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## THE COURSE OF SEIZURES AFTER TREATMENT FOR CEREBRAL CYSTICERCOSIS

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**Abstract Background.** Worldwide, cerebral cysticercosis is one of the most common causes of seizure disorders. Modern cysticidal drugs can usually eliminate the parasite from the brain, but there have been doubts as to whether such treatment improves the seizure disorder.

**Methods.** We studied 240 patients with seizures and cysticercosis of the brain parenchyma. Of these patients, 118 received cysticidal therapy (albendazole, praziquantel, or both) for lesions without inflammation on imaging studies (group 1); 49 patients with similar lesions either were not offered or refused cysticidal medication (group 2). Another 58 patients with inflammation around cysts (making spontaneous resolution more likely) also did not receive cysticidal medication (group 3), whereas cysticerci were removed surgically in 15 patients (group 4). The 240 patients were followed for a mean ( $\pm$ SE) of  $92 \pm 7$  months.

**Results.** In the patients treated with cysticidal medica-

tions, there was an 82 percent reduction in the mean number of brain cysts (from 5.0 to 0.9) and a 95 percent reduction in the mean frequency of seizures (from 11.3 to 0.6 per year;  $P < 0.001$ ). After three years of follow-up, 64 patients in group 1 (54 percent) were seizure-free. By contrast, the untreated patients (group 2) averaged 10.9 seizures per year; none were seizure-free. Among those with inflamed cysts (group 3), there was a 74 percent reduction in the frequency of seizures (from 7.5 to 2.7 per year), and 18 patients (31 percent) became seizure-free. After surgical treatment (group 4), there was an 87 percent reduction in the frequency of seizures (from 12.8 to 1.7 per year), and six patients (40 percent) became seizure-free.

**Conclusions.** After medical treatment of neurocysticercosis, there is usually remission or marked improvement in the associated seizure disorder. (N Engl J Med 1992;327:696-701.)

EPILEPSY is a common sign of a brain abnormality; however, little is known about its outcome when the primary cause is removed.<sup>1-10</sup> In the case of epilepsy due to neurocysticercosis, the epileptogenic area is in the brain tissue that surrounds the parasites and can be visualized by computed tomography or magnetic resonance imaging.

Epilepsy is the most frequent sign of neurocysticercosis.<sup>11</sup> In countries in which it is endemic, cysticercosis may affect between 2 and 4 percent of the general population<sup>12</sup>; it is also the main cause of late-onset epilepsy, accounting for more than 50 percent of such cases.<sup>13,14</sup> During the past few years, drugs that destroy parenchymal brain cysticerci have come into use.<sup>15-19</sup> Albendazole and praziquantel are highly effective in destroying cysticerci in the brain, but their effects on the evolution of late neurologic symptoms, such as epilepsy, headache, and motor, sensory, and psychiatric alterations, are unknown.<sup>15,20</sup>

In neurocysticercosis, the intermediate-stage larva (metacestode) of *Taenia solium* (the pork tapeworm) enters the brain tissue through the bloodstream. Within a few months, it evolves into a cysticercus that is approximately 1 cm in diameter and may eventually reach a diameter of more than 3 cm.<sup>21</sup> Once inside the brain parenchyma, this parasite causes inflammation, the severity of which depends on the degree of the host's immune response. In some cases, the parasite is surrounded by an intensely inflamed area, whereas in others there is minimal inflammation, and the cyst may grow and survive for several years.<sup>11</sup> The alterations in the brain tissue induced by the parasite and the chronic inflammation include displacement of neural structures, edema, the occurrence of mononu-

clear infiltrates, and reactive astrogliosis.<sup>21-23</sup> A frequent result is epilepsy.

The sudden destruction of the parasite by a cysticidal drug is accompanied by acute inflammation.<sup>15,20</sup> This therapy-induced inflammatory reaction could, it has been argued, result in additional nervous-tissue damage,<sup>24</sup> and this possibility casts into doubt the benefit of cysticidal therapy on the long-term evolution of neurologic symptoms caused by cysticercosis. We report the results of a long-term retrospective study of patients with epilepsy before and after drug therapy for parenchymal brain cysticercosis.

