Neurocysticercosis

Association between seizures, serology, and brain CT in rural Peru

S.M. Montano, MD, MPH; M.V. Villaran, MD, DTMPH; L. Ylquimiche, MDC; J.J. Figueroa, MD; S. Rodriguez, BS; C.T. Bautista, MS; A.E. Gonzalez, DVM, PhD; V.C.W. Tsang, PhD; R.H. Gilman, MD, DTMH; and H.H. Garcia, MD, PhD, for the Cysticercosis Working Group in Peru

Abstract—*Background:* Neurocysticercosis (NCC) is the commonest helminthic CNS infection and the main cause of adult-onset seizures in developing countries, also frequent in industrialized countries because of immigration from endemic zones. Although NCC is commonly seen in individuals with seizures in endemic areas, its role as a cause of epilepsy has been questioned on the basis of the poor methodology of published studies. *Objective:* To determine, in a cysticercosis-endemic area of the northern Peruvian coast, the frequency of 1) epileptic seizures, 2) serum antibodies to *Taenia solium*, 3) NCC-compatible findings on brain CT, and 4) the associations between these variables. *Methods:* A community-wide screening survey for possible seizure cases was performed using a validated questionnaire. Positive respondents were later examined in the field by neurologists. Seizure cases were categorized as single seizure, active epilepsy, or inactive epilepsy. Serology was performed for all consenting individuals using immunoblot. Noncontrast brain CT scans were performed in all individuals with seizures and two groups of control subjects without seizures (seropositive and seronegative). *Results:* The screening survey was applied to 903 permanent residents. Most positive respondents (114/137 [83.2%]) were examined by neurologists. The overall prevalence of epilepsy was 32.1 per 1,000 and that of active epilepsy was 16.6 per 1,000. Seroprevalence was 24.2% (200/825). Seroprevalence was associated with seizures (odds ratio 2.14; $p = 0.026$). Brain CT abnormalities compatible with NCC were more frequent in individuals with seizures and in those seropositive. *Conclusion:* In this hyperendemic area, an important proportion of seizure cases are associated with neurocysticercosis as demonstrated by serology or brain CT.

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Neurocysticercosis (NCC) is the infection of the CNS by the larval stage of *Taenia solium*, causing seizures and other neurologic disorders.[1,2] Infection is common; specific serum antibodies to *T. solium* infection can be found in up to 25% of the general population in endemic areas,[3-5] and NCC is commonly reported as the main cause of acquired epilepsy in developing countries.[1,6]

Whereas patients with NCC and seizures are a common event in clinical settings in endemic areas,[1,6] some authors have questioned the role of NCC as a contributor to the etiology of epilepsy and epileptic seizures in population terms.[7-9] Most published studies have relied on small sample sizes, inadequate population selection, and lack of accurate diagnostics. Of note, brain imaging is rarely available in endemic areas. We sought to determine the associations between seizures, serologic status, and brain image characteristics in a cysticercosis-endemic area comprising seven villages in the Tumbes River Valley (northern coast of Peru).

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the July 26 issue to find the title link for this article.

Methods. *Study site.* This cross-sectional study was conducted in the rural district of Matapalo, in the Zarumilla River Valley, near the Peru–Ecuador border (figure 1), between 1999 and 2000. The northern coast of Peru is a known cysticercosis-endemic area. Previous seroepidemiologic surveys in the study area using the enzyme-linked immunoelectrotransfer blot (EITB, western blot) assay[10] had found human seroprevalence levels of about 20% (unpublished data, Cysticercosis Working Group in Peru, 2004). The district of Matapalo includes seven villages: Isla Noblecilla, Quebrada Seca, Leandro Campos, Matapalo village, Nuevo Progreso,

From the School of Public Health and Administration (Dr. Montano) and Department of Microbiology (Drs. Villaran, Ylquimiche, Figueroa, Gilman, and Garcia), School of Sciences, Universidad Peruana Cayetano Heredia, US Naval Medical Research Center Detachment (Dr. Montano), Cysticercosis Unit (Dr. Garcia, S. Rodriguez), Instituto de Ciencias Neurologicas, and School of Veterinary Medicine (Dr. Gonzalez), Universidad Nacional Mayor de San Marcos, Lima, Peru; US Military HIV Research Program and Henry M. Jackson Foundation Inc. (C.T. Bautista), Rockville, MD, Department of International Health (Drs. Gonzalez, Gilman, and Garcia), Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, and Immunology Branch (Dr. Tsang), Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control, Atlanta, GA.

