Published in final edited form as:
Lancet Neurol. 2008 December ; 7(12): 1099–1105. doi:10.1016/S1474-4422(08)70243-6.

Perilesional brain edema and seizure activity in patients with calcified neurocysticercosis

Theodore E. Nash, MD, **E. Javier Pretell, MD**, **Andres. G. Lescano, PhD**, **Javier A. Bustos, MD**, **Robert H. Gilman, MD, DTMH**, **Armando E. Gonzalez, DVM, PhD**, and **Héctor H. Garcia, MD, PhD for The Cysticercosis Working Group in Peru.***
Laboratory of Parasitic Diseases. National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD (T.N.), Department of Transmissible Diseases, Instituto Nacional de Ciencias Neurologicas, Lima, Perú (E.P., H.G.); Currently, Department of Neurology of the Hospital Alberto Sabogal, Callao, Peru (EP); Facultad de Salud Pública y Administración, Peru (A.L.) and Department of Microbiology (J.B., H.G., R.G.) Universidad Peruana Cayetano Heredia, Lima, Perú; Department of International Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD (R.G., A.G, H.G..); Instituto Peruano de Parasitología Clinica y Experimental – INPPACE, Lima, Perú, (R.G., A.G., H.G.), and Department of Public Health, School of Veterinary Medicine, Universidad Nacional Mayor de San Marcos, Lima, Perú (A.G.)

Abstract

Background—Cysticercosis due to *Taenia solium* is a leading cause of adult acquired seizures and epilepsy that frequently occurs in patients with only calcified larval cysts. Transient episodes of perilesional brain edema occur around calcified foci but its importance, association with seizures, incidence, and pathophysiology are unknown.

Methods—One hundred and ten persons with only calcified lesions and a history of seizures or severe headaches were followed prospectively in a cohort design to assess the incidence of seizure relapses. In a nested case-control sub study, perilesional edema was assessed by MRI at the time a seizure occurred in the symptomatic patient and in a matched asymptomatic control, amongst the 110 followed.

Results—Median follow up was 32.33 months (SD 19.99). Twenty-nine people had an incident seizure with an estimated 5 year seizure incidence of 36%. Twenty-four patients of the 29 with seizure relapse had an MRI evaluation within five days of the event. Perilesional edema was found in 12 (50.0%) compared to 2 of 23 asymptomatic matched controls (8.7%).

Conclusions—Perilesional edema occurs frequently and is associated with episodic seizure activity in calcified neurocysticercosis. Our findings are likely representative of symptomatic patients in endemic regions and suggest a unique and possibly preventable cause of seizures in this population.

Communicating author: Theodore E. Nash, MD. Head, Gastrointestinal Parasites Section, Laboratory of Parasitic Diseases. National Institutes of Allergy and Infectious Diseases, National Institutes of Health. 9000 Rockville Pike, Bldg 4, Rm B1-01, Bethesda, MD 20892. Telephone (301) 496 6920, Fax (301) 402 2689, tnash@niaid.nih.gov.

Conflict of interest: The authors report no conflicts of interest.

Authors contributions: Dr. Nash was the principal investigator and Dr. Garcia had overall responsibility for running and performance of the trial in Peru. Dr. Pretell was the neurologist in charge of clinical evaluations and diagnosis and Dr. Bustos was responsible daily administration of the study. Drs. Lescano, Gilman Gonzales, and Garcia were responsible for study design, statistical design and analysis, critical review of the manuscript.

Keywords

Cysticercosis; Neurocysticercosis; Calcification; *Taenia solium*; Seizures; Epilepsy

Introduction

Neurocysticercosis (NCC), an infection of the larval form of the *Taenia solium* tapeworm, is the most common cause of acquired adult seizures and epilepsy in endemic regions [1]. After humans ingest raw or undercooked pork containing *T. solium* cysticerci (cysts), a tapeworm develops in the intestine. Tapeworm eggs released into the feces and ingested by free roaming pigs or accidently by humans hatch and the developing oncopheres are distributed most likely via the blood stream (mostly to the brain, muscles and subcutaneous tissues) and develop into cysts. In humans, the most serious disease manifestations are due to cysts that lodge in the brain or surrounding spaces, spinal cord, or eye.[2]

Viable brain cysts eventually degenerate provoking a host inflammatory response and later evolve into granulomas that frequently calcify.[3-6] Degenerating cysts are a frequent cause of morbidity and seizures, and most of the literature in NCC focuses on the clinical or therapeutic aspects of viable or degenerating cysts. Calcified lesions, however, are the most common cerebral finding of NCC because they accumulate in the brain and are a measure of prior infections.[7] This has been observed both in hospital settings (symptomatic cases) as well as in the general population of endemic regions where 10-20% of neurologically asymptomatic individuals demonstrate characteristic calcified cerebral lesions by CT examination.[7-12] However, the importance and disease manifestations associated with calcified lesions have not been well characterized. In fact, this stage of the disease is still regularly referred to as inactive NCC, implying an end stage and/or a state of less clinical importance.[13-15]

