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On the relationship between calcified neurocysticercosis and epilepsy in an endemic village. A large scale, CT-based population study in rural Ecuador

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SUMMARY

Objective—Using a large-scale population-based study, we aimed to assess prevalence and patterns of presentation of neurocysticercosis (NCC) and its relationship with epilepsy in community-dwellers aged 20 years living in Atahualpa (rural Ecuador).

Methods—In a three-phase epidemiological study, individuals with suspected seizures were identified during a door-to-door survey and an interview (Phase I). Then, neurologists evaluated suspected cases and randomly selected negative persons to estimate epilepsy prevalence (Phase II). In Phase III, all participants were offered non-contrast CT for identifying NCC cases. The independent association between NCC (exposure) and epilepsy (outcome) was assessed by the use of multivariate logistic regression models adjusted for age, sex, level of education and alcohol intake. CT findings were subsequently compared to archived brain MRIs in a sizable subgroup of participants.

Results—Of 1,604 villagers aged 20 years, 1,462 (91%) were enrolled. Forty-one persons with epilepsy (PWE) were identified, for a crude prevalence of epilepsy of 28 per 1,000 population (95% C.I.: 20.7 – 38.2). A head CT was performed in 1,228 (84%) out of 1,462 participants, including 39 of 41 PWE. CT showed lesions consistent with calcified parenchymal brain cysticerci in 118 (9.6%) cases (95% C.I.: 8.1% – 11.4%). No patient had other forms of NCC. Nine of 39 PWE, as opposed to 109 of 1,189 participants without epilepsy, had NCC (23.1% *versus* 9.2%,

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$p=0.004$). This difference persisted in the adjusted logistic regression model (OR: 3.04; 95% C.I.: 1.35 – 6.81; $p=0.007$).

Significance—This large CT-based study demonstrates that PWE had three times the odds of having NCC than those without epilepsy, providing robust epidemiological evidence favoring the relationship between NCC and epilepsy.

Keywords

Neurocysticercosis; Cysticercosis; Epilepsy prevalence; Rural areas; Population-based studies

INTRODUCTION

Neurocysticercosis (NCC) is a frequent helminthic infection of the nervous system that occurs when humans become intermediate hosts in the life cycle of the pork tapeworm *Taenia solium*, after ingesting its eggs. The disease is most often transmitted from tapeworm carriers to healthy individuals, through non-hygienic handling of food or by direct contact with human feces.¹ Ingestion of undercooked pork contaminated with cysticerci as the cause of human cysticercosis is a mistaken belief, since the role of pigs is to maintain the infection cycle by causing human taeniasis.²

Large hospital-based series have shown NCC as a pleomorphic disease, mostly presenting with recurrent seizures, but also causing more severe clinical manifestations such as intracranial hypertension, focal neurological deficits, or even death.^{3–5} This scenario is different at the population level, where most infected individuals are asymptomatic or remain asymptomatic for many years before presenting with symptoms.^{6–8}

Several studies have attempted to assess the relationship of this parasitic disease with epilepsy. Most of them have been based on serological tests, which are not reliable for assessing NCC prevalence in the absence of neuroimaging.^{9,10} More recently, other studies have attempted to estimate this relationship by the use of neuroimaging studies, providing more accurate information on the burden of NCC.^{11–18} However, the reliability of these studies has been partially hampered by the specific study design, selecting only persons with epilepsy (PWE) or seropositive individuals and controls (sometimes historical) for the practice of neuroimaging studies. To our knowledge, only one study was designed to perform neuroimaging studies in a representative sample of the population, and not only on the basis of the results of clinical interviews or immune diagnostic tests.¹⁹

The Atahualpa Project is an ongoing population-based cohort study, designed to assess and eventually reduce the increasing burden of neurological and cardiovascular diseases in rural Ecuador.²⁰ Using the structure of this study, we extended an invitation for the practice of a head CT to all community-dwellers aged ≥ 20 years enrolled in the Project, in order to better understand the patterns of disease expression of NCC in highly endemic villages and the relationship between NCC and epilepsy at the population level.

