Perilesional gliosis around solitary cerebral parenchymal
cysticerci and long-term seizure outcome: A prospective
study using serial magnetization transfer imaging

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SUMMARY

**Purpose:** Epilepsy following solitary cerebral cysticercosis (SCC) is possibly caused by perilesional gliosis, best visualized on magnetization transfer imaging (MTI). This study aims to describe development of gliosis around SCC by prospective serial MTI and to correlate this gliosis with long-term seizure outcome.

**Methods:** We randomized 123 patients with SCC and new-onset seizures to treatment with albendazole plus antiepileptics (treatment), or antiepileptics only (control), and performed magnetic resonance imaging (MRI) scans at 0, 3, 6, 12, and 24 months. Prospective follow-up data regarding seizure outcome up to 5 years later were collected. MRI studies were analyzed for lesion characteristics and perilesional magnetization transfer (MT) hyperintensity.

**Key Findings:** Clinical and radiologic data of 77 patients were analyzed. Demographic and seizure characteristics were similar in treatment and control groups. Clinical data were available up to 64 months after enrollment. At 12 months, 89.5% patients were seizure-free. MTI is more sensitive than routine imaging for detection of perilesional gliosis. Albendazole treatment did not affect imaging or clinical outcome, including development of gliosis. Independent of duration of follow-up, gliosis was associated with more seizures, and with seizure recurrence at 12 months; duration of seizures and antiepileptic therapy was longer. Gliosis was not dependent on seizure type or stage of degeneration at enrollment or persistence/calcification of the lesion.

**Significance:** Perilesional gliosis around SCC helps prognosticate seizure outcome. Poorer outcome in patients with persistent lesions is likely to be related to mechanisms other than gliosis. The lack of effect of albendazole on seizure outcome may be due to its inability to decrease formation of gliosis.

**KEY WORDS:** Solitary cerebral cysticercal lesion, Neurocysticercosis, Perilesional gliosis, Magnetic resonance imaging, Magnetization transfer imaging.

Seizures are an important clinical manifestation of *Taenia solium* infections in the brain, and are estimated to occur in 90% of patients with this disease (Chatterjee, 1973). In endemic areas, such as the Indian subcontinent, China, sub-Saharan Africa, and Central and South America, neurocysticercosis (NCC) contributes substantially to the burden of epilepsy (Gemmell, 1983; Román et al., 2000; de Souza et al., 2009). Seizures occur in any stage of NCC and can be partial, primary generalized, or partial with secondary generalization (Pradhan et al., 2003). However, the seizures of NCC are heterogeneous (Garcia et al., 1993; de Bittencourt et al., 1996; Proano et al., 2001): they include both acute symptomatic seizures, which occur when a parenchymal cyst starts degenerating (symptomatic of an acute inflammatory response), and chronic unprovoked seizures (i.e., epilepsy). Hence, a marker for unprovoked seizures is of prognostic importance in epilepsy due to NCC (Pradhan et al., 2003). Conventional magnetic resonance imaging MRI is of limited value for the assessment of therapeutic response because the cysticerci persist as fibrosed or calcific lesions for a long time (Kumar et al., 2002). Recent studies on patients with solitary cerebral cysticerci (SCC) have shown that presence of perilesional gliosis as visualized on magnetization transfer imaging (MTI) is associated with poor control of epilepsy and early recurrence of seizures after withdrawal of antiepileptic drug (AED) treatment (Gupta et al., 1999, 2000; Pradhan et al., 2000, 2003;
Agarwal et al., 2004). This perilesional gliosis, a sequel to perilesional inflammation seen in the stage of acute cysticercal degeneration, appears hyperintense on MTI with a low magnetization transfer (MT) ratio (Agarwal et al., 2004).

With one exception (Pradhan et al., 2000), studies on the relationship between perilesional gliosis in SCC and long-term seizure outcome published to date have all been retrospective and cross-sectional in nature (Gupta et al., 1999, 2000; Agarwal et al., 2004). We conducted the present study to describe the development of perilesional gliosis around an SCCL by means of prospective serial quantitative MRI in a cohort randomized to receive albendazole treatment or not, and to correlate the presence of this gliosis with long-term seizure outcome.

