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Neurocysticercosis in Persons with Epilepsy in Medellín, Colombia

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Summary: *Purpose:* A prospective series of 643 persons with epilepsy attending a reference neurologic center in Medellín, Colombia, was examined by computed tomography (CT scan) or serology or both with the enzyme-linked immunoelectrotransfer blot assay (EITB) to assess the prevalence of *Taenia solium* cysticercosis.

Methods: All presenting patients were consecutively enrolled in the study. Five hundred forty-six persons underwent cerebral CT scans; 376 of them also had serum EITB performed.

Results: Prevalence of neurocysticercosis by CT scan was 13.92%. Overall prevalence of *T. solium* antibodies with EITB was 9.82%, but for those with late-onset epilepsy (onset after age 30 years), prevalence increased to 17.5% and 19% for those who originated from outside urban Medellín. Seroprevalence in individuals with mixed lesions (cysts and calcifications) was 88.2% and 64.10% in those with live cysts. Conversely, only 2.72% of persons with CT findings not related to neurocysticercosis had positive EITB tests.

Conclusions: Our study shows that an important proportion of individuals with epilepsy have radiologic or serologic evidence of *T. solium* infection, suggesting that neurocysticercosis is an important etiology for epilepsy in Colombia. **Key Words:** Cysticercosis–*Taenia solium*—EITB—Epilepsy.

The incidence of epilepsy in developed countries is 50–100/100,000 population per year, with prevalence of 4–10/1,000 (1,2). In developing countries, the incidence and prevalence rates are higher, a difference that has been attributed to poorer standards of neonatal care and increased rates of infectious diseases (3). For example, most studies from Latin America have resulted in crude prevalence rates of 17–22/1,000, significantly higher than those for industrialized countries (4,5). *Taenia solium* cysticercosis of the nervous system (neurocysticercosis, NCC) is a major cause of epilepsy in most non-Muslim developing countries, accounting for ≤30–50% of late-onset cases (6–8), and is clearly an important contributor to the increase in rates (3,5). NCC is also being diagnosed with increasing frequency in the United States, where it is estimated that >1,000 cases occur each year, mostly due to immigration from countries in which the disease is endemic (9).

The adult *Taenia* tapeworm, measuring 2–8 m in length, develops in the human small intestine after ingestion of cysts in infected pork. Eggs are released individually or within gravid terminal proglottids in the stools. When accidentally ingested by a human or porcine host, the eggs hatch in the intestine, cross the intestinal wall, and find their way to various tissues, including those of the central nervous system, where they form cystic vesicles (10).

Clinical diagnosis of NCC is extremely difficult because of its unpredictable clinical presentation, resulting from the number, size, and location of parasitic lesions and the immune response of the host (11). Computed tomography (CT), introduced in 1978, has permitted visualization of parenchymal lesions and was initially regarded as highly sensitive (10), but later studies showed that its accuracy is far lower than expected (12,13). Immunologic tests lacked sensitivity and specificity until the introduction of the enzyme-linked immunoelectrotransfer blot (EITB) assay in 1989 (14). The EITB, now

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widely accepted as the test of choice for either clinical or epidemiologic uses (6,15), is 100% specific and 98% sensitive in patients with two or more lesions.

The prevalence of epilepsy in Colombia is ~20/1,000 (16,17). Although previous studies in the country have described risk factors for epilepsy that include heredity, perinatal hypoxia, and central nervous system infections (17–19), the only data available on the contribution of cysticercosis in persons with epilepsy is based on a serosurvey with enzyme-linked immunosorbent assay (ELISA) that found a prevalence of 23.4% (20). Our study attempted to quantify the contribution of NCC in the etiology of epilepsy by using both CT and EITB in a prospective series of patients with epilepsy in Medellín, Colombia.

MATERIALS AND METHODS

Patients

The study population consisted of all persons with epilepsy who attended any of the nine adult outpatient clinics of the Instituto Neurologico de Antioquia (INDEA), in Medellín, from March 30 to October 19, 1995. Medellín, with an urban center of 1.8 million, is the capital of the department of Antioquia, which includes eight regions. Inclusion criteria involved fulfilling the World Health Organization (WHO) criteria for the diagnosis of epilepsy (two or more afebrile seizures unrelated to acute metabolic disorders or to discontinuation of drugs or alcohol), and onset of crisis after age 10 years (21,22). This age limit was arbitrarily selected to evaluate the prevalence of NCC in adolescent and adult populations, excluding the pediatric population, in which the prevalence of NCC is much lower (23). The study was approved by the ethical review board of INDEA.

