HHS Public Access

Author manuscript

Epilepsy Behav. Author manuscript; available in PMC 2018 November 01.

Published in final edited form as:

Epilepsy Behav. 2017 November ; 76: 158–162. doi:10.1016/j.yebeh.2017.03.013.

Antiparasitic treatment of neurocysticercosis - the effect of cyst destruction in seizure evolution

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Abstract

Antiparasitic agents against *Taenia solium* cysticercosis are in use since 1979, although its use has been questioned on the basis that cysts would die naturally and thus treatment-induced inflammation is unnecessary. In addition, isolated reports have also questioned whether neurocysticercosis (NCC) is a cause of epilepsy. After more than three and a half decades, a large body of evidence is available. Little if any doubt exists on NCC as a cause of seizures - NCC is consistently associated with seizures when appropriate groups are compared, and in a large subset of cases, seizure semiology correlates with the anatomical location of lesions. Cyst degeneration and the subsequent inflammatory reaction increase seizure expression, although patients with non-inflamed cysts may show seizures, as do patients with long-standing, not inflamed calcified scars. Assessment of the evidence on cysticidal efficacy, safety, and the impact of cyst destruction in decreasing seizures leads to conclude that the benefits of antiparasitic treatment in parenchymal brain cysticercosis clearly overcome the risks, and have provided substantive evidence of the role of NCC as a cause of seizures and epilepsy. Antiparasitic therapy should be considered a primary option in the management of patients with live or degenerating brain NCC cysts.

Keywords

Cysticercosis; neurocysticercosis; seizures; epilepsy; albendazole; praziquantel; *Taenia solium*

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Authors' contributions: Oscar H. Del Brutto: study concept and design, manuscript drafting; Hector H. Garcia: study concept and design, manuscript drafting.

Disclosures. Dr. Garcia is supported by a Wellcome Trust International Senior Fellowship in Public Health and Tropical Medicine and is funded by FIC NIH Training Grant TW001140 and NINDS U01 NS086974. Dr. Del Brutto is supported by Universidad Espíritu Santo – Ecuador, Guayaquil – Ecuador.

1. INTRODUCTION

The use of antiparasitic drugs in the treatment of human neurocysticercosis (NCC) has been matter of a continuous and intense debate. More than 35 years after the introduction of PZQ as the first effective cysticidal agent,[1] there is now a large body of evidence to assess the benefits and contraindications of this therapy and, in particular, whether the destruction of parenchymal brain cysts reduces the risk of seizure recurrence in the long term. We provide here a description of the evidence linking NCC to seizures and epilepsy, a recount of the events that followed the adoption of praziquantel (PZQ) and albendazole (ABZ) as agents to destroy brain cyst in human NCC, and a compilation of controlled studies assessing seizure activity in relation to the efficacy of antiparasitic treatment.

2. ASSOCIATION BETWEEN NEUROCYSTICERCOSIS AND SEIZURES

NCC has been associated with epilepsy since its initial finding in 1558, when Rumler found “tumors” in the meninges of a patient with epilepsy.[2] There are numerous case series and case descriptions of patients with cysticercosis and epilepsy in the British and German literature from the late XIX and early XX Centuries,[3–5] but perhaps the most enlightening body of literature was crafted by medical officers of the British Army between 1932 and 1961, [6–9] where they described NCC as the cause of epilepsy in 450 British soldiers who were infected while on duty in India. From then on, thousands of NCC cases with seizures and epilepsy have been reported in medical journals.[10–13]

This abundant literature is further supported by epidemiological studies comparing the frequency of specific antibodies,[14–16] circulating parasite antigen,[17,18] or computed tomography (CT) or magnetic resonance imaging (MRI).[15,19] When comparable populations are assessed, NCC has been found to be two to four times more frequent in individuals with seizures or epilepsy than in control groups.

At an individual level, the cases of patients with seizures and NCC demonstrated in neuroimaging studies, in particular the large subset of cases where the semiology of the seizures correlates with the anatomical location of the cysticercosis lesions,[20–23] leave little space for doubt on whether the parasitic lesions can act as epileptogenic foci.