**Materials and Methods**

Patients were prospectively enrolled between May 2002 and October 2003 at a tertiary national referral center for neurologic diseases. After written informed consent was obtained, all patients presenting with new-onset focal or generalized seizures underwent contrast computed tomography (CT) scan of the brain followed by contrast MRI. Those with an MRI-confirmed solitary cerebral parenchymal cysticercal lesion were included in the study. Diagnosis of cysticercosis was based on criteria proposed earlier (Rajshke-khar et al., 1993; Del Brutto et al., 1996; Rajshhekhar & Chandy, 1997). Patients were excluded from the study if they had a past history of epilepsy, received albendazole or praziquantel in the past, evidence of other lesions on CT or MRI, significant neurologic deficits, raised intracranial pressure, or seizures refractory to acute treatment. Written informed consent for serial imaging procedures and enrollment into the study was obtained from all patients or guardians. Ethical clearance for the study was obtained from the hospital ethics committee of our institute. A detailed protocol was instituted for each patient at the time of entry.

Gadolinium-enhanced MRI of the brain was performed on a 1.5 Tesla MR system (Magnetom Vision 7252; Siemens AG, Erlangen, Germany) using a circular polarized head coil according to a predetermined protocol, which included pre- and postcontrast fast spin-echo (SE) T1-weighted sequences [time to pulse repetition (TR) 650, time to echo (TE) 12, number of excitations (n) 1], proton-density imaging (TR 4,800, TE 22, n 1), T2-weighted imaging (TR 4,800, TE 90, n 1), fluid-attenuated inversion recovery (FLAIR) [TR 9,000, TE 119, inversion time (TI) 1,200, n 1], constructive interference in steady state-three dimensional (CISS-3D) sequences (TR 12.25, TE 5.9, n 1), and proton (H1) MR spectroscopy. Imaging in the axial plane was performed using 5-mm slice thickness with an interslice gap of 0.5 mm, 24 × 24 cm field of view, and a matrix size of 256 × 256. MTI was carried out at the same time that the diagnostic MRI was performed with identical parameters as used for T1-weighted imaging except for the addition of an off-resonance saturation pulse with a frequency offset of 1,200 Hz and bandwidth of 250 Hz. Postcontrast MT spin-echo imaging was performed with gadolinium diethylene triaminopentaacetic acid (Gd-DTPA, 0.1 mmol/kg IV) as contrast.

The patients were randomized to two groups by means of a random-number table obtained from the Department of Biostatistics of our Institute. One group received AED only (usually phenytoin, carbamazepine, or oxcarba-zepine) and the second group was given albendazole at 15 mg/kg/day in two divided doses for 28 days in addition to antiepileptic medication. A second AED was added if the maximum tolerated dose of the first did not control seizures. Drug levels of AED were not obtained because of financial constraints.

Serial contrast MRIs were performed in each patient at 3, 6, 12, and 24 months after enrollment. The imaging protocol was similar for all follow-up evaluations. MRI was done in all cases >24 h after the last seizure. At 1 month after induction into the study and at every follow-up thereafter, at the time of obtaining repeat imaging the patients were evaluated regarding recurrence of seizures, any side effects of treatment, compliance with therapy, and the presence of fresh symptoms. Modification of AED therapy was done if required. Because these patients were widely dispersed in the community, we employed only self-reporting by the patient and caregivers using prospectively maintained seizure diaries to determine seizure recurrence and seizure number. In this cohort of patients with prior seizures, a recurrence was defined as any paroxysmal neurologic symptom without a definite alternative cause. The AED was tapered and stopped at the end of a 2-year seizure-free period. For assessment of long-term outcome, we contacted patients in October 2006 through a simple questionnaire posted with return-paid envelopes to every patient. Some patients came for follow-up in the outpatient clinic, whereas others communicated relevant details by post or telephone. Patients with >12 months follow-up period were included in the final analysis. The physicians who reviewed patient details at these follow-up visits were blinded to the two treatment groups.