### METHODS

#### Patients

During an eight-year period, from 1983 to 1990, 134 patients were treated for parenchymal brain cysticercosis at the National Institute of Neurology and Neurosurgery of Mexico. All had epilepsy, either as a unique manifestation or as part of a complex neurologic picture. All had been included in research protocols to assess the effectiveness of two cysticidal drugs, praziquantel and albendazole.<sup>15,18</sup> The criterion for the administration of cysticidal drugs was the demonstration on imaging studies of parenchymal brain cysticercosis without inflammation around cysts (Fig. 1A), so that spontaneous resolution of the lesions was not expected.<sup>11,15,18,20,25</sup> From the initial group of 134 treated patients, 16 were followed for fewer than 12 months. Most of these 16 patients had moved or had stopped coming to the outpatient clinic, and several attempts to locate them failed. By 1991, the remaining 118 patients (group 1) had been followed for at least 12 months after cysticidal therapy (range, 12 to 108; mean [ $\pm$ SE],  $44 \pm 3$ ). Most patients had been followed for long periods before cysticidal therapy was administered, so the patients served as their own controls. The duration of this pre-therapy follow-up ranged from 1 to 264 months (mean,  $56 \pm 6$ ).

We also studied an additional group of 49 patients with epilepsy due to parenchymal cysticercosis (group 2). They had been treated for epilepsy and followed for 12 to 366 months (mean,  $84 \pm 14$ ), but they had not been treated for cysticercosis, because they had refused treatment, because the treating physician decided not to give the cysticidal drug, or because they were followed between 1976 and 1983, after the introduction of CT but before the advent of cysticidal drugs. These patients had the same characteristics of cysticercosis as the patients in group 1, but had smaller parasite burdens, and for this reason, cysticidal therapy was either withheld or refused by

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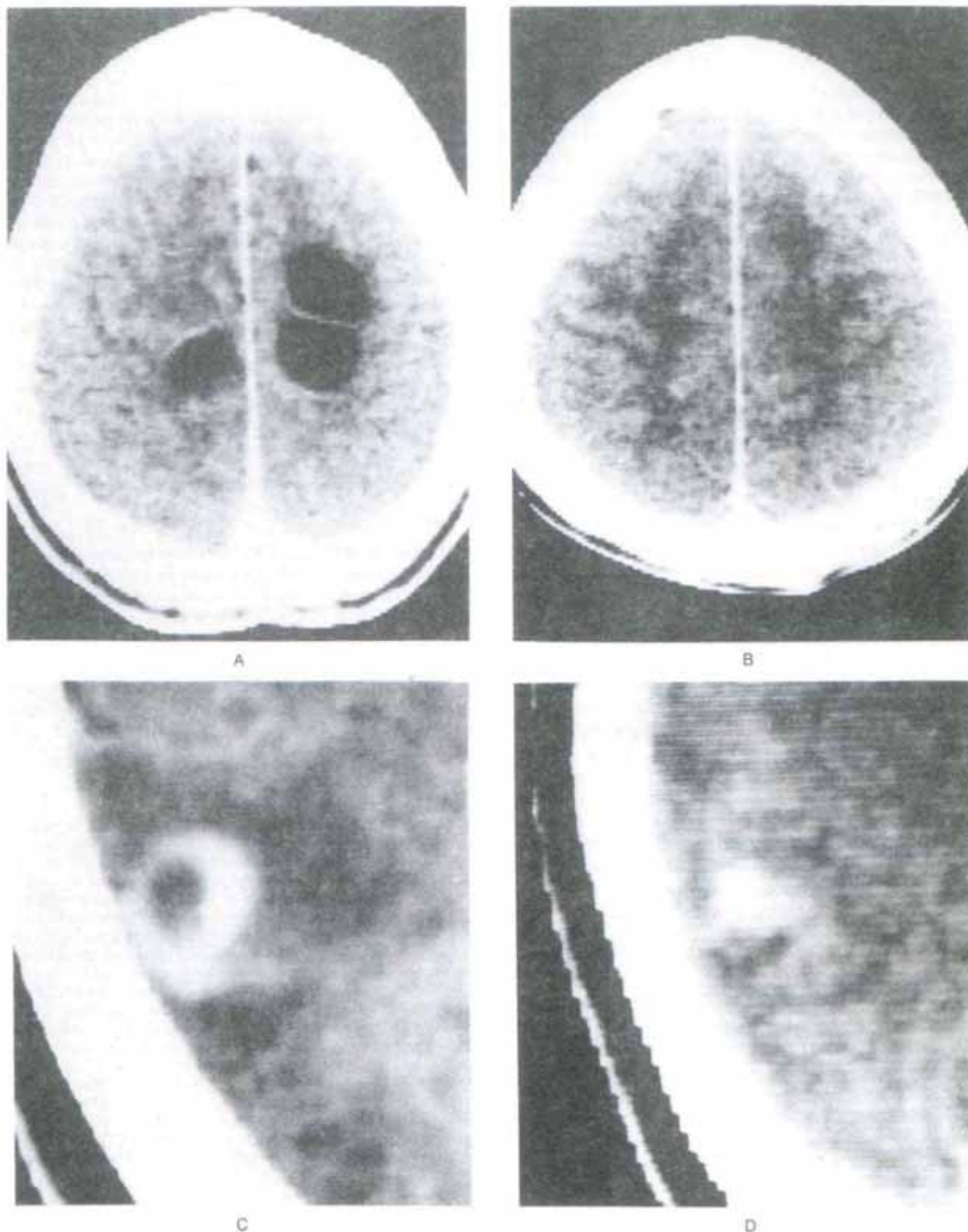


