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Predictors of refractory epilepsy in North India: A case–control study

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ABSTRACT

The study was done to identify the predictors of refractory epilepsy in the North Indian population attending a tertiary care centre. This case–control study from August 2006 to December 2008 enrolled 200 consecutive patients of intractable epilepsy and 200 age matched controls with well controlled epilepsy. The factors which were significant in univariate analysis were age of onset before fourteen years (OR 7.92), partial seizures (OR 6.27), presence of neurological deficits (OR 19.68), perinatal insult (OR 11.00), delayed milestones (OR 13.93), history of CNS infection (OR 7.45), febrile seizures (4.33), high initial seizure frequency of more than one per month (OR 14.26), non response to first Anti Epileptic Drug (AED) (OR 6.71) and abnormal brain imaging (OR 20.47). On multivariate analysis significant predictors were radiological evidence of structural cerebral abnormality (OR 20.47), non response to first AED (OR 19.21), delayed mile stones (OR 9.09), high initial seizure frequency of more than one per month (OR 6.71), partial seizure type (OR 6.27), febrile seizures (OR 5.66) and age of onset before fourteen years (OR 3.09). It is thus possible to identify a certain profile of patients with epilepsy who are likely to be refractory to medical therapy. These observations would be useful in selecting patients early for evaluation in Northern India where a high surgical treatment gap exists.

1. Introduction

It is estimated in various studies that the overall prevalence of epilepsy in India is 5.59–10 per 1000.[1–3] New onset epilepsy has a good prognosis, only 10–20% of the patients develop medically intractable epilepsy (MIE).[4,5] Studies have shown that addition of a second anti convulsant drug in patients with intractable epilepsy, controls seizures in an additional 10–25% of cases with chances of increased toxicity. Different risk factors have been associated with intractable epilepsy. Berg et al.[6] reported a history status epilepticus, infantile spasms, neonatal seizures, microcephaly to be associated with MIE. Kwan and Brodie[7] found patients having many seizures before treatment and inadequate response to initial treatment are likely to have refractory epilepsy. Similarly Kwong et al.[8] observed abnormal neurologic status and early breakthrough attacks after treatment initiation were predictors of MIE. Gururaj et al.[9] in their study population reported that developmental delay, neurological deficits, high frequency of seizures at onset and an abnormal brain imaging were associated with intractability. An earlier study done in the pediatric population in India by Singhvi et al.[10] found neuro infections to be a leading cause of intractable epilepsy.

However, the magnitude of MIE in India is unknown. Whether this can be predicted early on in the evolution of epilepsy is unknown and there is limited data available specifically addressing the risk factors and predictors associated with medically refractoriness. Besides, predictors of intractable epilepsy in an Indian population may be different in view of different etiologies in India compared to a developed country. Early identification of patients who are at high risk of developing intractable epilepsy would be essential in parental counseling and selecting patients for more intensive investigations and treatment for example early consideration of surgery and to prevent toxicity from a overdose and costs of AED, and useless poly therapy. It would be especially useful in a resource poor setting where a small number of neurologists deal with both pediatric and adult epilepsy patients and there exists a large treatment gap both medical and surgical. We therefore conducted this study in the realistic setting of this mixed population aiming to find early predictors of MIE.

2. Subject and methods

The present prospective case–control study was undertaken at a tertiary referral centre in India from August 2006 to December 2008 in consecutive patients between ages of 2–60 years who

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attended our epilepsy clinic. We included pediatric and as well as adult patients since adult neurologists in our country also attend many pediatric patients with epilepsy, especially those with MIE. This age range was defined to find controls easily. A total of 200 consecutive persons of intractable and 200 of well controlled epilepsy were included in this study.

Cases were defined as having intractable epilepsy when they had two or more seizures per month for a period of more than two years with two or more antiepileptic drugs (AEDs)[11] attending the intractable epilepsy outpatient clinic. Cases were consecutively recruited. We excluded patients whose seizures were poorly controlled but in whom compliance was poor, those with sub therapeutic serum drug concentration and those with non-epileptiform events. Compliance was determined by questioning the patients. Compliance was termed good if the patient answered: 'Yes, according to the given instructions' to the question: 'Have you taken your drugs regularly?' History of irregular medication breaks or discontinuation of medication or self manipulation of doses or intervals of dosing were interpreted as poor compliance. Whenever in doubt, the information was confirmed by drug levels.

Controls consisted of consecutive age matched patients, who had epilepsy and were attending the epilepsy outpatient clinic but had no seizures of any type for a minimum of two years while receiving the same dose of anti epileptic drugs. Patient with febrile seizures, acute neurological infection, space occupying lesions (SOL) or neurodegenerative diseases were excluded from the study.

Both cases and controls had a regular three monthly follow up in the respective outpatient clinics.