There is increasing recent evidence implicating calcified NCC in the genesis and/or maintenance of seizures and epilepsy in endemic populations. First, typical calcified brain lesions are common in CT studies of persons who present with seizures in endemic regions.[7] Second, in population-based studies using CT examinations, calcified lesions are much more frequent than viable cysts and more prevalent in symptomatic compared to asymptomatic patients. Lastly, when symptoms appear in individuals with only calcified disease, some show perilesional brain edema around one or more of the calcifications.[7]

Perilesional brain edema associated with calcified lesions is a recently described phenomenon.[16] Although it was first noted in the mid 1990's[17-19] its potential clinical significance and characteristics are not well defined. Even now, symptomatic patients with perilesional edema around calcifications are commonly misdiagnosed as refractory neurocysticercosis and unnecessarily treated with anthelmintics or even subject to brain biopsies. Collected series suggest that perilesional edema around calcified cysticerci occurs relatively frequently and can be associated with seizures or focal neurological deficits. [16,17,20-23] In a previous study by our group, perilesional edema was present in 34.5% of patients with only calcified lesions who presented with seizures.[20] However, little is known about the importance of perilesional edema around brain calcified lesions, its prevalence, natural history, treatment or pathophysiology. Since edema may occur in asymptomatic patients,[16] reliable estimates of its frequency and its association with seizures can best be approached in a prospective study. Here we report the results of a prospective cohort and nested case-control study evaluating the association between seizure relapse incidence and perilesional edema among calcified neurocysticercosis patients with a history of seizures or severe headache.

Methods

Study design

This is a prospective cohort study with a nested case-control sub-study aimed to assess the incidence of seizure relapses and its association with perilesional edema in patients with calcified cysticercosis.

Patients

Patients included 17 to 65-years-old patients attending the Instituto Nacional de Ciencias Neurologicas (INCN) in Lima, Peru, with calcified NCC and a history of one or more seizures or recurrent severe headaches within the previous 10 years. Calcified cysticercosis was defined as one of more calcifications < 1 cm in diameter by CT examination and current or past positive cysticercosis serology by western blot or documented evolution from viable cysts to calcified lesions. Patients were required to have been asymptomatic during the previous 3 months to allow adequate pre study assessment irrespective of whether or not they were receiving antiepileptic drugs. Patients with recent seizures (at least a seizure in the past six months) were placed on adequate anti-seizure medication (defined as therapeutic doses of at least one first line anti-epileptic drug, mainly phenytoin or carbamazepine, optimized as clinically indicated). Exclusions included a history of status epilepticus, focal MRI findings noted below (including viable cysticercosis, baseline perilesional edema and other brain lesions not due to NCC), taeniasis, pregnancy, intracranial hypertension, permanent neurological deficits, and a lack of willingness to comply with adequate regimes of anti-seizure medication. There was no requirement for anti-cysticercal treatment before entry although many patients had been previously treated successfully at the study site.

Patients who fulfilled the initial entry criteria underwent a baseline neurological examination by the staff neurologist of the Cysticercosis Unit at the INCN. Patients also received an off-site brain MRI including T1 (axial and sagittal), T2 (axial and coronal), and FLAIR (Fluid-Attenuated Inversion Recovery) (axial and coronal) protocols that excluded the presence of conditions that barred participation such as viable or dying cysts, baseline perilesional edema and focal findings not attributable to NCC (such as arteriovenous malformation, cerebral infarct, hemorrhage, and other conditions).[16] Perilesional edema was defined as the presence of transient T2 or FLAIR signals associated with calcified lesions at least twice the size of the implicated calcified focus. A persistent unchanging FLAIR signal around a calcified lesion was considered chronic gliosis. [24] Baseline MRI studies were assessed by an off-site neuroradiologist and again reviewed by the study team.

Prior CT examinations defined the number, location and size of calcified lesions and most were performed within 6 months to 1 year prior to assessment and/or demonstrated repeated examinations showing stable calcifications. Large calcifications were arbitrarily defined as more than 1 cm in diameter. Additional required studies included baseline CBC (complete blood count) and chemistry tests, and stool examination by microscopy and coproantigen detection to rule out taeniasis.[2]

Cohort Follow-up

Patients without exclusion criteria were prospectively followed and scheduled for clinical evaluations every three months at INCN. Additionally, patients and/or family were instructed to contact the clinic for evaluation as soon as possible following a potential symptomatic episode, namely a seizure, a suspected seizure or severe headache. The definition of seizure followed the criteria of the International League Against Epilepsy[25] in which more than one seizure in the same day is considered a single episode. A severe headache was defined as one significantly altering daily activities, seeking medical attention,

and requiring medication. Patients with symptomatic episodes underwent clinical and neurological examinations at INCN including an evaluation of the likelihood for seizure occurrence and to rule out causes other than cysticercosis, potential reasons for increased propensity for seizures (alcohol ingestion, failure to take medication, illicit drug ingestion, etc.), and, if indicated, measurement of anti-epileptic drug serum blood level. Patients were recruited and followed from November 1999 to December 2006.