Figure 1. CT Scans of Cysticerci in Brain Parenchyma of Two Patients.

In the first patient, three cysticerci were present in brain parenchyma before treatment, but there was no evidence of inflammation around the lesions after contrast enhancement (Panel A). The scan in Panel B was obtained eight months after cysticidal therapy; all cysticerci have disappeared, and there are no remnant granulomas. In the second patient, contrast-enhanced CT scanning showed one cysticercus that was surrounded by an area of intense inflammation and edema (Panel C). The patient did not receive cysticidal treatment. The scan in Panel D, obtained one year later, shows a calcified granuloma where the cyst was originally.

the patients. This group of patients was used as untreated controls. The selection criterion for inclusion in this group was the same as that for patients who received cysticidal therapy — namely, the presence of epilepsy due to parenchymal brain cysticercosis without inflammation around cysts, as confirmed by CT.<sup>15,20,25</sup> The follow-up for epilepsy in these patients began at the time of the CT diagnosis of brain cysticercosis.

A third group of 58 patients also had epilepsy due to brain cysticercosis, but CT scanning with contrast enhancement showed inflammation around the cysts (Fig. 1C) (group 3). In patients with such findings, the cysts are frequently destroyed spontaneously as a result of the immune response<sup>21,25-27</sup> (Fig. 1D); therefore, these patients were excluded from research protocols involving cysticidal therapy.<sup>15,17</sup> They were treated as an additional control group, and it was expected that the natural course of the disease would lead to the spontaneous resolution of many of the cystic lesions.<sup>25,26</sup> In this group, therapy was restricted to antiepileptic drugs and occasional brief courses of corticosteroid therapy. They were followed for a mean of  $36 \pm 7$  months before the parenchymal brain cysticercosis was diagnosed and for a mean of  $53 \pm 4$  months afterwards. The selection of patients for group 2 and group 3 was based exclusively on the results of the initial CT scan (the absence and presence of inflammation around cysts, respectively), and the scan was interpreted by someone who had no knowledge of the clinical course of each patient's epilepsy.

In one group of 15 patients with parenchymal brain cysticercosis but no evidence of inflammation around cysts on CT scanning, the cysts were surgically excised (group 4). Most of these patients chose surgical intervention over cysticidal therapy. The patients had been followed for epilepsy for a mean of  $27 \pm 10$  months before surgery and were followed for  $41 \pm 9$  months after surgery. No patient who had granulomas or calcifications in brain parenchyma at the time of the diagnosis of neurocysticercosis was included in the study, so that all patients had active brain cysticercosis lesions as described previously.<sup>11</sup>