3. FREQUENCY AND EVOLUTION OF SEIZURES IN PARENCHYMAL BRAIN CYSTICERCOSIS

A major contributor to the wide variability of clinical manifestations in parenchymal NCC is the stage of the parasitic larvae in the brain of the host, whether it is a viable larval cyst, a degenerating lesion, or a residual, calcified lesion.[24] The natural and post-treatment evolution of parenchymal cysts has been described elsewhere.[25,26] We will focus on the available information on seizure frequency and evolution by each stage.

3.1. Seizures in individuals with viable brain cysts

Patients with viable cystic brain lesions compose a significant proportion of all NCC cases in endemic countries.[27] Studies in British soldiers returning from India[6–9] showed that, in

many cases, seizures begin between 3 and 5 years after the end of exposure. It follows that established brain cysts can remain apparently asymptomatic for such periods. Some authors contend that seizures only occur after one or more of the cysts develop an inflammatory response.[27] This is frequently, although not necessarily always, the case. The initial trials of antiparasitic treatment in the 1980s claimed to recruit patients with no signs of inflammation on CT.[28–30] It could of course be argued that the sensitivity of old CT equipment was not that high and mild inflammation could have been missed. Symptomatic cases of viable NCC without apparent signs of inflammation on MRI can also be found in the literature. Moreover, seizures (and likely also pericystic inflammation), do not seem to prelude the degeneration of a viable cyst, at least in the short to medium term. Cases where a living cyst is associated with corresponding focal seizures for several years demonstrate that even if an inflammatory response is present, it would not necessarily evolve to the degeneration of the cyst. In a double blind, placebo-controlled treatment trial 49% (29/59) of cysts with signs of inflammation on baseline MRI in the placebo arm were still viable after six months of follow.[31] The possible explanations for seizures in NCC patients with only non-inflamed cysts are thus a) cysts without inflammation cause seizures, b) neuroimaging studies, even MRI, may also miss mild inflammation, and/or c) viable cysts may experience transient inflammation episodes and return to a viable, non-inflamed status.

3.2. Seizures in individuals with degenerating cysts

As the process of cyst involution is a continuum, there is not a defined point where a “cyst with signs of inflammation” becomes a “degenerating cyst”. Depending on the authors, this could be either when the cyst contents become proteinaceous and thus the signal of the cyst contents differs from that of the cerebrospinal fluid,[25] or when there are no discernible liquid cyst contents and only a ring or nodular enhancing signal is apparent.[31,32] Of note, the vast majority of patients with NCC in the Indian subcontinent presents with a single degenerating brain cysticercus.[33] Seizures in patients with degenerating cysts are more frequent, and thereafter decrease in frequency after inflammation resolves (along with resolution or calcification of the parasitic lesion).

3.3. Seizures in individuals with only calcified cysts

If well many patients with calcifications will never develop seizures or EEG abnormalities consistent with epileptiform discharges, a sizable number of these will do have seizures or epilepsy. In large series of symptomatic patients with NCC attending clinical centers, 20 to 40% of all cases present with only calcified lesions.[34,35] These individuals may have had seizures for years (thus making unclear if seizures begun before their cysts died), or may have all their lesions already dead by the time seizures started. Interestingly, a sizable proportion of individuals with symptomatic calcified NCC show peri-calcification edema around at least one of their lesions at the time of a seizure recurrence.[36] The most likely explanation for peri-calcification edema is an inflammatory response against residual antigens remaining within the calcified matrix, which periodically become exposed to the host immune system due to a process of calcification remodeling. However, it cannot be ruled out that edema and enhancement result from seizure-driven disruption of the blood-brain barrier.[36,37]

4. NEUROCYSTICERCOSIS AND EPILEPSY

NCC patients frequently present with repeated episodes of seizures of the same type. In one series of patients with live or degenerating cysts and a first seizure, relapses accounted for 32% in one year, and 48% in four years.[38]

