having unprovoked seizures [3]. NCC has an unpredictable clinical course, which makes it difficult to categorize all cases into the proposed classification of the ILAE Commission. For instance, a patient with chronic recurrent seizures, whose imaging studies show several non-inflamed parenchymal calcifications, should be categorized as having remote symptomatic unprovoked seizures. The same patient, some years later, can experience a recurrence of parenchymal transitional cysts. This case should be considered to have multiple episodes of NCC now resulting in acute symptomatic seizures.

The recent ILAE report defines comorbidity as the co-occurrence of two or more separate medical conditions in the same individual and includes NCC as a comorbid condition associated with epilepsy [6]. Ultimately, in patients with NC, what matters most is to

differentiate between provoked or acute symptomatic seizures and recurrent unprovoked seizures (epilepsy). This differentiation is very important, due to its implications concerning treatment and prognosis, as will be discussed below. Presumably, the inclusion of people with only acute symptomatic seizures as cases of epilepsy is one of the reasons for the high proportion of epilepsy reported in some studies [13].

4. Seizures as a main clinical manifestation of neurocysticercosis

In spite of the clinical heterogeneity and variability in the clinical forms of expression and evolution of NCC, all reports of medical literatures agree that seizures are the most common symptom of NC, occurring in 70-90% of patients [18,26]. However, seizure is more frequent when the parasite is located in the brain parenchyma of the patient, in comparison with the intraventricular or subarachnoid locations [20]. There is no uniformity in the reported distribution of seizure types in patients with NC. Some authors report a higher proportion of partial seizures, others conclude that generalized seizures are more frequent [1, 5, 27]. It seems that either generalized seizures or partial seizures with secondarily generalization are most commonly reported, while complex partial seizures are less frequent [1]

Seizures may occur at any evolutionary stage of the parasite. A recent prospective cohort study [28], whose aim was to describe seizure as a presenting symptom in individuals with recently diagnosed neurocysticercosis showed that most of the seizures in patients in the youngest age category (3–24 years old) appear to be provoked or acute symptomatic seizures due to transitional cysts in the brain parenchyma rather than new onset idiopathic ones. Thus, it appears that children are more likely to have NCC-related seizures than adults. The authors found transitional cysts to be associated with a significantly higher probability of seizure in the chi-square analysis; however, in the regression models that adjusted for patient age and gender as well as the number and location of the cysts, no specific cyst phase was found to be significantly associated with having seizures. Patients with cysts in the parietal lobe and with cysts in the frontal lobe were also more likely to present seizures.

It has been suggested that both age and gender influence the strength of the host's immune response. In a recent study [29] the odds of having transitional cysts were found to be 1.5-fold higher for the female patients than for the male; additionally, the number of transitional cysts was found to be 1.8-fold higher in the female patients than in the male, and this gender effect was not only statistically significant but also constant over time. It therefore appears that there are significant gender and age differences in the local immune response to NCC, even after adjusting for differences in healthcare access.

Some studies have also found familial aggregation of NCC infection [17, 30], as well as regional differences in the clinical manifestations of human NCC may indicate a role of host genetics [31]. However, in a recent study that investigated whether there is familial aggregation of seizures in first-degree relatives of NCC patients with seizure versus NCC patients without seizure as presenting symptom in a group of patients in Ecuador [32], there was no trend toward familial aggregation of seizures in NCC patients.

Neurologists from developing countries frequently see patients in whom the first seizure occurred many years before consultation; and when the second seizure occurs at the time of consultation, the imaging study shows one or more calcifications and one cyst in the transitional form with perilesional edema. We can assume that when the first seizures occurred, the patient had cysts in a transitional form, which eventually became calcified, and currently the patient has new acute seizures [1]. According to the ILAE Commission we should categorize these patients as having isolated epileptic events associated with a recurrent acute condition (transitional form) [3].