### Treatment

All subjects were treated for epilepsy according to the guidelines of the International League against Epilepsy and had periodic electroencephalographic assessments and plasma measurements of antiepileptic drugs.<sup>28,29</sup> We assessed any changes that occurred in antiepileptic therapy throughout the study and classified them in the following manner: withdrawal of antiepileptic drugs, a decrease in the dose or number of drugs, no substantial changes in the drug regimen, or an increase in the dose or number of drugs. Epileptic seizures were classified broadly as generalized or partial, regardless of secondary characteristics.<sup>29</sup> Approximately every three months, each patient was evaluated to assess the efficacy of the treatment of epilepsy. The number of seizures per year was calculated for a given period; however, in a few patients in all groups, before the trial began, the frequency of seizures varied widely from year to year. In these patients, the mean number of seizures was calculated only for the year before the study began. In most cases the number of seizures tended to decrease because of improved treatment with antiseizure medications. Seizures were categorized according to their yearly frequency in the following manner: no seizures, 1 seizure, 2 to 6 seizures, 7 to 12 seizures, and more than 12 seizures.

The patients treated with cysticidal drugs (group 1) were analyzed according to the drug used: praziquantel (50 mg per kilogram of body weight for 15 days), albendazole (15 mg per kilogram per day for 30 days), or sequential treatment with both drugs; the combination regimen was used for patients who still had cysts on CT scanning 3 months after single-drug therapy. During cysticidal therapy, 26 patients (22 percent) also received dexamethasone (8 mg intramuscularly every eight hours) for secondary reactions such as headache, vomiting, seizures, and neurologic symptoms attributed to the acute inflammation triggered by the destruction of cysticerci.<sup>30</sup> The dexamethasone was usually started on the second or third day of cysticidal therapy and stopped two or three days later. All secondary reactions subsided quickly after dexamethasone therapy was instituted, and no patient had a serious or persistent secondary reaction attributable to the cysticidal therapy. All patients continued to receive antiepileptic therapy during cysticidal treat-

ment. The evolution of parenchymal brain cysticerci was followed with successive CT scans and in some cases with magnetic resonance imaging.<sup>20</sup> The mean and total numbers of cysts were counted during the initial and final imaging studies. In groups 1 and 4, CT scanning was performed before and after cysticidal therapy. In groups 2 and 3, CT scanning was done at the time of the diagnosis of cysticercosis and at various intervals during follow-up. Patients were divided into three subgroups according to the number of cysts: those with a single cyst in brain parenchyma, those with two to seven cysts, and those with more than seven cysts. In the group of patients with more than seven cysts, there were large differences in the number of cysticerci, ranging from eight to uncountable. For the purposes of statistical analysis, those with too many cysts to count were considered to have eight cysts (which reduced the variation around the group mean). The evolution of neurocysticercosis in every group was measured by calculating both the mean reduction in the total number of cysts and the percentage of patients free of cysticerci, as demonstrated by successive CT scans. We also counted the number of cysts that left permanent calcified granulomas after the disappearance of the cysticerci.

### Statistical Analysis

The evolution, number, and characteristics of epileptic seizures and parenchymal brain cysticerci were compared within and between groups for the various follow-up periods. The results obtained before and after cysticidal therapy were analyzed by the paired t-test and the nonparametric Wilcoxon signed-rank test. Comparisons between group 1 and the other groups were done with the t-test for independent samples and the nonparametric Mann-Whitney U test. Comparisons within groups were made by one-way analysis of variance and the nonparametric equivalent Kruskal-Wallis test. Odds ratios and 95 percent confidence intervals were obtained by logistic-regression analysis. All P values of 0.05 were considered to indicate statistical significance.<sup>31-33</sup>

### RESULTS

The 240 patients with epilepsy in this study were followed for a mean ( $\pm$ SE) of  $92 \pm 7$  months, for a total of 22,157 months of observation. The 118 patients who received cysticidal therapy with albendazole, praziquantel, or both (group 1) had a mean of  $11.3 \pm 2.0$  seizures per year over a mean period of  $56 \pm 6$  months before treatment. After treatment the mean number of cysts decreased from  $5.0 \pm 0.3$  to  $0.9 \pm 0.2$ , an 82 percent reduction (Table 1). The mean number of seizures declined to  $0.6 \pm 0.1$  per year, a reduction of 10.7 seizures per year ( $P < 0.001$ ; 95 percent confidence interval, 6.4 to 15.0), for a 95 percent decrease in the number of seizures during a mean follow-up of  $44 \pm 3$  months (Table 2). At the end of the trial, 64 patients in group 1 (54 percent) were free of seizures, and in most cases the seizures stopped shortly after cysticidal therapy was begun, so that the improvement was attributed to the elimination of parenchymal cysticerci rather than to an adjustment in antiepileptic therapy.

