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Epilepsy and Neurocysticercosis in Atahualpa: A Door-to-Door Survey in Rural Coastal Ecuador

*Oscar H. Del Brutto, *†Rocío Santibáñez, *Luis Idrovo, ‡Silvia Rodrìguez, †Enrique Díaz-Calderón, †Carlos Navas, §‖Robert H. Gilman, *Fausto Cuesta, ¶Aurelio Mosquera, **Armando E. Gonzalez, ††Victor C. W. Tsang, and ‡§Hector H. García

*Department of Neurological Sciences, Hospital-Clínica Kennedy, and †Neurology Service, Hospital Teodoro Maldonado Carbo, Guayaquil, Ecuador; †‡Cysticercosis Unit, Instituto Nacional de Ciencias Neurológicas and §Department of Microbiology, Universidad Peruana Cayetano Heredia, Lima, Perú; ‖Department of International Health, Johns Hopkins University Bloomberg School of Hygiene and Public Health, Baltimore, Maryland, U.S.A.; ¶Military Hospital, Guayaquil, Ecuador; **School of Veterinary Medicine, Universidad Mayor de San Marcos, Lima, Perú; and ††Division of Parasitic Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, U.S.A.

Summary: *Purpose:* To determine the prevalence of epilepsy and the role of neurocysticercosis in the occurrence of epilepsy in Atahualpa.

Methods: We used a door-to-door survey to detect subjects with epileptic seizures, to collect a blood sample for determination of anticysticercal antibodies, and to evaluate social characteristics of the population, including household pig ownership. Neurologists examined suspected cases and a sample of negative individuals. Then patients with epilepsy, as well as age- and sex-matched controls, underwent a head computed tomography (CT) and a scalp EEG.

Results: The questionnaire was answered by 2,415 of 2,548 residents of Atahualpa, and cysticercosis serology was performed in 1,687 consenting individuals. Cysticercosis seroprevalence was 145 (8.6%) per 1,686). Neurologic examination confirmed 24 patients with epilepsy (crude prevalence, 9.9 per 1,000 population, and 10.8 per 1,000 when adjusted to the United States population). After adjustment by age, sex, and pig raising, positive serology was strongly associated with epilepsy (odds ratio (OR), 4.16; 95% confidence interval (CI), 1.6–11.2). CT findings compatible with neurocysticercosis were found in five patients with epilepsy and also were more frequent than in controls, although this did not reach statistical significance (five of 19 vs. one of 19; $p = 0.125$, McNemar's test). Besides these five cases, three other patients with epilepsy had positive serology (one with a normal CT and two who did not have a CT).

Conclusions: Neurocysticercosis is associated with one-third of cases of epilepsy in Atahualpa and may be a major contributory factor for the excess fraction of epilepsy seen in this population. **Key Words:** Epilepsy—Cysticercosis—Neurocysticercosis—Community survey—Ecuador.

Epidemiologic studies have shown that epilepsy is more common in developing countries than in the developed world (1). It has been suggested that part of this higher prevalence could be related to an increased number of patients with secondary epilepsy related to neurocysticercosis (NCC) (2). However, contrasting data have been obtained in community surveys performed in developing countries because of the lack of neuroimaging studies or the inadequate selection of controls (3–7). To determine the role of NCC in the occurrence of epilepsy, we carried out a cross-sectional study in Atahualpa, by using a door-to-door questionnaire, neurologic examination, and complementary examinations [cysticercosis serology, head computed tomography (CT), and scalp EEG].

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Address correspondence and reprint requests to Dr. O.H. Del Brutto at Air Center 3542, P.O. Box 522970, Miami. FL 33152-2970, U.S.A. E-mail: odbp@gye.satnet.net

METHODS

Atahualpa is a rural village of coastal Ecuador, located 10 miles east of the Pacific Ocean (2°18'S, 80°45'W). The weather is hot and dry, with scarce rains from January to April. The entire population belongs to the Mestizo ethnic group (a racial admixture of Spaniard and Amerindian). All inhabitants speak Spanish, and most have a low economic income; men work as carpenters, farmers, or laborers, and women are housewives (8).