METHODS

Study population

Atahualpa is a rural village located in coastal Ecuador, known to be endemic for NCC.^{15,21,22} Atahualpa residents are homogeneous regarding race (95% belong to the native/mestizo ethnic group), living conditions, socio-economic status, and dietary habits, as detailed elsewhere.²⁰ Atahualpa is a closed village with a low migration rate (less than 30 adults leave the village every year), which make it an optimal setting for conducting population-based studies. The village has electricity but, until recently, most houses did not have pipe water and most streets were not paved. During the past five years this has changed, and nowadays, up to 40% of streets are paved and up to 80% of houses have closed systems for sewage disposal. The remaining houses still have open latrines for feces disposal.

Domestic pig raising is common. The last census conducted by our group revealed about 600 pigs in the village. Pig corralling was noticed in about 60% of cases, and the rest were allowed to roam free in and around the houses and streets. Despite the pig-raising culture of Atahualpa residents, they are not frequent pork consumers. Pigs are most often sold in neighboring villages, and only eaten by Atahualpaians for special celebrations. Treatment of pigs with antiparasitic drug or passive immunization has never happened in the village. In contrast, over the past decade children in school age have been deparasited with albendazole and secnidazole (an antiprotozoal agent) once a year every other year, as part of a public campaign of the Ministry of Health.

Study design

Using a population-based 3-phase study design, we aimed to assess the prevalence of seizures and epilepsy in Atahualpa residents aged ≥ 20 years, and to estimate the prevalence and patterns of disease expression of NCC and its relationship with epilepsy. The study followed the recommendations of the standards of reporting of neurological disorders (STROND) guidelines,²³ and was approved by the Institutional Review Board of Hospital-Clinica Kennedy, Guayaquil, Ecuador (FWA 00006867).

Door-to-door surveys (Phase I)

All Atahualpa residents aged ≥ 20 years were invited to participate. After a comprehensive informed consent process, eligible individuals who accepted and signed a written consent form were enrolled. During the surveys, personnel of the Atahualpa Project, including trained rural doctors and a neurology resident conducted face-to-face interviews to identify individuals with a suspected seizure disorder, departing from the field instrument developed and validated by Placencia et al.^{24,25} Demographics, level of education and alcohol intake were also inquired during the survey to be used as covariates in subsequent analyses.

Neurological examination (Phase II)

Certified neurologists, blinded to the results of the survey, examined all suspected cases, as well as a random 5% sample of non-suspected individuals to estimate the reliability of the field instrument for detection individuals with seizures, and to assess the crude prevalence of recurrent unprovoked seizures (epilepsy). During this phase, history taking to determine

whether the individual actually had epilepsy was directed to assess family history of seizures, the age of onset and date of the last seizure, the circumstances that surrounded the seizure episodes, the number of lifetime seizures, the type of seizures, and the use and efficacy of antiepileptic drugs. A thorough neurological examination was performed in all cases.

Neuroimaging studies (Phase III)

All participants – being identified as a PWE or not – were offered a non-enhanced CT scan of the head, and those who accepted the practice of this procedure and had no contraindications were enrolled. Women of childbearing age had a pregnancy test before the scan. All CTs were performed with a Philips Brilliance 64 CT scanner (Philips Medical Systems, The Netherlands) at Hospital-Clínica Kennedy, Guayaquil. Slice thickness was 3mm, with no gap between slices. A neurologist and a neuroradiologist independently read all CTs with attention to the presence of parenchymal brain calcifications as well as other intracranial lesions suggestive of NCC.²⁶ As detailed elsewhere, rounded and homogeneous non-physiological supratentorial calcifications, measuring <1cm in diameter, not associated with other neuroimaging findings suggestive of alternative etiologies, and not explained by any other causes, were considered to be of cysticercotic origin.²⁷ Images corresponding to all identified lesions were sent to another expert for further confirmation. Inter-reader agreement was excellent ($k=0.92$) and disagreements were resolved by consensus.

