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Cysticercosis as a major cause of epilepsy in Peru

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In countries where cysticercosis is endemic, the proportion of epilepsy due to cysticercosis is not well documented. To investigate the association between cysticercosis and epilepsy, we used the enzyme-linked immunoelectrotransfer blot (EITB) assay to detect serum antibodies to *Taenia solium* in 498 consecutive outpatients at a neurology clinic in Lima, Peru. Every patient was classified as epileptic (n=189) or non-epileptic (n=309) after neurological, and where possible electroencephalographic, examination. A substantially higher proportion of epileptic than non-epileptic patients was seropositive in the EITB (22 [12%] *vs* 8 [3%], p<0·001). 19% of epileptic patients born outside Lima, 20% of those with late-onset epilepsy, and 29% of patients with both these characteristics were seropositive. Thus, in Peru, cysticercosis is an important aetiological factor for epilepsy.

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Introduction

Neurocysticercosis is common in rural areas of developing countries where free-ranging pigs are raised.[1,2] Clinically, the disorder can include many neurological symptoms, but epilepsy is the most common.[2–5] Rural areas of developing countries have higher rates of epilepsy[6,7] and of *Taenia solium* infection[8] than do urban areas and developed countries. Neurocysticercosis resulting from the higher *T solium* infection rate may contribute to higher rates of epilepsy in these areas.[9]

The proportion of epilepsy cases associated with neurocysticercosis has not been well documented. Serological tests used to measure the prevalence of cysticercosis in epileptic populations were not highly sensitive or specific.[10,11] However, the enzyme-linked immunoelectrotransfer blot (EITB) assay[12,13] is 98% sensitive and 100% specific and can accurately diagnose *T solium* infection. We used the EITB assay to define the relation between epilepsy and cysticercosis in individuals attending a neurology outpatient clinic in Lima, Peru.

Patients and methods

The Instituto Nacional de Ciencias Neurológicas is the neurological reference centre for Peru and mainly serves the lower and middle class sectors of the population. New patients are randomly assigned to one of six neurology outpatient clinics for evaluation. All new patients attending one such clinic (consultorio no 2) between April, 1990, and June, 1991, were enrolled in this study after they had given informed consent. The study was approved by the ethical review boards of the Universidad Peruana Cayetano Heredia and the Johns Hopkins University.

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TABLE I—CHARACTERISTICS OF 498 PATIENTS

—	Epileptic (n=189)	Non-epileptic (n=309)	p
No (%) male	129 *(68%)*	204 *(66%)*	0·677
Age (yr)			
Mean (SD)	28·2 (14·7)	36·1 (16·6)	<0·001
Range	8–76	14–77	<0·001
No (%) of patients			
EITB seropositive	22 *(12%)*	8 *(3%)*	<0·001
Born outside Lima	101 *(53%)*	179 *(58%)*	0·375
Who had raised pigs*	78/179 *(44%)*	110/291 *(38%)*	0·253
Who had passed flatworms*	28/158 *(18%)*	22/256 *(9%)*	0·009
With abnormal EEG	53/107 *(50%)*	22/131 *(17%)*	<0·001

*Some patients could not answer some questions.

A study nurse recorded information on birthplace, educational level, number of family members, and type of household (number of rooms, construction materials, source of water, and type of sewage facilities). Birthplace was classified as in Lima or outside Lima. This city (population 7 million) is the main urban centre of Peru, with about 35% of the country's population. Nearly all pigs in the city are free of cysticercosis and are killed and processed in slaughterhouses with veterinary inspection.[14] Patients were also asked whether they or close relatives had raised pigs, had passed flatworms, or had a history of seizures. Every patient was examined by a hospital neurologist and classified as epileptic or non-epileptic, and a venous blood sample was obtained. Clinical follow-up included electroencephalographic (EEG) examinations when possible. Computed tomography scans are rarely available for this population because of their high cost.

Serum samples were assayed by the EITB assay for antibodies specific to *T solium*.[13] Seven lentil-lectin-purified *T solium* glycoprotein antigens were used in an immunoblot format to detect specific antibodies in serum. Antibody binding to these glycoproteins was visualised with the hydrogen peroxide/diaminobenzidine substrate, and a sample showing reactions to one or more glycoproteins was taken as positive. The assay was repeated when results were ambiguous. Tests were done at the Laboratory of Parasitology of the Universidad Peruana Cayetano Heredia and repeated at the Centers for Disease Control in Atlanta, USA, for quality control.