Relapses in patients with NCC and more than one previous seizure are frequent, more in individuals with multiple viable cysts or calcifications, and a bit lower in individuals with a single degenerating brain parasite. The scarce data on the frequency of seizures in individuals with viable NCC who are not treated with antiparasitic drugs suggests high rates of seizure relapses. Initial case-control studies demonstrated 100%[39] and 74%[40] of seizure relapses by one year in patients who did not receive antiparasitic treatment, although these numbers are likely increased by non-compliant patients, self-selected when they refused antiparasitic treatment. The only placebo-controlled trial in viable NCC that used MRI to define cases reported seizure relapses in 29/59 (50%) control patients receiving antiepileptic drug treatment along 2 1/2 years of follow up.[31] In another study, a steroid-treated control group is reported to have a proportion of patients seizure free at 12 months of follow-up of 0.52 using Kaplan–Meier survival analysis.[41] In patients with viable cysts who receive antiparasitic treatment, seizure relapses are associated with having surviving cysts[32] or residual calcifications.[42]

Seizure relapses in patients with a single degenerating cysticercus are less frequent, around 20 to 30% in the initial year of follow up.[43–48] Single brain lesions leaving a residual calcification are strongly associated with an increased risk of seizure relapse.

In individuals with only calcified NCC the rate of seizure relapse is high (30–50% in two years),[36,37] and a sizable proportion of them show peri-calcification edema around at least one of their lesions at the time of a seizure.[38]

According to the International League Against Epilepsy (ILAE), epilepsy is now defined as *"a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (3) diagnosis of an epilepsy syndrome".*[49] Most cases of symptomatic NCC seen at clinical centers fulfill one or both of the initial two criteria.

4.1. Neurocysticercosis, seizures and inflammation

There are multiple potential factors contributing to seizure activity in NCC, including the location and evolutionary stage of each lesion, as well as the individual genetic background and the presence of concomitant or secondary comorbidities.[50] Inflammation seems a major driver for seizures in NCC, evident both in viable cysts with perilesional inflammatory reactions, degenerating cysts and in calcified cysts with perilesional edema. Some authors have claimed that seizures associated with viable or degenerating cysts are transient (reactive seizures), merely as the result of a temporary episode of inflammation and thus with no impact in future seizure relapses.[51] This erroneous conceptualization assumes that the

parasite does not cause a permanent damage in the brain and thus increase subsequent susceptibility to seizures.

It is difficult to accept cysticerci as a transient insult to the surrounding brain parenchyma. Initially, the parasitic cysts establish and modulate the immune response, with minimal pericystic inflammation and focal reactive gliosis.[52,53] Once the host's immune system breaks the immune evasion defenses of the cyst, a focal inflammatory response involving cytokine production and cellular infiltration initiates the process of destruction of the cyst,[53–55] with an evident inflammatory reaction involving BBB rupture and perilesional edema. Then the parasite is destroyed and the inflammatory process subsides, with eventual resolution on neuroimaging, or leaving a residual calcification. Seizures also occur from calcified cysts, sometimes with perilesional edema at the time of a seizure, sometimes without it. Additionally, multiple reports suggest that NCC may lead to mesial temporal sclerosis as a secondary epileptogenic focus.[56–59] Repeated focal seizures along years or even decades in patients with NCC suggest a structural damage and formation of epileptogenic circuits, independent of the contributory effect of transient episodes of inflammation.

5. ANTIPARASITIC AGENTS IN NEUROCYSTICERCOSIS

It was only in 1979 that PZQ was described as the first etiological treatment against cysticerci in the human brain, using a dose (50 mg/kg/day) and time (15 days) estimated based on experiments in animals.[1] The initial reports were followed by multiple case reports and case series, and the enthusiasm was fostered by the availability of CT to demonstrate the disappearance of brain cystic larvae following PZQ therapy. However, treating physicians also became rapidly aware that the use of PZQ in NCC was not such an easy job. Patients presented increased neurological symptoms during the initial days of antiparasitic treatment, including seizures and intracranial hypertension, with some patients dying.[60,61] This was interpreted as the result of an inflammatory response and successfully managed by concomitant use of corticosteroids.[62] Albendazole was later introduced as a more available and cheaper agent, with apparently more cysticidal efficacy than PZQ.[30,63–65]