So far, the mechanism by which the calcified neurocysticercal lesions (CNL) cause seizures or epilepsy is not known [1,33,34]. This has been attributed to residual perilesional gliosis that results in chronic epileptogenic foci [33]. CNL are frequently encountered on CT scans of asymptomatic individuals, and studies from Latin American countries report that the majority are incidental lesions [30,35]. These observations would question the epileptogenicity of CNL. On the contrary, based on epidemiological studies, patients with epilepsy have a higher prevalence of calcified lesions than controls [19].

Another potential evidence for the epileptogenicity of CNL is the episodic appearance of edema surrounding the CNL after seizures. Some studies have suggested that perilesional oedema is associated with episodic seizure activity in patients with CNL [36]. The authors argue that episodic release of cysticercal antigens from the calcified lesions can lead to inflammation, perilesional edema, and seizures. These studies have not been replicated so far. Anyway, it is not clear whether this edema is causal or a consequence of the seizure [34]. Transient cortical edema after seizures, a rare neuroimaging finding, was described more than 20 years ago [37,38] but its mechanism has not been entirely clarified. The empirical observation of neurologists from NCC endemic countries is that perilesional oedema around calcification in patients with epilepsy are extremely rare and, when it happens, perilesional oedema disappears in a few days without any additional treatment, except for antiepileptic drugs.

Another study designed to analyze epileptogenesis in calcified neurocysticercosis using dynamic contrast-enhanced MRI [39], reported quantitative differences between symptomatic and asymptomatic groups in various perfusion indices. Median values of the rate transfer constant and leakage volume were higher in symptomatic patients than in asymptomatic patients, indicating a higher degree of blood brain barrier permeability in symptomatic individuals. This study also showed increased MMP-9 (R279Q) gene polymorphisms in subjects with seizures compared with those in asymptomatic and control subjects. Therefore, the epileptogenicity in patients with CNL could be related to degree of inflammation, which also may be partly determined by genetic factors. This study was carried out with a small sample of patients and should be confirmed in the future.

Single enhancing lesion and seizures. A single enhancing lesion on CT (SECTL) or hyperintense lesion on MRI is a common finding in patients with newly identified seizures in developing countries [40,41]. The patients, mainly children and young adults, have some benign and transitory clinical manifestations, predominantly partial or partial secondary

generalized seizures, and occasionally Todd's paresis or focal neurological deficits. These lesions have been attributed mainly to cysticercosis or to tuberculosis; however, similar lesions have been reported in other inflammatory pathologies such as pyogenic abscess, histoplasmosis, blastomycosis and sarcoidosis, post-infectious vasculitis, and to primary and metastatic brain tumors.

The natural history of these lesions usually takes one of two forms: it becomes isodense on CT, or isointense on MR, and then either resolves entirely, or a punctuate calcification may be left as a residue [41]. The time till resolution of the lesion is quite variable ranging from a few weeks to more than a year. SECTL are benign and tend to resolve spontaneously, without anticysticercal drugs or surgery, since the parasite is already in the degenerative phase and will eventually disappear or become calcified [1]. Treatment should be limited to medication required to control the acute symptoms, such as antiepileptic medication [2].

5. Neurocysticercosis as etiology of epilepsy

Analytical studies designed to establish associations and determinants of epilepsy have been scarce in DC. Comparing results of studies of etiology is difficult because of differences in definitions and lack of diagnostic criteria [3]. Most studies lack information on the latency between the first acute symptomatic seizure and the first unprovoked seizure, as well as age at onset of seizures and age at diagnosis. In studying etiology, it is preferable to use incident cases, not prevalent cases, because one cannot distinguish the potential etiological factors that preceded the onset of epilepsy from those which occurred after the disease developed. Cause and effect become confused. This is why it is extremely difficult to compare results of studies of epilepsy due to NC. These studies are few, and are frequently targeted at all seizures, instead of epilepsy alone. There are broad differences in the definition of NC, as well as failure to define criteria for diagnosis of either seizures or epilepsy.

