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Original Research Article

Childhood epilepsy: a study of etiological and prognostic factors for failure of remission at a tertiary care government hospital, a prospective COHORT study

Pinto Nathaniel[1], D'Lima Annely[2]*, Pinto Jessica[3], Maria Piedade Silveira[2]

[1]Manipal Hospital, Goa, India
[2]Department of Pediatrics, Goa Medical College, Bambolim, Goa, India
[3]DEIC, North Goa District Hospital, Goa, India

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***Correspondence:**
Dr. D'Lima Annely,
E-mail: annelydlima@yahoo.com

ABSTRACT

Background: This study was carried out to identify early predictive factors of medically intractable childhood epilepsy. We also aimed to explore the prognosis in terms of remission with anti-epileptic drug (AED) treatment and to identify the predictors of poor prognosis (failure of remission) in relation to the control of epilepsy.
Methods: Children with epilepsy were included. Information recorded at the time of the first visit: age, gender, age at onset of epilepsy, patient history, AED treatment and Seizure control. Details of general and neurological examination were also recorded. These patients were then followed up over a one-year period to assess for remission and patient compliance with medication.
Results: A total of 239 patients between the ages of 1 month and 12 years were diagnosed with epilepsy according to the International league against epilepsy (ILAE) classification. Of these 213 patients followed up. Among these, 126 (59.1%) patients attained remission while 87 (40.8%) patients failed to attain remission. Age of onset less than 1 year, microcephaly, developmental delay at diagnosis, a definite etiology, infantile spasms, structural abnormality detected on neuroimaging, abnormal electro-encephalography (EEG) and the requirement for polytherapy to achieve seizure control were found to be associated with a poor prognosis (failure of remission).
Conclusions: The poor prognostic factors for childhood epilepsy at diagnosis are age of onset <1 year, microcephaly, infantile spasms, structural abnormality on neuroimaging and abnormal EEG. At follow up patients requiring an add-on AED to pre-existing treatment regimen is associated with a lesser likelihood of achieving remission.

Keywords: Pediatric epilepsy, Prognosis, Neuroimaging, EEG, Follow-up

INTRODUCTION

The prevalence of active epilepsy in India is 5.59 per 1000 population with no gender or geographical difference.[2] It has been estimated that 3% to 5% of the general population experience one or more seizures at some time during their lives.[3] In many patients, seizures are well controlled with AEDs, but approximately 25% to 30% continue to experience recurrent seizures despite optimal therapy.[4] These patients have medically refractory epilepsy. Several prognostic factors have been identified, such as seizure type, neurologic and psychiatric deficits, electroencephalographic abnormalities, and acquired brain lesions.[5-7] Several studies have shown that one of the most important risk factors for poor prognosis (failure of remission) is related to the type of epilepsy.[5-7] The early identification of intractability may be useful in designing alternative therapies such as anti-inflammatory agents or surgical

interventions. It would also be essential in parental counselling and individual support.[8]

METHODS

The study was carried out at the Goa medical college and hospital a tertiary care government hospital in West India. All the patients who were diagnosed to have epilepsy as per the new definition of epilepsy according to the ILAE classification of epileptic seizures were included in the study.[1] The study was approved by the institutional ethics committee. The study was a retrospective observational study. The patients were recruited in the study over a period of 1 year from 1st September 2015 to 31st September 2016. The patients were selected by simple random sampling. These patients were then followed up for a period of 1 year, until 31st September 2017. At each follow-up visit the patients were assessed for compliance towards the medications and seizure control. Also, any associated co-morbidities like visual and hearing impairments and delayed development were appropriately managed by referring the patient to the respective specialty. Informed consent for participation in the study was obtained from the parent or legal guardian of each patient.

The following information was registered on a case-record form at the time of the first visit: age, gender, age at onset of epilepsy, patient history, seizure type/epilepsy syndrome according to the ILAE classification of epileptic seizures, EEG and neuro-imaging data, AED treatment and seizure control. A detailed general examination and neurological examination were then carried out by the principal investigator and the findings were recorded in a case sheet.