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Address correspondence and reprint requests to Dr. H.H Garcia, Department of Microbiology, Universidad Peruana Cayetano Heredia, Lima, Peru; e-mail: hgarcia@jhsph.edu

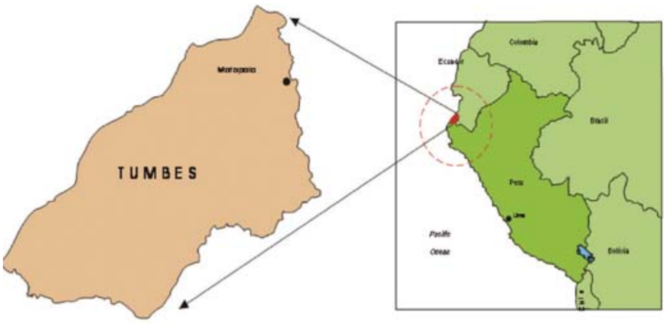

Figure 1. Study site.

Totora, and Tutumo. The entire population belongs to the Mestizo ethnic group (a racial admixture of Spaniard and Amerindian). All inhabitants speak Spanish.

Enrollment and census. A door-to-door baseline census was carried out for demographic information as part of a large project in control of *T. solium* taeniasis/cysticercosis. A record was set with individual information, including complete name, gender, age, and residential status, as well as characteristics of the household (number of persons, number of rooms, water source, sewage, use of latrines, electricity) and presence of pigs in the household. All participants received a complete explanation of the study procedures and signed a written consent form. The study was approved by the institutional review boards of the Universidad Peruana Cayetano Heredia and the Johns Hopkins University Bloomberg School of Public Health.

Survey. An adapted form of a previously validated screening questionnaire[11-13] was applied by trained field workers to identify all potential cases of epileptic seizures. The questionnaire comprised nine questions (see table E-1 on the *Neurology* Web site at www.neurology.org). Positive respondents to the survey were interviewed in situ by a neurologist, who obtained a careful seizure history to confirm or reject the diagnosis of seizures according to the criteria of the International League Against Epilepsy (figure 2).[14,15] All individuals diagnosed as having seizures were later examined by a different physician to reconfirm the diagnosis.

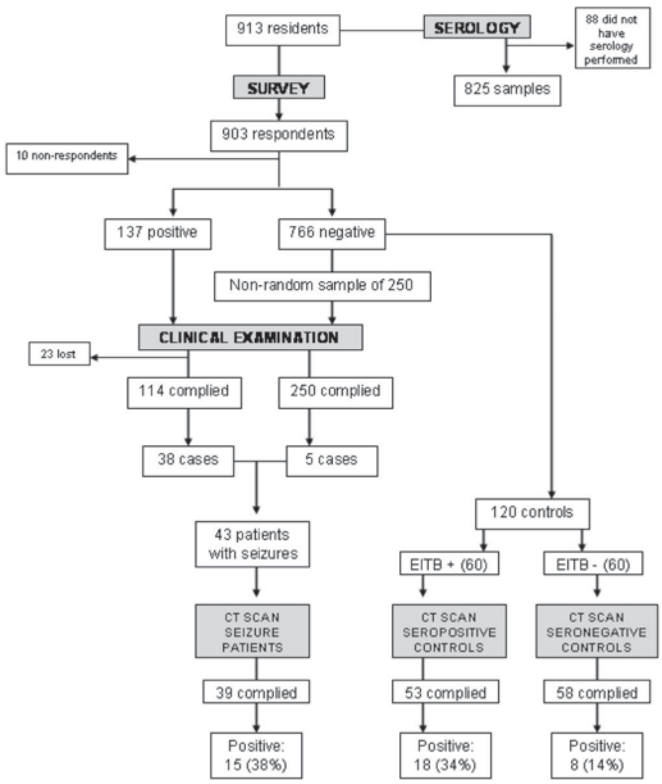

Figure 2. Study flowchart.

During the visits for neurologic examinations, other villagers asked to be examined because of either headaches or nonneurologic complaints. They were seen by the physicians and registered as a separate group.

Operational definitions. Resident. A resident was an individual who had slept in the village at least 2 nights per week during the last 6 months.

Eventual resident. An eventual resident slept in the village <2 nights per week but more than once a month during the last 6 months.

