Neurocysticercosis among People Living Near Pigs Heavily Infected with Cysticercosis in Rural Endemic Peru

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Abstract. Neurocysticercosis causes substantial neurologic morbidity in endemic regions around the world. In this cross-sectional study, we describe the frequency of neurocysticercosis among a presumed high-risk group of people in an endemic community in northern Peru. Participants who screened positive on a nine-question seizure survey were evaluated clinically to diagnose epilepsy using International League Against Epilepsy criteria. Those with epilepsy were offered a noncontrast computerized tomography (CT) of the head. We also tested sera from all participants using the lentil lectin-bound glycoprotein enzyme-linked immunoelectrotransfer blot (EITB) to detect anti-cysticercus antibodies and enzyme-linked immunosorbent assay (ELISA) B60/B158 to detect cysticercosis antigens. Participants with strongly positive ELISA (ratio ≥ 3) were offered a noncontrast magnetic resonance imaging (MRI) of the brain. We diagnosed 16 cases of epilepsy among 527 people screened (lifetime prevalence 30 per 1,000). Twelve with epilepsy accepted CT scan and five (41.7%) had parenchymal calcifications. None had viable cysts. Of the 514 who provided a blood sample, 241 (46.9%) were seropositive by EITB and 12 (2.9%) were strongly positive by ELISA (ratio ≥ 3). Eleven accepted MRI and eight (72.3%) had neurocysticercosis, including five with extraparenchymal cysts, five with parenchymal vesicular cysts, and two with parenchymal granulomas. These findings show that clinically relevant forms of neurocysticercosis and epilepsy can be found by applying screening interventions in communities endemic to *Taenia solium*. Longitudinal controlled studies are needed to better understand which subgroups are at highest risk and which are most likely to have improved prognosis as a result of screening.

INTRODUCTION

Neurocysticercosis (NCC) is an infection of the central nervous system by larval cysts of the zoonotic cestode *Taenia solium*. The infection occurs via fecal–oral transmission when eggs shed in the feces of a human with the intestinal form of the pork tapeworm infection are ingested (Figure 1). These eggs release oncospheres that penetrate the intestinal wall and circulate through the bloodstream to form cysticerci. Cysticerci that form in the brain may lead to neurologic manifestations, including seizure, headache, intracranial hypertension, encephalitis, cognitive impairment, and stroke.^{1,2} The burden of NCC in endemic regions can be substantial, and this disease remains the leading cause of acquired epilepsy across much of Asia, Africa, and Latin America.^{3,4} In Latin America alone, up to 1.35 million people have seizure disorders secondary to NCC.^{5,6} Strategies to reduce this large burden of neurologic disease are needed.

Neuroimaging either using computerized tomography (CT) or magnetic resonance imaging (MRI) is required for clinical diagnosis of NCC.⁷ CT scan tends to capture more cases of calcified NCC, are more widely available, and less expensive than MRI but also impart some risk through exposure to radiation. Several studies have used CT scan in the community setting to detect cases of NCC, although typically only among symptomatic or seropositive participants.^{8–11} A couple of studies have applied CT to adults without prescreening and found the prevalence to be 9–19%, with the vast majority of

cases being calcified NCC.^{12,13} MRI is a more sensitive tool for detecting viable cysts, particularly small cysts, as well as cysts in the base of the brain, ventricles, or subarachnoid spaces. MRI does not subject the participant to radiation but is less widely available and more expensive than CT. The only study to use MRI in the community setting reported the prevalence of viable cysts to be 5%.¹⁴ No studies have used both modalities, an approach which may capture more cases of NCC.

The goal of this study was to describe the frequency of NCC diagnosed using both CT and MRI among a presumed high-risk group of residents in a *T. solium* endemic community in northern Peru, using both symptom screening and serology to select participants eligible for neuroimaging.

MATERIALS AND METHODS

Study site. The study site was the village of Surpampa (population 1,058) in the northern coastal region of Piura, Peru, where *T. solium* is known to be endemic.^{15–17} In this arid agricultural region, villagers raise pigs by allowing them to roam free and forage for food. Many households lack latrines and open defecation is common. Pigs are therefore able to access and consume human feces contaminated with *T. solium* eggs.