Information available in developing countries shows that the proportion of idiopathic (60-70%) to symptomatic epilepsy (30-40%) is similar to that reported in studies from developed countries [8]. Among the symptomatic group, infection and parasitic diseases, particularly neurocysticercosis, perinatal brain damage, and head trauma are the most frequent disorders reported as a cause of epilepsy [5,42]. In a prospective cohort study of patients with newly-diagnosed epilepsy seen at the five main hospitals in the three major cities of Ecuador, perinatal brain damage (9%), neurocysticercosis (8.3%), central nervous system infections (4.2%), stroke (4.8%), and head trauma (4.2%) were the most frequent disorders reported as causes of epilepsy [42]. Although NCC is one of the most frequent antecedents among the symptomatic group, this disease is not necessarily the main cause of epilepsy, as has been previously suggested [11,17,43,44].

Hospital-based studies to analyze NCC as etiology of epilepsy are shown in Table 1. Studies of highly selected patients with seizures in neurologic services of hospital settings from some DC reported NCC as the main cause of epilepsy, accounting for 30% to 50% of patients [11,43]. In a study carried out in 212 patients with epilepsy, a rural sub-Saharan Africa area

endemic for porcine cysticercosis [45], 2.4% were identified as definitive and 11% had lesions highly suggestive of NCC, using CT scan as part of the diagnoses. In another study from Africa, 37% of patients with epilepsy had NCC [46]. In studies from India, in which acute symptomatic seizures were excluded, only 11% (47) cases with epilepsy had NC; conversely, in a study of 572 patients with acute symptomatic seizures 67% had SECTL [48]. Another study was carried out in India [49] to determine the etiologic role of NCC in a hospital-based sample in 1026 patients with epilepsies divided according to the ILAE epidemiological criteria. NCC was diagnosed in imaging studies in 59% of those with acute symptomatic seizures, but only 2.0% with prevalent epilepsy, and none of the cases of incident epilepsy.

Author Country/year (reference)	# Pts.	Case Ascertainment	Type of study	NCC (%)
Medina et al México/1990 (11)	100	All seizures, CT scan	Prevalent cases	50%
Del Brutto et al Ecuador/1991 (43)	225	All seizures, CT scan	Prevalent cases	40%
Murthy et al India/1999 (48)	572	Acute seizures CT scan	Retrospect (SCTEL)	67 %
Sawhney et al India/1996 (47)	407	Single Sz. Excluded CT scan	Prevalent and incident cases	11 %
Singh G, et al India/2006 (49)	1026	Single, incident and prevalent seizures CT scan	Single Sz Prevalent cases Incident cases	59 % 2 % 0 %

Table 1. Neurocysticercosis as etiology of epilepsy: Hospital-based studies

The above mentioned studies confirm the necessity to differentiate between acute seizure and recurrent unprovoked seizures (epilepsy). It is likely that most of the patients with NCC have acute symptomatic seizures which do not necessarily evolve into epilepsy. Similarly, it is crucial to determine NCC as etiology of epilepsy in incident cases instead of prevalent ones. These are probably some of the reasons of over diagnosis of epilepsy in some hospital-based studies [3]

Community-based studies in which CT scan was used to diagnose NCC are shown in Table 2. In a study carried out in Ecuador [43], the authors concluded that NCC is associated with one in three cases of epilepsy and was possibly the cause of the excessive proportion of epilepsy in that population. However, only three (8%) of 24 people with epilepsy had “definitive” NCC. Another community survey [44] carried out in Peru showed that seroprevalence (using the enzyme-linked immunoelectrotransfer blot (EITB) assay) was positive in 24.2% (200/825); 15 of 39 individuals with seizures (38.5%) had lesions compatible with NCC on CT scan. The authors concluded that brain CT abnormalities compatible with

NCC were more frequent in individuals with seizures and in those with positive EITB for cysticercosis. Most of the patients who were diagnosed with NCC in this study had only calcifications (half of them had just one calcification); however, it is well known that brain calcifications do not necessarily mean NC. The small population samples of the above studies do not allow generalizations.