These patients were then followed up over a 1-year period to assess for remission, patient compliance with medication and any side-effects towards the medications were also noted. 1) Monthly if seizures were not controlled (failed to achieve remission) and 2) Three monthly if seizures were controlled (achieved remission).

An EEG was performed on all the patients at the time of inclusion in the study to facilitate classification of the epilepsy. The EEG was performed including standard stimulation procedures (photic stimulation and hyper-ventilation). Magnetic resonance imaging (MRI) of the brain was performed using a high resolution 3.0 Tesla MRI machine. All MRI scans were conducted by a specialized neuro-radiologist using standard MRI protocols to screen for underlying structural abnormalities.

Inclusion criteria

Inclusion criteria included children aged 1 month to 12 years presenting to Neurology clinic with epilepsy.

Exclusion criteria

Exclusion criteria excluded children who were diagnosed with Febrile seizures and acute symptomatic seizures were excluded from the study.

Definitions

According to the ILAE classification of epileptic seizures, seizure types were categorized into generalized (tonic, clonic, or tonic-clonic) or focal (simple or complex partial) and spasms. The etiologies of epilepsy were grouped into genetic, structural, metabolic, post infectious sequelae and unknown cause. Remission was defined as an achievement of at least one year free of seizures.

The patients at follow-up were the categorized as ‘good outcome’ meaning seizure free for at least 1 year during follow-up and ‘poor outcome’ meaning failure to achieve good seizure control (remission) for at least 1 year during the follow-up period. Seizure control was assessed based on the year preceding the patient's last visit

Treatment

Patients were prescribed AEDs based on patient profile (age, sex), seizure type and drug characteristics (efficacy, side effects and drug interaction profiles). AEDs prescribed to the patients included sodium valproate, carbamazepine, levetiracetam, oxcarbazepine, topiramate, clobazam and lamotrigine. Monotherapy was tried initially in all patients. In patients who failed to achieve good seizure control, the AEDs were first titrated to the maximum tolerated dose, before prescribing an add-on. Combination therapy was commenced if the first AED was well tolerated but failed to achieve seizure control. Compliance with the treatment regimen was monitored during the follow up visits.

Statistical analysis

All analysis was performed using SPSS 13.0 software (IBM, Chicago, USA). Data was stored in an electronic database and analysis was based on all the information available at the time of the patient's first visit. They were first assessed by examining the univariate relation between each variable (characteristics of patients and epilepsy) and seizure control. For categoric variables, the comparison of percentages according to treatment response (seizure control) was made using chi-square analysis or Fisher's exact test if chi-square was not a valid test. The odds ratio (OR) and 95% confidence interval (CI) were calculated. The two tailed $p<0.05$ was considered as statistically significant.

RESULTS

A total of 239 patients between the ages of 1month and 12 years were diagnosed with epilepsy according to the

ILAE classification during the study period from 1st September 2015 to 31st September 2016. These patients were then followed up for a period of 1 year, until 31st September 2017. Among the 239 patients included in the study, 22 patients were lost to follow up and 4 patients expired during the course of the study period. At the end of the follow up period of 1 year the data of 213 (89.12%) patients was available for analysis.