Study design and participants. This cross-sectional descriptive study was conducted at the end of a 1-year prospective community-based trial that evaluated a targeted screening strategy for control of *T. solium* taeniasis.¹⁸ In that trial, we offered stool screening and treatment of taeniasis to a subset of the population residing in areas of increased transmission (referred to as rings). At the end of the trial, we conducted a survey in this same group of high-risk residents using multiple tools to identify symptomatic cases of NCC and provide treatment of taeniasis to all participants. No control

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FIGURE 1. Lifecycle of *Taenia solium*.

group was included. A total of 576 people were eligible for the cross-sectional survey with children < 2 years old excluded. Participation is shown in Figure 2.

Screening for seizures and clinical evaluation for epilepsy.

We screened all participants for a history of seizures using a validated nine-question survey that has been used in community-based studies in Latin America.^{10,19,20} The survey was administered by a team of nurses, nursing technicians, and midwives who had been specifically trained for this purpose. Participants who screened positive were then evaluated in their homes by a study physician who used International League Against Epilepsy guidelines to diagnose seizures and epilepsy. The following definitions were used.²¹

Seizure. A clinical manifestation presumed to result from an abnormal and excessive discharge of a set of neurons in the brain, which is perceived by the patient or an observer, and which includes an alteration of consciousness, or an unexplained motor, sensory, autonomic, or psychic event.

Epilepsy. A medical condition defined by the occurrence of two or more unprovoked seizures in a period of more than 24 hours. Multiple seizures occurring within a single 24-hour period are considered a single event.

Active epilepsy. A subcategory of epilepsy in which the patient has experienced at least one seizure in the preceding 5 years, regardless of whether the patient is taking antiepileptic drug (AED) treatment.

Nonactive epilepsy. A subcategory of epilepsy in which the patient has not experienced at least one seizure in the

previous 5 years, regardless of whether the patient is taking AED treatment.

Serologic screening. We collected a 5-mL peripheral venous blood sample from all participants to screen for circulating antigens or antibodies indicating infection with or exposure to *T. solium* cysticercosis, respectively. The blood samples were stored on ice in coolers and then centrifuged in a field laboratory. Serum aliquots of 1.5 mL were then frozen at -20°C and shipped to the Universidad Peruana Cayetano Heredia (UPCH) (Lima, Peru) for further analysis. We used an enzyme-linked immunoelectrotransfer blot (EITB LLGP) to detect antibodies against *T. solium* cysts as previously described.²² The EITB LLGP assay uses an enriched fraction of homogenized *T. solium* cysts containing seven *T. solium* glycoprotein antigens: GP50, GP42, GP24, GP21, GP18, GP14, and GP13. Reaction to any of these seven glycoprotein antigens is considered positive. The assay was first reported to be 98% sensitive and 100% specific to *T. solium* larval stage but has since been shown to have sensitivity < 70% for NCC with single viable cysts or calcified cysts only.^{23,24} The presence of antibodies does not distinguish active infection from cleared infection or egg exposure without infection.

We also analyzed human sera for the presence of cysticercosis antigens using a previously described enzyme-linked immunosorbent assay (antigen-ELISA, i.e., Ag-ELISA) based on a combination of two monoclonal antibodies (B158/B60).²⁵ The presence of these antigens in human sera indicates active infection with *T. solium* cysts, with the amount of antigen

FIGURE 2. Study flow diagram showing the number of residents participating in screening and diagnostic activities.

present thought to vary depending on the number, size, and location of cysts.^{26–28} The sensitivity is reported at ~85%, although it may be lower for infections with one or few brain cysts.²⁹ Results of the ELISA were expressed as a ratio, calculated by dividing the optical density (OD) of the sample by the mean OD of eight known negative samples plus three standard deviations. A ratio greater than or equal to 1 was considered positive. An arbitrarily defined ratio greater than or equal to 3 was considered strongly positive.