Methods

At the time of consultation, the attending neurologist obtained a thorough clinical history and completed a form designed for the study. Information recorded included age, sex, age of onset of epilepsy, city/town of residence, and socioeconomic status. Patients were then offered cerebral CT scans of the brain, performed at INDEA, with a Siemens Somatom ART Scanner. Before and after contrast injection, slices of 10-mm thickness were obtained for the anterior or middle fossa and 5-mm slices for the posterior fossa. The types of NCC lesions were defined as follows:

Live cysts: hypodense, rounded lesions visible in noncontrasted series;
Degenerating cysticerci: isodense zones that became hyperdense after the injection of contrast dye, or
Calcified lesions: hyperdense images that did not alter in appearance after the injection of contrast dye.

Patients were classified as "CT positive" with at least one of the following CT criteria compatible with NCC: one or more living or degenerating cysticercosis lesions, regardless of the presence of a visible scolex, or two or more calcifications compatible with NCC (nodular or annular, smaller than 1 cm, and not located in areas of physiologic calcifications (24). Patients were classified under the "CT nonspecific" group if they had hydrocephalus only, or a single calcified lesion with characteristics possibly compatible with NCC but not specific enough to establish the diagnosis. A classification of "CT negative" was given to those patients whose CT scans were normal or showed other defined neurologic conditions.

Individuals who had a CT scan performed were offered serum EITB tests. If the patient accepted the offer, 5 ml of blood was taken by venipuncture, and the plasma was separated and stored at –20°C. EITB tests were performed at the National Center for Infectious Diseases (CDC), Atlanta, GA, U.S.A., as originally described (14). EITB diagnostic criteria for cysticercosis were the presence of antibody reaction to at least one of the seven specific glycoprotein bands. EITB results were provided to the patients and to the attending neurologists for patient management. No systematic analysis of cerebrospinal fluid (CSF) was performed in this population.

Statistical analysis

EpiInfo, version 6.1 (Centers for Disease Control and Prevention) was used for descriptive analysis. χ^2 tests were used to evaluate differences between continuous variables, and Student's t test or Mann–Whitney tests for continuous ones. CT scan sensitivity and specificity were determined, with the EITB results as the standard. EITB sensitivity and specificity also were calculated against CT results.

RESULTS

A total of 643 individuals with epilepsy were included in the study. Of these, 324 (50.4%) were male subjects. Mean age was 32.9 ± 15.3 (mean ± standard deviation). Three hundred sixty-three (56.5%) belonged to the lower socioeconomic strata, 626 (97.4%) lived in the Department of Antioquia, and 472 (73.4%) of them in the metropolitan area of Medellín; 104 (16.2%) came from rural areas; 373 (58.0%) attended INDEA for the first time. The mean age of onset of epilepsy was 24.0 ± 13.7 years.

Of the 643 persons, 546 (84.9%) received CT scans. Persons who had a CT scan were similar to those who did not in terms of male/female ratio and first-time attendance at INDEA. However, as a group, they were older (mean age, 33.6 ± 15.6 vs. 29.1 ± 12.9 years; $p = 0.01$) and had older age of onset of crisis (24.6 ± 14.1 vs. 20.7 ± 10.2 years; $p = 0.02$). Among those who had CT, 76

(13.9%) were diagnosed as CT positive; 52 (9.5%) had single calcifications or hydrocephalus alone, belonging to the CT-nonspecific group; 418 (76.56%) had normal scans or conditions other than NCC, and thus were assigned to the CT-negative group (Table 1).

Of the 546 patients who underwent a CT scan, 376 (68.86%) also had EITB tests. More EITB tests were performed for patients with a CT scan compatible with NCC 119 (93.0%) of 128 than those with other diagnoses 257 (61.5%) of 418; ($p < 0.001$). The 257 CT-negative patients who had EITB tests did not differ from the 161 who did not in terms of sex ratio or first-time attendance, but they were older (mean age, 34.5 ± 15.9 vs. 29.9 ± 15.1 years; $p = 0.001$), more likely to be from the metropolitan area [221 (86%) of 257 vs. 99 (61.5%) of 161; $p < 0.001$], and had slightly older age of onset of epilepsy (25.4 ± 14.6 vs. 22.6 ± 13.7 years; $p = 0.05$).