Nested Case-control Study of Perilesional Edema

When a patient experienced a symptomatic episode, a MRI was obtained as soon as possible but no later than 5 days following the event. A matched asymptomatic control was also selected to undergo a brain MRI, chosen from cohort members who had not had a seizure by the time the case subject had a seizure episode. Seizure relapsed patients were matched to controls by age (+/- 5 years), sex and strata defined by the numbers of brain calcifications. Four strata based on the number of brain calcifications were used: 1 or 2 calcifications, 3 to 5 calcifications, 6 to 20 calcifications and >20 calcifications. A control was selected from the respective strata using a random number list. If no eligible control existed, the next closest match, chosen first by age and then by sex, was selected. The presence or absence of perilesional edema on MRIs was assessed by the study neurologist as soon as possible after the examination, by the PIs twice yearly and by a neuroradiologist unaware of the previous interpretations. There were no disagreements in the interpretation of MRIs. Patients with seizure relapses were treated symptomatically except for subjects who were entered into another trial to assess the usefulness of corticosteroids for the treatment of perilesional edema.

Statistical analyses

Cumulative seizure relapse incidence in the cohort study was estimated using the Kaplan-Meier approach. [26] The Log-rank test was used to evaluate the association between relapse and potential covariates. The association between relapse and edema in the nested case-control was analyzed with the McNemar's test for paired observations.[27] As case-control pairs were matched on sex, age and overall number of cysts by strata, results are already adjusted for these potential confounders. Only bivariate associations were evaluated, because the small number of case-control pairs precluded a more detailed multiple regression analysis. Additionally, associations between edema and other variables were explored with the Mann-Whitney rank sum test and Fisher's exact tests among incident seizure cases only. Significant differences at the 0.05 level are reported. Results that showed strong trends and a significance of 0.15 or less (marginally significant) are also noted as marginally significant since this information may be of potential use for future studies. All analyses were conducted with Stata 9.0 (College Station, TX, 2007).

Ethical review and approval

The study and written consent forms were reviewed and approved by the IRBs of the Universidad peruana Cayetano Heredia, the Johns Hopkins Bloomberg School of Public Health, and the National Institute of Allergy and Infectious Diseases, NIH. All study participants signed the approved written consent.

Results

Study population

One hundred and ten individuals out of the 153 who signed the consent entered the study cohort. Reasons for exclusion are outlined in Figure 1.

Cohort patients

Baseline characteristics of the cohort are summarized in Table 1. Women were slightly older than men (37.16 +/- 14.10 versus 32.75 +/- 11.32, p=0.072, Student's T test). All patients had a positive serology except for two patients in whom the serology had reverted to negative at the time of study entry. Almost all patients (106 of 110) in the cohort had a history of seizures, and the remaining 4 had a history of severe episodic headache. One patient was excluded on retrospective evaluation because her presumed seizures were later diagnosed as episodes of vertigo. Analyses excluding patients with headaches did not significantly change the results.

The duration of prior seizure activity and types of seizures are also summarized in Table 1. Presence of occipital calcifications at enrollment was associated with having had a higher previous frequency of visual seizures. This was true when analyzed for the absence or presence of occipital calcifications (3/55=5.4% versus 17/55=30.9%, p<0.001), as well as for the number of occipital calcifications divided in tertiles (3/55=5.4%, 4/24=16.7%, and 13/31=41.9%, p<0.001). Time to last seizure is outlined in Table 1. Sixty-one (55%) of the 110 patients had received anti-parasitic treatment with either albendazole or praziquantel. None of the four patients with only headaches had received antiparasitic treatment. Of those on antiepileptic medications twenty-three were receiving phenytoin, 33 were on carbamazepine, 2 were on valproic acid, one on phenobarbitone only, and one on gabapentin.

Baseline imaging characteristics

All patients had only calcifications that were due to cysticercosis because of known or prior positive cysticercosis serology. The number, size and location of the calcifications are outlined in Table 1 (non exclusive categories).

Follow up

Patients were followed for 1 day to almost 80 months (mean 34.30 months, median 32.33 months, SD 19.99). New, incident seizures occurred in 29 patients, 28/105 with a history of previous seizures (incidence of seizure relapse in this group is thus calculated as 9.37 per 100 person/year), and 1/4 patients with a history of only headaches. A quarter of all cohort patients had an incident seizure within 39 months from entry into the cohort (Figure 2). The estimated 5-year incidence of seizure relapses was 36% (95% CI: 25, 49%). Eleven patients had partial seizures, 17 had generalized seizures, and one patient had both. No cases of severe headaches occurred in the absence of seizures. Analyses excluding patients with headaches did not significantly change the results.

The propensity to develop new seizures in this heterogenous group of patients with calcifications and a history of seizures or severe headache varied. Patients who were still taking anti-epileptics medications (AEDs) on entry had a significantly greater tendency to have subsequent seizures (hazard ratio: 5.29, 95% CI: 2.01, 13.94, p<0.001). This is not unexpected because AEDs are discontinued in patients whose seizure activity is quiescent. Other associations that demonstrated reasonably strong trends but with $p \geq 0.05$ included the number of frontal lobe calcifications (p=0.057), number of previous generalized tonic-clonic seizures (p=0.084), and the age of the patient (p=0.140), all categorized in tertiles. Also, patients with previous partial sensory seizures tended to have less seizures (p=0.080), and patients with large calcifications or more than one previous seizure had marginally more seizures (p=0.125 and p=0.129, respectively). There was a mild association of seizures with the presence of an increased number of occipital calcifications, p=0.143, the highest tertile at greatest risk. No association was found between incident seizures and sex, headache,

duration of seizure activity, number of calcifications, dominant hemisphere or temporal lobe calcifications, partial visual seizures or prior albendazole treatment.