Computed tomography (CT) of the head. Participants diagnosed with epilepsy by the study physician were offered noncontrast CT scan of the head using a helicoid scanner (Siemens AG, Munich, Germany). Cranial CT was chosen for the epilepsy group because it is the most sensitive modality for detecting calcifications, which can cause seizures, and is often sufficient to identify parenchymal cysticerci.

MRI of the brain. Participants with a strongly positive Ag-ELISA (ratio ≥ 3) were offered noncontrast MRI using T1, T2, and fluid-attenuated inversion recovery sequence; MRI is better than CT for detection of viable cysts, including small cysts and extra-axial cysts.³⁰ A cutoff of ≥ 3 was used to increase the positive predictive value of the assay for detecting viable cysts and thereby reduce the number of unnecessary MRIs. We provided transportation for participants to and from for these procedures. Participants diagnosed with epilepsy or NCC were referred to the local ministry of health facility for further evaluation and treatment.

Statistical methods. All data were analyzed using STATA SE14 (StataCorp, College Station, TX). Fisher's exact or χ^2 tests were used to compare distributions of proportions or to examine association between pairs of categorical measures, and t-tests to compare means of continuous variables.

Variables potentially associated with the seropositivity on the serologic assays were evaluated individually by logistic regression. Those variables with significance at or below the 0.25 level were included in a multivariable logistic regression model, and the effect measure is reported as an adjusted odds ratio with 95% confidence intervals. All tests were two-sided with significance threshold set at 0.05.

Ethics. This study was reviewed and approved by the Institutional Review Boards at the UPCH and at Oregon Health & Science University. All adult participants provided written informed consent. Written informed consent from a parent or guardian was required for participation of minors.

RESULTS

Characteristics of eligible population. Of the total population of 1,058 residents, 24 (2.3%) were ineligible for participation in the study based on age < 2 years old. Of the remaining 1,034 residents, 576 (55.6%) resided within any of 31 rings formed in the parent study.¹⁸ We were able to screen 534 (94.3%) of these ring residents using either the neurologic survey or the serologic assays for cysticercosis (Figure 1). Demographic characteristics of the residents living within rings are shown in Table 1.

Serologic results. We collected blood samples from 514 (89.2%) of the 576 eligible participants. There were 241 (46.9%) with positive serology on EITB LLGP; 111 (21.6%) had one to two reactive bands, 98 (19.1%) had three reactive bands, and 32 (6.2%) had four to seven reactive bands. There were 39 (7.6%) individuals with positive Ag-ELISA (ratio ≥ 1). Twelve (2.3%) had a strongly positive result on Ag-ELISA (ratio ≥ 3). The proportion of individuals with positive Ag-ELISA increased with greater number of reactive bands present on

TABLE 1

Demographic characteristics of residents who were eligible for screening based on residing within 100 meters of a heavily infected pig

	Residents within a screening ring	
	N = 576	
Male sex, no. (%)	306 (53.1)	
Age, median (IQR)	26 (14–45)	
Households that have latrine, no. (%)	311 (54.0)	
Households that raise pigs, no. (%)	406 (70.5)	
Corral present on property, no. (%)	184 (45.3)	
No. of pigs raised, mean (SD)	5.3 (4.1)	
No. of residents per house, mean (SD)	6.0 (2.2)	

IQR = interquartile range; SD = standard deviation.

EITB LLGP, with a substantial increase when four or more bands were present (Table 2). The seroprevalence of anti-cysticercus antibodies increased with increasing age whereas the seroprevalence of cysticercosis antigens remained relatively constant across age categories (Figure 3). Residing within the same household as someone who was diagnosed with taeniasis was the strongest risk factor for seropositivity, with the odds of having circulating anti-cysticercus antibodies or cysticercus antigens being 6.1 and 5.7 times higher, respectively (Tables 3).

