Original article

Factors influencing the prognosis of epilepsy in children: A Hospital-based study

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Abstract

Introduction: Epilepsy is a chronic cerebral disorder with many medical and social implications. Predicting prognosis of an individual patient is imperative to tailor the treatment strategy and to improve the quality of life.

Objective: To study the factors which influence the prognosis of epilepsy in children.

Design: Prospective , observational study

Methods: All consecutive children between 2 to 12 years diagnosed to have epilepsy for atleast 6 months were enrolled. Children with febrile seizures , acute symptomatic seizures and static /progressive neurological disorders were excluded. The demographic characteristics, clinical details and investigations of each subject were recorded. Each child was followed up for a period of 6 months to determine the treatment outcome. Data was analysed using Pearson Chi Square test

Results: The mean age of onset of epilepsy was 6.41 year (SD = 2.69) .Fifty eight children (58%) went into conditional remission, 25 (25%) were treatment resistant and 17 (17%) achieved remission. Major factors associated with poor prognosis were multiple seizures prior to treatment (p=1.12E-14), low TDM levels at 3 months of treatment (p=4.95E-09) and polytherapy (p=4.48E-15). Early age of onset (p=0.0065), generalized seizure (p=0.0069), abnormal birth history (p=0.0028), family history of epilepsy in first degree relatives (p=0.023) and abnormal neuroimaging (p=0.00065) were other factors predicting poor prognosis.

Conclusions: Multiple seizures, generalized seizure , symptomatic epilepsy, early onset of epilepsy, abnormal birth history and abnormal neuroimaging are associated with poor prognosis. Determining prognosis of epilepsy helps in predicting the clinical course and response to treatment.

Key words: Epilepsy, prognosis, factors, children

Introduction

Epilepsy is one of the most common treatable serious neurological disorders of childhood. It is a condition in which seizures are triggered recurrently from brain due to aberrant electrical activity. The prevalence rate in a study in North India was 6.24 per 1000 population. [1] A recent study conducted in Kolkata's urban population showed an annual incidence rate of 27.27 per 100,000 per year. [2] For children with epilepsy, the prognosis is generally good, but 10-20% can have persistent seizures refractory to drugs and those can pose a diagnostic and management challenge. Epidemiological studies showed that up to 70% of patients with epilepsy entered remission, many of them did so early within the first year of treatment. [3]

The term prognosis generally refers to the probability of attaining seizure remission while on treatment and after drug withdrawal. [4] The prognosis of childhood epilepsy has important epidemiological, social and clinical implications. Therefore, determining prognosis is significant not only to the patient but also to his/her family, treating doctor and society. It is important to

predict the likely clinical course of childhood onset epilepsy within a year of diagnosis and starting treatment both in terms of seizure control, clinically relevant intractability and increased risk of death. This could allow for more aggressive treatment with modern anti epileptic drugs and if possibly early neurosurgical intervention in suitable cases. Many factors like etiology, seizure frequency, seizure type and others influence the prognosis of epilepsy.

There are very few studies in literature which have assessed the factors influencing the prognosis of epilepsy in children. Looking at the paucity of the studies and implications of prognosis of epilepsy, we conducted a study with an **objective** to determine the factors influencing the prognosis of epilepsy in children and its correlation with outcome.

Methods

This prospective observational study was conducted over a period of 18 months at a tertiary care centre and teaching hospital. Approval from Institutional Ethics Committee was obtained. Consecutive children between the age group of 2 to 12 years diagnosed to have epilepsy for at least 6 months at enrollment were included. Children with situation related epilepsy (febrile seizures and acute symptomatic seizures) and static or progressive neurological disorder were excluded.

After receiving informed consent, the subjects' demographic characteristics, clinical details of epilepsy, investigations and treatment were recorded in a predetermined proforma. Each child was followed up for a period of 6 months to determine the treatment outcome.The seizure type was classified according to the International League Against Epilepsy (ILAE) 1981. The etiology of epilepsy was classified according to the 1989 ILAE Classification & 2001 ILAE proposal. The age of onset of epilepsy was grouped as early childhood (</=5 years) and late childhood (> 5 years). We recorded the clinical details emphasizing on duration of epilepsy, frequency of seizures prior treatment as 2, 3-5, 5-10 and multiple (>10) episodes, family history of epilepsy in the first degree relatives and abnormal birth history. Serum calcium, blood sugar, EEG and neuroimaging were done in all patients. TDM levels at 3 months of initial treatment were recorded which were categorized as normal, low or high. Treatment r eceived was split as monotherapy (receiving 1 drug) and polytherapy (receiving more than 1 drug).