Epileptic seizure. An epileptic seizure was a clinical manifestation (sudden and transitory abnormal phenomena) presumed to result from an abnormal and excessive discharge of a set of neurons in the brain, perceived by the patient or an observer. It might include alteration of consciousness or motor, sensory, autonomic, or psychic events.[16] Febrile and eclamptic seizures were excluded from analyses.

Epilepsy. Epilepsy consisted of two or more unprovoked epileptic seizures.[16] An episode of status epilepticus or multiple seizures occurring in a 24-hour period were considered a single event.

Active epilepsy. A person with active epilepsy had at least one epileptic seizure in the previous 5 years, regardless of antiepileptic drug treatment.[16]

Blood sampling/serology. Blood samples were taken from all consenting individuals by finger prick and stored on filter paper. The EITB assay for diagnosis of human NCC using lentil lectin, affinity-purified *T. solium* metacestode glycoprotein antigens was carried out on these samples as previously described.[3,10] The sensitivity of this assay is 98%, and its specificity reaches 100% in individuals with two or more viable lesions found by imaging.[3,10]

Brain CT. All patients with a diagnosis of epileptic seizures confirmed by neurologic examination were offered a brain CT scan in the nearest city. Two groups of controls (60 seropositive and 60 seronegative individuals without a self-reported history of seizures) were randomly selected and also invited to have a brain CT scan performed. Seronegative controls were selected from a list of houses without seropositive individuals.

Statistical analysis. χ^2 or Fisher exact tests were used to compare differences in proportions. Prevalence was defined as the number of seropositive individuals detected per 100 participants or individuals with a seizure disorder detected per 1,000. CI for prevalence was estimated based on exact binomial method. Odds ratios (ORs) and adjusted ORs (AORs) controlling for gender and age were estimated in univariate and multiple logistic regression analysis as well as associated 95% CI. Given that the study population included sets of familial members, the data were presumed to violate the standard logistic regression assumption of independent response probabilities across observations. ORs and AORs were estimated using random effects logistic regression, defining household as the group variable. All reported probability (p) values were two sided; p values of <0.05 were considered to be significant. Statistical analyses were carried out using SPSS version 12.1 (SPSS Corp., Chicago, IL) and SAS version 8.0 (SAS Institute, Cary, NC).

Results. In the baseline census, 1,004 individuals (574 men, 430 women) were registered in 237 houses. No potable running water was available in the study area (127 households [53.6%] declared to obtain water from a nearby river and 85 [35.9%] from wells). A minority of the households had sewage (17 [7.2%], all of which belonged to the village of Matapalo) or latrines (28 [11.8%]). Most families (146 [61.6%]) raised pigs.

From the total census population of the district of Matapalo, 913 (90.9%) individuals were permanent residents and 37 (3.7%) were eventual residents. Fifty-four (5.4%) did not fit in the resident definition and were excluded from the analyses. Therefore, our study population comprised 950 individuals (residents and eventual residents): 542 (57.1%) men and 408 women. Their mean age was 26.8 years (SD 19.63 years). Of these, 903 agreed to participate in the survey, and 137 were positive respondents for seizures (survey coverage 95.1% of all villagers). This coverage was similar among villages. Most of them (114/137 [83.2%]) complied with the neurologic evaluation. The 23 positive respondents to the survey who did not have a confirmatory clinical examination were not considered in further analyses involving categories by clinical diagnosis (performed with n = 880; 766 negative respondents to the survey and 114 positive respondents with neurologic evaluation).

Besides the 114 positive respondents to the survey, a nonrandom group of 250 negative respondents volunteered for neurologic evaluation (mainly because of headache or nonneurologic complains), adding up to a total of 364 evaluated individuals. Compared with the remaining 516 negative respondents, these 250 individuals were more frequently female (131/250 [52.4%] vs 209/516 [40.5%]; $p = 0.002$) and raised pigs in a higher proportion (203/250 [81.2%] vs 354/516 [68.6%]; $p < 0.001$), but a lower proportion of them had latrines (77/250 [31.3%] vs 187/516 [38.7%]; $p = 0.048$). They were, however, similar in regard to age, village distribution, number of rooms in the house, source of water, electricity, sewage, and mean number of pigs raised. On neurologic interview and examination, 39 of 114 positive respondents to the survey and 6 of the 250 volunteers were identified to have had seizures (see figure 2). These 45 individuals were examined a second time by a different neurologist. The diagnosis was not confirmed in 1 individual from each group, leaving 43 individuals positive for seizures (38/114 [33.3%] and 5/250 [2.0%]). Thus, the survey had a positive predictive value of 0.33 (38/114; 95% CI 0.25 to 0.43). The negative predictive value could not be calculated from the study design.