Seizure screening and clinical evaluation. Of the 576 eligible participants, 527 (91.5%) were screened for seizures in their homes using the short questionnaire. In all, 114 (21.6%) were positive on this screening tool. Our study physician evaluated 108 (94.7%) of those who screened positive, verifying a history of seizure in 35 (32.4%); eight had febrile seizure, 11 had a single seizure episode, 11 had inactive epilepsy, and five had active epilepsy. None of the five with active epilepsy were presently taking AEDs. Fifteen participants with epilepsy provided a blood sample; nine (60.0%) had one or more reactive bands on EITB LLGP whereas three (20.0%) had an Ag-ELISA ratio ≥ 1 .

Computed tomography of the head. Of the 16 participants with epilepsy, 12 (75%) received CT scan of the head; five (41.7%) had parenchymal calcifications consistent with NCC and none had cystic lesions. Of the five with calcifications, one (20%) had active epilepsy whereas four (80%) had inactive epilepsy. There was no association between EITB positivity and the presence of calcifications in the 12 who had CT scan; 2/5 (40%) of those with calcifications were EITB LLGP positive whereas 4/7 (57%) of those without calcifications were EITB LLGP positive ($P = 0.6$).

MRI of the brain. Of the 12 participants with an Ag ratio ≥ 3 , ten (83.3%) had four or more reactive bands on EITB, one

TABLE 2

Proportion of individuals with circulating cysticercosis antigens by number of reactive bands present on the EITB LLGP

EITB LLGP (no. of reactive bands)	Number	Ag-ELISA	
		ODR ≥ 1	ODR ≥ 3
0	273	3 (1.1)	1 (0.4)
1–2	111	11 (9.9)	0 (0)
3	98	8 (8.2)	1 (1.0)
4–7	32	17 (53.1)	10 (83.3)

EITB = enzyme-linked immunoelectrotransfer blot; ELISA = enzyme-linked immunosorbent assay; ODR = Optical density ratio.

FIGURE 3. Seroprevalence of anti-cysticercus antibodies (EITB LLGP) and cysticercus antigens (Ag-ELISA) among residents living within 100 meters of a heavily infected pig with cysticercosis. EITB = enzyme-linked immunoelectrotransfer blot; ELISA = enzyme-linked immunosorbent assay.

(8.3%) had three reactive bands, and one (8.3%) was negative on EITB. Eleven (92.7%) received MRI of the brain; eight (72.3%) had cystic lesions consistent with NCC including five (45.5%) with extraparenchymal cysts, five (45.5%) with parenchymal vesicular cysts, and two (18.2%) with parenchymal granulomas. No basal subarachnoid cysts (racemose NCC) were detected. None of the eight with viable cysts had a history of epilepsy although two reported severe headaches. Two additional participants were suspected of having NCC despite having a normal MRI. These individuals had very high Ag-ELISA ratios, suggesting the presence of cysts in a region not imaged such as the spine. One was a 45-year-old male with inactive epilepsy who had mild hippocampal asymmetry, Ag-ELISA ratio of 87.0, and four reactive bands on EITB. The other was a 39-year-old female with a history of a single seizure episode, active taeniasis infection, Ag-ELISA ratio of 47.7, and six reactive bands on EITB. A summary of the laboratory, imaging, and clinical results for the 13 people diagnosed with NCC using either CT or MRI is shown in Table 4.

DISCUSSION

The objective of this study was to describe the frequency of NCC among a presumed high-risk group of residents in an endemic community. Using a combination of neurologic surveys and serologic testing for the presence of cysticercosis antibodies or antigens, with confirmation of positive results through clinical evaluation and neuroimaging, we identified 13/543 (2.4%) people with NCC, including eight with viable cysts. We also identified 16 people with epilepsy of multiple causes, including five with active epilepsy who were not receiving AED therapy. These findings illustrate the potential to identify affected individuals in the community setting who may benefit from clinical management.