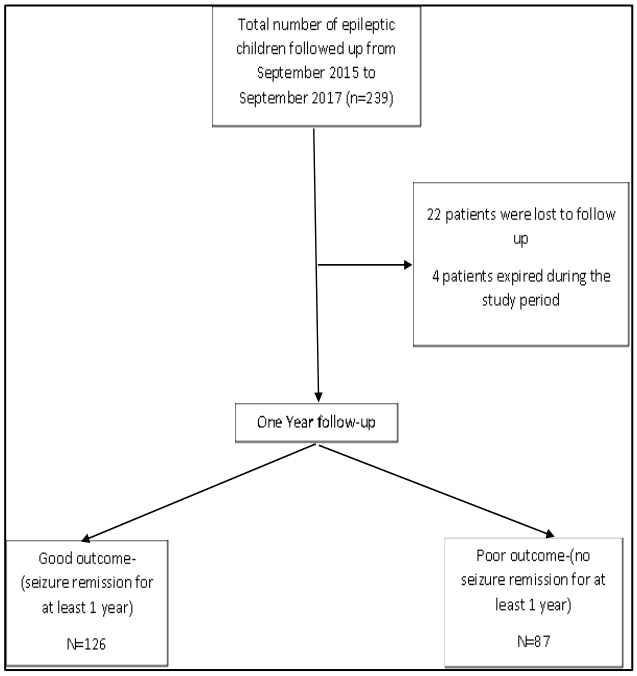

Figure 1: Participants included in the study.

Age of onset

Among the study population 94 (44.1%) patients developed seizures during their first year of life as against 119 (55.9%) who had seizures beyond one year of age. Among those with seizure onset before 1 year of age, 48 (55%) had a poor outcome (failure of remission) ($p<0.05$), as compared to children who had their first seizure after 1 year of age.

Sex

The 131 (61.5%) of the study population comprised of males, the rest were females. A larger percentage (64.8%), of males achieved seizure remission as compared to only 35.2% of females. This was not statistically significant ($p=0.317$).

Etiology

In this study idiopathic epilepsy was the commonest with 124 (58.2%) patients wherein the cause of seizures could not be identified. Also, idiopathic epilepsy was found to have the best prognosis in terms of remission, with 90 (71%) among these achieving good seizure control. The children who were found to have a structural abnormality on neuroimaging comprised of 66 (30.9%) of the study population. Among these 43 (65%) had failure of remission (poorly controlled seizures). This was found to be statistically significant, $p<0.05$. A very small proportion of the study population, 6 (2.8%) were found to have a genetic or metabolic etiology contributing to seizures. Among these 4 (66.7%) of patients failed to achieve remission. This small number is probably because genetic testing is not routinely done as part of diagnostic work-up.

Table 1: Analysis of patient characteristics, type of epilepsy and seizure control.

Patient characteristics	Remission (126)		No remission (87)		P value
	N	%	N	%	
Age (years)					
<1 year	46	36.5	48	55.2	0.007
Gender					
Male	81	64.3	50	57.5	0.317
Female	45	35.7	37	42.5	
Semiology					
Generalized	97	76.9	63	72.4	0.446
Focal	28	22.2	18	20.6	0.794
Spasms	1	0.79	6	6.8	0.015
Etiology					
Genetic	2	1.6	0	0.0	0.239
Structural	23	18.3	43	49.4	0.001
Infective	3	2.4	3	3.4	0.644
Metabolic	2	1.6	2	2.3	0.707
Idiopathic	90	71.4	34	39.1	0.645
Neurocutaneous markers	7	5.6	6	6.9	0.688
Microcephaly	24	19.0	39	44.8	0.009
Developmental delay	97	77.0	27	31.0	0.451
Polytherapy: >2 drugs	12	9.5	58	66.7	0.001
Abnormal EEG	59	46.8	59	67.8	0.002
Abnormal neuroimaging	29	23.0	50	57.5	0.001

Semiology

The seizure type or epilepsy syndrome was classified according to the ILAE classification of epileptic seizures. Generalized seizures were found to be the most common semiology seen in 160 (75.1%) as compared to focal seizures which were seen in 46 (21.6%) patients. Among those with generalized seizures 63(72.4%) failed to achieve remission. Among those with focal seizures 18 (20.6%) failed to achieve remission. This however, was not statistically significant. The semiology with the worst prognosis as far as seizure control was Infantile spasms with the highest rate of recurrence. Among the 7 patients with infantile spasms only 1 achieved remission. This was found to be significant with a $p=0.015$.

Neurocutaneous markers

The prevalence of neurocutaneous markers was relatively low in the study population. Only 13 (6.1%) of the patients were noted to have some type of neurocutaneous marker. Only 1 patient was diagnosed to have tuberous sclerosis. The patients with neurocutaneous markers were found to have poor prognosis as far as seizure control with 6 (46%) of the patients failing to achieve remission. This however was not statistically significant, p=0.68.