Since the use of AEDs was associated with a majority of subsequent seizure activity, all 60 patients using AEDs were analyzed separately. Statistically significant associations were similar to those found in the entire group and included the number of prior seizures (p=0.053), prior generalized tonic-clonic seizures (p=0.025), presence of large calcifications (p=0.032), and frontal calcifications (p=0.125). While statistical assessment of factors associated with seizures in patients not receiving AEDs at cohort entry was limited by the small number of seizure events (n=4), the presence of frontal calcifications was still significantly associated to seizure relapse (p=0.016).

Nested matched case-control study

Twenty-four patients with seizure relapse had an MRI evaluation within five days of the event. Perilesional edema was found in 12 (50.0%, 95% confidence interval 29.1-70.9%) (Figure 3). Twenty-three age-, sex- and calcifications-matched controls were examined and perilesional edema was found in only two of them (8.7%). The cases and controls had similar characteristics (Table 2). Ten case-control matched pairs differed in the presence of edema; all ten cases had edema but their corresponding controls did not. These resulted in a highly significant association between perilesional edema and seizure relapse, although an actual matched odds ratio (OR) could not be estimated (95% CI > 2.24, p=0.002). One of the two controls with positive MRI findings had very mild edema while the second had marked and more widespread edema (Figure 3). Interestingly, this second control experienced a seizure relapse a few months later.

Among patients with seizure recurrence, perilesional edema was marginally more frequent in subjects who had received albendazole compared to those who had not received albendazole (9/14, 64.3% vs 3/10, 30%, p=0.107). There was also a trend for subjects with perilesional edema to have experienced more partial sensory seizures in the past (p=0.149). No association was found with use of antiepileptic medications at baseline, type of seizure, and number and location of calcifications.

Discussion

This is the first prospective study of the incidence and clinical significance of perilesional edema around calcified *T. solium* granulomas. There are three important findings of this study. First, seizures were relatively frequent in this closely followed population. Seizures occurred in 26.36% (29/110) of the cohort and 26.67% (29/105) of those with a history of seizures over the course of the study, reaching an estimated 36 % incidence in 5 years of follow up. Second, perilesional edema around calcified cysticerci is very common occurring in 50% (12/24) of studied patients with seizures, and third, perilesional edema is strongly associated with seizures since it was only present in 8.7% (2/23) of asymptomatic controls, or 3.6% (5/138) of all eligible patients at baseline.

The phenomenon of perilesional edema around calcified NCC lesions suggests a unique and specific underlying pathophysiology of seizures in this subpopulation. Because much of the injury and disease due to cysticercosis are secondary to inflammation, the most plausible hypothesis is that edema represents an inflammatory response to calcified granulomas. We and others earlier speculated that antigen is either sporadically released and/or recognized by the host.[16,18] If this speculation is true, how or why this occurs is unknown and why perilesional edema occurs in one patient and not another or associated with only one or a few of the many calcified lesions an individual has is also puzzling. A plausible explanation is that not all calcified lesions are the same. They may differ in the manner, amount and

form of calcium deposition;[16] quantity, type and degree of antigen that can be recognized by the host,[28], the presence and level of residual inflammation,[24,29-32] or its closeness to a blood vessel.

Nearly 26% of the cohort developed recurrent seizures, for an extremely high incidence of recurrent seizures in this group (9.37 incident seizure events per 100 person/year). The most useful prediction of continued seizure activity was previous seizure activity as judged by the requirement for continued AED use. A large majority of the cohort who had recurrent seizures was taking AEDs.

Half of the persons with seizures did not show perilesional edema. Whether this represents one or more alternative pathways that can cause seizures or a partial or perhaps non-visualizable manifestation of the same mechanism requires a better understanding of the pathophysiology involved. No feature, finding or characteristic predicted who would develop perilesional edema, although this analysis may have been limited by the relatively small number of events. Contrast enhancement around brain calcifications predicted future perilesional edema episodes according to our previous findings[20] and was associated to enhanced seizure activity in other reports.[21] We could not confirm these associations since contrast enhancement was not employed in all individuals who had an MRI.

Our study group differed from an unselected population of persons with seizures and neurocysticercosis, treated or untreated adults presenting with viable cysts.[3,33,34] and residents of endemic communities. Unique to our study, the cohort consisted of patients with only neurocalcifications due to cysticercosis who fulfilled entry conditions. Selection criteria that could have increased the propensity for seizures in this population compared to a similar unselected population with calcifications include an increased number of persons seeking/requiring specialty care, the exclusion of patients with no symptoms for the prior 10 years, and the requirement for a present or past positive cysticercosis serology. Also, patients with more subtle symptoms associated with perilesional edema, in the absence of seizures, may have been excluded from the group initially or overlooked during assessment. On the other hand, some criteria that could have decreased the seizure rates in this population include the exclusion of patients with gliosis or those suffering frequent seizures and/or perilesional edema episodes. Despite the unique selection criteria, a large subset of the cohort was representative in many ways of patients with calcified neurocysticercosis who seek treatment and care.