All the subjects were followed up for 6 months at the end of which treatment outcome was determined. Treatment outcome as regards to seizures was classified into two groups; one as remission (no seizures without drug treatment) plus conditional remission (no seizures under treatment) and second as treatment resistance (seizures even on 2 or more appropriate anti epileptic drugs). These clinically relevant factors of epilepsy were then correlated with treatment outcome.

Data was analysed using Pearson Chi Square test and statistical tool used was SPSS version 13.0. Statistical significance was accepted if *P* value was less than 0.05.

Results

A total of 100 children (n=100) satisfying the inclusion criteria were enrolled. The subjects ranged from 3 years to 12 years; mean and median age were 8.82 year SD = 2.43)and 9.5 years respectively. Male: Female ratio was **1.8** (65 boys, 35 girls). Sixty children (60%) were in the age group of 5-10 years while there were 33 children

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(33%) in >10 yearsand 7 children (7%) in <5 years age group. Abnormal birth history was seen in 27% of children. Family history of epilepsy in first degree relatives was found in 16%. The **mean age of onset of epilepsy was 6.41 year** (SD = 2.69) and median was 7 years. Twenty four (24%) children had their onset of epilepsy between 6-7 years of age and 22(22%) had between 2-3 years.Generalised seizure were observed in 65%, partial in 18% and partial with secondary generalisation in 17% of the subjects.In our study population, 67%had idiopathic and 33% had symptomatic etiology. The **mean duration of epilepsy was 2.37 year** (SD = 1.542) and the median was 2 years. Multiple episodes of seizures were observed in 26% children. EEG was abnormal in 99% and predominant pattern seen on EEG was generalized seizure activity in 64% children followed by focal activity in 24%. Other EEG abnormalities seen were 3 Hz/sec spike and wave (5), centrotemporal spikes (3), hypsarrythmia (2),.Abnormality on neuroimaging was present in 19 (19%) children which included cerebral atrophy (8 children), gliotic scars (7), old infarcts (2), encephalomalacia (1) and frontal porencephalic cyst (1). Mean duration of treatment received in our study population was 2.12 year. Seventy three children were on monotherapy while 27 were on polytherapy. Normal TDM were observed in 88 children, low in 12 and none had high levels. At the end of follow up, 58 children went into conditional remission, 25 were treatment resistant and 17 achieved remission.

Data analysis revealed that association between seizure frequency, drug therapy, TDM levels and the outcome was highly significant. **(Table 1)**. Multiple seizure frequency and children on polytherapy were associated with poor prognostic outcome; *p* value being 1.12E-14 and 4.48E-15 respectively both of which were statistically highly significant. 84.6% of children with multiple seizures were associated with treatment resistance. it was observed that all children with seizure frequency < 3 remitted. Also, 88.9% of children on polytherapy had treatment resistance as compared to only 5.6% on monotherapy. The low levels of TDM was associated with poor prognosis; *p* value was statistically highly significant (*p* = 4.95E-09). It was observed that exclusively all children (100%) with low TDM levels had treatment resistance. It was observed that 100% of children with low TDM had treatment resistance; p value was statistically highly significant (p=4.95E-09) . In this study 88.9% of children on polytherapy had treatment resistance as compared to only 5.3% on monotherapy; p value was statistically highly significant (p=4.48E-15).88.9% of children on polytherapy had treatment resistance as compared to only 5.3% on monotherapy; p value was statistically highly significant (p=4.48E-15).

