Prognosis for seizure recurrence in patients with newly diagnosed neurocysticercosis

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Abstract—Objective: To determine the risk of seizure recurrence after a first seizure due to neurocysticercosis (NC) and to evaluate risk factors for seizure recurrence, including the influence of antihelminthic treatment. Methods: The authors prospectively followed 77 patients with a first seizure and active or transitional NC for >7 years (median 24 months). Results: Thirty-one patients (40.3%) experienced seizure recurrence. Kaplan–Meier estimated recurrence was 22% at 6 months, 32% at 12 months, 39% at 24 months, and 49% at 48 and 84 months. Treatment with an antihelminthic (albendazole) did not influence recurrence. On multivariable analysis, none of the following predicted recurrence: sex, presenting seizure type, classification of NC, localization of cysts, Todd paralysis, neurologic deficits at presentation, EEG abnormalities. Only change in CT predicted recurrence: 22% in patients in whom cysts disappeared and 56% in patients with persistent cysts ($p < 0.05$). In this latter group, recurrence was associated with persistence of an active lesion. Of those with two seizures, estimated risk of a third seizure was 68% by 6 years after the second seizure. Conclusions: Seizure recurrence is high after a first acute symptomatic seizure due to NC, but this seems related to persistence of active brain lesions. Recurrence risk is low and in keeping with seizure risk following other brain insults leading to a static encephalopathy in those in whom the NC lesion clears. Patients with NC should receive antiseizure medications until the acute lesion clears on CT. There is no correlation between treatment with antihelminthic agents and seizure recurrence.

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Taeniasis/cysticercosis remains a world public health problem, both in developing and in developed countries; infection is becoming increasingly common in the latter because of the immigration from endemic regions. Epidemiologic surveys for human cysticercosis, using EITB, report a seroprevalence from 8 to 12% in some regions of Latin America.1 Studies of highly selected patients with seizures in neurologic services of hospital settings from some Latin American countries report neurocysticercosis (NC) as the main cause of epilepsy.2 NC is commonly associated with clinical manifestations such as seizures, headache, and focal neurologic deficits. Seizures are the most common presenting symptom, occurring in up to 90% of patients.1,2 These seizures are related to the acute reaction occurring at the time of the cyst degeneration, are probably dependent on cyst localization and extent of edema associated with cyst degeneration, and fall into a classification of acute symptomatic seizures.

There is no agreement on prognosis for further seizures in these patients. Some report that NC patients with acute symptomatic seizures have a good prognosis in terms of risk for subsequent unprovoked seizures.3,4 Others report a high risk of further seizures and suggest that prognosis improves after antihelminthic treatment.7,8 In most studies, sample size has been small, assessment has been done retrospectively, and optimal analytic methods have not been used. Knowledge of the risk of seizure recurrence is a necessary prerequisite for making rational decisions regarding short-term treatment of the acute condition and the need for long-term treatment with antiepileptic drugs (AED). To our knowledge, there are no data from prospective cohort studies to ascertain the prognosis for unprovoked seizures following an acute episode of NC.

We prospectively assessed the risk of seizure recurrence in patients who have a first acute symptomatic seizure due to NC. We have also evaluated potential risk factors for seizure recurrence, and we compared the seizure recurrence risk in those with and without treatment with the antihelminthic drug (AHD) albendazole.

Methods. Subjects. This study is a consecutive case series of all patients seen for a first seizure and evidence of an active or transitional form of NC (with or without calcifications) in the emergency room or outpatient departments of the Vicente Corral Moscoso Hospital of Cuenca.
Based on our previous publications,1,7,8 it seems that the study. A follow-up CT scan was obtained between 6 seizure recurrence or until August 2001, the termination of visits. For analytic purposes, patients were followed until the first seizure were considered to have a single episode of acute symptomatic seizures. This is in accord with strategies used for classification of acute symptomatic seizures from other causes.10