Although 10-20% of the general population in cysticercosis-endemic villages have brain calcifications, only a small proportion of them have a history of seizures or epilepsy. This symptomatic group, however, accounts for about 1/3 of all epilepsy cases in these endemic villages. Our cohort is similar to the subset of the population in endemic villages who have brain calcifications and develop seizures and/or epilepsy and there is no reason to believe that the presence and characteristics of perilesional edema would be different in this symptomatic group.

Neurocysticercosis is the most common cause of late-onset epilepsy in endemic areas accounting for a sizable proportion of epilepsy cases in endemic countries. Neurocysticercosis due to only calcified granulomas is a frequent presentation of NCC and there is substantial evidence implicating calcified lesions as seizure causing foci. In this study, perilesional edema around calcified lesions newly occurred in 50% of the participants who manifested seizures. Therefore, perilesional edema will likely be an important cause of NCC-associated morbidity. The unusual and distinct nature of perilesional edema indicates a specific pathophysiology that may be amendable to unique interventions and treatments.

Acknowledgments

We wish to thank the neurologists of the San Vicente Infectious Disease Service, who helped in patient care and management, and the neurologists of other services at the Instituto de Ciencias Neurologicas in Lima, Peru, for patient referral.

Financial support / role of the funding source: Support for this study was received from intramural National Institutes of Allergy and Infectious Diseases (NIAID), National Institutes of Health, NIH, USA and Fogarty International Center FIRCA grant R03 TW05562. The funders had no role (other than required IRB reviews) in study design, data collection, data analysis, data interpretation, or writing of the report. All coauthors had full access to all the data in the study. Drs. Nash and Garcia had final responsibility for the decision to submit for publication

References

1. Commission on Tropical Diseases of the International League Against Epilepsy. Relationship between epilepsy and tropical diseases. Commission on Tropical Diseases of the International League Against Epilepsy. Epilepsia. 1994; 35(1):89–93. [PubMed: 8112262]
2. Garcia HH, Del Brutto OH. Neurocysticercosis: updated concepts about an old disease. Lancet Neurol. 2005; 4(10):653–61. [PubMed: 16168934]
3. Del Brutto OH, Santibanez R, Noboa CA, Aguirre R, Diaz E, Alarcon TA. Epilepsy due to neurocysticercosis: analysis of 203 patients. Neurology. 1992; 42(2):389–92. [PubMed: 1736171]
4. Vazquez V, Sotelo J. The course of seizures after treatment for cerebral cysticercosis. N Engl J Med. 1992; 327(10):696–701. [PubMed: 1495522]
5. Rajshekhar V. Etiology and management of single small CT lesions in patients with seizures: understanding a controversy. Acta Neurol Scand. 1991; 84(6):465–70. [PubMed: 1792850]
6. de Aluja A, Vargas G. The histopathology of porcine cysticercosis. Vet Parasitol. 1988; 28(1-2):65–77. [PubMed: 3388737]
7. Nash TE, Del Brutto OH, Butman JA, et al. Calcific neurocysticercosis and epileptogenesis. Neurology. 2004; 62(11):1934–8. [PubMed: 15184592]
8. Garcia-Noval J, Allan JC, Fletes C, et al. Epidemiology of Taenia solium taeniasis and cysticercosis in two rural Guatemalan communities. Am J Trop Med Hyg. 1996; 55(3):282–9. [PubMed: 8842116]
9. Montano SM, Villaran MV, Ylquimiche L, et al. Neurocysticercosis: association between seizures, serology, and brain CT in rural Peru. Neurology. 2005; 65(2):229–33. [PubMed: 16043791]
10. Medina MT, Duron RM, Martinez L, et al. Prevalence, incidence, and etiology of epilepsies in rural Honduras: the Salama Study. Epilepsia. 2005; 46(1):124–31. [PubMed: 15660778]
11. Fleury A, Gomez T, Alvarez I, et al. High prevalence of calcified silent neurocysticercosis in a rural village of Mexico. Neuroepidemiology. 2003; 22(2):139–45. [PubMed: 12629280]
12. Cruz ME, Schantz PM, Cruz I, et al. Epilepsy and neurocysticercosis in an Andean community. Int J Epidemiol. 1999; 28(4):799–803. [PubMed: 10480714]
13. Carpio A, Placencia M, Santillan F, Escobar A. A proposal for classification of neurocysticercosis. Can J Neurol Sci. 1994; 21(1):43–7. [PubMed: 8180904]
14. Bittencourt PR, Costa AJ, Oliveira TV, Gracia CM, Gorz AM, Mazer S. Clinical, radiological and cerebrospinal fluid presentation of neurocysticercosis: a prospective study. Arq Neuropsiquiatr. 1990; 48(3):286–95. [PubMed: 2264783]
15. Sotelo J, Guerrero V, Rubio F. Neurocysticercosis: a new classification based on active and inactive forms. A study of 753 cases. Arch Intern Med. 1985; 145(3):442–5. [PubMed: 3977513]
16. Nash TE, Patronas NJ. Edema associated with calcified lesions in neurocysticercosis. Neurology. 1999; 53(4):777–81. [PubMed: 10489040]
17. Del Brutto OH. Prognostic factors for seizure recurrence after withdrawal of antiepileptic drugs in patients with neurocysticercosis. Neurology. 1994; 44(9):1706–9. [PubMed: 7936301]
18. White AC Jr. Neurocysticercosis: a major cause of neurological disease worldwide. Clin Infect Dis. 1997; 24(2):101–13. quiz 114-5. [PubMed: 9114131]