The presentation of NCC in the community setting follows a spectrum of clinical severity. In most of the cases, disease is limited to calcified scars in the brain parenchyma that may form after cyst death (calcified NCC). The prevalence of calcified NCC in endemic areas ranges from 9% to 19%.^{12,13} Although most are asymptomatic and do not require regular treatment or clinical follow-up, in an unknown proportion,

TABLE 3

Factors associated with seropositivity for antibodies against *Taenia solium* cysticercosis on EITB LLGP and for the presence of cysticercosis antigens on Ag-ELISA

Variable	EITB LLGP				Ag-ELISA			
	OR	P value	aOR	95% CI	OR	P value	aOR	95% CI
Age	1.03	< 0.01	1.03	(1.02–1.04)	1.01	0.20	1.01	(1.00–1.03)
Male sex	0.97	0.85	–	–	1.05	0.88	–	–
Number of residents in the house	0.97	0.46	–	–	1.03	0.72	–	–
Households that have latrine	0.82	0.28	–	–	0.66	0.22	0.79	(0.40–1.57)
Households that raise pigs	1.44	0.07	1.64	(1.07–2.54)	0.76	0.45	–	–
Corral present on property	0.94	0.73	–	–	1.24	0.54	–	–
Number of pigs raised	1.01	0.53	–	–	0.7	0.54	–	–
Household member with taeniasis*	4.85	< 0.01	6.05	(3.22–11.4)	5.7	< 0.01	5.72	(2.79–11.7)

aOR = unadjusted odds ratio; CI = confidence interval; EITB = enzyme-linked immunoelectrotransfer blot; ELISA = enzyme-linked immunosorbent assay; OR = odds ratio.

* Confirmed by stool screening during the parent study using light microscopy for *Taenia* sp. material and ELISA for *Taenia* sp. coproantigens (optical density ratio ≥ 20).

calcifications will become chronic epileptogenic foci.³¹ The treatment gap of epilepsy in impoverished rural regions endemic to *T. solium* remains high.³² Identifying untreated cases of epilepsy in these regions, due to NCC or other cause, could substantially reduce morbidity provided appropriate clinical management with AEDs. The lifetime prevalence of all epilepsy in this study was 29/1,000 and that of active epilepsy was 9/1,000. None of the five individuals with active epilepsy were on AED therapy when identified. Of the nine people with inactive epilepsy, four had calcified NCC.

A smaller subset of individuals with NCC in the community setting have living, viable cysts in their brain, ranging from

less than 1% in studies using CT scan^{12–14} to 5% in a single study that used the more sensitive modality MRI. Viable cysts that occur in the brain parenchyma are typically asymptomatic until the parasite dies, at which point the host inflammatory response provokes seizures as the cyst degenerates. The clinical course of most untreated infections with a single or few intraparenchymal cysts is relatively favorable. However, clinical management of these patients with antiparasitic drugs along with steroids to control inflammation does reduce the risk of seizures in the long term.³³ We found two individuals in this category with single viable parenchymal cysts.

TABLE 4

Neuroimaging characteristics (i.e., MRI or CT) of participants with neurocysticercosis found among residents of a screening ring in Piura, Peru

Case number	Age	Sex	Ag-ELISA (ODR)	EITB (no. of bands)	Neuroimaging findings	Number of lesions	Clinical diagnosis and history
1	73	M	30.9	4	MRI: Multiple bilateral parenchymal vesicular cysts with surrounding edema. Two extraparenchymal cysts including one in the lateral ventricle and one subdural.	7	Negative epilepsy screen. Not evaluated by study physician.
2	24	M	65.4	7	MRI: Multiple bilateral parenchymal vesicular cysts without surrounding edema. Multiple extraparenchymal cysts including cysts in the fourth ventricle, lateral ventricle, and subdural regions.	> 24	Headaches
3	58	F	13.1	7	MRI: Single temporal–occipital vesicular cyst with surrounding edema	1	Negative epilepsy screen. Not evaluated by physician.
4	78	M	16.5	6	MRI: Single cyst in Sylvian fissure	3	Headaches. History of traumatic brain injury.
5	41	M	23.2	7	MRI: Single cyst in Sylvian fissure and two parenchymal granulomas	3	Single seizure. Active taeniasis infection.
6	13	F	37.5	4	MRI: Single vesicular cyst in the central sulcus	1	Negative epilepsy screen. Not evaluated by physician.
7	7	F	3.2	0	MRI: Single parenchymal vesicular cyst without edema	1	History of febrile seizure
8	13	F	25.9	5	MRI: Multiple small parenchymal vesicular cysts without edema. Single calcified cyst with surrounding edema.	> 50	History of unexplained fall Active taeniasis infection
9	43	F	0.3	0	CT: Calcifications in left temporal and lenticular regions	2	Active epilepsy
10	60	M	1.2	0	CT: Single calcification in left lenticular region	1	Inactive epilepsy
11	25	F	0.5	0	CT: Single calcification in right frontal cortex	1	Inactive epilepsy Headaches
12	56	M	0.6	2	CT: Single calcification in left posterior temporal region	1	Inactive epilepsy
13	31	F	1.5	2	CT: Single calcification in right paramedial frontal cortex	1	Inactive epilepsy