Definitions. Type of initial seizure was classified in accordance with recommendations of the International League Against Epilepsy.11 Seizure recurrence was defined as any seizure occurring >1 week after the index seizure. A diagnosis of NC was made if a patient presented with any of the following: 1) one or more active parenchymal cysts, 2) one or more transitional or degenerative parenchymal cysts, 3) one or multiple calcifications associated with one or more active cysts with or without transitional or degenerative cysts, 4) any of the above descriptions associated with the extraparenchymal forms. The characterization and classification of these NC forms were performed according to the criteria of our previous publication.12

Treatment strategies. All patients received prednisone (1 mg/kg/day for 8 days and then decreasing doses the following 8 days) and AED (the routine practice in the Vicente Corral Moscoso Hospital for these patients is administration of phenytoin or carbamazepine). Depending on the preference of the treating physician, some patients received the AHD albendazole 15 mg/kg/day for 8 days in addition to the symptomatic treatment (Treatment Group 1). Other patients received only symptomatic treatment (Treatment Group 2). Assignment was not random but depended on the neurologist on call at the time of presentation.

If a patient had no further seizures for 1 year, medication was withdrawn over a 1-month period. If the patient experienced a seizure recurrence on withdrawal, AED were restarted.

Follow-up. Patients were followed up by means of clinical interviews every 2 months. If patients did not return to the clinic, they were contacted by telephone or by home visits. For analytic purposes, patients were followed until seizure recurrence or until August 2001, the termination of the study. A follow-up CT scan was obtained between 6 and 12 months after the first CT scan in 72 patients. Based on our previous publications,5,7,8 it seems that follow-up CT scan between 6 and 12 months after presentation is advisable to track resolution of the lesions.

Analysis. Univariate analyses for dichotomous variables were performed using Kaplan–Meier survival analysis,13 and statistical significance was calculated using the Mantel method. Results are displayed as Kaplan–Meier survival curves with the cumulative probability of seizure recurrence plotted as a function of time after the first seizure. Univariate analysis for all risk factors and multivariable analysis were performed using the Cox proportional hazard model.14 Distribution of variables among groups was analyzed by the χ² test. Differences were considered significant at p < 0.05 (two tailed). The ethical committee of the University of Cuenca approved the study.

Results. Ninety-three patients with a first seizure associated with NC were initially identified. Ten had only classifications, leaving 83 patients with a first acute symptomatic seizure related to NC. There were no deaths in the cohort. There were 51 patients who returned for follow-up visits who were prescribed and continued AED for 1 year. Thirty-two patients did not return for routine clinical evaluation after their first medical examination. Of these 32, 18 patients were contacted by telephone and 8 were interviewed by means of home visits. All gave information regarding seizure history and medication use. Of the 26 patients who did not return, only 8 continued taking AED for 1 year. The remaining 18 patients discontinued the AED completely. Serum drug levels were not readily available in the hospital at the time of this study and could not be used to monitor compliance in those prescribed medication.

Six patients were lost during follow-up; four cared for by other neurologists and two cared for by the author. The final study group of 77 patients included 36 men (47%) and 41 women (53%) (table 1). Their mean age was 27 years (±18 years) with a range from 3 to 78 years. Twenty-five patients (34%) were children (≥15 years old). Thirty-five patients (45%) had clinical manifestations of neurologic deficit, and 11 (14%) had Todd paralysis. Forty-four (57%) patients received AHD treatment with albendazole in addition to symptomatic treatment; 33 (43%) received no AHD.

At presentation, partial secondarily generalized seizures were the most frequent type of seizures (40%). A single transitional or degenerative cyst was the most frequent abnormality (60%) at initial CT scan (see table 1). Anatomically, the parietal lobe was the most frequent area of cyst involvement (38 patients, 49%). Lesions were multifocal in 26 patients (34%).

A single brief seizure occurred in 59 patients. This occurred on the day of admission in 49 and between 24 hours and 7 days of clinical presentation in 10 (13%). Seventeen patients (22.1%) had multiple seizures in the first 24 hours and one patient (1.3%) had status epilepticus.