Author Country/year	Patients with epilepsy	Inclusion criteria	Diagnosis of NCC	NCC No. (%)
Montano, et al Perú/2005 (44)	39	All seizures Prevalent cases	CT scan, > 50% only 1 calcification	15 (38)
Del Brutto, et al Ecuador/2005 (43)	19	Recurrent seizures Prevalent cases	CT scan, All pts had only 1 calcification	5 (26)
Medina et al Honduras/2005 (11)	100	Recurrent seizures Prevalent cases	CT scan,	37(37)

Table 2. Neurocysticercosis as an etiology of epilepsy: Community-based studies

There are several studies in the medical literature that have reported an association between epilepsy and NCC based on positive serum antibodies to *Taenia solium*/cysticercosis [17,50,51]. Unfortunately, the presence of antibodies may indicate only previous exposure to or infection with the parasite, but not necessarily brain infection. This information has created some distortion in the current perception of NCC epidemiology. A systematic review of the literature on the frequency of NCC, diagnosed with neuroimaging, has been published [15]. Overall, 565 articles were retrieved and only 26 had reliable information to estimate the frequency of NCC in various populations worldwide. The authors concluded that the prevalence of NCC worldwide remains unknown; however, the proportion of NCC among persons with epilepsy was very consistent and estimated at 29.6% (95%CI: 23.5%–36.1%) from 12 studies conducted in Latin America, Sub-Saharan Africa, and Southeast Asia.

6. Inconsistencies in the relationship between neurocysticercosis and epilepsy

There are clinical inconsistencies in the link between epilepsy and NCC. Parasite location may be remote from the apparent epileptogenic region [3]. There is also no correlation between the NCC burden of lesions and the severity of the epilepsy. Patients with severe refractory seizures may have only one calcified lesion; on the other hand, there are patients with multiple cysts or calcifications but no seizures.

EEG has been found to be abnormal in 30-50% of patients with seizures due to NC. It is assumed that EEG findings have poor correlation with symptoms and CT lesions in patients with NCC [52,53]. A positive correlation between CT lesions and localizing or lateralizing

EEG abnormalities has been reported for only 15-30% of patients. Similarly, the correlation between seizure type and EEG abnormalities ranges from around 7% to 20% [53]. Discrepancies between clinical localization based on seizure semiology and location of the lesion on neuroimaging is a not uncommon feature in patients with NC. A non-causal relationship between epilepsy and cysticercosis in some cases might explain these apparent discrepancies [54,55]. Further prospective cohort studies, properly designed to study ictal and interictal EEG abnormalities in patients with seizures, correlated with the different evolutionary stages of the parasite, may clarify the relationship between NCC and epilepsy.

The coexistence of hippocampal atrophy and extrahippocampal pathological abnormalities, such as cortical dysgenesis and gliosis, referred to as "dual pathology", has been reported in 5 to 30% of patients with medically refractory partial seizures [56]. Dual pathology implies that both lesions somehow interact with each other and contribute to epileptogenesis through mechanisms still poorly understood. Some authors have also attributed hippocampal sclerosis to NCC [54,57,58]. Patients with calcifications due to NCC and mesial temporal lobe epilepsy (hippocampal sclerosis) became seizure free after anteromesial temporal lobectomy, without resection of the cysticercotic lesion [35], suggesting the two phenomena are independent. The presence of CNL does not influence the clinical and pathologic profile of patients with hippocampal atrophy. An irritative zone in the temporal lobe is more relevant in determining the severity, symptomatology and frequency of seizures than the number and location of calcifications [59]. The possibility of dual pathology related to NCC needs further clarification in prospective cohort studies.

NCC and epilepsy are common diseases in most developing countries. Because of their high prevalence, a causal as well as fortuitous relationship between the two conditions might exist [35,54,60] NCC is also an uncommon cause of intractable epilepsy, even in endemic regions and that it may only represent a coexistent pathology, according to a cross sectional study investigating the etiology of intractable epilepsy in 512 patients in Brazil [61].