The effect of treatment was evaluated regarding seizure recurrence and radiologic outcome. Clinical outcome parameters included total number of seizures, time to become seizure-free, duration of AED treatment, time since AEDs were stopped at the last visit, and the length of time seizure-free after the last episode. Lesion characteristics, staging of the cyst, and the presence of perilesional hyper-intensity on conventional FLAIR, proton density (PD), and T2-weighted images as well as T1-weighted with and without MTI were analyzed separately by two trained, independent physicians and a neuroradiologist, who were unaware of treatment administered. The lesion was described with regard to the appearance of the scolex, cyst fluid, cyst wall, and the perilesional area. The region of interest in the perilesional area was selected so as to include any perilesional...
MT hyperintensity seen on later scans, or was chosen arbitrarily if no such hyperintensity was seen. These imaging characteristics were analyzed for temporal variation and for variability between albendazole and nonalbendazole groups. Staging of the cysticercal lesion on serial MRI was done using standard criteria described in our earlier report (de Souza et al., 2010a). SPSS version 15.0 (SPSS Inc., Chicago, IL, U.S.A.) was used for statistical analysis. Descriptive statistics such as mean, standard deviation, standard error, frequencies, and percentages were used to express data. The independent sample t-test was used to compare continuous variables between two groups, including between the treatment and control groups. Chi-square test was employed for categorical variables. Pearson’s correlation coefficient was used to establish relationships between continuous variables. One-way analysis of variance (ANOVA) followed by post hoc tests was carried out to compare mean values when the number of groups was more than two. Wilcoxon test and Kruskal-Wallis test were used to compare seizure frequency between the various groups. Risk estimates were expressed in terms of the odds ratio. Breslow-Day, Tarone, Cochran, and Mantel-Haenszel tests were used to test the homogeneity and conditional independence of the odds ratio (OR). A p-value of <0.05 was considered statistically significant.

**Key Findings**

One hundred twenty-three patients were recruited from October 2002 to May 2003. Among these, 77 patients had a minimum follow-up period of 12 months, and had at least four MRI examinations. Sixty patients in this group had five MRI scans. The remaining 46 patients were excluded because their follow-up period was <12 months or as they did not have four MRI scans. Demographic profile, seizure type, and MRI findings in the latter set of patients did not differ from the group that was analyzed. Among the 77 patients analyzed, 34 (44.2%) responded to our postal and telephonic enquiries and attended the outpatients clinic during October 2006. Data regarding the remaining had been entered prospectively during each follow-up. The randomized study design and the pattern of follow-up are depicted in Fig. 1.

No statistically significant difference was seen between the albendazole and treatment groups in demographic parameters such as age and sex distribution, seizure semiology, cyst characteristics on the first MRI, and duration of illness prior to presentation. The mean duration of follow-up was $33.9 \pm 13.7$ months, and no difference was noted between the albendazole and control groups. Follow-up ranged from 12–64 months from the time of diagnosis, and 42 patients (51.9%) had follow-up data available for a period of 3 years or more from the time of enrollment. Baseline characteristics of the patient population, including seizure semiology and details of follow-up available are represented in Table 1, and age and sex distributions in Fig. 2.

AEDs used included phenytoin, phenobarbital, carbamazepine, oxcarbazepine, and clobazam; 77.6% of patients were controlled on a single AED, whereas 15.8% required two AEDs and 6.6% needed three drugs for seizure control. The most common AEDs used were carbamazepine or its analog oxcarbazepine (60.5%), followed by phenytoin in 42.5%. Phenobarbital and clobazam were also administered as add-on therapy to <15% of patients each. There was no significant difference between albendazole and control groups in the type, dosage, or number of AEDs used.