A baseline census was performed to identify all the residents of Atahualpa and to collect sociodemographic information including household pig ownership. During *Phase I*, rural doctors carried out a door-to-door survey to detect

subjects with epileptic seizures by using a validated questionnaire (9). Individuals aged 15 years or older were interviewed directly unless mentally impaired; in such cases, caregivers answered the questions. Children were interviewed indirectly through their parents or guardians. At this stage, field personnel also obtained a capillary blood sample of consenting individuals for cysticercosis serology by immunoblot (10). In *Phase II*, two neurologists examined all suspected cases, as well as a sample of age- and sex-matched negative individuals. Neurologists were blinded as to whether the individual was a positive case or a randomly selected control. Epilepsy was diagnosed in subjects who had two or more unprovoked epileptic seizures (11). Seizure type was classified according to the International League Against Epilepsy (12). Active epilepsy was diagnosed in patients who had at least one epileptic seizure in the previous 5 years, regardless of antiepileptic drug (AED) treatment. An incident case was defined as someone having had the first epileptic seizure in the year preceding the prevalence day (October 15, 2003). In *Phase III*, patients with epilepsy, as well as healthy age- and sex-matched individuals, were invited to undergo a head CT (before and after contrast injection) and a scalp EEG. The study was approved by the IRB of the Hospital-Clinica Kennedy, Guayaquil, Ecuador. Methodologic details on design, procedures, and instruments of this study have been published elsewhere (8).

The χ^2 test and Fisher's exact test were used to analyze associations for discrete variables, and Student's *t* test or Mann–Whitney test for continuous variables; the McNemar test was used for matched data. A multiple logistic regression model with stepwise forward variable selection was fitted by using serologic status as the dependent variable and a history of epilepsy, age, history of pig raising, and sex as independent variables in the final model.

RESULTS

Atahualpa had 2,548 residents distributed in 445 houses (mean, 5.7 ± 3.3 individuals per house). Pig husbandry was common (198 families, 44.5%). Ninety-five percent of the population (2,415 individuals) were interviewed. There were few open refusals to the survey (not registered, estimated in fewer than five). The 133 nonrespondents corresponded mainly to individuals who worked out of town or were traveling. Only one individual died between the census and the survey. Thirty suspected cases with epileptic seizures were detected. From these, neurologic evaluation found recurrent epileptic seizures in 23, a single seizure in three, and nonepileptic events in four. Examination of 120 negative respondents [matched 4:1 to the positives by age (±5 years) and sex] disclosed one additional patient with recurrent epileptic seizures. Thus the questionnaire had a positive predictive value of 0.77 (23 of 30; 95% CI, 0.6–0.9) and a negative predictive value of 0.99 (119 of 120; 95% CI, 0.98–1.00). The prevalence rate of epilepsy was 9.94 per 1,000 population (95% CI, 5.98–13.9 × 1,000) (10.76 per 1,000 when adjusted to the U.S. population). No differences were found in the prevalence of epilepsy by sex (12 of 1,177 men and 12 of 1,238 women). Age-specific prevalence rates are shown in Table 1.

TABLE 1. *Age-stratified prevalence rates of epilepsy in Atahualpa, Ecuador*

Age (yr)	Persons with epilepsy	Prevalence (×1,000)	95% CI
0 to 9	1/571	1.75	0–5.2
10–19	5/512	9.77	1.1–16.4
20–29	7/366	19.13	5.1–33.2
30–39	4/256	15.63	0.4–30.8
40–49	2/241	8.30	0–19.7
50–59	3/220	13.64	0–29
60–69	2/109	18.35	0–43.5
70+	0/140	0.00	0–21
Total	24/2,415	9.94	6–13.9

CI, confidence interval.

The 24 patients with epilepsy were 12 men and 12 women (mean age, 31.9 ± 17.6 years) distributed in 22 houses. Eighteen (75%) patients had active epilepsy. We found no incident cases. Fourteen patients have had >20 seizures during their lives, seven had from six to 20 seizures, and three had fewer than five seizures. One of the 18 patients with active epilepsy had daily seizures, two have monthly seizures, and the remaining 15 have sporadic seizures. Seizures had started at a mean age of 12.4 ± 13.7 years (age range, 1–48 years). Neurologic examination was normal in 18 of 24 cases, five had intellectual impairment, and two had focal deficits (one had both conditions). Seizures were tonic–clonic generalized in 12 patients, simple partial with or without secondary generalization in six, and complex partial in two; the remaining four patients had mixed seizures. Twenty-two of these patients had been evaluated by a physician at a given moment of their disease. However, at the time of this study, only 13 patients were taking AEDs, which were taken irregularly in all cases. Eleven of the 24 patients admitted some degree of stigmatization caused by the seizure disorder, that interfered with their education, marriage, or employment.