Statistical analyses

Data analyses were carried out by using STATA version 14 (College Station, TX, USA). In univariate analyses, continuous variables were compared by linear models and categorical variables by χ^2 or the Fisher exact test as appropriate. Continuous variables were presented as means $\pm$ standard deviations and categorical variables as percentages with 95% confidence intervals (C.I.). Reliability of the field instrument was assessed by calculating its sensitivity and specificity, as well as its positive and negative predictive values (using numbers of true and false positive suspected cases, and those of true and false negative non-suspected individuals). The crude prevalence of epilepsy was calculated by dividing the number of confirmed PWE by the total number of participants enrolled at the survey (per 1,000 population). The independent association between NCC (as the exposure) and epilepsy (as the outcome) was assessed by the use of a multivariate logistic regression model adjusted for age, sex, level of education and alcohol intake. Similar models were constructed to evaluate variables associated with the presence of NCC. Models were fitted with robust standard errors to account for household clustering and were evaluated for possible collinearity among covariates and fit the data by the use of Akaike's information criteria. Predictive probabilities of NCC prevalence according to the age of the subjects (in quartiles) were estimated to assess whether age is a factor increasing the prevalence of NCC.

RESULTS

Figure 1 is a flow diagram depicting the process of enrollment and the reasons for not including potentially eligible individuals at each step of the enrollment process. Of 1,604 Atahualpa residents aged ≥ 20 years identified during the door-to-door survey, 1,537 (96%)

signed the informed consent and were interviewed with the aforementioned screening questionnaires. Seven of these persons had incompletely filled forms and 75 declined further consent (mostly because of their unwillingness to participate in further phases of the study) and were excluded, leaving 1462 (91%) participants. Mean age of enrolled individuals was 45.4 ± 18.5 years, 786 (54%) were women, 612 (42%) had primary school education only, and 302 (21%) admitted moderate-to-severe alcohol consumption (all of them were men).

The field instrument for seizure detection, applied in the settings of personal interviews by trained rural doctors and a neurology resident, revealed 51 suspected cases. Of these, 38 had recurrent non-provoked epileptic seizures according to the neurological interview (Phase II). Seven of the remaining 13 subjects had a single seizure episode (to have occurred more than 5 years before the survey) and the other six had non-epileptic events (syncope or paroxysmal vertigo). Neurologists also interviewed a randomly selected sample of non-suspected individuals (71 [5%] out of 1,411), and found that three of them had recurrent non-provoked epileptic seizures. These findings gave the questionnaire a sensitivity of 93.6% (95% C.I.: 81.4 – 98.3), a specificity of 90.7% (95% C.I.: 81.1 – 95.8), a positive predictive value of 0.86 (95% C.I.: 0.73 – 0.94) and a negative predictive value of 0.96 (95% C.I.: 0.87 – 0.98) for seizure detection, irrespective of the number of events (single or recurrent seizures).

The total of 41 PWE found among 1,462 participants gave a crude prevalence of epilepsy of 28 (95% C.I.: 20.7 – 38.2) per 1,000 Atahualpa residents aged ≥ 20 years. PWE were less educated than those without epilepsy (66% versus 41% individuals had only primary school education, $p=0.002$), but there were no significant differences in the mean age (49.6 ± 18.3 versus 45.3 ± 18.5 , $p=0.142$), proportion of women (56% versus 54%, $p=0.761$), or severity of alcohol intake (12% versus 21%, $p=0.174$) across PWE and those without it. The age of onset of seizures in PWE ranged from 1 to 80 years (mean age of onset 17.7 ± 18 years, median age of onset: 13 years), with nine persons (22%) presenting with late-onset epilepsy (seizures starting after the age of 20 years²⁷). Only seven persons had a positive family history of epilepsy. Eleven PWE have had less than 5 seizures, four from 6 to 10, two from 10 to 20, and the remaining 24 recalled more than 20 lifetime seizures. Twenty persons (50%) had active epilepsy, defined as the presence of seizures during the past five years. Seizures were referred as tonic-clonic generalized in 31 cases (76%). In the other 10 cases, seizures had a focal onset with or without secondary generalization. The physical and neurological examination was normal in all but two cases, one presenting with hemiparesis and the other with phocomelia in an arm. Five individuals had a history of status epilepticus (more than once in three of them). Thirty-three PWE received or were currently taking AEDs. Drugs most frequently used were carbamazepine, phenytoin and phenobarbital, alone or in combination. Length of therapy and dosages varied, but AEDs have most often been taken at suboptimal doses and for inadequate periods. Eight (20%) PWE never received AEDs.