19. Sheth TN, Lee C, Kucharczyk W, Keystone J. Reactivation of neurocysticercosis: case report. Am J Trop Med Hyg. 1999; 60(4):664–7. [PubMed: 10348245]
20. Nash TE, Pretell J, Garcia HH. Calcified cysticerci provoke perilesional edema and seizures. Clin Infect Dis. 2001; 33(10):1649–53. [PubMed: 11595994]
21. Sheth TN, Pillon L, Keystone J, Kucharczyk W. Persistent MR contrast enhancement of calcified neurocysticercosis lesions. AJNR Am J Neuroradiol. 1998; 19(1):79–82. [PubMed: 9432161]
22. Park SY, Barkovich AJ, Weintrub PS. Clinical implications of calcified lesions of neurocysticercosis. Pediatr Infect Dis J. 2000; 19(6):581–3. [PubMed: 10877183]
23. Antoniuk SA, Bruck I, Dos Santos LH, et al. Seizures associated with calcifications and edema in neurocysticercosis. Pediatr Neurol. 2001; 25(4):309–11. [PubMed: 11704400]
24. Gupta RK, Kathuria MK, Pradhan S. Magnetisation transfer magnetic resonance imaging demonstration of perilesional gliosis--relation with epilepsy in treated or healed neurocysticercosis. Lancet. 1999; 354(9172):44–5. [PubMed: 10406368]
25. Commission on classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981; 22:489–501. [PubMed: 6790275]
26. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Assoc. 1958; 53:457–81.
27. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika. 1947; 12:153–157. [PubMed: 20254758]
28. Gupta RK, Kumar R, Chawla S, Pradhan S. Demonstration of scolex within calcified cysticercus cyst: its possible role in the pathogenesis of perilesional edema. Epilepsia. 2002; 43(12):1502–8. [PubMed: 12460252]
29. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 24-2000. A 23-year-old man with seizures and a lesion in the left temporal lobe. N Engl J Med. 2000; 343(6):420–7. [PubMed: 10933742]
30. Wang IC, Fan PC, Lu SC, Fan CK, Su KE. Suppression of host Th1-type granulomatous inflammation by Taenia solium metacestodes is related to down-regulation of osteopontin gene expression. Int J Parasitol. 2008; 38(2):239–48. [PubMed: 17765901]
31. Henneberg, R. Die tierischen parasiten des zentralnervensystem. In: Lewandowsky, M., editor. Handbuch der neurologie. Berlin: Verlag Von Julius Springer; 1912. p. 643-712.
32. Pradhan S, Kathuria MK, Gupta RK. Perilesional gliosis and seizure outcome: a study based on magnetization transfer magnetic resonance imaging in patients with neurocysticercosis. Ann Neurol. 2000; 48(2):181–7. [PubMed: 10939568]
33. Garcia HH, Pretell EJ, Gilman RH, et al. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. N Engl J Med. 2004; 350(3):249–58. [PubMed: 14724304]
34. Carpio A, Santillan F, Leon P, Flores C, Hauser WA. Is the course of neurocysticercosis modified by treatment with antihelminthic agents? Arch Intern Med. 1995; 155(18):1982–8. [PubMed: 7575052]

