Incidence of seizures due to degenerative phase of neurocysticercosis: A study in a cohort of primary school children in south India

Shyam K Jaiswal, Jagarlapudi MK Murthy, Mreddy Padmanabh Reddy, Surampudi Srikrishna

Department of Neurology, CARE Institute of Neurosciences, CARE Hospitals, Hyderabad; NICE Hospital and NICE Foundation, Hyderabad, India

Abstract

Objective: To study the incidence of seizures due to degenerative phase of neurocysticercosis (NCC) in a cohort of primary school children in south India. Methods: The study cohort included 7,408 (age 5-15 years, boys 44.5% and girls 55.5%) children registered on roles on the date of start of study. The children were followed through first to fifth standard for new-onset of seizures. The data collected included demographic data, date of seizure, any antecedent events, seizure semiology, neurologic findings, 40 minutes EEG findings, and contrast CT brain findings. This analysis is limited to seizures due to degenerative phase of NCC. The average annual incidence rates (AAIR) and 95% confidential intervals (CI) were calculated. Results: During the study period, of the 58 children with new-onset seizure, 19 (32.7%) had seizure due to degenerative phase of NCC [mean age 9.42 years; range 7-13 years; 8 boys and 11 girls]. Contrast CT scans in all the 19 children showed solitary cysticercus granuloma (SCG). The common seizure type by mode of onset was focal. The AAIR of seizure disorder was 36.64 (95%CI 22.1-57.2) per 100,000. All the children received antiepileptic drug treatment and four weeks of albendazole and steroids. The seizure disorder resolved with the resolution of the lesion on follow-up CT scan and AEDs were withdrawn. Conclusions: In this highly selective cohort of primary school children from low economic strata, the AAIR of seizure disorder due to degenerative phase of NCC, SCG was high. Seizure disorder due to SCG has an enduring predisposition for seizure recurrence and need AEDs for the period of resolution of lesion and AEDs could safely be withdrawn with the resolution of the lesion.

Keywords: Acute symptomatic seizures, neurocysticercosis, solitary cysticercus granuloma, average annual incidence rate

INTRODUCTION

Epileptic seizures are the common presenting feature of all the evolutive stages of neurocysticercosis (NCC). Colloidal and granular-nodular evolutive stages of NCC represent the degenerative phase or transitional form of NCC. This includes solitary cysticercus granuloma (SCG) which represents single parenchymal cysticercal cyst in degenerative phase. Seizures due to degenerative stage including SCG are categorized under acute symptomatic seizures. In countries, endemic to cysticercosis, degenerative phase of NCC is the common cause of acute symptomatic seizures. There were a few community-based studies estimating the prevalence of seizure disorder due to degenerative phase of NCC, but no incidence studies. In the Comprehensive Rural Epilepsy Study in South India in a rural community the prevalence of seizure disorder due to degenerative phase was 0.14 (95%CI 0.08-0.26) per 1,000 population. The study population in these studies included all age group. We studied the incidence of seizures due to degenerative phase of NCC in a cohort of school children accessing education in government primary schools in south India.

METHODS

The study cohort included children accessing education in 18 Government Primary School in five mandals (revenue division) in Hyderabad district, Telangana State, a state in India. These schools were randomly selected from among 250...
schools adopted by NICE Foundation, Hyderabad, under its School Health Program. On the date of start of study, January 1, 2006, there were 7,408 children aged between 5-15 years were on rolls. This cohort was followed for the incidence of new-onset seizure through first standard to fifth standard, study period January 1, 2006 and December 31, 2012. Students admitted in the subsequent years were excluded from the study. Children with febrile seizures were excluded from the study. This study has the approval of Institute’s Ethics Committee, CARE Hospitals Hyderabad.

Children with new-onset seizures were identified by the pediatrician in the School Outpatient Clinics run by the NICE foundation and referred to the Neurology Department, CARE Hospitals, Hyderabad, for further evaluation and management. Help of school teachers and coordinators was taken to identify any child with new-onset seizures who did not attended the School Outpatient Clinics. All the children were clinically evaluated in detail. The data collected included: demographic details, date of onset of first ever seizure, seizure semiology (eye witness account), neurologic findings, EEG features (40 minutes record), and findings on contrast computed tomography (CT) brain done within one week of the event seizure.