A head CT was performed in 1,228 (84%) out of 1,462 participants (77% of the entire Atahualpa population aged ≥ 20 years), including 39 of 41 PWE, the seven persons with a single seizure, and 1,182 of 1,414 without seizures. CT showed lesions consistent with NCC in 118 cases (9.6%; 95% C.I.: 8.1% – 11.4%). All these patients had calcified lesions in the brain parenchyma, and there was no single case with other forms of the disease, such as

living or degenerating parenchymal, subarachnoid or ventricular cysts, or hydrocephalus. In addition, none of these patients had previously been diagnosed with NCC and no one received cysticidal agents in the past. Four PWE without evidence of NCC had CT abnormalities likely explaining their seizure disorder, including focal areas of atrophy in the temporal lobe in two, cerebral hemiatrophy in one, and a congenital subarachnoid cyst in the other.

Due to the potential lack of resolution of CT to detect small cystic lesions in the brain parenchyma, subarachnoid space or ventricular cavities, we used information provided by brain MRIs performed in the same population for other research purposes, as part of the Atahualpa Project.^{22,29,30} As detailed elsewhere, MRIs were performed with a Philips Intera 1.5T (Philips Medical Systems, the Netherlands) at Hospital-Clínica Kennedy, and included two-dimensional multi-slice turbo spin echo T1-weighted, fluid attenuated inversion recovery (FLAIR), T2-weighted, and gradient-echo sequences in the axial plane, as well as a FLAIR sequence oriented in the sagittal plane; slice thickness was 5mm with 1mm gap between slices.²⁹ A total of 452 MRIs, all performed in Atahualpa residents aged 40 years, were reviewed. As expected, the mean age of individuals who had a brain MRI (64.8 ± 14.2 years) was higher than those who had a head CT (46.2 ± 18.4 years).

These 452 MRIs corresponded to 81 of the 118 participants with evidence of NCC on CT and to 371 of the 1,110 without NCC. MRIs did not detect any cysticercotic lesion missed on CT with the possible exception of an old focus of gliosis surrounding one calcified lesion. Likewise, MRIs did not identify new NCC cases among those with a negative CT scan. On the other hand, MRIs detected five lesions likely responsible for the epileptic disorder in non-cysticercotic cases (that were not seen on CT), including hippocampal sclerosis in three, cortical heterotopia in one, and a cavernous angioma in the remaining case. In addition, the case with cerebral hemiatrophy, the congenital arachnoid cyst and the two cases with focal areas of atrophy in the temporal lobe (as a probable sequelae of herpetic encephalitis), that were already noticed on CT, were easily demonstrated on MRI.

There were a total of 193 calcifications in the 118 patients. Eighty-four (71%) had a single calcification, 29 (25%) had from 2 to 4 calcifications, and the remaining five had 5 calcifications (mean calcifications per person: 1.6 ± 1.7). Lesions were located in the left cerebral hemisphere in 49 cases, in the right cerebral hemisphere in 46, and in both cerebral hemispheres in the remaining 23. No single case had calcifications located in the brainstem or cerebellum. Regarding the cerebral lobes involved, the parietal lobe was more frequently affected (77 calcifications), followed by the frontal ($n=44$), the occipital (40), and the temporal lobes ($n=11$). The remaining calcifications were located in the basal ganglia or thalami ($n=11$).

Patients with calcified cysticerci on CT were older (51.4 ± 17.2 versus 45.7 ± 18.5 years; $p=0.001$), and more often women (65% versus 54%; $p<0.001$) than those without NCC, but there were no differences in the level of education ($p=0.263$) or severity of alcohol intake ($p=0.886$) across groups. A logistic regression model, adjusted for sex, level of education and alcohol intake, showed significantly increased odds for the prevalence of calcified cysticerci in the 2nd, 3rd and 4th quartiles of age when compared with the 1st quartile used as

the referent category (Table 1). In this model, being woman remained as the only significant covariate ($p=0.006$). Predictive probabilities of NCC prevalence (with 95% confidence intervals) according to quartiles of age (adjusted for sex and alcohol intake) showed a lower prevalence of NCC among subjects in the 1st quartile when compared to those in the 4th quartile (Figure 2).