Soon after the introduction of PZQ as the first specific agent against NCC some authors raised concerns about the need for antiparasitic therapy, based on the assumption that brain parasites in symptomatic NCC cases were already in degeneration, so parasite destruction by drug therapy should not affect the evolution of the underlying seizure disorder.[66,67] Other authors even questioned whether antiparasitic drugs really destroyed the parasites.[66] The arguments in favor and against the use of antiparasitic drugs for NCC are varied and we have tried to summarize them in Table 1.

Key to understand this bipolarity in arguments is the varied clinical expression of NCC and its different spectra in most endemic countries (where multiple brain cysts and subarachnoid disease, variants associated with chronic disease and higher morbidity occur with frequency), compared to its presentations in non-endemic countries or the Indian subcontinent, where severe NCC is much less frequent.[24,33] Claims for the use of antiparasitic agents came principally from countries where multicystic disease was frequent

(Mexico, Brazil, Ecuador),[11,28–30,40,60] while with rare exceptions, claims against the use of antiparasitic treatment came from non-endemic countries (USA, UK) or the Indian subcontinent.[67–70]

5.1. The role of steroids

As mentioned lines above, steroids are given concomitantly with antiparasitic agents to reduce the inflammation that is triggered by the death of the parasites. A wide variety of regimes can be found in the literature, with different steroid drugs (dexamethasone, prednisone, prednisolone, etc), doses, time of administration, and length of steroid administration. Most authors use dexametasone at 0.1 to 0.2 mg/k/d, from one day before the onset of antiparasitic therapy, with gradual tapering. Steroids may also be required to control perilesional edema or other causes of intracranial hypertension not related to antiparasitic treatment.[71]

6. EVOLUTION OF SEIZURES IN RESPONSE TO ANTIPARASITIC TREATMENT

Seven blinded randomized controlled trials have assessed the evolution of seizures in patients treated with antiparasitic drugs.[31,41,43–46,48] Five prospective controlled studies evaluating seizures after antiparasitic treatment in NCC included only patients with one or two small, degenerating lesions (all conducted in India). Four of these five studies in degenerating lesions found fewer seizure relapses in patients treated with ABZ and steroids (ORs 1.5, 2.4, 2.4 and 3.2),[43–46] and one found fewer seizures in patients who did not receive antiparasitic drugs (OR 0.3).[48]

Three randomized controlled trials related to antiparasitic treatment in patients with viable NCC cysts have been published, two of which were placebo controlled. In the first one, patients with epilepsy and viable parenchymal cysts were randomized to receive ABZ plus dexamethasone (n=60) or two placebos (n=60). There were fewer seizures in patients in the ABZ group (significant for seizures with generalization, non-significantly higher for partial seizures). Subgroup analysis also demonstrated fewer seizures in patients whose cysts resolved, independently of treatment group.[31]

A second trial compared patients with at least one viable or transitional parenchymal cyst receiving ABZ plus prednisone (n=90) versus placebo of ABZ plus prednisone (n=88), including 28 patients with also extraparenchymal cysticercosis. This study was initially reported as finding no differences in seizures between groups,[41] although further exploratory analysis found significantly fewer seizures with generalization in the ABZ group.[72] Of note, the antiparasitic efficacy of ABZ in this study markedly differed from that in a previous open study by the same group, that concluded that *“at 6 months and at 1 year after treatment, there were no differences in the three treatment groups in terms of the proportion of patients who were free of cysts or the relative reduction of number of cysts.”*[66] There is no information in either of the publications regarding the numbers of seizures in patients whose cysts resolved compared to those with remaining live cysts. In addition, a randomized trial

comparing two antiparasitic regimes[32] demonstrated fewer partial seizures (and thus fewer overall seizures) in patients whose cysts resolved after antiparasitic treatment.