Perilesional gliosis was defined as an MT hyperintensity visible around the lesion, without hyperintensity on $T_2$ or FLAIR and with isointensity or hyperintensity on $T_1$-weighted imaging (Pradhan et al., 2000). This gliosis was not seen at baseline or at 3 months in any patient. In subsequent scans, perilesional gliosis was visible in 22.2–39.2% (Table 2A). MTI and contrast MTI sequences showed a significantly higher incidence of perilesional hyperintensity than routine pre- and postcontrast $T_1$-weighted images ($p < 0.001$). There was no difference between the treatment and control groups in the occurrence of perilesional gliosis. Perilesional gliosis as seen on MTI is depicted in Figs. 3 and 4 and shows serial evolution of gliosis in one of our patients. The cysticercal lesion persisted in a significant proportion of patients (82.2%) at 6 months, but the proportion of patients with visible lesions fell steadily through later scans. Staging of the lesion based on MR characteristics was done in accordance with criteria described in detail in our previous report (de Souza et al., 2010a). At baseline, all the lesions were in stage 2 (early degeneration, 69.8%) or stage 3 (late degeneration, 30.2%). As cysticercal degeneration progressed, the lesions progressed from these stages to stage 4, or resolved and became invisible on MRI. At the time of the last MRI, 40.8% of lesions had resolved, whereas 39.5%
had calcified and 19.7% showed a persistent granuloma. Treatment with albendazole did not affect the radiologic stage of the lesion or its persistence on serial MRI. Forty-five patients (59.2%) did not have recurrence of seizures beyond 1 month after enrollment in the study. After 1 year, a further 30.3% were free of seizures, leading to a cumulative seizure remission rate of 89.5% at 1 year. Just over half the patients (39, 53.4%) had four seizures or less; 18.4% of patients in the whole cohort had a poor outcome, with continuing seizures in the 12 months preceding the last visit. Although 60.5% were free of seizures for 2 years or more at the time of the last visit, AED treatment exceeded 2 years in duration in nearly two thirds (62.3%). Fifty-four patients (71.1%) remained on AEDs at the time of the last visit, whereas the rest had been off treatment for 2–34 months. There was no difference in the clinical outcome between the treatment and control groups (Table 2B).

Using survival analysis, the median seizure-free period among 17 seizure-free patients was 11.0 [standard error (SE) 1.24] months with a maximum seizure-free period of 58.0 months.

The presence of perilesional gliosis at 12 months after enrollment was significantly related to recurrence of seizures despite AED treatment (p = 0.021, Table 3 and Fig. 5). No significant effect of gliosis on seizure

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### Table 1. Details of baseline demographic characteristics of the patient population, types of seizures at presentation, and follow-up available

| Variable                        | Entire cohort (n = 77) | Treatment group (n = 35) | Controls (n = 42) | p-value<sup>a</sup> |
|---------------------------------|------------------------|--------------------------|------------------|---------------------|
| Age in years, mean ± SD (Range) | 19.1 ± 10.8 (5–52)     | 20.6 ± 9.9 (5–42)        | 17.8 ± 11.5 (6–52) | 0.41                |
| M:F                             | 39:38                  | 21:14                    | 18:24            | 0.09                |
| **Semiology**                   |                        |                          |                  |                     |
| Generalized (%)                 | 4 (5.2)                | 2 (5.7)                  | 2 (4.8)          | 0.86                |
| SS (%)                          | 14 (18.2)              | 6 (17.1)                 | 8 (19.0)         | 0.86                |
| SS with gen (%)                 | 51 (66.2)              | 23 (65.7)                | 28 (66.7)        | 0.86                |
| CPS (%)                         | 1 (1.3)                | 1 (2.9)                  | 0                | 0.86                |
| CPS with gen (%)                | 7 (9.1)                | 3 (8.6)                  | 4 (9.5)          | 0.86                |
| **Onset**                       |                        |                          |                  |                     |
| Single seizure (%)              | 58 (72.5)              | 28 (80)                  | 30 (71.4)        | 0.27                |
| Cluster/EPC                     | 15/4                   | 4/3                      | 11/1             | 0.54                |
| **Follow-up**                   |                        |                          |                  |                     |
| Response to letter (%)          | 34 (44.2)              | 13 (37.1)                | 21 (50)          | 0.18                |
| Follow-up from presentation (month), mean ± SD (range) | 33.9 ± 13.7 (12–60) | 31.9 ± 14.2 (12–56) | 35.6 ± 13.3 (13–60) | 0.59                |
| Duration of illness (month) before enrollment, mean ± SD (Range) | 1.4 ± 2.8 (0–13) | 1.8 ± 3.3 (0–13) | 1.0 ± 2.3 (0–13) | 0.67                |
| Total FU from first seizure (month), mean ± SD (range) | 35.3 ± 14.1 (12–64) | 33.8 ± 14.8 (12–58) | 36.6 ± 13.9 (13–64) | 0.78                |
| Percentage of patients with follow-up duration |                      |                          |                  |                     |
| 12–23 month                     | 24.7                   | 28.6                     | 21.4             | –                   |
| 24–35 month                     | 20.8                   | 22.8                     | 21.5             | –                   |
| ≥36 month                       | 54.5                   | 48.6                     | 57.1             | –                   |

<sup>a</sup>p-value calculated for comparison between the treatment and control groups.