From these 43 individuals with seizures, 15 had active epilepsy, 14 had inactive epilepsy, and 14 had had a single seizure. An overall epilepsy prevalence of 32.1 per 1,000 was determined in our study population (95% CI 21.6 to 45.8). The prevalence for active epilepsy was 16.6 per 1,000 (95% CI 9.3 to 27.3). These are minimal estimates, given that another 23 individuals who were positive respondents to the survey did not comply with neurologic examination. Seizures were generalized in 36 cases, partial in 5 cases, and not classified in 2 cases. The ages at which a seizure first presented were as follows: 8 before age 5 (3 of these before the first year), 8 between 6 and 10 years, 8 between 11 and 15 years, 8 between 16 and 20 years, and 11 older than 20 years (see table E-2). At the time of this study, only two individuals had received antiepileptic drugs, both irregularly.

Factors associated with seizures. To raise pigs (OR 2.77; 95% CI 1.09 to 7.04; $p = 0.032$) and to have more than four pigs in the household (OR 3.09; 95% CI 1.18 to 8.10; $p = 0.022$) were significantly associated with seizures. Other potential variables such as water, latrine, sewage, electricity, and number of inhabitants per room did not have significant associations with seizures in univariate logistic regression analysis (table 1). The proportion of the variance explained by seizure seropositivity by household was 25.3 (95% CI 9.4 to 52.5; $p = 0.012$), and the interclass cluster correlation (degree of similarity) was 0.04.

Serology. Eight hundred twenty-five blood samples were collected, of which 200 (24.2%) were positive to western blot for cysticercosis. Seroprevalence for cysticercosis was similar between men (113/469 [24.1%]) and women (87/356 [24.4%]). The only factor associated with a positive serology was to have sewage installations in the house (23/65 [35.4%] vs 32/175 [18.3%]; OR 2.45; 95% CI 1.30 to 4.68; $p = 0.006$; calculated only in the Matapalo village, where some houses had sewage). Although all age groups had high seroprevalence, an increased ratio was found in the group between ages 51 and 60 (figure 3). Seizures were more frequent in seropositive individuals than in seronegative individuals (17/200 [8.5%] vs 26/625 [4.2%]; OR 2.14; 95% CI 1.08 to 4.20; $p = 0.026$). From the 43 cases with seizure disorder, 5 of 15 (33.3%) active epilepsy cases, 6 of 14 (42.9%) nonactive epilepsy cases, and 6 of 14 (42.9%)

Table 1 *Factors associated with seizures in rural villagers on the Peruvian northern coast (n = 880)*

Variable	Frequency, no. (%)	Odds ratio (95% CI)	p Value
Water			
River	21/342 (6.1)	Ref.	
Well/ditch	16/456 (3.5)	0.62 (0.32–1.19)	0.149
Other	2/27 (7.4)	0.91 (0.21–3.87)	0.896
Sewage*			
No	6/179 (3.4)	Ref.	
Yes	4/73 (5.5)	1.65 (0.46–5.89)	0.443
Latrine			
No	32/554 (5.8)	Ref.	
Yes	9/286 (3.1)	0.53 (0.25–1.11)	0.094
Raise pigs			
No	5/230 (2.2)	Ref.	
Yes	38/650 (5.9)	2.77 (1.09–7.04)	0.032
No. of pigs			
None	5/230 (2.2)	Ref.	
1–4	14/313 (4.5)	2.35 (0.85–6.54)	0.1
>4	24/337 (7.1)	3.09 (1.18–8.10)	0.022
Electricity			
Yes	5/118 (4.2)	Ref.	
No	33/668 (4.9)	0.80 (0.31–2.05)	0.644
No. persons/ room			
1–4	29/673 (4.3)	Ref.	
>4	9/134 (6.7)	1.39 (0.66–2.94)	0.384