CT = computerized tomography; EITB = enzyme-linked immunoelectrotransfer blot; ELISA = enzyme-linked immunosorbent assay; MRI = magnetic resonance imaging.

We found several more individuals (6/543, 1.1%) whose infections involved ventricular cysts and/or many parenchymal cysts. Although these forms of infection are the least common in the population setting, they generally have a higher degree of mortality and worse clinical prognosis, due to resulting obstructive hydrocephalus, elevated intracranial pressure, seizures or stroke.³⁴ Interestingly, 6/11 (54.5%) of those with Ag ≥ 3 had these more severe forms of infection. This suggests that Ag-ELISA screening with an elevated cutoff may be able to identify individuals with the most severe disease manifestations. Although there is sufficient clinical rationale to suspect that early identification and treatment may improve clinical outcomes, there are no definitive data to support this.

This study had some secondary findings worth noting briefly here. With respect to serology, we noted a large increase in the proportion of individuals who had detectable Ag levels as the number of reactive bands present on EITB increased from three to four (Table 3); 19% of individuals with three or more reactive bands on EITB had Ag ratio ≥ 1 compared with 53.3% when four or more bands were present. This suggests that the lower molecular weight bands (14, 18, and 21 kDa), which typically appear as the fourth or higher band on EITB, may correlate with active infection more strongly than the higher molecular weight bands (24, 39, 42, and 50 kDa). On a population level, there was a relatively linear increase in the prevalence of EITB positivity with increasing age, whereas the prevalence of Ag positivity remained relatively static across age groups (Figure 3). This suggests that risk of infection is not age dependent although there is accumulation of persistent anti-cysticerci antibodies with increasing age. By far, the strongest risk factor we found for positive serology was living in the same household of someone with taeniasis, an exposure that increased the risk of having positive Ag or EITB by 6-fold each.

This was a small descriptive study and as such it has important limitations to consider. The fact that we limited our screening to a presumed high-risk subset of the population implies that the results may not be generalizable to the overall population. In fact, the seroprevalence on EITB (46.9%) in this study, which is higher than any previous reports from Peruvian communities, suggests that this was not a representative group. Because we limited screening to this subset only, we have no direct comparison group to evaluate this possibility, a factor which is further complicated by the small overall number of CTs and MRIs performed. In addition, the Ag cutoff level required to be eligible for MRI screening was arbitrarily selected given the absence of existing data for this type of community screening. The four participants with Ag > 3 but without findings of NCC on brain MRI could reflect cyst infection outside the brain, although we cannot confirm this because imaging was limited to the brain. Optimal cutoff levels need to be explored in future studies. Nevertheless, we found viable NCC in eight people, corresponding to a minimum of 0.8% (8/1,034) in the entire population including the nonsampled areas. Longitudinal controlled studies are needed to better understand which subgroups are at highest risk and which are most likely to have improved prognosis as a result of screening.

In conclusion, this pilot study suggests that applying screening interventions in communities endemic to *T. solium* may identify clinically relevant forms of NCC and epilepsy. Different screening modalities and approaches can be used,

depending on whether the intent is to identify people with epilepsy (with or without NCC) or people with NCC and viable cysts. Screening should only be pursued in regions that have adequate diagnostic and clinical infrastructure and expertise to manage patients who are found.

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