Of the 1,228 participants with a head CT, seven had a single seizure, 39 had recurrent unprovoked seizures (epilepsy), and 1,182 did not recall seizure episodes. Two of the seven persons (29%) with a single seizure had calcified cysticerci on CT, and the others had a normal CT. Since the main objective of this analysis is to assess the independent association between NCC and epilepsy, persons with a single seizure with or without NCC, were considered as epilepsy-negative subjects (particularly because the seizure episode occurred more than five years before the interview in all cases). Of the 39 PWE, nine (23.1%) had calcified cysticerci on CT as opposed to 109 (9.2%) out of the 1,189 participants without epilepsy ($p=0.004$). This difference persisted in a logistic regression model adjusted for age, sex, education and alcohol intake (OR: 3.04; 95% C.I.: 1.35 – 6.81; $p=0.007$). In this model, the only covariate that remained significant was level of education ($p=0.007$).

The mean age of seizure onset in PWE and NCC was somewhat higher than that of PWE without NCC (23.2 ± 21.3 versus 15.3 ± 16.5 years), but the difference did not reach significance ($p=0.246$). Likewise, there was a non-significant trend for PWE in the NCC group to have more often late-onset epilepsy than in PWE without NCC (44% versus 16%, $p=0.087$), but PWE and NCC did not have more life-time seizures than those without NCC ($p=0.711$). On the other hand, the mean number of calcifications in PWE was not different from that of those without epilepsy (1.3 ± 0.7 versus 1.6 ± 1.8 , $p=0.621$).

DISCUSSION

The relationship between NCC and epilepsy has been suggested in several studies but it is not universally accepted.³¹ There is a great heterogeneity in study designs, with some diagnosing NCC only on the basis of low accuracy serological assays (hemagglutination tests, serum ELISA) or X-ray films, and others restricting the sample to selected groups or to small numbers of participants. Moreover, some authors still argue that cysticercotic lesions in the brain can be innocent bystanders present in many PWE living in regions where this parasitic disease is endemic.^{32,33} While this is theoretically possible – and must indeed occur in a reduced percentage of cases – several pieces of evidence favor a causal relationship between NCC and recurrent nonprovoked seizures. Published evidence include abundant descriptions of cases with focal epilepsies related to the location of a single parasite in the brain parenchyma,^{34–38} the higher prevalence of epilepsy in cysticercosis-endemic areas when compared with non-endemic regions,³⁹ and the occurrence of inflammatory changes surrounding parenchymal brain cysticerci immediately after a seizure in up to 50% cases.⁴⁰ In addition, while it has been suggested that some degenerating cysticerci may induce reactive seizures due to transient episodes of inflammation, calcified cysticerci – as those found in the present series – represent enduring epileptogenic lesions due to the gliosis that develops around dead parasites, as well as late exposure of residual antigenic material to the brain parenchyma.⁴¹

In this study, assessing a large and unbiased population of community-dwellers (living in an endemic village) with high-resolution CT, PWE had three times the odds of having NCC than those without epilepsy, providing robust epidemiological evidence favoring the association between NCC and epilepsy. As occur in all cross-sectional studies, correlation (or association) does not imply causation. However, biological plausibility strongly suggests a cause-and-effect relationship between NCC as the exposure and epilepsy as the outcome, since the opposite is highly unlikely and there were no other evident confounders that might explain the outcome. The present study fulfills the standards for the conduction of well-designed epidemiological studies attempting to assess a potential relationship between NCC and epilepsy, as proposed elsewhere.³¹

The absence of viable brain cysticerci in the study population (even when a sizable proportion of participants were also evaluated with MRI), and the similar prevalence of NCC across participants older than 30 years deserve further attention. Brain calcifications have been found as the only form of NCC in other population studies conducted in endemic villages, where smaller numbers of participants have been scanned.⁶ It is however surprising not to find a single case of viable NCC in a population of more than 1,200 individuals where 118 cases of calcified NCC were detected. Being Atahualpa a cysticercosis-endemic village, where all the inter-related stages in the life cycle of *Taenia solium* apparently exist (free roaming pigs, open-air defecation with inadequate disposal of human feces, and pork consumption), recent human infections presenting on CTs as living cysts or degenerating granulomas should be expected. Another unexpected finding was the similar prevalence of patients with NCC across different age groups with the exception of those younger than 30 years of age. Since calcifications are permanent lesions except in very rare cases,⁴² new infections should result in a cumulative effect increasing prevalence in older ages. Moreover, in the present series, the mean number of calcifications per patient did not increase with advancing age, suggesting that reinfections in already infected individuals were unlikely. These findings would be explained if transmission has stopped and infected pigs do not longer habit in Atahualpa. Alternatively, transmission may still be present and people may had been infected at early ages and then protected from further infections due to less-well understood immune mechanisms.