The patients were recruited by UPP, MT and MVPS based on the inclusion and exclusion criteria. There were monthly consensus meeting amongst the assessors. Patients and their families were interviewed and relevant records relating to the patient's illness were reviewed. The following data was obtained in a structured questionnaire, age of onset of unprovoked seizure, initial seizure type, number of seizures at baseline before start of treatment, and onset seizure frequency (first one year), present seizure frequency, longest seizure free interval and details of AEDs and response to first AED, any history of status epilepticus (SE) before or as a part of presentation, febrile convulsion, perinatal insult,[12] delayed mile stones, head trauma or any family history of seizure disorder. Other clinical parameters included mental retardation (defined as IQ of less than 70) or behavioral abnormality, focal motor deficits and neuroimaging. Computed tomography was done in all patients, epilepsy protocol magnetic resonance imaging was performed in all patients with MIE. Previous relevant medical records were reviewed and additional studies were carried out as clinically indicated EEG, VEEG, Interictal and Ictal SPECT (SISCOS—Ictal and Interictal SPECT subtraction). The syndromic diagnosis was made according to the revised classification by ILAE, 1989.[13] Cases and controls were classified according to the risk factors and clinical features in each group as well as epilepsy syndromes.

Ethical clearance was taken from Institutional Ethical Committee. The study was conducted after taking written informed consent from all patients, explaining the nature and need of the information.

2.1. Statistical analysis

We used chi square test for comparison of categorical data and Mann–Whitney test for comparison of non parametric continuous data. Odds ratios (OR) and 95% confidence interval were calculated. Potential interaction between factors was examined by logistic regression method. Statistical calculations were performed with use of SPSS software (version 16). A P value of <0.05 was considered significant.

3. Results

This case–control study was conducted from August 2006 to December 2008. 200 patients of intractable epilepsy (case) and 200 patients of well controlled epilepsy conforming to eligibility criteria were included in this study.

A comparison of intractable and well controlled groups showed several differences (Table 1). Age of onset varied from 1 year to 55 years and majority of patients in the intractable group had onset of seizures before the age of 14 years. Most of the cases and controls were males (71% and 64% respectively). This is due to the socio cultural referral bias of families of giving better medical attention to male subjects. In intractable group 83% of patients had partial seizures, 7% had a generalized onset, 6.5% had myoclonic seizure at onset and 3.5% had presented with multiple seizure types, where as in the well controlled group 56.5% patients presented with partial seizures, generalized seizure was the clinical presentation in 30.5% patients, and 12.5% patients had myoclonic seizures as the initial presentation. Status epilepticus was seen in 7% of patients in the intractable epilepsy group and 2.5% in patients with good control. History of delayed mile stones was found in 18% of patients of intractable epilepsy and only 1% in well controlled group, similarly history of perinatal insult was found in 23% of patients. 10% of patients of intractable group had history of febrile seizure where as only 2.5% patients of control had febrile seizures. More than 90% patients in the well controlled group had favorable response to first AED where as only 10% of the intractable group had reported initial favorable response to first AED. Abnormal brain imaging was seen in 79% of the patients in intractable group and only 39% of the patients in well control group. Post infectious causes, predominantly neurocysticercosis (NCC) were associated in 13% of the intractable group. 83% of the patients of intractable group had history of high seizure frequency (more than one per month) in their initial two years of onset of seizures where as only 25% of patients in the well control group had a frequency of more than one per month. However family history of seizures, history of head trauma and behavioral disorders were not found to be significantly different between the two groups. The present study is tertiary care hospital-based wherein independent predictors of intractability showed strong univariate association between the age of onset before the age of 14 yrs, high initial seizure frequency, partial seizure types, presence of neurological deficits, perinatal insult, history of status epilepticus, febrile convulsions, history of delayed mile stones, febrile encephalopathy, non response to first AEDs and presence of known radiological epileptogenic structural lesions (Table 2). These variables were factored for multivariate analysis.

The cases and controls were categorized according to the ILAE, 1989 classification,[13] and further subdivided into age groups of <14 years and ≥ 14 years. The maximum numbers of patients were

Table 1
Characteristics of intractable and well controlled seizure.

	Case ($n=200$)	Control ($n=200$)	P-Value
Age at onset of seizures	5.18 ± 7.62	5.62 ± 9.18	0.20
Gender			
Male	142(71%)	128(64%)	0.13
Female	58(29%)	72(36%)	
Initial seizure type			
Partial onset	166(83)	113(56.5)	<0.05
Generalized	14(7)	61(30.5)	
Myoclonic	13(6.5)	25(12.5)	
Mixed	7(3.5)	1(0.5)	
Present seizure frequency			
1–4/month	74(37%)		
1–6/week	48(24%)		
Daily	78(39%)		