

Research paper

Recurrence rate and risk factors for recurrence of seizures after withdrawal of antiepileptic drugs (AED) in Indian children treated for epilepsy



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1. Introduction

Epilepsy is a major public health problem affecting about 50 million people worldwide. Even though it is a chronic condition, it may not remain life-long. The causes are variable and hence the outcome is also heterogeneous.¹ There are considerable disadvantages of continuing AEDs indefinitely as they have potential adverse cognitive and behavioral side effects along with cost implications.²

The decision to discontinue AED therapy is weighed against the chances of recurrence by the physicians. Previous studies in children have shown a risk of recurrence ranging from less than 10–70%.^{3–15} A few Indian studies have looked at risk factors of seizure recurrence in adults,^{16,17} but there is none such study in Indian children.

In India, the epidemiology of epilepsy is different from western countries in view of high burden of symptomatic epilepsy due to prevalence of birth asphyxia, neonatal hypoglycemia, etc. resulting from poor antenatal and natal care services.¹⁷ These children suffer from epilepsy of variable severity and the duration of treatment given is usually for 2–3 seizure free years after which the AED is/are withdrawn. We did this study to evaluate the rate of recurrence in children after AED withdrawal and the associated risk factors and reviewed the literature for similar such studies.

2. Methods

Patients were selected from the Pediatric Epilepsy Clinic in a referral Medical College between July 2005 and December 2013. Out of 2200 patients referred for seizures, 1108 children were diagnosed with epilepsy. Children (below the age of 18 years) with unequivocal epilepsy, who had been treated for a seizure free period of 2–3 years, after which their anti-epileptic drugs (AED) were slowly tapered over 2–3 months were selected, who were followed up for a minimum period of 6 months. 148 such children were identified in whom recurrence and presence of risk factors was noted (Fig. 1).

2.1. Inclusion criteria

- (1) Age below 18 years
- (2) Children who had 2 or more unprovoked seizures
- (3) Treated with anti-epileptic drugs (AED)
- (4) Had been seizure free for 2–3 years
- (5) Follow-up of minimum 6 months was available after withdrawal.

2.2. Exclusion criteria

- (1) Children with single seizure but received AED
- (2) Those with acute symptomatic seizures but received prolonged AED therapy
- (3) Those on prolonged AED since neonatal period (after perinatal insult)
- (4) Those diagnosed with inborn errors of metabolism
- (5) Infants/Children with West syndrome.

The following factors were studied in these children: age of onset of seizures, sex, type of seizures, total duration of epilepsy, duration to control seizures after initiation of AED, number of AED used, number of seizures before starting AED, number of seizures after AED was started, total number of seizures, duration of AED therapy, age at withdrawal of AED, follow-up period after withdrawal, interval between AED withdrawal and seizure recurrence. To find the etiology, prior history of neonatal seizures,

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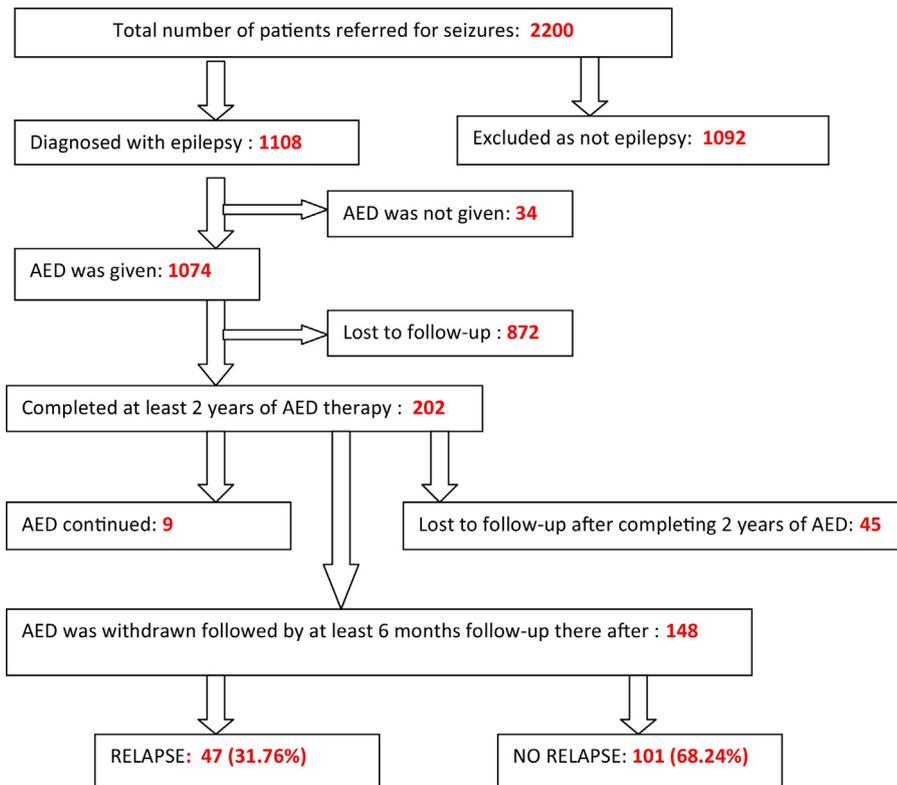