Recurrence risk. The mean follow-up of the 77 patients was 24 months (SD 20 months, range 1 to 84 months). The median was 15 months. There was a total of 1,891 person-months of observation. During this time, 31 (40.3%) of the 77 patients in the study had further seizures. There was no difference in the recurrence of seizures among any of the groups detailed in table 1. The cumulative estimate of recurrence for all patients was 22% at 6 months, 32% at 12 months, 39% at 24 months, and 49% at 48 and 84 months (figure 1). As treatment with AED could have masked potential seizure cases, we evaluated the recurrence risk after medication discontinuation. Among the 46 who remained seizure-free for 1 year and were followed for >1 year, 8 experienced a recurrence. Estimate of cumulative seizure recurrence in those seizure-free for 1 year based upon Kaplan–Meier analysis was 18%.

Of the 31 patients who had a seizure recurrence, 16 (52%) had a third seizure during the follow-up period. The Kaplan–Meier estimates of recurrence from the second seizure to the third were 23% within 6 months, 27% within 12
months, 42% within 24 months, and 68% within 48 and 85 months.

**Clinical predictors of recurrence.** Seizures recurred in 23.6% of those with multiple seizures during the acute clinical phase and in 46% of patients with only a single seizure \( (p < 0.05) \). The only patient who had status epilepticus did not have a recurrence. On multivariable analysis, neither age (adults versus children), gender, type of initial seizure, type of NC, localization of cysts in the brain, Todd paralysis, neurologic deficit, nor EEG abnormalities were predictive of further seizures.

A second CT scan was performed on 72 patients between 6 and 12 months following presentation and compared with the first CT scan (table 2). There was no change in the number of cysts in 13 patients, and their crude seizure recurrence was 61%. In three patients, there was reduction of the number of cysts but not total resolution of all cysts. A seizure recurred in one (33%). In 23 patients, the cysts became calcified, and seizures recurred in 67%. In 32 patients, the CT scan showed disappearance of cysts and seizures recurred in 22% \( (p = 0.05) \). When stratified by treatment group, distribution of change in CT findings over time was similar.

**Effect of treatment strategies on seizure recurrence.** There was no significant difference in risk for a seizure recurrence between those treated with AHD when compared with those receiving symptomatic therapy alone (figure 2). Overall recurrence risk was 40% in both groups. There was no difference in risk for recurrence based upon treatment group in those remaining seizure-free for 1 year.

**Discussion. Overall recurrence.** Parenchymal cysticercosis (the most frequent form of NC) is unique in that virtually all cases present with an acute symptomatic seizure. In the current study in which patients were followed prospectively from time of presentation with acute symptoms of NC, we estimate that 50% of cases will experience a seizure recurrence in the 7-year period following first symptoms. Almost half of these recurrences will occur in the first year.

**Risk factors for recurrence.** Among a large array of variables that we assessed as potential risk factors for recurrence, we find only persistence of abnormalities on follow-up CT scan to be predictive of seizure recurrence. Recurrences were identified in only 22% of those with disappearance of all cysts, 56% in those with persistent cysts, and 52% of those with calcification of cysts.

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**Table 1** Characteristics of 77 patients with a first seizure due to neurocysticercosis

| Feature                        | No. (%) | Recurrence, % | \( \chi^2 \), two-sided |
|--------------------------------|---------|---------------|--------------------------|
| Sex                            |         |               |                          |
| Male                           | 36 (47) | 44            | .49                      |
| Female                         | 41 (53) | 37            |                          |
| Median age at diagnosis, y (SD) |         |               |                          |
| Children \( \leq 15 \)          | 25 (32.5) | 40 | 1.0   |
| Adults                         | 52 (67.5) | 40 |        |
| Todd paralysis                 | 11 (14) | 45            |                          |
| Neurologic deficit             | 35 (45) | 43            |                          |
| Seizure type                   |         |               |                          |
| Generalized tonic-clonic       | 19 (25) | 42            | .50                      |
| Partial simple                 | 23 (30) | 35            |                          |
| Partial complex                | 4 (5)   | 75            |                          |
| Partial secondarily generalized| 31 (40) | 39            |                          |
| CT scan image                  |         |               | 1.49                     |
| Single transitional cyst       | 46 (60) | 41            |                          |
| Multiple active cysts          | 9 (12)  | 22            |                          |
| Active + transitional cysts    | 3 (4)   | 33            |                          |
| Multiple transitional cysts    | 6 (8)   | 83            |                          |
| Active cysts + calcifications  | 6 (8)   | 50            |                          |
| Transitional cysts + calcifications | 7 (9) | 14            |                          |
| Anthelmintic treatment         |         |               |                          |
| Albendazole                    | 44 (57) | 39            | 1.81                     |
| No treatment                   | 33 (43) | 42            |                          |