Diagnostic clinico-radiological criteria for NCC proposed by Del Brutto et al. were used for the diagnosis of NCC.\textsuperscript{14} CT features compatible with a diagnosis of SCG included: single small (<20 mm), well defined lesion, contrast-enhancing (closed ring, disc, or nodular type) with or without peri-lesional edema and associated with minimal mass effect and no midline shift.\textsuperscript{15} Criteria proposed by International League Against Epilepsy (ILAE) Commission were used to categorize seizures due to SCG under acute symptomatic seizures.\textsuperscript{1,4} Seizure type was classified into generalized and focal onset using the new 2017 seizure classification.\textsuperscript{16}

SCG has an enduring predisposition for seizure recurrence for the period of resolution of the CT lesion.\textsuperscript{15,17,18} All children received antiepileptic drugs (AEDs) mostly monotherapy for the period of resolution of the lesion on follow-up CT. NICE Foundation provided, mostly standard AEDs free of cost. The systematic review suggests that cysticidal agents hasten the resolution of this lesion, thus reducing the period needed for AED treatment.\textsuperscript{15} For these reasons, all children received a course of cysticidal drug, albendazole (15 mg/kg x 4 weeks)\textsuperscript{19} and short course of oral prednisolone (1mg/kg) with tapering dose over 4 weeks. Children were followed at an interval of three months or whenever required. During the follow-up, the data collected included: seizure freedom or recurrence, drug adherence, and adverse drug events. First follow-up contrast CT was done at 6 months in all the children. In children with non-resolution of the CT lesion, subsequent scans were done at 3 to 6 months intervals.

The Foundation support for this study included: (1) identifying all the children with new-onset seizures and referring them for further management to Neurology Outpatient Clinic, CARE Hospitals; (2) bearing the costs of all investigations; (3) providing AEDs free of cost; and (4) allowing access to the school records.

Statistical analysis

The average annual incidence rate (AAIR) was calculated from that of the seven consecutive years (January 2006 to December 2012). The 95% confidence intervals (CI) of the incidence were calculated assuming a Poisson distribution for the observed cases.

RESULTS

The number of children registered on rolls on the date of start of the study (January 1, 2006) was 7,408; 3297 (44.5%) boys and 4111 (55.5%) girls and age ranged between 5 and 15 years. All the children were from low socio-economic strata, mostly from the surrounding slums with stray pigs strolling around the areas of domicile. During the study period, 58 children had new-onset seizures. This included 21 (36.2%) children with new-onset acute symptomatic seizure and 37 (63.2%) children with new-onset unprovoked seizures. The aetiology of new-onset acute symptomatic seizures included: degenerative phase of NCC in 19, brain tuberculoma in 1 and cerebral venous thrombosis in 1. The aetiology of unprovoked seizures included: focal structural lesion in 9, genetic or probable genetic in 11, and unknown cause in 10.

Clinical characters

In all the 19 children with seizure disorder due to degenerative phase of NCC, contrast showed SCG. The mean age of children with SCG was 9.42 years (7-13 years) and the gender distribution was 8 boys and 11 girls. The common seizure type was focal onset motor. (Table 1)
Incidence

The average number of cases per year was 2.7. The crude AAIR of seizure disorder due to SCG was 36.64 (95% CI 22.1 – 57.2) per 100,000. For age-specific incidence children were divided into two groups: 5-10 years and 11-15 years. Age-specific AAIRs for the age group 5-10 years was 30.95 (95% CI 16.5-52.9) per 100,000 and for the age group 11-15 years it was 60.88 (95% CI 22.3-132.5) per 100,000 and gender-specific AAIR for girls was 34.75 (95% CI 16.7-63.9) per 100,000 and for boys was 39.00 (95% CI 17.8-74.0) per 100,000 (Table 2).

Treatment and follow-up

All children received AED monotherapy, mostly carbamazepine. Five children had breakthrough seizures despite good drug adherence; in 3 at 3 months, in 1 at 4 months and in 1 at 12 months. AEDs were withdrawn in all the children, with the resolution of the lesion in the follow-up contrast CT scan (in 14 children at 6 months, in 4 children at 9 months, and in 1 child at 18 months). None of the children had recurrence of seizures during the follow-up period of 1 to 5 years.

DISCUSSION

Degenerative stage of NCC is one of the common causes of acute symptomatic seizures in children in India.\textsuperscript{20,21} In this study all the children had SCG on the contrast CT scan. The AAIR of seizure disorder due to SCG was 36.64 (95% CI 22.1-57.2) per 100,000. Focal onset seizure was the common seizure type. Children in this cohort were from low socioeconomic strata and from slum areas with poor hygienic environment and pig population. There were no incidence studies on seizure disorder due to SCG for comparison. In Latin American countries, the estimated median NCC (all evolutive stages) proportion among children with seizure disorder was 3.6 per 1,000 (95% CI: 1.4-6.9).\textsuperscript{22} SCG is the most frequent presenting form of NCC in India.\textsuperscript{15} In a hospital-based study in south India, all evolutive stages of NCC accounted for 51% of the etiologic spectrum in 558 children with focal seizures, SCG for 16.5%.\textsuperscript{20} In other endemic countries for NCC, SCG accounts for about 20% of all cases of active NCC.\textsuperscript{23,24}