Forty-seven patients tested positive by EITB [47 (12.5%) of 376]. Sampling coverage was similar for both sexes, but there were more EITB-positive cases in male than female subjects [34 (17.5%) of 194 vs. 13 (7.1%) of 182; OR = 2.76; $CI_{95\%}$ = 1.34–5.78; $p < 0.005$]. There was no difference in seropositive group with regard to socioeconomic status, but persons who originated from outside the metropolitan area of Medellín tended to have a higher proportion of seropositive cases [13 (18.6%) of 70 vs. 34 (11.1%) of 306; $p = 0.09$; OR = 1.82; $CI_{95\%}$ 0.85–3.08]. The proportion of EITB-positive individuals increased with age (Fig. 1), and was found more frequently in patients with late-onset epilepsy (Table 2).

TABLE 1. *CT and EITB results for cysticercosis in epileptic patients in Medellín, Colombia*

CT results	No. of patients	EITB +/Total sampled	EITB % Positive
CT positive			
Single cysts	17	7/17	41.2
Multiple cysts	5	3/5	60.0
Two or more calcifications	36	12/33	36.4
Mixed lesions	18	15/17	88.2
Subtotal	76	37/72	51.4
CT nonspecific			
Hydrocephalus alone	4	1/3	33.3
Single calcification	48	2/44	4.5
Subtotal	52	3/47	6.4
CT negative			
Normal	337	4/305	1.31
Neoplasia	6	1/2	50.00
Atrophy	13	1/8	12.50
Arteriovenous malformation	3	0/3	0
Cerebral vascular accident	1	0/1	0
Others	58	1/38	2.63
Subtotal	418	7/357	1.96
Total patients	546	47/376	12.5

CT, computed tomography; EITB, enzyme-linked immunoelectrotransfer blot assay.

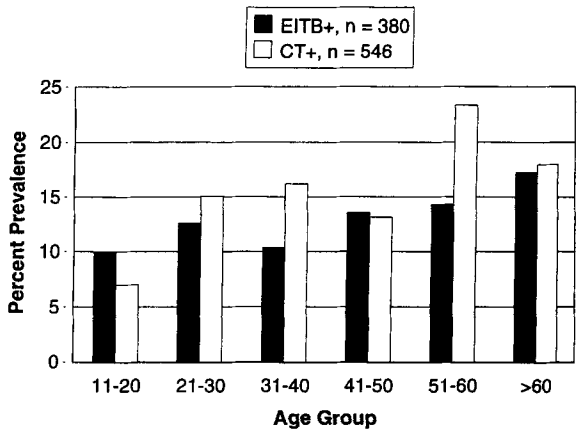

FIG. 1. Prevalence of cysticercosis by computed tomography (CT) and immunoelectrotransfer blot assay (EITB) in all outpatients with epilepsy who were seen at the clinics of the Instituto Neurologico de Antioquia (INDEA), Medellín, Colombia, stratified by age.

The EITB was positive in 15 (88.2%) of 17 patients with mixed lesions (cysts and calcifications), and 25 (64.1%) of 39 patients with live cysts, but in only seven (41.2%) of 17 of patients with a single live cyst. Interestingly, only two (4.5%) of 44 patients with a single calcification tested seropositive. Only seven (2.0%) of 357 patients with conditions other than NCC were seropositive (Table 1). One of these patients had an initial CT diagnosis of cerebral glioma, confirmed by MRI, and had a surgical biopsy performed (Fig. 2). Results of the biopsy showed nonspecific vasculitis, and excision surgery was delayed. The EITB was positive in this patient, and when the patient came for follow-up 6 months later, the lesion had resolved without treatment. Because the biopsy results were nonspecific, the EITB was positive, and the lesion resolved without treatment, we can conclude only that this patient did not have a cerebral glioma, but instead was probably infected with NCC.

A weighted seroprevalence rate may be calculated by extrapolating the EITB prevalence in CT-positive, CT-nonspecific, and CT-negative persons to the total population in each group, assuming that sampled patients are not different from those not sampled. By using this method, the overall seroprevalence in this series of patients with epilepsy is 9.82% (76 CT-positive patients at 51.38% prevalence, 52 CT-nonspecific patients at 6.38% prevalence, and 418 CT-negative patients at 2.72%

TABLE 2. *Proportion of EITB-positive patients relative to the age of onset of epilepsy*

Age of onset	EITB+	Percentage
≤20	18/185	9.73
21–30	11/92	11.96
>3	18/103	17.48

EITB, enzyme-linked immunoelectrotransfer blot assay.