The chi-square and Fisher's exact tests were used for the analysis of categorical variables and Student's *t* test and the Mann-Whitney test for continuous variables, by means of SPSS statistical software (SPSS Inc, Chicago, USA). With either the result of the EITB test or the presence or absence of epilepsy as the outcome variable, we tested several logistic regression models to assess the individual contribution of each of the following variables: birthplace, education, history of raising pigs, history of passing flatworms, property status (owner, tenant, or lodger), presence of dirt floor or adobe or cane walls, number of rooms and number of inhabitants in house, source of water, and presence of household sewage connections. Significance was set at 0·05. Statistical significance was assessed by the likelihood ratio test in the logistic regression analysis with EGRET statistical software (Statistic and Epidemiology Research Corporation, Seattle, USA).

TABLE II—COMPARISON OF SEROPOSITIVE AND SERONEGATIVE PATIENTS

—	EITB positive (n=30)	EITB negative (n=468)	p
No (%) male	25 *(83%)*	308 *(66%)*	0·076
Age (yr)			
Mean (SD)	38·5 (15·7)	32·9 (16·4)	0·056
Range	18–71	8–77	<0·001
No (%) of patients			
Born outside Lima	26 *(87%)*	254 *(54%)*	<0·001
Who had raised pigs*	20/28 *(71%)*	169/443 *(38%)*	0·001
Who had passed flatworms*	8/26 *(31%)*	42/389 *(11%)*	0·007
With abnormal EEG	8/15 *(53%)*	67/223 *(30%)*	0·111
With family history of seizures*	6/25 *(24%)*	86/392 *(22%)*	1·000
With family history of taeniasis*	2/21 *(10%)*	10/367 *(3%)*	0·270

*Some patients could not answer some questions.

Results

Of the 506 patients examined, 8 (2%) refused to take part. 189 (38%) of the remaining 498 patients were classified as epileptic. Epileptic patients were younger than non-epileptic patients and higher proportions had passed flatworms or were seropositive for cysticercosis by the EITB assay. As expected, more epileptic than non-epileptic patients had abnormal EEGs (table I).

Table II compares patients who were positive and negative in the EITB; there were significant differences between these groups in the proportions born outside Lima, who had raised pigs, and who had passed flatworms. Male patients had a higher frequency of seropositivity than female patients and the proportion seropositive was higher among patients older than 20 years than in younger patients (27/357 [8%] *vs* 3/141 [2%], p=0·037).

The age of seizure onset was recorded for 166 of the 189 epileptic patients. There were no significant differences between these patients and those with unknown age of seizure onset in age, birthplace, history of pig raising, history of passing flatworms, or proportion of abnormal EEGs. Among the patients with known age of epilepsy onset, the 20 seropositive patients were older at onset than were the 146 seronegative patients (mean 30·0 [SD 13·2] *vs* 22·8 [14·4] years, p<0·01). The proportion seropositive was significantly greater among patients with late-onset (after age 20) epilepsy than in those with epilepsy of earlier onset (15/74 [20%] *vs* 5/92 [5%], p=0·007, odds ratio 4·4). The highest proportion of seropositives was found among patients with late-onset epilepsy who had been born outside Lima (14/49 [29%] *vs* 6/117 [5%] of other patients, p<0·001, odds ratio 7·4, table III).

Of the 23 patients with unknown age at epilepsy onset, 14 (12 EITB negative, 2 EITB positive) were older than 20 years at the time of the study. If all 12 seronegative patients are taken as late onset and the 2 seropositive patients as early onset, the association between late-onset epilepsy and seropositivity remains significant (p=0·041, odds ratio 2·9).

A family history of epilepsy was more common among epileptic than among non-epileptic patients (44/92 [48%] *vs* 112/324 [35%], p=0·028). Patients with a family history of epilepsy were younger than those without such a history (mean 28·8 [14·4] *vs* 34·9 [17·0] years, p<0·005) and a greater proportion had raised pigs (46/91 [51%] *vs* 119/324 [37%], p=0·024). These groups did not differ as regards sex ratio, EITB results, flatworm passage, or the proportion with abnormal EEG findings.