There is only scarce information on the natural evolution of untreated NCC infections in endemic settings. Residual calcifications have been found in approximately 55% of Indian patients presenting with a single degenerating brain cyst and not receiving cysticidal drugs.⁴³ In multi-cystic infections, seen more frequently in Latin America than in India, this prevalence is likely higher. It is possible that in our series, there is a subgroup of individuals who completely cleared their NCC infections, which might be either included in the group of PWE or in that of people without epilepsy. However, their numbers can not be estimated. In addition, we can not rule out that some of our patients with calcified NCC and no current epilepsy will have nonprovoked seizures in the future.

Major strengths of this study include the population-based design with unbiased selection of participants, the systematic procedures used for detection of individuals with suspected seizure disorders (using a validated field instrument) and the further assessment of positive epilepsy cases by certified neurologists, together with the high number of neuroimaging

studies performed (1,228 CT scans) and the high level of inter-rater agreement for CT readings. A potential limitation is the lack of MRI exams in younger individuals, which could have unveiled viable NCC lesions not detected by CT, and the lack of serological investigation of pigs, which would help to elucidate whether active transmission still exists in the village.

In addition, immune tests (such as the enzyme-linked immunosorbent assay) were not performed, and this could be seen as a limitation of our study. However, all our NCC cases were in the calcified state and this is not an appropriate population to compare the performance of antibody serology because only a small proportion of them will test positive because antigenic stimulation disappeared and the antibody response wanes along time, and even those with a positive test will likely have very low antibody levels compared to individuals with viable infections.⁴⁴

In conclusion, this study demonstrate a robust relationship between epilepsy and NCC (OR: 3.04; 95% C.I.: 1.35 – 6.81) in a village endemic for NCC – where 9.6% of community-dwelling individuals aged 20 years are infected – with a prevalence of epilepsy two or three times higher than in the developed world. These figures are likely similar in many endemic villages in most non-Muslim developing countries, where NCC greatly contributes to the global burden of epilepsy.

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KEY BULLET POINTS

- Few imaging-based studies have examined the association between neurocysticercosis and epilepsy at the population level.
- Previous studies face problems related to small sample sizes or biased selection of participants.
- In this large population study, persons with epilepsy had three times the odds of having neurocysticercosis than those without epilepsy.
- All detected NCC patients had calcified lesions. Whether younger individuals have viable lesions can not be assessed from this data.

Figure 1. Flow diagram depicting the process of enrollment and the reasons for not including potentially eligible individuals at each step of the enrollment process.

Figure 2.

Graph plot showing predictive probabilities of neurocysticercosis prevalence (with 95% confidence intervals) according to quartiles of age (adjusted for sex and alcohol intake). The plot shows a lower prevalence of neurocysticercosis among subjects in the 1st quartile when compared to those in the 4th quartile.

Table 1

Logistic regression model, adjusted for sex, level of education and severity of alcohol intake, showing prevalence of patients with calcified neurocysticercosis across quartiles of age, and the size of the difference in this prevalence according to age (using individuals in the lowest quartile as the referent category).

	Total series (n=1,228)	NCC cases, n (% , with 95% C.I.)	Adjusted OR (95% C.I.)	p value
Quartile 1 (20–30 years)	296	15 (5.1; 3.1 – 8.2)	Ref	Ref
Quartile 2 (31–41 years)	303	29 (9.6; 6.8 – 13.4)	2 (1.07 – 3.71)	0.029
Quartile 3 (42–60 years)	316	36 (11.4; 8.3 – 15.4)	2.31 (1.22 – 4.37)	0.010
Quartile 4 (>60 years)	313	38 (12.1; 8.9 – 16.2)	2.61 (1.35 – 5.04)	0.004