7. Effect of antihelminthic drug treatment on recurrence of seizures

Treatment for NCC with antihelminthic drugs (AHD) such as praziquantel and albendazole has been available for at least 25 years, and since then its use has been controversial. Praziquantel was used for the first time in México [62]. Albendazole was used for the first time in China [63].

To date, there are no controlled clinical trials to establish definitive doses and duration of treatment. A meta-analysis was published in 2005 [64], in which only 11 studies, among 764, were selected, only 6 with viable cysts and 5 with degenerative or coloidal cysts. The authors reported disappearance of viable cysts in 44% of patients who were treated with albendazole vs. 19% of the placebo group ($p < 0.025$). They also reported disappearance of degenerative cysts in 72% of patients of the albendazole group, and 63 % of the placebo group, but there was no statistical significance ($p < 0.38$). The Editors of the journal where this meta-analysis was published affirmed that selected studies were small and heterogeneous, and only 5 of 11 were good quality. They concluded that studies provided

limited evidence of a modest effect of NCC treatment, since the effects of cysticidal treatment on neuroimaging end points were relatively small (OR <2.2). A recent Cochrane review [65] of 21 randomized controlled clinical trials of cysticidal therapy concluded that with adults with viable cysts the use of albendazole is associated with a decrease in the number of cysts but not in the recurrence of seizures lesions.

One of the main reasons for which there is a lot of confusion in the medical literature and a supposed controversy regarding the effectiveness of AHD, is that most of the publications report “reduction of the number of lesions” as a valid endpoint to measure effectiveness of the treatment, which is misleading. We should wonder, for example, in the hypothetical event that a person with 10 viable cysts has been administered AHD, whether, as a consequence of the treatment, 8 parasites die (80% reduction of lesion/successful treatment?), but two cysts remain which may provoke seizures or headache: Is this a successful treatment? Maybe not.

The appropriate end point to evaluate the effectiveness of AHD could be the disappearance of cysts. Strictly speaking, even in the case that treatment with AHD may kill all parasites in a patient, it is not possible to talk about “cure” because, as we know, most cysts once they die become calcifications, a permanent sequel, which could aggravate seizures long life. If we compare those studies in which one of the end points to evaluate effectiveness of AHD is disappearance of cysts (table 3), including the results of the abovementioned meta-analysis, where about 30% to 40% of patients had disappearance of cysts [66-68]. Therefore, there is no controversy; we can affirm that, according to available evidence based medicine, AHD are effective in one third of patients, approximately.

8. Risk of seizure recurrence in patients with neurocysticercosis

Some authors report that NCC patients with acute symptomatic seizures have a good prognosis in terms of remission of seizures [69-73]; others report that most patients have a high risk of seizure recurrence, and suggest that prognosis improves after antihelminthic treatment. [66]. Prospective cohort studies have determined the risk of seizure recurrence after a first seizure due to NCC is between 17% to 56%, depending on the viability of the parasite. The risk is greater in the transitional forms and it diminishes in the viable or calcified forms [73-76]. Overall, the risk of seizure recurrence involves around one third of patients.

It has also been suggested that seizure control in patients with NCC is improved and that the chance of remaining seizure-free after the withdrawal of antiepileptic drugs is greater after a course of AHD, when compared with seizure control in those in whom the disease is left untreated [66]. However, current reliable information has shown that AHD treatment in patients with seizures due to NCC is not associated with the recurrence of seizures at all [67,68] (Table 3).

Regarding the duration for which antiseizure medication should be continued following an acute NCC episode, some clinicians routinely continue antiseizure medication for 1 year, but

shorter and longer intervals have been recommended [1]. One assumes that the risk of seizures is substantial as long as there is an active ongoing process as characterized by persistence of edema around the degenerating lesion. Because of this, CT scan is a useful tool for these treatment decisions. It is appropriate to monitor cyst activity with CT scanning and to continue antiseizure medication until resolution of the acute lesion. After this time antiseizure medication may be discontinued [1]. Seizures occurring in individuals after resolution of edema and resorption or calcification of the degenerating cyst should be considered unprovoked and, in this situation, long-term antiseizure medication is warranted.