Most often acute symptomatic seizures are unlikely to recur unless the underlying causal condition recurs.\textsuperscript{25} Seizures in the active phase of central nervous system (CNS) infections can occur beyond seven days, with persistent clinical or laboratory findings.\textsuperscript{4} There is a mounting evidence from the observational studies to suggest that seizure disorder due to the degenerative stage of NCC, in particular due to SCG has an

### Table 1: Seizure type by ILAE 2017 seizure classification in the 21 children with acute symptomatic seizures

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=21 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. <strong>Focal seizures</strong></td>
<td></td>
</tr>
<tr>
<td>Focal aware motor onset seizures</td>
<td>2 (9.5)</td>
</tr>
<tr>
<td>Focal impaired awareness motor to bilateral tonic-clonic</td>
<td>12 (57.2)</td>
</tr>
<tr>
<td>II. <strong>Unknown onset motor seizures</strong></td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>III. <strong>Generalized – tonic-clonic</strong> (in any combination)</td>
<td>2 (9.5)</td>
</tr>
</tbody>
</table>

### Table 2: Acute symptomatic seizures – epidemiology

<table>
<thead>
<tr>
<th>Variable</th>
<th>Average Annual incidence per 100,000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute symptomatic seizures</td>
<td>40.50 (25.1-61.9)</td>
</tr>
<tr>
<td>Solitary cysticercus granuloma</td>
<td>36.64 (22.1-57.2)</td>
</tr>
<tr>
<td>• Age specific (5-10 years)</td>
<td>30.95 (16.5-52.9)</td>
</tr>
<tr>
<td>• Age specific (11-15 years)</td>
<td>60.88 (22.3-132.5)</td>
</tr>
<tr>
<td>• Gender specific (girls)</td>
<td>34.75 (16.7-63.9)</td>
</tr>
<tr>
<td>• Gender specific (boys)</td>
<td>39.00 (17.8-74.0)</td>
</tr>
</tbody>
</table>
enduring predisposition for seizure recurrence for the period of resolution of the CT lesion.\textsuperscript{15,20} The natural history of a SCG is quite variable, in a hospital-based study in south India, the proportion of lesions that resolved completely at 6 and 12 months was 36.4\% and 62.5\% respectively.\textsuperscript{27} In the study by Carpio and Hauser, the authors estimated that 50\% of cases would experience a seizure recurrence in the 7-year period following the first symptoms and almost half of these recurrences would occur in the first year. The seizure recurrence was associated with persistent of lesion.\textsuperscript{27} The seizure disorder due to SCG is “self-limiting”, resolves with the resolution of the CT lesion.\textsuperscript{15,17-19} and is “pharmaco-responsive”.\textsuperscript{15,26} Seizure disorder (acute symptomatic seizures) due to certain central nervous (CNS) infections like the degenerative phase of NCC, may have enduring predisposition for seizure recurrence. These patients may need long-term AED prophylaxis for the period of resolution of the pathology. It may be appropriate to subclassify seizure (acute symptomatic seizures) disorder due to CNS infections into “those with enduring predisposition for seizure recurrence” and “those without”. Such a classification has clinical implication, as in patients with enduring predisposition for seizure recurrence institution of AED prophylaxis may be appropriate to avoid seizure-related adverse effects including stigma and SUDEP. Other infective CNS lesions associated with enduring predisposition for seizure recurrence include CNS tuberculoma.\textsuperscript{29,30}

In the recent ILAE 2017 classification of epilepsies\textsuperscript{34}, the concept of an infectious etiology is that it directly results from a known infection in which seizures are a core symptom of the disorder. The ILAE Commission categorized seizure disorder due to NCC under focal epilepsy due to infectious etiology.\textsuperscript{31} Conceptually epilepsy is a disorder of the brain characterized by an enduring predisposition to generate unprovoked epileptic seizures.\textsuperscript{32} By this definition of epilepsy, it may not be appropriate to classify the seizure disorder due to SCG under epilepsy due to infectious etiology, though seizures are the core symptom of the lesion and the lesion has an enduring predisposition for seizure recurrence.\textsuperscript{15,27}

The findings in this study have a public health importance. Children living in the slum areas with poor hygienic environment and pig population in this part of the world are at a greater risk of developing seizure disorder due to NCC. This cohort reflects the real-world situation of epilepsy care in resource poor countries, particularly countries endemic to NCC. Seizure disorder due to all the evolutive stages is potentially preventable by appropriate public health measures.

The major limitations of the study are: (1) the study cohort was highly selective; children were from low socioeconomic strata and from slums with high risk for tape worm infestation; and (2) small study sample. The observations in this study may not be generalizable.

In conclusion, this study suggests that the incidence of seizure disorder due to degenerative phase of NCC would likely to be high in child population with high risk for NCC. Seizure disorder due to SCG is self-limiting and needs AEDs for the period of resolution of the lesion on repeat contrast CT.

**DISCLOSURE**

Financial support: None

Conflict of interest: None

**REFERENCES**