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![Figure 2](image)

**Figure 2.**
Age (A) and sex (B) distributions of the patient population. 
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recurrence could be demonstrated at 6 and 24 months. There was a significant increase in the number of seizures throughout the illness—from the time of onset till the last follow-up—in the subgroup with gliosis, independent of the time at which MRI was done (Table 4). The total number of seizures did not depend on the duration of follow-up. The time taken to become seizure-free was significantly longer in the subgroup with gliosis (mean of 9.41 ± 15.4 months, compared to 3.41 ± 9.77 in patients without gliosis). The duration of treatment with AEDs was longer in the subgroup with gliosis (mean duration of 31.53 ± 12.39 months, compared to 27.98 ± 10.57 in patients without gliosis), but this was not statistically significant (p > 0.05). Similarly, there was no significant

| Time of scan | Whole cohort (n = 77) | Treatment group (n = 35) | Controls (n = 42) | p-value* |
|-------------|----------------------|--------------------------|------------------|-----------|
| (A) Imaging outcome | | | | |
| Perilesional gliosis (%) | 6 month | 22.2 | 12.5 | 30.0 | 0.07 |
| 12 month | 39.2 | 32.4 | 45.0 | 0.19 |
| 24 month | 36.8 | 25.0 | 48.3 | 0.13 |
| Lesion persistence (%) | 6 month | 82.2 | 81.3 | 82.9 | 0.55 |
| 12 month | 69.0 | 75.0 | 64.1 | 0.23 |
| 24 month | 55.0 | 56.7 | 53.3 | 0.50 |
| (B) Clinical outcome | | | | |
| Time to cessation of seizures (month, mean ± SD) | 5.9 ± 12.7 | 6.1 ± 12.8 | 5.8 ± 12.8 | 0.33 |
| Months seizure-free at last visit (mean ± SD) | 28.6 ± 15.8 | 26.1 ± 16.6 | 30.7 ± 14.9 | 0.70 |
| Total number of seizures (mean ± SD) | 11.5 ± 22.6 | 9.7 ± 18.5 | 12.9 ± 25.3 | 0.68 |
| Duration of AED therapy (month, mean ± SD) | 28.6 ± 11.3 | 27.8 ± 11.8 | 29.3 ± 11.1 | 0.58 |
| Months off AED therapy at last visit (mean ± SD) | 5.4 ± 9.7 | 3.8 ± 8.2 | 6.8 ± 10.7 | 0.30 |

*p-value calculated for comparison between the treatment and control groups.

Figure 3.
Postcontrast MTI at 6 months after enrollment in the study, showing peripheral enhancement of the lesion with perilesional hyperintensity suggestive of gliosis in three axial sections.

Figure 4.
Pre- and postcontrast serial MTI, showing perilesional hyperintensity suggestive of gliosis not visible in T₁-weighted images.
difference in the number of AEDs needed for adequate seizure control in the groups with and without gliosis: two of five patients on three AEDs and 6 of 12 patients on two AEDs had perilesional gliosis. When only patients with at least 36 months of follow-up were analyzed (n = 42), time to seizure freedom, total duration of AED therapy, number of AED used, and seizure frequency per month were not affected by the presence of gliosis.

Persistence of the cysticercal lesion on serial MRI was compared with the later development of perilesional gliosis and with seizure recurrence. The incidence of gliosis was not higher in those patients in whom the cysticercal lesion remained visible at 3, 6, 12, or 24 months as compared to those in whom the lesion resolved. Calcification of the lesion did not affect the presence of gliosis. Seizure recurrence was significantly higher in patients with a visible lesion at 6 months [OR 1.33 with 95% confidence interval (CI) 1.14–1.56], but no similar correlation was seen at 12 or 24 months (OR 1.05, 95% CI 0.70–1.56) and OR 1.22, 95% CI 0.65–2.28, respectively. Presentation with an initial cluster of seizures or epilepsy partialis continua did not affect the later development of gliosis. Similarly, the initial stage of degeneration of the cysticercal lesion did not have any effect on the development of perilesional gliosis (Table 5).