Fewer seizure recurrences do not necessarily mean a seizure-free state. Independently of receiving antiparasitic drugs or not, a sizable proportion of patients with cystic disease will have at least one seizure in their follow up. The proportion of patients free of seizures in the follow up is usually around 50%, although relapses are significantly more frequent when calcifications are left on the brain parenchyma after therapy.[31,42] Repeated seizures in patients in whom their cysts had resolved suggests that epileptogenic foci established before the parasite died.

Most authors now accept that antiparasitic treatment should be used in patients with viable cysts. Reasons include not only the evidence for fewer seizures in the follow up but also the decreased risk for disease progression, although the real proportion of patients whose cysts grow or cause other types of complications, or the proportion of patients initially diagnosed of parenchymal NCC who will later unveil extraparenchymal lesions cannot be assessed because of the lack of untreated patient cohorts. Side effects of antiparasitic treatment (most frequently headache and seizure events) occur with relative frequency but are easily managed by interrupting antiparasitic therapy and increasing the concomitant steroid therapy.[71] Serious side effects occur rarely and involve stroke and acute hydrocephalus, mainly observed in patients with subarachnoid cysts or basal arachnoiditis.[73] So far, there is no evidence to sustain that histological and immunological sequels of parenchymal NCC treated with antiparasitic drugs could be worse than those arising from the natural involution of the cyst.

7. CONCLUSIONS

Assessment of the published evidence on cysticidal drug efficacy, safety, and the impact of cyst destruction in decreasing seizures, leads to conclude that the benefits of antiparasitic treatment in parenchymal brain cysticercosis clearly overcome the risks, and have provided substantive evidence of the role of NCC as a cause of seizures and epilepsy. Antiparasitic therapy should be considered a primary option in the management of patients with live or degenerating parenchymal brain cysts. Before considering the start of antiparasitic treatment, patients should have their symptoms well controlled, with particular attention to the presence of intracranial hypertension, and side effects should be beard in mind and weighted according to the number, size and location of cysts.

Acknowledgments

Funding: No external funding.

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Highlights

- Neurocysticercosis is a major cause of seizures and epilepsy in vast regions of the world.
- Antiparasitic agents against *Taenia solium* cysticercosis destroy parasitic cysts and have been used since 1979
- Benefits of antiparasitic treatment in parenchymal brain cysticercosis (in terms of efficacy, safety, and the impact of cyst destruction in decreasing seizures) clearly overcome the risks.
- Antiparasitic therapy is a primary approach for the management of patients with live or degenerating brain NCC cysts.

Table 1

Arguments in favor and against the use of antiparasitic treatment in NCC

In favor	Against
• Rapid disappearance of cysts. • Series of ABZ or PZQ-treated patients have better clinical evolution (have less seizures) than not-treated patients seen at the same centers. • Severe cases are seen less frequently now	• Anti-parasitic treatment causes severe, acute, unnecessary brain inflammation. • Treatment-induced inflammation or stroke can be fatal. • No need: NCC becomes symptomatic after several years, when the parasite dies.

Table 2

Prospective randomized controlled trials assessing seizure frequency after antiparasitic treatment in patients with single degenerating cysticerci

Trial	N	Intervention	Comparator	Seizures
Baranwal et al [45]	63	ABZ 15 mg/kg/d x 28 days	Placebo	4/31 cases (13%) versus 10/32 controls (31%), OR 2.4
Chaurasia, et al [48]	67	ABZ 15 mg/kg/d x 3 days	Placebo	3/33 cases (9%) versus 1/34 controls (3%), OR 0.3
Gogia et al[43]	51	ABZ 15 mg/kg/d x 28 days	Placebo	3/24 cases (13%) versus 5/27 controls (19%), OR 1.5
Kalra et al[44]	89	ABZ 15 mg/kg/d x 28 days	No ABZ	6/44 cases (14%) versus 15/45 controls (33%), OR 2.4
Singhi et al[46]	73	ABZ 15 mg/kg/d x 28 days	No ABZ	4/35 cases (11%) versus 14/38 controls (37%), OR 3.2