The 49 patients with untreated lesions and no inflammation around cysts (group 2) had a mean of  $10.9 \pm 3.0$  seizures per year during  $84 \pm 14$  months of follow-up. In these patients the mean number of parenchymal cysts increased 15 percent, from  $4.0 \pm 0.5$  to  $4.6 \pm 0.8$ . The mean number of seizures did not vary significantly in most patients during follow-up despite adjustments in the antiepileptic-drug regimen.

The 58 patients with cysts and inflammation who did not receive cysticidal therapy (group 3) had a mean of  $7.5 \pm 1.0$  seizures per year during a mean peri-

Table 1. Characteristics of Parenchymal Brain Cysticercosis in 240 Patients with Epilepsy.\*

GROUP	NO. OF PATIENTS	AGE yr	MALE SEX %	NO. OF CYSTS		TREATMENT/ NO. OF PATIENTS	TIME BETWEEN INITIAL AND FINAL CT mo	NO. OF CYSTS		PATIENTS FREE OF CYSTS %
				AT INITIAL CT†	TOTAL			AT FINAL CT	% IMPROVEMENT	
1. Cysticidal treatment	118	38±1	66	5.0±0.3	591	Albendazole/42 Praziquantel/60 Albendazole-praziquantel/16	10±1	0.9±0.2	82	71
2. No cysticidal treatment	49	39±2	65	4.0±0.5	195	None	7±1	4.6±0.8	0	4
3. Inflammation around cysts	58	28±2	64	2.5±0.3	146	Occasional steroids	16±2	0.7±0.3	72	83
4. Surgical treatment	15	39±3	67	1.9±0.6	29	Surgery	8±3	1.0±0.7	47	87

\*Plus-minus values are means ±SE. Values in parentheses are percentages.

†For the purposes of statistical analysis, patients who had more than seven cysts or too many to count on CT imaging were considered to have eight cysts.

od of 36±7 months before the diagnosis of parenchymal cysticercosis. Without treatment the mean number of cysts declined from 2.5±0.3 at diagnosis to 0.7±0.3 over a mean interval of 16±2 months, a reduction of 72 percent. The mean number of seizures per year declined by 64 percent to 2.7±0.9 during 54±4 months of follow-up, a decrease of 4.8±0.1 seizures per year (P<0.002; 95 percent confidence interval, 1.6 to 8.0).

The 15 patients who had uninflamed cysts that were surgically excised (group 4) had a mean of 12.8±3.0 seizures per year during a mean period of 27±10 months, with a mean of 1.9±0.6 cysticerci before sur-

gery. After surgery the number of cysts was reduced to 1.0±0.7. The number of cysts that remained after surgery was high because two of the patients had several cysts, and in each case only a single, large clump of cysticerci was removed, leaving many other cysts. The other 13 patients only had a single cysticercus before surgery, and all of them were free of cysts after surgery. In this group the mean number of seizures per year declined after surgery to 1.7±0.8, a reduction of 11.1±2.2 seizures per year (P<0.009; 95 percent confidence interval, 2.9 to 16.7), for an improvement of 87 percent after a mean follow-up of 41±9 months.

When the course of the epilepsy was compared in

Table 2. Characteristics of Epilepsy in 240 Patients with Parenchymal Brain Cysticercosis.\*