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**Table 2** Percentage of seizure recurrence after first seizure in patients with neurocysticercosis according to differences between first and second CT scan

| CT scan results, no. (%) | Seizure recurrence |
|--------------------------|--------------------|
| No change                | Cyst reduction     | Cyst disappearance | Calcified lesions |
| No                       | 5 (38)             | 2 (67)             | 25 (78)           | 11 (48)          |
| Yes                      | 30 (42)            | 12 (52)            | 7 (22)            | 42 (58)          |

* CT scan performed 6–12 mo after the first.
and longer intervals have been recommended. 4 The AED for 1 year (the practice in Cuenca), but shorter acute NC episode. Some clinicians routinely continue for which AED should be continued following an NC. There are no guidelines regarding the duration therap
er elaboration.

"Implications for management of people with NC. There are no guidelines regarding the duration for which AED should be continued following an acute NC episode. Some clinicians routinely continue AED for 1 year (the practice in Cuenca), but shorter and longer intervals have been recommended.4 The AED currently used have no antiepileptogenic effect but do effectively prevent acute symptomatic seizure occurrence, at least in the context of traumatic brain injury.15 One assumes that the risk for seizures is substantial as long as there is an active ongoing process as characterized by persistence of edema about a degenerating lesion. Because of this, we feel that CT is a useful tool for these treatment decisions. Seizures in the context of edema and a degenerative lesion should be considered acute symptoms—even if they occur many months after presentation. It is appropriate to monitor cyst activity with CT scanning and to continue AED until resolution of the acute lesion. After this time, AED may be discontinued. Other authors have also suggested that AED can safely be withdrawn once the follow-up CT shows resolution of the lesion.16,17

Unprovoked seizures and epilepsy. Seizures occurring in individuals after resolution of edema and resorption or calcification of the degenerating cyst should be considered unprovoked. It is these individuals who truly have epilepsy, and in this situation, long-term AED are warranted.

Seizure recurrence among those with cyst resolution was about 22%, a figure in accord with those in studies evaluating unprovoked seizure risk among individuals with structural brain abnormalities and acute symptomatic seizures.18-23 In the current study, about two-thirds of cases with a recurrence experienced a third episode. This proportion is similar to recurrence risk following a first unprovoked remote symptomatic seizure.24-26

Effect of antihelminthic treatment on seizure recurrence. It has been suggested that patients with NC are more likely to remain seizure-free if antihelminthic treatment is administered.7,8 In the current study, we failed to find any correlation between treatment with antihelminthic agents and seizure recurrence. The current report was not a randomized clinical trial (one is currently being conducted), but there were no obvious differences in the characteristics of patients in the two treatment arms and the findings are similar to those reported in previous clinical trials of AHD in the treatment of NC.2,27,28

Although no long-term effect on cyst reduction has been demonstrated in randomized trials of NC comparing AHD with placebo, there are trends toward more rapid resolution of the lesion in those treated with AHD.16,17 Although not the case in the current study, a higher risk for seizures has also been reported in the first month following presentation in those treated with AHD when compared with those not treated.37

The similarities in seizure recurrence within treatment groups, even using optimal analytic methods, may be related to differential effects of treatment strategies on unprovoked and acute symptomatic seizures. It seems that interpretation of prognosis for continuing seizures and epilepsy after an acute presentation of NC provided in previous studies is difficult because of the failure to distinguish acute symptomatic seizures from epilepsy. This distinction must be considered in future studies of the effects of AHD treatment on seizure recurrence in people with NC. Meanwhile, people with acute NC should be treated with AED until cyst resolution on CT.

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Figure 2. Probability of seizure recurrence after a first seizure in 77 patients with neurocysticercosis as function of cysticidal treatment. Circles = patients who received antihelminthic medication; squares = patients who received no antihelminthic medication.
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