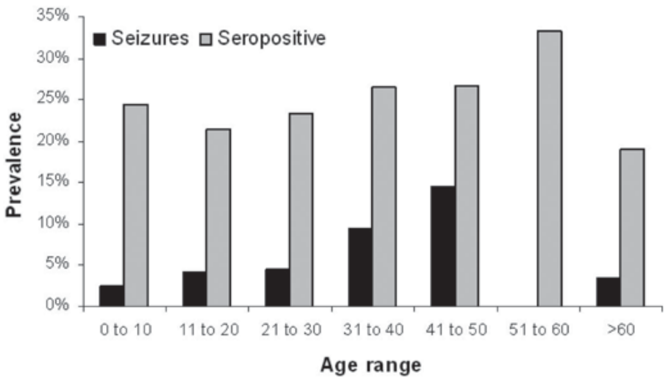

Figure 3. Age-specific prevalence of seizures (black) and seropositivity to cysticercosis (gray).

Table 2 Brain CT scan findings according to clinical and serologic status, Matapalo, Peru, 2001 n = 150)

Group	Neurocysticercosis on brain CT	Odds ratio (95% CI)	*p* Value	Adjusted odds ratio (95% CI)	*p* Value
No seizures, seronegative	8/58 (13.8%)	Ref.		Ref.	
No seizures, seropositive	18/53 (35.0%)	3.21 (1.26–8.21)	0.015	3.49 (1.34–9.11)	0.011
Seizures, seronegative	8/25 (32.0%)	2.94 (0.96–9.05)	0.06	3.33 (1.05–10.62)	0.042
Seizures, seropositive	7/14 (50.0%)	6.25 (1.73–22.62)	0.005	6.05 (1.61–22.77)	0.01

Adjusted odds ratio, by age and sex.

cases of individuals with a single crisis were seropositive. The proportion of the variance explained by cysticercosis seropositivity by household was 18.7 (95% CI 10.1 to 32.1; $p < 0.001$), and the interclass cluster correlation was 0.12.

Brain CT scan. One hundred fifty brain CT scans were performed in individuals with a confirmed history of seizures (n = 39; 4 individuals with seizures did not comply), seropositive nonconvulsive control subjects (n = 53), or seronegative nonconvulsive control subjects (n = 58). Lesions compatible with NCC on CT scan[17] were found in 15 of 39 individuals with seizures (38.5%) and18 of 53 seropositive controls (34.0%) but in only 8 of 58 (13.8%) seronegative control subjects. Calcifications were by far the most frequent finding (single calcification in 22 of 41 CT-positive cases, and multiple calcifications in another 11). Four individuals presented viable cysts only, three had cysts plus calcifications, and one had a single inflammatory lesion. The individuals with cysts on CT were seropositive with exception of one asymptomatic control subject with a single cystic image.

Compared with the seronegative individuals without seizures, all other groups had higher frequencies of lesions compatible with NCC on brain CT. The higher frequency was found in individuals with seizures and a positive serology (AOR 6.05; 95% CI 1.61 to 22.77; $p = 0.008$), followed by the seropositive individuals without seizures (AOR 3.49; 95% CI 1.34 to 9.11; $p = 0.011$) and those with seizures but seronegative (AOR 3.33; 95% CI 1.05 to 10.62; $p = 0.042$) (table 2). Multiple logistic regression including the 150 patients with CT scans and serology, after adjustment for sex and age, showed that the strongest predictor for having brain images compatible with NCC was a positive serology (table 3).

NCC-attributable fraction of seizure cases. There were 803 individuals with serology and seizure status defined. Applying to this population the proportions of NCC-compatible CT findings according to seizures and serologic results, we obtain an expected number of 160 individuals with NCC on CT, 17 of whom would be individuals with seizures (leaving 26 individuals with seizures in the remaining 643 residents). Thus, the population-attributable fraction of seizure disorders associated with NCC based on CT scan findings gives 24.8%, calculated as $p_e \times ([q+/q-] - 1)/(p_e \times [(q+/q-) - 1]) + 1$, where p_e is the prevalence of NCC-compatible findings on CT in the overall population, $q+$ is the proportion of individuals with seizures among those with abnormal CT, and $q-$ is the proportion of individuals with seizures among those with normal CT.[18] In a similar manner, if we calculate the proportion of individuals with seizures in the seropositive group (16/200 [8.0%]) and compare it with the proportion in the seronegative group (27/625 [4.3%]), the population-attributable fraction based on serology is 16.9%. Given that these two fractions do not completely overlap but are highly correlated, a reasonable estimate of the overall NCC-attributable fraction would be between 25 and 30% of seizure disorder cases in the district of Matapalo. Repeating the above calculations for epilepsy instead of all seizure cases, the estimates are 23.7% based on CT and 13.0% based on serology, which again gives 25 to 30% as an overall estimate of the NCC-attributable fraction of epilepsy cases in this area.