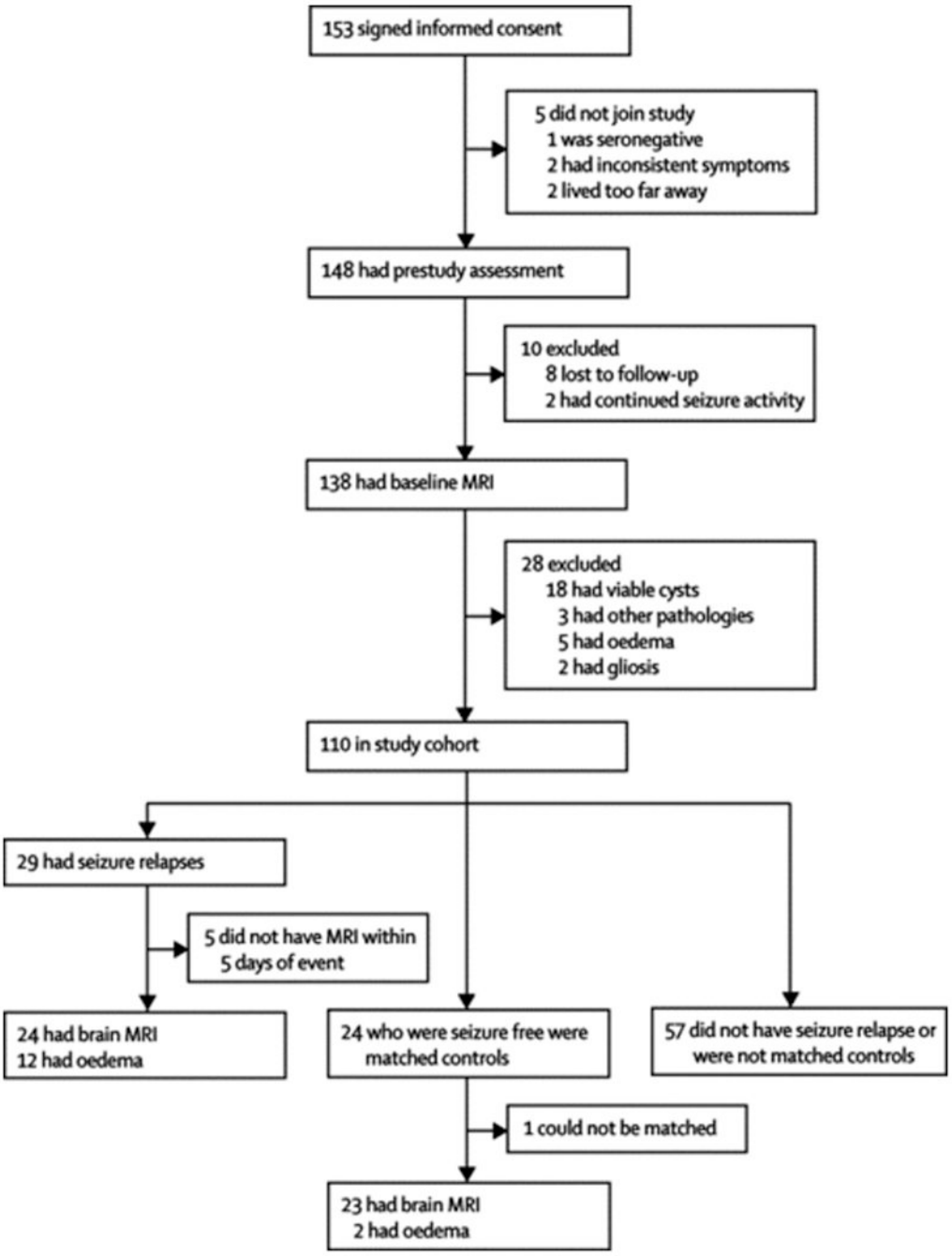

Figure 1.
Entrance selection into the cohort and outcome.

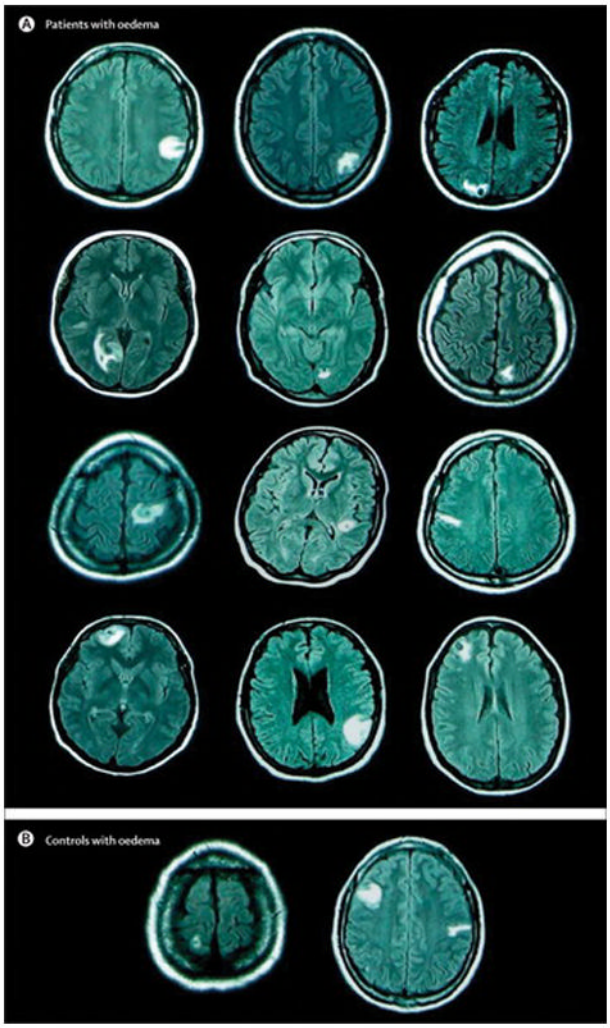

Figure 2. Kaplan-Meier estimate of the rates of seizure presentation of the entire cohort over time