CC serology was performed in 22 of 24 patients with epilepsy and in 1,664 of 2,391 without epilepsy. The 860 individuals not sampled were slightly younger (mean age, 26.9 vs. 29 years; $p = 0.023$), were more frequently men (347 of 860 vs. 940 of 1,688; $p < 0.001$), but had raised pigs with similar frequency (410 of 860 vs. 872 of 1,688; $p = 0.059$) than had those not sampled. Results were positive (presence of one or more reactive bands against *Taenia solium* antigens) in six of 22 patients with epilepsy and in 139 of 1,664 without epilepsy (OR, 4.11; 95% CI, 1.3–11.3; $p = 0.009$). Multivariate analysis (logistic

TABLE 2. *Multivariate analysis (forward logistic regression) for seropositivity to cysticercosis in the general population of Atahualpa, Ecuador*

	B	Standard error	Wald	df	p Value	Odds ratio	95% CI
Epilepsy	1.425	0.504	7.977	1	0.005	4.157	1.5–1.2
Age	0.031	0.004	66.358	1	0.000	1.032	1.02–1.04
Pig raising	0.514	0.182	7.929	1	0.005	1.672	1.2–2.4
Sex[a]	−0.305	0.187	2.679	1	0.102	0.737	0.5–1.1

[a]Reference category, female.

regression), with epilepsy as the dependent variable and adjusting by age, sex, and a history of raising pigs, confirmed this association (OR, 3.9; $p = 0.008$). Seropositive individuals were older than seronegative subjects (mean age, 43.8 vs. 27.6 years; $p < 0.001$). We also found a significant relation between household pig ownership and positive serology in that house. Seropositive individuals were found in 65 of the 198 houses where pigs were raised and in 49 of the 247 houses without pigs (OR, 1.97; 95% CI, 1.3–3.1; $p = 0.002$). Multivariate analysis with seropositivity as the dependent variable confirmed the significance of these associations and showed an additional association between seropositivity and age (Table 2).

Nineteen of 24 patients with epilepsy accepted the practice of complementary examinations and were matched 1:1 on age and sex to healthy individuals chosen from the sample of 120 negative respondents to the survey. The EEG was abnormal in nine patients and in one control ($p = 0.008$, McNemar's test). Of the nine patients with an abnormal EEG, five had diffuse slowing of background activity or nonparoxysmal bursts of hypervoltage theta waves; two had focal paroxysmal activity; and two had generalized paroxysmal activity. The control with an abnormal EEG had diffuse slowing of background activity. CT findings in patients with epilepsy included parenchymal brain calcifications in five, diffuse brain atrophy in one, focal brain atrophy related to head trauma in one, and a brain tumor in the remaining patient. One control had parenchymal brain calcifications, and the other had a congenital arachnoid cyst in the sylvian fissure. Thus CT findings compatible with NCC were found in five of 19 patients with epilepsy and in one of 19 controls ($p = 0.125$, McNemar's test).

After interpretation of data from clinical examination, EEG, CT, and serum immunoblot, one (5.3%) of 19 patients had idiopathic epilepsy (rolandic epilepsy), seven (36.8%) had secondary epilepsy, and 11 (57.9%) had probable secondary (cryptogenetic) epilepsy. Five of the seven patients with secondary epilepsy had NCC, which, according to current diagnostic criteria (13), was definitive in three (calcifications and a positive immunoblot) and probable in two (calcifications and a negative immunoblot). One of the remaining two patients with secondary epilepsy had a brain tumor, and the other had focal brain atrophy related to a head trauma. Besides these five patients with NCC-compatible CT findings, three other cases had positive serology (one with a normal CT, plus two of the five patients who did not come for complementary examinations), making a total of eight patients (33%) with epilepsy associated with cysticercosis infection (Table 3).

TABLE 3. *Diagnosis of neurocysticercosis[a] in eight patients with epilepsy in Atahualpa, Ecuador*

Age/Sex	Diagnostic criteria[b]	Degree of diagnostic certainty[c]
54 F	Two major (CT and immunoblot), one minor, one epidemiologic	Definitive neurocysticercosis
21 M	Two major (CT and immunoblot), one minor, one epidemiologic	Definitive neurocysticercosis
60 F	Two major (CT and immunoblot), one minor, one epidemiologic	Definitive neurocysticercosis
37 M	One major (CT), one minor, one epidemiologic	Probable neurocysticercosis
57 M	One major (CT), one minor, one epidemiologic	Probable neurocysticercosis
31 F	One major (immunoblot), one minor, one epidemiologic	Probable neurocysticercosis
22 M	One major (immunoblot), one minor, one epidemiologic	Probable neurocysticercosis
3 M	One major (immunoblot), one minor, one epidemiologic	Probable neurocysticercosis

NCC, neurocysticercosis; ELISA, enzyme-linked immunosorbent assay.