Table 3 Logistic regression analysis of factors associated with presenting neurocysticercosis-compatible lesions on brain CT (n = 150)

Variable	Coefficient	SE	Odds ratio (95% CI)	*p* Value
Positive serology	1.04	0.39	2.83 (1.31–6.13)	0.012
Seizures	0.9	0.44	2.46 (1.05–5.76)	0.039
Age	0.02	0.01	1.02 (0.99–1.04)	0.13
Male	0.26	0.4	1.29 (0.59–2.84)	0.525

Discussion. The prevalence of active epilepsy in industrialized countries with well-organized health care and reporting systems varies from 3 to 9 per 1,000 inhabitants.[19-24] In the developing world, it is usually two to three times these numbers,[24] although, depending on the methodology used, it may vary from very low ranges such as 2.5 per 1,000 in India[25] to a strikingly high 49 per 1,000 in Liberia.[26] In Latin America, active epilepsy prevalences include 5.8 to 18 per 1,000 in Guatemala,[27,28] 6.7 to 9.9 per 1,000 in Ecuador,[13,29,30] 8.2 to 12.4 per 1,000 in Brazil,[31] and 11.1 in Bolivia.[32] Using a door-to-door survey, we found a prevalence of 16.6 per 1,000 active epilepsy cases in this rural population in the northern coast of Peru, one of the highest figures reported in this region. The overall prevalence of epilepsy was as high as 32.1 per 1,000, and the total prevalence of seizure disorders, including single crisis, was 47.6 per 1,000. The fact that a group of 23 positive respondent individuals for the screening questionnaire were not evaluated by neurologists might have led to underestimation of the actual prevalence. In this series, women were more likely than men to have seizures, as in other Latin American series.[32,33] Other studies have reported no significant differences in epilepsy prevalence between men and women[20,21] or higher prevalence in men.[34] Most patients had never sought or received antiepileptic treatment. Poor epilepsy case management, based mainly on economic hardship, is also a usual scenario in most developing countries[9] and worsens the prognosis of these individuals.

Infectious diseases are assumed to be an important contributor to the etiology of seizures and epilepsy in developing countries, and from these, cysticercosis is identified as the leading cause.[6] Our data strongly support this affirmation. In this endemic district, there was a high prevalence of seizures and epilepsy, seizures were associated with pig raising as well as with positive serology, and both seizures and positive serology were associated with NCC on CT. In this study, only noncontrast CT scans were performed. Parasites in late stages of degeneration appear as a small ring or nodule, visible only after the administration of contrast medium,[17] and thus we may have underestimated the number of subjects with NCC determined by brain CT. These enhancing lesions, however, are rarely found in field studies. In contrast to what is usually seen in hospital series, in field conditions (mostly asymptomatic individuals), viable cysts or degenerating parasites are only a small minority of NCC cases.[13,28,36,37] Also, most individuals with seizures and only calcified lesions had negative serology, thus diluting the strength of the association between serology and seizures. It has been previously shown that antibodies disappear months or years after parasite death.[35]

This study adds to a short list of field studies using CT to assess the impact of NCC.[13,28,36-38] In all these studies, most of the lesions on CT were calcifications, also found in a sizable proportion of individuals without seizures. Thus, many individuals can follow an asymptomatic course of the disease in which the parasite will die without treatment. Whether this is the effect of genetic predisposition,[39] hormonal or sex-related factors,[40] acquired immunity,[41] or infective dose remains to be determined. It is probable that the existence of this subset of asymptomatic individuals (probably the majority of all infections) led to confusion in some authors about whether NCC causes epilepsy, ignoring the bulk of evidence provided by the symptomatic cases.

Confirmatory information on the association between NCC and seizure disorders should lead to implementation of control and prevention measures with the goal of decreasing the numbers of individuals with seizures, as NCC is a preventable and eradicable disease.[42] A cysticercosis eradication program, funded by the Bill and Melinda Gates Foundation, is already established in the area and may provide the first population-based evidence of a decrease in seizures following sustained control of an infectious disease.

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