**DISCUSSION**

Neurocysticercosis serves as a biologic marker of socioeconomic development (Sarti et al., 1992; Carpio et al., 1998) and is an important cause of seizures and epilepsy in endemic areas. Epilepsy due to NC is heterogeneous and includes partial seizures, primary generalized seizures, and partial seizures with secondary generalization (Del Brutto et al., 1992; de Bittencourt et al., 1996). Chronic unprovoked seizures or epilepsy due to NCC is a sequel to degeneration and death of the cysticerci. Cysticercal degeneration is characterized pathologically by neuronal necrosis, fibrillary deposits, fibrosis, gliosis, calcification, and hemosiderosis. An inflammatory infiltrate comprising mainly lymphocytes and macrophages with occasional eosinophils and giant cells is associated with glial cell proliferation and cellular pleomorphism. Adjacent neurons undergo necrosis probably due to compression by the parasite or due to secretion of mediators of inflammation by the cysticercus itself or by the infiltrate (Chung et al., 1998; Lino-Junior Rde et al., 2007). In focal-acquired epilepsy such as NCC, the role of this gliosis in the genesis of epilepsy has not been adequately investigated (Kathuria et al., 1998). It has been postulated that modifications in astroglial structure and properties can influence neuronal activity by influencing the volume and chemical environment of the extracellular space, including the development of gap junctions with altered ion channel permeability, and changes in the buffering of electrolytes (Pradhan et al., 2000). Neurons lose their normal connections and form new, abnormal ones. These changes increase neuronal membrane excitability via down-regulation of inhibitory γ-aminobutyric acid (GABA) receptors and upregulation of excitatory N-methyl-D-aspartate (NMDA) receptors, potentiating the action of glutamate and thereby predisposing to the development and synchronous spread of abnormal electrical discharges (Pradhan et al., 2003).

Newer MR techniques such as MTI and T2-relaxometry augment the visual evaluation of the perilesional area in patients with NCC (Kumar et al., 2002). Consequent to the changes described in preceding text, neurodegeneration, microglial proliferation, β-amyloid deposition, and astrogliosis lead to signal intensity changes on MTI (Kumar et al., 2003). This relatively novel imaging technique determines the contribution of macromolecular proteins to the MR signal, by suppressing signal from tissue with high interaction between macromolecules and water (Kathuria et al., 1998). MT contrast results from interaction between protons in free fluid in a tissue and those proteins in macromolecules (Filippi & Rocca, 2007), and provides a reliable index of the structural integrity of tissue (Sinson et al., 2001). This technique is superior to conventional MRI in the accurate detection and quantification of subtle changes in cerebral white matter (Fazekas et al., 2005), being able to detect additional
regions of abnormality in areas not apparent on T2-weighted imaging (Gupta et al., 1999; Kumar et al., 2003). MT hyperintensities and consequent alterations in the MT ratio have been attributed to increased water content, neuronal loss, gliosis, and damage to myelin (Kimura et al., 1996), and such signal intensity changes have been noted in histologically abnormal areas that appeared normal to routine T2-weighted imaging in diverse diseases of cerebral white matter like multiple sclerosis (Filippi & Rocca, 2004) and traumatic brain injury (Gupta et al., 1999; McGowan, 1999; Sinson et al., 2001; Kumar et al., 2003; Filippi & Rocca, 2004), as well as NCC (Kathuria et al., 1998; Gupta et al., 1999, 2000; Pradhan et al., 2000; Kumar et al., 2002; Pradhan et al., 2003; Chawla et al., 2004).

The present report is the first study evaluating the effect of perilesional gliosis on long-term seizure outcome in parenchymal NCC using prospective serial MRI and MTI. Therefore, we have attempted to correlate long-term seizure outcome with the presence or absence of perilesional gliosis on qualitative MTI at specified times after onset. Our cohort

Figure 5.
Occurrence of perilesional gliosis in patients with and without seizure recurrence at 6 months (A), 12 months (B), and 24 months (C) after enrollment. Epilepsia © ILAE
has a long follow-up period, and the effect of treatment with albendazole in these patients has also been studied. Previously published studies on this subject have failed to consider the effect of albendazole treatment on long-term seizure outcome, and have largely been concerned with single MRI evaluations at a specified time after enrolment.