Microcephaly

At the first visit on general examination, microcephaly (head circumference of less than third centile or less than 2 SD as per CDC charts was noted to be a prominent finding in 63 (29.6%) patients. Among the children who were noted to have microcephaly, 39 (61.9%) had poor seizure control i.e., they failed to achieve remission, p<0.05.

Developmental delay

Developmental delay was defined according to the developmental quotient (DQ) assessed according to the milestone history. Patients with a DQ of less than 70 in two or more domains were considered to be developmentally delayed. Among the study population 124 (59.2%) patients had a DQ of less than 70. Among these 27 (21.8%) had failure of remission in terms of seizure control.

EEG and neuroimaging findings

The 118 (55.4%) of the children included in the study had abnormal EEG findings. Of these children, 59 (67%) had failure of remission (p<0.05). Fifty (56.8%) of children with poor outcome had associated abnormal neuroimaging (p<0.05).

Efficacy of AED therapy

Among 213 patients with newly diagnosed epilepsy, 125 (58.6%) patients were seizure free for 1 year during the follow up period. Of these 125 patients who achieved good seizure control 113 (90.4%) patients did so with a single AED while 12 (9.6%) patients required the use of two or more AEDs to achieve remission. Eighty-seven (40.9%) patients however, continued to have seizures despite the use of two or more antiepileptics (Table 2).

Table 2: Efficacy of AED therapy.

Number of AEDs	Remission (126)		No remission (87)	
	N	%	N	%
1	84	66.6	5	5.74
2	30	23.8	24	27.5
>2	12	9.52	58	66.6

Analysis of predictors related to poor seizure outcome

At the end of one-year follow-up 87 patients never achieved remission and were classified in the poor outcome group and remaining 126 patients were classified in the good outcome group.

Univariate logistic regression analysis of these two groups of patients demonstrated that generalized seizures and infantile spasms, presence of microcephaly, EEG and neuroimaging abnormalities, age of onset less than 1 year and polytherapy were associated with a poor outcome.

DISCUSSION

Two hundred and thirty-nine children who were diagnosed with epilepsy as per the ILAE classification were included in the study. Of these 213 were followed up for a period of 1 year after inclusion, giving us a follow-up percentage of 89.12%. During this 1year, 126 (59.1%) children achieved remission, whereas 87 (40.9%) children failed to achieve remission. An epidemiological review by Beigi indicates that in several studies it has been shown that among newly diagnosed patients of epilepsy 55-68% of cases tend to achieve prolonged seizure remission.[9] Cockrell et al in his study which followed up children with epilepsy for a period of 9 years found that the overall prognosis in terms of seizure remission was good with most patients (>90%) achieving at least a 1-year remission period; by 9 years, 86% can expect to have achieved a 3-year remission and 68% can expect to have achieved a 5-year remission.[10]

Among our study population it was found that 94 (44.1%) patients had onset of epilepsy before the age of one year with 48 (51%) of these failing to achieve remission (p<0.05). Seizures occurring in the first year of life might have an evolution ranging from benign to severe with variable prognosis, particularly those categorized as epileptic encephalopathies where the prognosis is poor.[11] Chawla et al, Ohtsuka et al and Yilmaz et al all in their studies, support the hypothesis that early-onset seizures indicate a predisposition to epileptogenesis in the developing brain, which can cause medical intractability.[8,12,13] Evaluation of the seizure frequency in our study revealed that, children who had the first seizure after the 1st year of life were found to have a better outcome in terms of seizure control as compared to those who developed seizures in infancy. Thus, onset of seizures in the first year of life is a risk factor for poor prognosis.[14,15]