It was also observed that a statistically significant relation existed between other factors *viz* age of onset of seizure, type of seizure, birth history, family history and the outcome. **(Table 1)** .Treatment resistance was more in children </= 5 years (41%) as compared to > 5 years (14.8%); this difference was statistically significant (p =0.0065).In our study, generalised seizure was associated with more chances of treatment resistance (33.8%) as against partial seizures which was 8.6% with p valu e of 0.0069. . Children with abnormal birth history (48.1%) as compared to children with normal birth history (16.4%) had a higher possibility of treatment resistance and the

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correlation was found to be statistically significant (p =0.0028). In our study, 50% of the study population with family history of epilepsy in first degree relatives had treatment resistance as compared to 20.2% with no family history and the correlation between the two was statistically significant (p=0.023).

TABLE 1 : ***Correlation of factors with treatment outcome***

Parameter	*R/#CR (no./%)	$TR (no./%)	p value	Correlation
Frequency of seizures prior to treatment (episodes)				
1 to 2	29 (100)	0 (0)	1.12E-14	Highly significant
3 to 5	33 (97.1)	1 (2.9)		
5 to 10	9 (81.8)	2 (18.2)		
Multiple (>10)	4 (15.4)	22 (84.6)		
TDM levels at 3 months of treatment initiation				
Low	0 (0.0)	12 (100.0)	4.95E-09	Higly significant
Normal	75 (85.2)	13 (14.8)		
Drug therapy				
Monotherapy	69 (94.7)	4 (5.3)	4.48E-15	Highly significant
Polytherapy	3 (11.1)	24 (88.9)		
Age of onset of epilepsy (yrs)				
<=5	23 (59.0)	16 (41)	0.0065	Significant
>5	52 (85.2)	9 (14.8)		
Seizure type				
Generalised	43 (66.2)	22 (33.8)	0.0069	Significant
Partial	32 (91.4)	3 (8.6)		
Birth History				
Abnormal	14 (51.9)	13 (48.1)	0.0028	Significant
Normal	61 (83.6)	12 (16.4)		
Family history of epilepsy				
Yes	8 (50.0)	8 (50.0)	0.023	Significant
No	67 (79.8)	17 (20.2)		
Neuroimaging findings				
Abnormal	8 (42.1)	11 (57.9)	0.00065	Significant

*R: Remission; #CR: Conditional remission; $TR: Treatment resistance

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Table 2: Prognostic factors and their significance: Comparison of studies.

Prognostic Factors	Present study	Cockrell OC, *et al*	Berg AT, *et al.*	Udani,*et a*l.	.MuhammerAkbar,*et al.*	Ada Geerts, *et al.*
Age of onset of epilepsy	+	NS	NS	+	+	+
Initial seizure frequency	++	NS	+	NS	+	NS
Seizure type	+	+	+	+	NS	+
Seizure etilogy	-	+	+	NS	NS	+
Birth history	+	+	NS	+	NS	+

***++ :** highly significant for predicting prognosis**; +** : Significant factor for predicting prognosis*

--: not significant; NS Not studied

Discussion

Long-term prognosis of epilepsy is favorable in the majority of children, with up to 70% having long-term remission with or without continuation of antiepileptic drugs (AEDs). [5] Whilst most are able to achieve remission, 9-24% of children will run an intractable course, the variation in percent accountable by different definitions. [6] Although patients with medical intractability only represent a minority, a disproportionate amount of resources is required to treat this group. Many factors namely age of onset, gender, etiology, seizure type, frequency of seizure, birth history, family history of epilepsy, neuroimaging , EEG features and drug therapy influence the prognosis of epilepsy. Numerous studies have been conducted to determine the influence of these factors on prognosis of epilepsy.

We found that at the end of our study period 75 (75%) children achieved remission or conditional remission while 25 (25%) were treatment resistant. In studies conducted by Sander, *et al.* [7] , Udani, *et a*l. [8] and Finnish study by Sillanpaa M, *et al* remission was found to be in 60-70% of the subjects which is comparable to our study. However, in the Connecticut study [9] , NGPSE study [10] and Dutch study by Ada Geerts, *et al* [11] remission was 53%, 86% and 90% respectively; which was not comparable to our study probably due to a longer follow up period.