Over 18 months, we recruited 123 patients with new-onset seizures and solitary cerebral parenchymal cysticerci in this prospective serial imaging study. Although a significant proportion dropped out (37.4% did not have adequate clinical or radiologic follow-up), we were able to perform at least four serial MRI examinations in 77 patients and correlate data thus obtained with long-term clinical outcome, beyond 1 year from presentation. Although we included all patients with >12 months of follow up, most of our cohort had much longer follow-up data available.

The incidence of perilesional gliosis as seen on qualitative MTI increased steadily from the third MRI to the fifth. A lower number of patients in absolute terms had gliosis at 24 months, but this was due to patient dropout. MTI was markedly more sensitive than routine T1-weighted sequences for the detection of this perilesional gliosis. Perilesional gliosis was seen in 39.2% of patients, comparable to the figure of 33% reported previously (Kumar et al., 2002). An association between perilesional gliosis visible on MT imaging at 12 months and seizure recurrence was observed. The presence of gliosis at 6, 12, and 24 months was associated with more seizures than in those patients without such gliosis, although this parameter may be affected by self-reporting and by patients who had a large number of seizures. In the only earlier prospective study on this aspect, Pradhan and coworkers has shown that seizure recurrence was higher in patients with gliosis and that perilesional gliosis has a predictive value of 86% for seizure recurrence after stopping AED therapy. The absence of perilesional gliosis had a predictive value of 90% for remaining seizure-free (Pradhan et al., 2000). In agreement with these conclusions, we found that the presence of perilesional gliosis on MTI has a high specificity but low sensitivity when predicting seizure recurrence. Gliosis as seen on MRI has been shown to facilitate seizure recurrence after traumatic brain injury (Angeleri et al., 1999).

The development of perilesional gliosis was independent of the stage of the lesion at presentation, the type of seizure at presentation (single seizure, cluster, or epilepsy partialis continua), nature and duration of AEDs used, or calcification of the lesion on serial MRI. Although up to 82.2% of lesions remained visible at 6 months, this did not help predict the subsequent development of perilesional gliosis. These findings are similar to the ones reported previously (Pradhan et al., 2000). Similarly, eventual calcification of the lesion did not predispose to gliosis, unlike the patients reported by Pradhan et al. (2003). Only 19.7% of lesions remained visible at 24 months, unlike a previous report in which as many as 38% of cysticercal lesions were persistently visible (Pradhan et al., 2000). Earlier studies, due to their cross-sectional nature, had included patients with persistent lesions as well as those that had resolved. Therefore, it was not clear whether gliosis occurred more frequently around a persistent lesion. In this study we have demonstrated that there is no difference in the development of gliosis between lesions that persist and those that become MR-invisible. This finding validates the conclusions made in earlier reports, as their patients had both persistent and invisible lesions (Pradhan et al., 2000). However, as reported by us and others previously (Rajeshkhar & Chandy, 1997; Murthy & Reddy, 1998; Agarwal et al., 2004; de Souza et al., 2010a).

| Table 4. Effect of perilesional gliosis at various periods after enrolment on the total number of seizures in each patient |
|---|---|---|---|
| Time of scan | Perilesional gliosis | Number of seizures | p-value* |
| 6 month | Absent | 8.26 | 14.71 | <0.001 |
| 12 month | Absent | 6.91 | 7.59 | <0.001 |
| 24 month | Absent | 6.38 | 7.42 | <0.001 |

*p-value calculated for seizure number and presence of perilesional gliosis.

| Table 5. Effect of persistence of the lesion on serial MRI and of the stage of the lesion at enrollment on the subsequent occurrence of perilesional gliosis |
|---|---|---|---|---|---|---|
| Time of scan | Lesion persistence | Relative risk of gliosis | p-value* | Time of scan | Stage of lesion on baseline scan | Relative risk of gliosis | p-value† |
| 6 month | Persistent | 0.86 | 0.72 | 6 month | Stage 2 | 1.34 | 0.28 |
| 12 month | Persistent | 1.05 | 1.00 | 12 month | Stage 2 | 0.92 | 0.76 |
| 24 month | Persistent | 0.94 | 1.00 | 24 month | Stage 2 | 0.94 | 1.00 |