GROUP	DURATION OF EPILEPSY BEFORE TREATMENT FOR CYSTICERCOSIS mo (total)	SEIZURES			FOLLOW-UP†			CHANGE IN ANTI-EPILEPTIC DRUG REGIMEN % of patients	
		GENERALIZED PARTIAL %	NO. PER YR; NO. OF PATIENTS	MEAN NO. PER YR	MEAN	TOTAL	NO. OF SEIZURES PER YR; NO. OF PATIENTS		MEAN SEIZURES PER YR
1. Cysticidal treatment (n = 118)	56±6 (6640)	32/68	1; 20 (17) 2-6; 64 (55) 7-12; 17 (14) >12; 17 (14)	11.3±2.0	44±3	5196	0; 64 (54) 1; 38 (32) 2-6; 15 (13) 7-12; 1 (1) >12; 0 (0)	0.6±0.1	Withdrawn: 22 Decreased: 22 Unchanged: 48 Increased: 8
2. No cysticidal treatment (n = 49)	—	47/53	—	—	84±14	4101	0; 0 (0) 1; 7 (14) 2-6; 29 (60) 7-12; 5 (10) >12; 8 (16)	10.9±3.0	Withdrawn: 12 Decreased: 10 Unchanged: 66 Increased: 12
3. Inflammation around cysts (n = 58)	36±7 (2102)	43/57	1; 11 (19) 2-6; 28 (48) 7-12; 11 (19) >12; 8 (14)	7.5±1.0	53±4	3094	0; 18 (31) 1; 20 (34) 2-6; 17 (30) 7-12; 1 (2) >12; 2 (3)	2.7±0.9	Withdrawn: 14 Decreased: 22 Unchanged: 38 Increased: 26
4. Surgical treatment (n = 15)	27±10 (410)	20/80	1; 2 (13) 2-6; 6 (40) 7-12; 1 (7) >12; 6 (40)	12.8±3.0	41±9	614	0; 6 (40) 1; 4 (27) 2-6; 2 (13) 7-12; 2 (13) >12; 1 (7)	1.7±0.8	Withdrawn: 7 Decreased: 3 Unchanged: 63 Increased: 27

\*Plus-minus values are means ±SE. Values in parentheses are percentages.

†For group 1, follow-up began at the time of cysticidal therapy; for group 2, it began at the time of the diagnosis of epilepsy; for group 3, it began at the time of the CT-based diagnosis of neurocysticercosis; and for group 4, it began at the time of surgery.

the four groups, patients in group 1 had 94 percent fewer seizures per year than those in group 2, 78 percent fewer than those in group 3, and 65 percent fewer than those in group 4.

Antiepileptic therapy was withdrawn or the dosage was reduced during follow-up in 44 percent of the patients in group 1, in 22 percent of those in group 2, in 36 percent of those in group 3, and in 10 percent of those in group 4 — differences that were not significant. More than half the patients in group 1 were free of seizures during a mean follow-up of three years after cysticidal therapy. None of the patients in group 2 were free of seizures, whereas 31 percent of those in group 3 and 40 percent of those in group 4 were free of seizures at follow-up. If poor control of epilepsy is defined as the occurrence of more than 12 seizures per year,<sup>34</sup> at the end of the study eight patients in group 2 (16 percent), two in group 3 (3 percent), one in group 4 (7 percent), and none in group 1 had poor control of epilepsy.

Statistical comparisons between groups showed that the outcome was significantly better for patients in group 1 than in any other group with respect to the following variables: the number of seizures, number of antiepileptic drugs administered, number of patients free of seizures, and number of patients with poor control of seizures (Table 2). Multivariate analysis showed that the improvement in epilepsy in patients in group 1, as compared with all other groups, was not due to differences in antiepileptic therapy, indicating that it could be due to cysticidal treatment.

On follow-up CT scanning, 71 percent of the patients in group 1, 4 percent of those in group 2, 83 percent of those in group 3, and 87 percent of those in group 4 were free of brain cysticerci and were considered cured of neurocysticercosis (Table 1). In patients treated with cysticidal agents, 80 percent of the cysts that were eliminated from brain parenchyma left no granulomas (Fig. 1B). By contrast, 80 percent of the cysts that spontaneously disappeared in patients in groups 2 and 3 left visible granulomas where the cysticerci had been<sup>35</sup> (Fig. 1D). In patients treated with cysticidal agents, the cystic lesions disappeared within three months after treatment, whereas the cysts that disappeared spontaneously in the patients in group 3 usually did so after more than six months.<sup>25,26</sup>