On correlation of our results, we found that seizure frequency prior to treatment, polytherapy, low TDM levels at 3 months of treatment and abnormal neuroimaging were the highly significant factors associated with poor prognosis. Even early age of onset of epilepsy, generalized seizure, abnormal birth history and family history of epilepsy in first degree relatives were other factors of prime statistical significance predicting poor prognosis . Whereas age, gender, etiology of epilepsy and abnormal EEG findings did not have any influence on the prognosis of epilepsy.

In the NGPSE study by Cockrell OC, *et al.* which enrolled 1091 patients, partial seizure, symptomatic etiology and neurological birth deficit were the factors associated with medical intractability. [10] The Connecticut study

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conducted by Berg AT, Shinner S, *et al*. done in 613 children suggested factors like specific syndrome/etiology, generalized seizure, high initial seizure frequency, focal EEG slowing as early predictors of intractability. [9] In these studies factors like seizure frequency and seizure type influencing prognosis were comparable to our study. Muhammer Akbar, *et al.* showed male gender, seizure onset in infancy, abnormal EEG and 10 or more seizures to be associated with poor prognosis. [12] In an Indian study by Udani VP, *et al*. on 123 difficult to control epileptic children, risk factors for intractability were onset below 2 years of age, male sex, neurological and developmental handicaps and certain seizure types (generalized tonic clonic, complex partial and mixed). [8] Results of Dutch study showed younger age of seizure onset, symptomatic etiology and mental retardation to be associated with poor outcome of epilepsy. [11] In the present study, it was observed that age of onset was one of the important factors strongly influencing the prognosis of epilepsy. Earlier the age of onset, poorer the prognosis. .This finding was consistent with other studies. K wong KL, *et al*. suggested abnormal neurological status and lack of early response to treatment as predictors of developing intractable epilepsy. Independent predictors of intractability with multiple regression were abnormal neurodevelopmental status, symptomatic etiology, and more than three seizures in the second 6 months after treatment. [13] In a study by Kwan P and Brodie MJ, the prevalence of persistent seizures was higher in patients with symptomatic or cryptogenic epilepsy than in those with idiopathic epilepsy (40 percent vs. 26 percent, P=0.004) and in patients who had had more than 20 seizures before starting treatment than in those who had had fewer (51 percent vs. 29 percent, P<0.001). They also showed that the probability of seizure remission decreases significantly with each successive treatment failure. [14] Many of these findings are consistent with the findings of the present study. Mac Donald, et al. suggested high seizure frequency (>10) in the early phase of epilepsy as the single most important predictive factor for both early and long-term remission with 95% of those with 2 seizures achieving a 5 year remission compared with only 24% of those with more than 10 seizures. [15] Hauser Wa, *et al*. [16] showed a positive correlation between family history of epilepsy and relapse rate of seizure. The results of both of these studies are comparable to our study. In a study by Shinnar, *et al*[17] , the pooled recurrence risk in patients with idiopathic seizure was 32% compared with 57% for a symptomatic seizure which is not consistent with the findings in our study.

Comparing results of numerous studies it was found that **(Table 2)** , essentially early age of onset (<2years) of epilepsy, multiple seizures, seizure type , seizure etiology and abnormal birth history predict poor prognosis. These findings were comparable with our study except seizure etiology which did not bear any statistical significance to prognosis in our study. Other factors which we found highly statiscally significant were drug therapy, low TDM levels and abnormal neuroimaging which were probably not studied as individual parameters by many authors.

Given the unrelenting rise in childhood epilepsy rates having both medical and social implications,

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determining prognosis is significant not only to the patient but also to his/her family, treating doctor and society. Assessment of risk profile could allow for more aggressive and tailored treatment with modern anti epileptic drugs (AED) .Ours was the first type which had studied multiple factors of epilepsy affecting prognosis. However, our drawback was that sample size was small and follow up period was short.

To **conclude** our study, children with one or more factors such as multiple seizures prior to treatment, early onset of epilepsy (< 2 years of age), generalized seizures, low TDM level, polytherapy, abnormal neuroimaging , abnormal birth history and family history of epilepsy are likely to have poor outcome of epilepsy and high degree of treatment resistance. Although this group of patients is small ,in clinical practice, it is important to identify them early to allow for more aggressive treatment with modern AEDs and, if needed, early neurosurgical intervention in select cases.

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