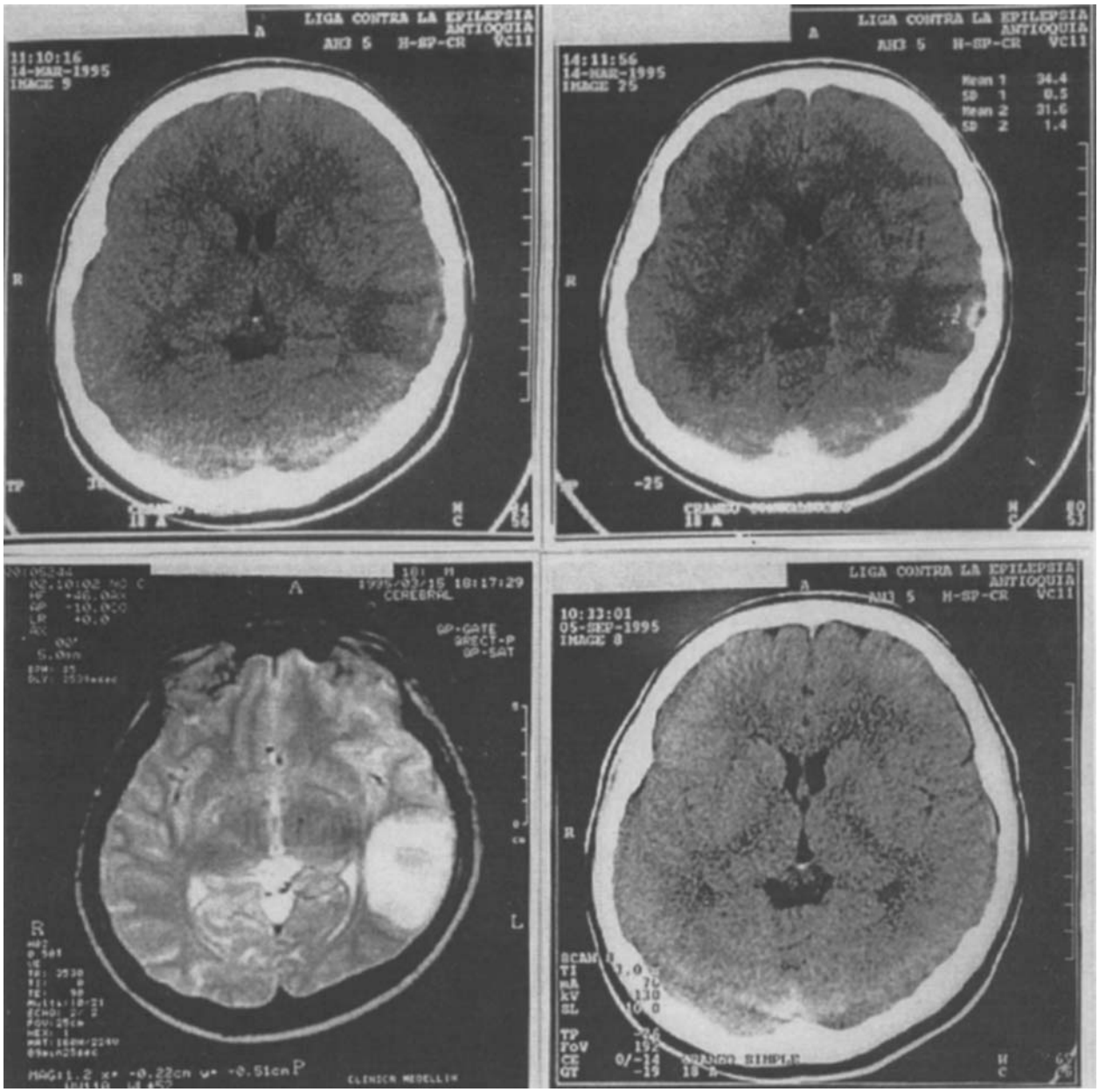

FIG. 2. Radiograph of a patient with suspected cysticercosis. The biopsy result of the cyst was inconclusive. EITB test for cysticercosis was positive. Pre- **(upper left)** and postcontrast **(upper right)** computed tomography (CT) scan, and T_2 magnetic resonance imaging (MRI; **bottom left)**, showing a degenerating cysticerci in the left hemisphere. The lesion resolved without treatment **(bottom right)**.

prevalence). The sensitivity and specificity of CT scanning with respect to EITB testing was 84.1% (37 of 44) and 87.7% (250 of 285), respectively. Conversely, the sensitivity and specificity of the EITB when calculated against CT scanning was 51.4% (37 of 72) and 97.3% (250 of 257).