Logistic-regression analysis showed that the odds that seizures would persist increased by 10 percent for every year that seizures had occurred before cysticidal therapy (odds ratio, 1.1;  $P < 0.002$ ; 95 percent confidence interval, 1.0 to 1.2). Patients who were given two or more antiseizure medications had a risk of persistent seizures that was three times greater than that for patients who received only one medication (odds ratio, 3.1;  $P < 0.001$ ; 95 percent confidence interval, 1.7 to 5.5). According to the multivariate analysis, patients who did not receive cysticidal treatment had almost twice the odds of persistent seizures (odds ratio, 1.7;  $P < 0.001$ ; 95 percent confidence interval, 1.3 to 2.3). Men seemed to have a higher risk of persistent seizures than women (odds ratio, 1.6;  $P = 0.11$ ;

95 percent confidence interval, 0.9 to 3.0). In group 1, patients who received praziquantel had a higher risk of persistent seizures than those who received albendazole (odds ratio, 2.3;  $P = 0.10$ ; 95 percent confidence interval, 0.8 to 6.3); however, patients treated sequentially with both drugs did better than those treated with either drug alone (odds ratio, 4.0;  $P = 0.06$ ; 95 percent confidence interval, 1.0 to 5.7). Regression analysis showed no significant differences in the course of seizures according to the patients' age or type of seizure.

## DISCUSSION

In this study we found that the outcome for patients with epilepsy due to neurocysticercosis was better after treatment with cysticidal agents than when the primary disease was left to follow its natural course. This was true both for those in whom the cysticerci remained unchanged for long periods and for those in whom there was an intense inflammatory reaction that eventually destroyed the cysticerci. There were also fewer seizures after medical treatment than after surgical extirpation of the cystic lesion, perhaps because surgical excision carries its own risk of tissue damage.<sup>2</sup> Multivariate analysis showed that the difference in the number of seizures was more strongly associated with cysticidal therapy than with any of the other variables studied.

At the beginning of the trial, the patients in group 1 had 40 percent more parenchymal brain cysticerci than the patients in the other three groups combined (5 vs. 3 cysts per patient). At the end of the trial, the patients in group 1 had greater improvement, as measured by the number of cysts remaining, than the other groups. Although at the end of the study more patients in group 3 were free of cysticerci than in group 1 (83 percent vs. 71 percent), this difference was mainly due to the far heavier parasite burden in group 1 (5 vs. 2.5 cysts per patient). Cysticercus infestation is typically more severe in those with little apparent immune response to the parasites (group 1) than in those with intense responses (group 3).<sup>15,17</sup> In this study, 50 percent of the patients in group 1 had more than seven cysts, whereas 62 percent of the patients in group 3 had only a single cyst (Table 1). In agreement with other reports, we found that albendazole was superior to praziquantel, with an 80 percent reduction in the total number of cysts after a single course of therapy, as compared with a 65 percent reduction after praziquantel.<sup>18,20</sup>

There are two major arguments about the value of cysticidal therapy. One argument is that in the absence of inflammation, cysticerci can remain in brain parenchyma indefinitely without producing any neurologic complications but seizures, and these can be easily managed with antiepileptic therapy.<sup>24</sup> This was the situation for our untreated control patients in group 2. Although in fact for most of our patients the only clinical manifestation was epilepsy, most had frequent seizures for years, probably because of the persistence of the parasite as the epileptic focus. The oth-

er argument against medical treatment is that cysts may be destroyed by the host's immune response without the aid of cysticidal agents.<sup>24,36</sup> This was the case for our patients in group 3, in whom a high percentage of cysts disappeared without cysticidal treatment; however, the number of seizures per year in this group was 31 percent higher than in those who received medical treatment. Eighty percent of the cysts destroyed by the host's immune mechanisms induced granulomas, and this result may account for the high incidence of persistent seizures. Another fact that supports this explanation is the common finding of granulomas in patients with late-onset epilepsy in countries in which cysticercosis is endemic.<sup>13,14,35,37</sup> In such cases epilepsy is due to the persistence of granulomas in the brain in the absence of evidence of live cysticerci.<sup>13,14,35,37</sup> The endogenous destruction of cysticerci carries the additional risk of scarring brain tissue and thus providing an epileptic focus that the live cysticerci never provided.

In agreement with other studies, we found that the duration of epilepsy and the use of two or more anti-convulsant agents were additional risk factors for persistent seizures.<sup>1,6,38,39</sup> We conclude that treatment of the parenchymal lesions in the brain greatly improves the prognosis of patients with epilepsy due to cysticercosis.

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