In this study idiopathic epilepsy was the commonest with 124 (58.2%) patients wherein the cause of seizures could not be identified. This was found to have the best prognosis in terms of remission, with 90 (71%) among these achieving good seizure control. The children who were found to have a structural abnormality on neuroimaging comprised of 66 (30.9%) of the study population. Among these 43 (65%) had failure of

remission (poorly controlled seizures). This was found to be statistically significant, p<0.05 which was similar to the results obtained by Semah et al and Yilmaz et al where abnormal magnetic resonance imaging findings occurred significantly more often in the group with intractable epilepsy.[5,13] Wirelle et al also concluded that the prognosis for seizure remission is much grimmer in those with abnormal neuroimaging.[7] A very small proportion of the study population, 6 (2.8%) were found to have a genetic or metabolic etiology contributing to seizures. Among these 4 (66.7%) of patients failed to achieve remission. This small number is probably because genetic testing is not routinely included as part of the diagnostic work-up. The strongest prognostic predictor for seizure recurrence in patients with epilepsy is the etiology of the epilepsy.[16] Idiopathic epilepsy enjoys a better chance of seizure remission than symptomatic or cryptogenic epilepsy. A documented etiology has been found to be a significant predictor of intractability or failure of remission.[16] Specific syndrome / known etiology, high initial seizure frequency, and focal EEG slowing were noted to be early predictors of poor prognosis.[16] A documented etiology of the seizure and an abnormal (epileptiform and/or slow) electroencephalogram (EEG) pattern are the 2 most consistent predictors of recurrence.[9] Similar results were also noted in our study, 118 (55.4%) of the children included in the study had abnormal EEG findings. Of these children, 59 (67%) had failure of remission (p<0.05). EEG abnormalities were also observed to be prognostic significance in different studies, although the type of abnormality which predicted poor prognosis differed.[12,13,17]

The relationship between semiology and the prognosis of seizures was also analysed. Generalized seizures were found to be the most common semiology seen in 160 (75.1%) patients as compared to focal seizures which were seen in 46 (21.6%) patients. Among those with generalized seizures 63 (72.4%) failed to achieve remission. Among those with focal seizures 18 (20.6%) failed to achieve remission. This however, was not statistically significant. Focal seizures are also correlated with a higher risk of recurrence.[9] History of acute symptomatic seizures prior to the first unprovoked seizure has been found to increase the risk of relapse, while evidence is inconclusive or lacking for sex, age, and status epilepticus.[9] Infantile spasms were seen in 7 of the study population out which 6 failed to achieve remission (p<0.05). Similar findings were reported in the study carried out by Yilmaz et al and Berg et al.[13,17]

Children noted to have microcephaly and developmental delay at the initial presentation were found to have poor prognosis at follow up (p<0.05). Studies by Berg et al, Ohtsuka et al and Yilmaz et al identified mental and motor deficiencies as significant predictors of intractability.[12,13,17] Also, Abdel-Salam et al noted an inverse correlation between severity of epilepsy and IQ.[18]

Among the study population, patients who required an addition of another AED to the existing treatment regimen had a lesser likelihood of achieving remission (p<0.05). This was similar to the findings of Atugonza et al wherein the study participants managed with multiple AEDs were almost four times more likely to have poor seizure control compared to those using monotherapy.[19] Malik et al also concluded that the response to the first antiepileptic drug was also a powerful prognostic factor.[14] Poudel et al also concluded that when seizure does not respond to one anticonvulsant drug, i.e., the need of polytherapy is the strongest predictor of poor outcome.[6]

Limitations

A longer follow up period would be ideal for better assessment of seizure control. Identification and classification of epilepsy syndromes would have given more information and provided us better assessment on seizure recurrence. The non-availability of video EEG to confirm the semiology of seizures led to dependence on patient's description to confirm the semiology in most cases. Also, a genetic analysis of all the seizure cases would add to the information.

CONCLUSION

The predictors for non-remission of childhood epilepsy at diagnosis are age of onset less than 1 year, microcephaly, infantile spasms, structural etiology, abnormal EEG and neuroimaging findings. At follow up patients requiring an addition of a second AED to the current treatment regimen is associated with a lesser likelihood of achieving remission.

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