Table IV gives unadjusted odds ratios for risk factors associated with epilepsy or with EITB seropositivity. By multiple logistic regression, the best-fit model for epilepsy as outcome variable included a positive EITB result (adjusted odds ratio 4·7) absence of drinking water in the house (2·3),

TABLE III—ASSOCIATION OF BIRTHPLACE AND AGE OF ONSET OF EPILEPSY WITH SEROPREVALENCE TO *T SOLIUM* INFECTION AMONG EPILEPTIC PATIENTS

—	Total	EITB positive	
		No (%)	95% CI (%)
All epileptic patients	189	22 *(12%)*	7–16
All epileptic patients born outside Lima	101	19 *(19%)*	11–26
Late-onset epileptic patients	74	15 *(20%)*	11–29
Late-onset epileptic patients born outside Lima	49	14 *(29%)*	16–41

TABLE IV—RISK FACTORS ASSOCIATED WITH EPILEPSY OR WITH EITB SEROPOSITIVITY

—	Odds ratio (95% CI)
Factors associated with epilepsy	
EITB	4·96 (2·04–12·41)*
No drinking water in house	2·54 (1·31–4·94)*
History of passing flatworms	2·29 (1·21–4·35)*
Adobe or cane walls	1·75 (1·06–2·90)*
Fewer than four rooms	1·59 (1·07–2·37)*
No sewage connection	1·65 (0·98–2·76)
Dirt floor	1·62(0·84–3·14)
Lodger status	1·37(0·92–2·03)
>7 inhabitants	1·30(0·82–2·04)
History of raising pigs	1·27(0·85–1·89)
<6 years' education	1·22 (0·70–2·11)
Birthplace outside Lima	0·83 (0·57–1·22)
Factors associated with EITB seropositivity	
Birthplace outside Lima	5·48 (1·78–18·82)*
History of raising pigs	4·08 (1·66–10·33)*
History of passing flatworms	3·66 (1·36–9·61)*
Lodger status	2·85 (1·17–6·86)*
No sewage connection	2·65 (1·05–6·55)*
No drinking water	2·21 (0·69–6·61)
>7 inhabitants	1·82 (0·75–4·32)
Adobe or cane walls	1·81 (0·64–5·01)
Dirt floor	1·62 (0·45–5·26)
Fewer than four rooms	1·22 (0·53–2·80)
<6 years' education	0·96 (0·27–3·02)

*p<0·05.

and fewer than four rooms in the house (1·6); the likelihood ratio of the model statistic (4 df) was 52·71 ($p < 0·001$). The model that best fitted the data when the probability of a positive EITB result was the outcome variable included birthplace outside Lima (adjusted odds ratio 3·3) and a history of raising pigs (2·7); the likelihood ratio statistic of this model (3 df) was 456·57 ($p < 0·001$).

A higher proportion of epileptic patients underwent EEG examinations than did non-epileptic patients (107/189 [57%] *vs* 131/309 [42%], $p = 0·003$). The 238 patients who had EEGs were significantly younger than those who did not, but they were similar as regards sex, birthplace, EITB results, and histories of pig raising and passing flatworms. Seropositive patients tended to have a higher frequency of abnormal EEG findings than did seronegative patients (table II). The proportion of seropositivity was similar for patients with focal EEG abnormalities (3/31 [10%]) and for those with generalised abnormalities (5/43 [12%]). 1 case reported as "abnormal" had no further information in the notes. Of the 8 EITB-positive patients classified as non-epileptic, 5 underwent EEG examinations; 4 were abnormal. 2 showed general paroxysmal activity, 1 had focal paroxysms, and the other had an abnormal basal rhythm. 7 EITB-positive patients had cerebral computed tomography scans; 6 were epileptic. 6 scans showed cysticercoid lesions, and the other was normal. However, this patient had an EEG with focal abnormalities. 6 EITB-negative patients also underwent computed tomography; 1 (showing a single calcification) was diagnosed as showing cysticercosis.