Author/year, reference	Treatment groups (No. patients)	Cysts disappearance* No./%	Seizures recurrence** No./%
Garcia H, et al. 2004 (66)	Albendazole (55) Placebo (54)	21 (38%) 8 (15%)	32 (56%) 32 (54%)
Carpio A, et al. 2008, (73)	Albendazole (51) Placebo (50)	18 (35%) 6 (12%)	19 38%) 27 (48%)
Das K, et al. 2007 (68)	Albendazole (148) Placebo (150)	10 (7%) 12 (8%)	40 (27%) 24 (16%)

* CT scan at 6 months after finishing treatment

** Seizures recurrence at one year follow-up

Table 3. Effects of cysticidal drugs on resolution of parenchymal viable cysts and seizures recurrence in patients with neurocysticercosis (randomized, placebo-controlled studies)

It seems that interpretation of risk of seizures after neurocysticercosis is difficult. These difficulties are increased in those patients who have mixed forms, including active, transitional, and calcified lesions. Further studies should be performed in order to estimate recurrence risk in those patients with seizures due to calcifications alone, in comparison with patients with acute seizures due to transitional cysts.

9. Conclusions

Epilepsy and NCC are common diseases in poor countries, and NCC is increasingly diagnosed in developed countries due to migration from endemic regions. However, reliable data concerning prevalence and incidence of NCC is lacking worldwide.

Seizures are the most common symptom in patients with the parenchymal location of the parasite. Seizures may occur at any evolutionary stage of the parasite, but acute symptomatic seizures are more frequent in the transitional form, due to the inflammatory response of the brain. Most people with NCC have acute symptomatic seizures that do not necessarily evolve into epilepsy. This is one of the reasons that epilepsy is over diagnosed in some studies. The ILAE's Commission on Epidemiology includes NCC as a comorbid condition associated with epilepsy.

There are inconsistencies in the link between epilepsy and NC. Because of the high prevalence of each condition, a causal as well as fortuitous relationship between the two pathologies might exist. NCC is not necessarily the main cause of epilepsy in endemic countries, although it is one of the most frequent antecedents among adult patients with symptomatic epilepsy.

Several studies have reported an association between epilepsy and NCC based on positive serum antibodies to *Taenia solium*/cysticercosis. This information has created distortion in the perception of NCC epidemiology

Seizures in the context of edema and a degenerative lesion should be considered acute symptomatic even if they occur many months after presentation. After resolution of the acute lesion antiseizure medication may be discontinued. Seizures occurring after resolution of edema or calcification of the degenerating cyst should be considered unprovoked and, in this situation, long term antiepileptic medication is warranted. There is no correlation between treatment with antihelminthic agents and seizure recurrence

The prognosis of seizure in patients with NCC is good. In about two thirds of the patients with acute symptomatic seizures due to NCC the seizures do not recur [67] People with acute seizures NCC should be treated with antiseizure medication until cyst resolution on CT scan. The risk of seizure recurrence (epilepsy) occurs in the inactive or calcified form of NC.

Recommendations: Further research should be undertaken in order to clarify: -the natural history of *T.Solium*/cysticercosis disease, -the variability of antihelminthic treatment efficacy, -the factors that contribute to clinical heterogeneity of NC, -immunological response of the host. It is also recommended to standardize a common methodology, including definitions, in order to propose new diagnoses criteria for NCC.

Health authorities should focus on prevention and eradication of taeniasis/cysticercosis in order to decrease the number of individuals with seizures/epilepsy and other consequences.

Author details

Arturo Carpio

School of Medicine, University of Cuenca, Ecuador

G.H. Sergievsky Center, Columbia University, New York, USA

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