DISCUSSION

This study shows that cysticercosis is an important cause of epilepsy in Antioquia. The study population consisted of a consecutive group of incident and prevalent cases of epilepsy attending the only neurologic center in a densely populated city (1.8 million) plus its surroundings. Although the study was not designed to extrapolate conclusions regarding the whole population of Colombia, there is no reason to expect marked differences when comparing with patients with epilepsy in other regions of the country. Several other characteristics are delineated in the analysis: the disease is more common in individuals from rural areas and, as expected, is more common in late-onset epilepsy. Almost 20% of those patients with age of onset of epilepsy after 30 years had antibodies to *T. solium* by EITB.

Previous studies on the epidemiology of epilepsy in Colombia are rare. One of these showed antibodies to *T. solium* by ELISA in 23.3% of 240 persons with epilepsy (20), but this result is difficult to interpret because of the poor performance of the test (15,25) and unclear inclusion criteria. Several studies reported a high prevalence of cysticercosis in patients with epilepsy in India (8), Mexico (7), and Peru (6). Clear concordance is found between studies, supporting the hypothesis that NCC is the single most important factor that accounts for the difference in prevalence of epilepsy between developed and developing countries (3,5).

Selection of patients is always an important issue in epidemiologic studies of epilepsy (2,26). In this study, all patients were consecutively included and sent to CT. They were offered serum EITB assays, which were ultimately performed in almost all patients with CT findings compatible with NCC and in >60% of those with negative scans. There is no reason to suspect that CT-negative patients who did not have a serology test will have a different prevalence than those sampled. The onset age of their epilepsy was only slightly lower and might have diminished the prevalence, but more of them came from rural areas, which would have increased the seroprevalence. Although there was not a nonneurologic control group to test for population baseline seroprevalence, antibodies to *T. solium* were present in only four of >300 individuals with normal scans.

Important factors that may lead to confusion in analyzing data from serologic surveys for cysticercosis is the area where the samples were derived (they may be from a major city or an endemic village), and what characteristics defined the study population (general population, neurologic patients, inpatients or outpatients, patients with epilepsy, or even those with late-onset epilepsy). Seroprevalences in persons with epilepsy have been reported in hospital settings: 26% in India by using indirect hemaglutination (8), 12% in Peru by using EITB (6), and in rural settings: 34% in Peru by EITB (27) and in Mexico, 29% by EITB (15).

Some discordance was found between EITB and CT. Almost half of those diagnosed as having NCC by CT were seronegative, especially patients with only calcified lesions. In these cases, the antibody response may have disappeared after the death of the parasites, although a recent report indicates that, at least in albendazole-treated patients, this process usually takes >1 year (28). Seroprevalence in patients with a single calcification was very low, probably reflecting three factors: lower sensitivity of the EITB in patients with a single lesion, loss of antibody after the death and calcification of the parasite, and calcifications due to other causes, including cytomegalovirus, tuberculosis, toxoplasmosis, abscesses, and many other causes (24). Similar variation in potential causes of enhancing lesions exists, although no patient in this series had this type of lesion alone. A few EITB-positive cases were negative by CT. Some patients with NCC and normal scans will have lesions detected only by MRI, reflecting the lower sensitivity of CT (current evidence indicates that MRI is more useful than CT for the detection of parenchymal, subarachnoidal, or intraventricular cysts, but not for calcified lesions), or they may have cysts located elsewhere in their bodies (13). Other possibilities include naturally resolved cysticercosis infections, intestinal *T. solium* tapeworm, or incorrect serologic diagnosis.

Cysticercosis is a preventable disease that is responsible for a significant proportion of cases of epilepsy in most developing countries. Its control and eradication will be possible only by improving living and sanitary conditions in areas in which it is endemic or, still to be demonstrated, by applying intervention and control programs (29–31). Until this disease is eradicated, a diagnosis must always be considered when evaluating patients with epilepsy living in or migrating from these zones.

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