Discussion

12% of epileptic patients attending an outpatient clinic in Peru had serological evidence of *T solium* infection. 29% of patients with late-onset epilepsy who were born outside Lima were seropositive, compared with only 1–2% of control populations living in Lima.[15] Our results accord with those of a Mexican study, in which 50% of patients with late-onset epilepsy were diagnosed as having cysticercosis on the basis of computed tomographic appearance.[16]

Known causes of epilepsy include cerebrovascular disease, neoplasia, trauma, alcohol use, birth injury, and central nervous system (CNS) infections.[7,9] Both birth injury and parasitic CNS infections are more common in rural than in urban settings.[7] Although cysticercosis is often cited as a major cause of epilepsy in countries where *T solium* is endemic,[4,5,16,17] few accurate data are available. In one serological study,[17] 25% of a highly selected group of epilepsy patients were seropositive, but the test used was not highly sensitive or specific. Perhaps the best demonstration of the close relation between epilepsy and cysticercosis was in New Guinea; cysticercosis was introduced by imported pigs in 1972 and there was a substantial increase in the number of burns because this population commonly uses open fires, and burns occurred when individuals having seizures fell into fires.[18,19]

In cysticercosis, the average time between the acquisition of infection and development of symptoms is about 7 years,[5] but it can vary widely. Therefore, a proportion of seropositive patients in any population will be symptom-free. In cysticercosis-endemic communities, it is likely that most seropositive patients either do not have symptoms or do not seek medical attention.[20,21] In addition, the number of seropositive individuals with subclinical abnormalities (ie, EEG changes) is unknown. In our "non-epileptic" group 4 of 5 seropositive patients tested had abnormal EEG results. Our study was hospital-based, however, and results may differ from those obtained in the community.

Ownership of a latrine, type of sewage facilities, and number of bedrooms were recorded but not included in the models because of the low significance. 94% of our patients lived in houses with toilets (80%) or latrines (14%).

The finding that the major risk factor for epilepsy was a positive EITB result confirms the strong connection between *T solium* infection and epilepsy in Peru. Factors protecting individuals against *T solium* infection were birth in Lima and no history of pig raising. Both variables incorporate many others, such as endemicity of disease, environmental contamination, slaughterhouse inspection of pork, and better sanitary conditions.

Further elucidation of the natural history of cysticercosis and the response to treatment of patients with cysticercosis-associated epilepsy is needed. Community-based studies on the linkage between epilepsy and cysticercosis are being conducted in Peru. Cysticercosis should be strongly suspected in developing countries among patients with late-onset epilepsy, especially those from pig-raising areas.

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Influence of non-inherited maternal HLA antigens on occurrence of rheumatoid arthritis

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Many HLA-associated diseases occur in patients not carrying the putative predisposing antigen. The suggestion that this might be due to disease heterogeneity is not sufficiently supported by available data. We hypothesise that HLA-DR4-associated genetic susceptibility to rheumatoid arthritis is due to an effect of DR4 on T-cell receptor repertoire expression and that the presence of antigen in the mother is capable of producing this effect in her children, even when DR4 is not inherited by them.

To investigate this possibility we HLA typed 94 rheumatoid arthritis patients and their parents and 86 control families. An increased frequency, compared with controls, of non-inherited maternal HLA-DR4 was found predominantly in the mothers of DR4-negative patients. Unexpectedly, we also found an increased frequency of non-inherited maternal HLA-DR6 and a decreased frequency of non-inherited maternal HLA-DR3 in the mothers of DR4-positive patients.

The results of our analyses are consistent with our hypothesis.

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Introduction

Rheumatoid arthritis, ankylosing spondylitis, and coeliac disease are significantly more frequent in individuals carrying the HLA antigens DR4, B27, and DR3 and DR4, respectively.[1] But only a fraction of the individuals that carry these HLA alleles are affected by the diseases. This observation is assumed to be due to an additional requirement for exogenous factors, including microbial and viral infections, which in conjunction with the genetic predisposition lead to disease. However, with rare exceptions, such as narcolepsy, ankylosing spondylitis, and insulin-dependent diabetes mellitus, a sizeable proportion of patients with an HLA-associated disease do not carry the predisposing allele(s). Suggestions to explain why so many patients lack the HLA allele associated with a disease include presence of non-HLA Ir genes, heterogeneity of the disease, and epitope sharing between serologically different HLA alleles.[1]

An important factor determining susceptibility to immunopathological disease is the expressed T-cell receptor repertoire. This repertoire may be determined not only by the genetic make-up of an individual but also by environmental factors. We have evidence that the T and B cell repertoire for HLA class I alloantigens is governed by the "self" HLA antigens of a given individual and also by non-inherited maternal HLA class I antigens (NIMAs).[2] This observation suggests that if susceptibility to autoimmune disease is related to the nature and extent of T-cell receptor variability, then susceptibility may depend on the effects of both inherited and non-inherited maternal HLA class II antigens. We studied patients with rheumatoid arthritis to test the hypothesis that HLA-DR4-

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