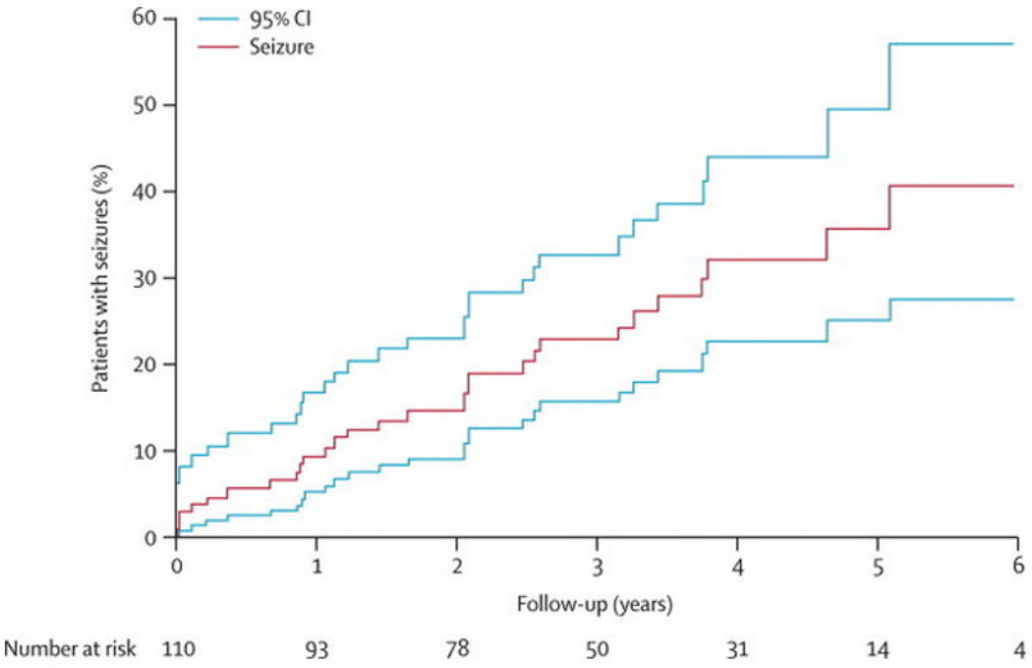

Figure 3.
Representative MRI FLAIR images of symptomatic patients with perilesional edema and in the two asymptomatic controls with perilesional edema.

Table 1

Baseline characteristics of the patients.

Sex = male		59 (53.6%)
Age	Mean +/- SD Range	34.79 +/- 12.82 17 - 65
Prior antiparasitic treatment		61(55.5%)
Seizures		105 (96%)
Number of previous seizures	1	20 (19.0.%)
	2 to 5	30 (28.6%)
	6 to 10	17 (16.2%)
	11 to 51	18 (17.1%)
	>51	20 (19.0%)
Types of seizures (non-inclusive)	Partial	49
	Complex partial	3
	Partial with secondary generalization	40
	Generalized tonic- clonic	66
Length of disease (seizures) in months	Mean +/- SD	83.59 +/- 67.68
Time from last seizure to study entry (months)	3 to 6 months	35 (33.3%)
	6 months to 1 year	11 (10.5%)
	1 to 2 years	16 (15.2%)
	2 to 5 years	22 (21.0%)
	> 5 years	21 (20.0%)
On AEDs		60 (54.5%)
Number of brain calcifications	1 to 2	40 (36.4%)
	3 to 5	28 (25.5%)
	6 to 20	30 (27.3%)
	>20	12 (10.9%)
At least one large calcification		55 (50.0%)
Calcifications in *	Dominant hemisphere	88 (80.0%)
	Frontal lobes	75 (68.2%)
	Temporal lobes	47 (42.7%)
	Parietal lobes	86 (78.2%)
	Occipital lobes	45 (40.9%)

* Non-exclusive categories

Table 2

Comparison of baseline characteristics of cases and controls.

	Patients (n=23)	Controls (n=23)	p
Age (years)	31.52 (9.10)	32.17	0.63
Calcifications	7(9)	8(12)	0.47
Percentage men	16 (70%)	15 (65%)	0.76
Oedema	12 (52%)	2 (9%)	0.002
Used AED	19 (83%)	9 (39%)	0.006
Number of seizures	43.5 (46.0)	21.1 (32.8)	0.05
Length of disease (months)	84.3 (62.7)	68.3 (52.6)	0.37
Used albenzadole	14 (61%)	15 (65%)	1.0
Number of large calcifications	3.30 (6.08)	1.74 (4.61)	0.08
Number of calcifications per area			
Dominant hemisphere *	3.7 (4.8)	2.6 (3.6)	0.54
Frontal lobes	2.8 (3.6)	3.4 (8.4)	0.17
Temporal lobes	1.0 (1.8)	1.3 (2.7)	0.64
Parietal lobes	2.3 (3.4)	3.8 (10.4)	0.80
Occipital lobes	1.5 (1.7)	1.6 (3.6)	0.28
Types of seizure			
Partial	9 (39%)	14 (61%)	0.07
Partial with secondary generalisation	12 (52%)	7 (30%)	0.39
Generalised tonic-clonic	11 (48%)	13 (57%)	0.79

Data are mean (SD) or number (%)

* One case-control pair was excluded from this calculation because the control had many (>99) brain calcifications but the actual number was not recorded exactly, preventing calculation of the mean.