[a]According to Del Brutto et al. Proposed diagnostic criteria for neurocysticercosis. *Neurology* 2001; 57:177–83.

[b]Diagnostic criteria: *Major*: Lesions highly suggestive of NCC on imaging studies, positive serum immunoblot for the detection of anticysticercal antibodies, resolution of intracranial lesions after cysticidal therapy, and spontaneous resolution of small single enhancing lesions. *Minor*: Lesions compatible with NCC on imaging studies, clinical manifestations suggestive of NCC, positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens, and cysticercosis outside the CNS. *Epidemiologic*: Evidence of a household contact with *T. solium* infection, individuals coming from or living in an area where cysticercosis is endemic, and history of frequent travel to disease-endemic areas.

[c]Degrees of diagnostic certainty: *Definitive diagnosis*: Presence of two major plus one minor and one epidemiologic criteria. *Probable diagnosis*: Presence of one major plus two minor criteria, presence of one major plus one minor and one epidemiologic criteria, or presence of three minor plus one epidemiologic criteria.

DISCUSSION

The crude point-prevalence rate of epilepsy in Atahualpa (9.9 per 1,000) is similar to those found in other Latin American community surveys (3–5), suggesting that epilepsy is more common in rural areas of developing countries than in industrialized nations, where prevalence rates range from 4.2 to 6.8 per 1,000 population (1). Several conditions could account for this excess fraction of epilepsy, including NCC, other infectious diseases of the CNS, poor obstetric care, birth trauma, or parental consanguinity (2,14).

Our determined prevalence does not account for potential lack of sensitivity of the instrument. Placencia (3), in its initial application, calculated a sensitivity of almost 100%. We found one false-negative case among a sample of 120 nonsuspected individuals. The design of our study did not permit assessing the sensitivity of the survey because of the relatively small sample of negative respondents clinically examined, the low frequency of false negatives, and the wide variability associated with this estimate (1 of 120; 95% CI, 0.04–4.04). The false-negative case we found, however, opens the possibility that other persons with epilepsy were missed and that the prevalence of epilepsy in Atahualpa could be even higher than that here reported.

Only three controlled studies previously assessed the relation between NCC and epilepsy by using CT scans in field settings. In the Andean region of Ecuador, Cruz et al. (6) found CT abnormalities compatible with NCC in 14 of 26 patients with epilepsy and in 17 of 118 nonmatched healthy controls (OR, 6.93; $p < 0.001$). If we apply current diagnostic criteria for NCC to that population of patients with epilepsy, 23% had definitive and 30.8% had probable NCC (6). In Mexico, CT findings compatible with NCC were found in seven of 10 patients with epilepsy and in 15 subjects taken from a mixed group of 109 seropositive individuals and tapeworm carriers (OR, 14.62; $p < 0.001$) (15). In Guatemala, 36 of 76 individuals with seizures had lesions compatible with NCC on CT, compared with 12 of 51 controls without a history of seizures (OR, 2.92; $p = 0.011$) (16,17).

In our survey, a positive serum immunoblot was significantly associated with the occurrence of epilepsy. Other population-based controlled studies also attempted to assess the relation between epilepsy and CC on the basis of the results of serologic assays for the detection of anticysticercal antibodies (18,19). Although most seroepidemiologic studies found a significant association between epilepsy and a positive immunoblot (18,19), this association could not be demonstrated in the Ecuadorian study (6) (marginal significance) or in the Guatemalan study (16,17) and could not be extracted from the Mexican study (15) because of inadequate selection of controls. It must be noted that circulating antibodies may indicate only exposure to the parasite or systemic disease, and not necessarily cerebral infection (13). Conversely, serology also may be negative in NCC patients with only calcified, dead parasites. The study design is correlative, and it cannot establish that CC caused the observed epilepsy.

In summary, we found evidence of CC in eight (33%) of 24 patients with epilepsy. Diagnosis was based on both CT and serology in three patients (definitive diagnosis), and on either CT or serology in the remaining five (probable diagnosis) (see Table 3). Our data point toward NCC as a major contributory factor for the occurrence of epilepsy in Atahualpa. NCC is a potentially eradicable disease, and its control may reduce the prevalence of epilepsy in developing countries.

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