*Stage of degeneration of the cysticercal lesion based on imaging characteristics (de Souza et al., 2010a).
†p-value calculated for relative risk of gliosis with lesion resolution and persistence on MRI.
‡p-value calculated for relative risk of gliosis with stage of lesion degeneration on baseline MRI.
Rajshekhar & Jeyaseelan, 2004; de Souza et al., 2009), lesion persistence is associated with poorer long-term seizure outcome. In the present cohort too, long-term seizure outcome was worse if the lesion remained visible on the 6-month MRI. Because our findings indicate that this is likely not due to perilesional gliosis, it is possible that recurrence of seizures with persistent cysticercal lesions may be due to other mechanisms. In particular, it has been hypothesized that episodic antigen release from the dead cysticercus may provoke inflammation, leading to recurrent seizures. According to this model, cyst antigens sometimes remain sequestered in the granuloma or in the calcified dead cyst, and these antigens are released through partial decalcification or micromodeling of the lesion, which triggers a host immune response (Pradhan et al., 2000; Chawla et al., 2004).

Seizure outcome in our patients with solitary parenchymal NCC was generally good, with more than half having four or less seizures and 89.5% being free of seizures after the first year of illness. Therefore, we have found no significant difference in the number of AEDs used or in the duration of AED therapy between patients with and without gliosis. It has been shown that patients with NCC relapse more frequently than those with idiopathic epilepsy after withdrawal of AED, with relapse rates of >50% (Del Brutto, 1994). In Pradhan’s study, 86% of patients with gliosis had recurrences of seizures on stopping AED, compared to just 10% in those without gliosis (Pradhan et al., 2000). Moreover, the effect of AED on long-term seizure outcome in the face of permanent structural damage to brain parenchyma is under debate (Pradhan et al., 2003). Although in our study patients with gliosis did receive AED for a longer duration on average, this was not statistically significant. In earlier studies, 36–73% of patients with perilesional gliosis needed more than one AED for satisfactory seizure control, whereas only 7–9% of patients without gliosis were on two AEDs. All patients on more than two AEDs had perilesional gliosis. Furthermore, interictal electroencephalography (EEG) is more often abnormal in the gliosis group (Pradhan et al., 2000; Kumar et al., 2002; Pradhan et al., 2003).

Our patients demonstrated no difference in either clinical or radiologic outcome between treatment and control groups. Therefore, the possibility of albendazole treatment confounding our results is unlikely. In earlier studies with CT scan (Ferreira et al., 2001; Kuruvilla et al., 2001; Sujit Kumar & Rajshekhar, 2004; Wallin & Kurtzke, 2004; Udani, 2005) and in our previous report using serial MRI (de Souza et al., 2009), it has been shown that albendazole leads to faster resolution of perilesional inflammation soon after onset of cysticercal degeneration, and may contribute to radiologic resolution of the enhancing lesion. However, despite this early action, it has no effect on long-term seizure outcome. It has been proposed that albendazole and other anthelmintic drugs only improve imaging without modifying the clinical course of the disease (Kramer et al., 1989). Our results suggest that long-term seizure outcome is strongly influenced by the development of perilesional gliosis. In a previous report based on the same cohort of patients (de Souza et al., 2010b) we have shown that albendazole does not affect the development of perilesional gliosis around the cysticercus, thus providing a possible explanation for its demonstrated lack of effect on seizure outcome.

In conclusion, perilesional gliosis as seen on qualitative MTI around SCC is of value in prognosticating seizure outcome. Although patients with SCC in general have a good prognosis for seizures, the number of seizures as well as the risk of seizure recurrence is higher in patients with visible gliosis. Poorer seizure outcome in patients with persistent lesions is likely to be related to mechanisms other than the development of perilesional gliosis. The lack of effect of treatment with albendazole on seizure outcome may be due to its inability to decrease the formation of perilesional gliosis.

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**DISCLOSURE**

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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