Fig. 1. Patient flowchart.

febrile seizures and family history of seizures was taken in detail. The motor and cognitive development and any morbidities were noted. Investigations included EEG at onset of AED, EEG before withdrawal, type of EEG abnormality and neuro-imaging findings (preferably MRI).

The data was entered on excel sheet. Those patients who did not follow up were called telephonically to check for seizure recurrence.

2.3. Statistical analysis

The information was collected and analyzed through SPSS (Statistical package for social sciences) version 17.0. For univariate analysis we have used Chi-square test, Fisher’s exact test to find the association between recurrence and various risk factors. A multivariate analysis was carried out using Cox proportional Hazard model.

P value <0.05 was significant, <0.01 – highly significant

A detailed review of literature was performed by entering the key words – AED withdrawal, recurrence, relapse, risk factors. Databases searched were Pubmed, Embase, various articles in journals related to epilepsy and neurosciences and their cross references.

3. Results: background data: see Table 1

3.1. Rate and timing of recurrence

Recurrence was seen in 47 cases, with a recurrence rate was 32%. The time to recurrence varied from 1 month to 10 years (mean of 1.189 years) after withdrawal of AED. 68% of total relapses occurred within 1 year, while 89% of relapses were within 2 years of withdrawal of AED. Thus only 11% relapse happened after 2 years of withdrawal (Fig. 2).

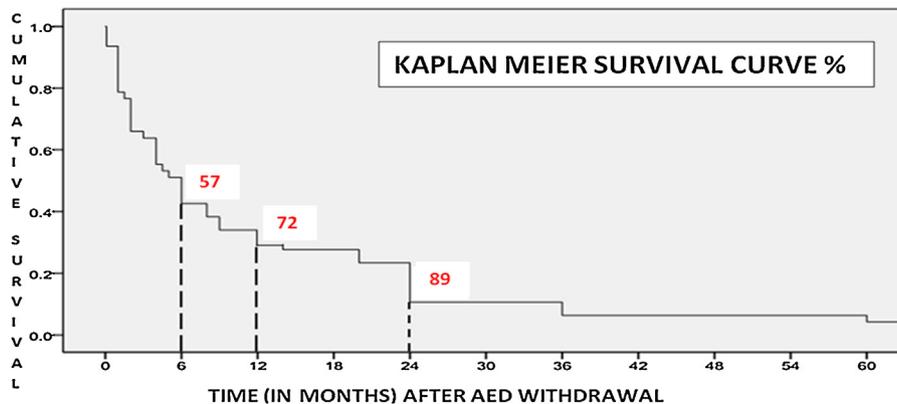


Fig. 2. Kaplan Meir curve for rate of recurrence.

Table 1

Background data.

Study parameter	Details
Age (in years)	Range: 2.8–20 years. Mean 4.34 years.
Sex	Males: 96 (65%), Females: 52 (35%)
Age of onset	Range: 2 months to 16 years. Mean: 4.99 years
Duration of active epilepsy (from 1st to last seizure)	Less than 1 month (31), 2–6 months (33), 6 months to 1 year (24) 1–3 years (29), 3–6 years (22), 7–10 years (9) Mean: 1.89 years
Type of seizures	Focal/secondarily generalized: 94, generalized: 40, multiple types: 11
Focal epilepsy (111)	Carbamazepine (26) – 6 symptomatic focal, 20 cryptogenic: 10 recurred
Total recurrence in 30.	Phenytoin (8) – 2 symptomatic: 1 recurred
Details of drugs used:	Phenobarbitone (10) – 2 symptomatic: 5 recurred Valproate (26) – 11 symptomatic: 8 recurred 2 drugs (14): 4 had recurrence, 3 drugs (8): 1 had recurrence 4 and 5 drugs (1 each): 1 had recurrence Valproate alone (16): 5 had recurrence Valproate with other drugs (22): 8 had recurrence
Generalized epilepsy (37) – recurrence in 13	Single (112), Two (23), Three (11), Four (1), Five (1) 2 (61), 3–5 (51), 6–10 (18), 10–20 (6), More than 20 (12) 0 (71), 1–2 (26), 3–10 (34), 10–20 (11), More than 20 (6) 2–5 (82), 6–10 (28), 10–20 (18), More than 20 (20) Range: 1.2–10 years (Mean: 3.31 years). 2 years (42), 3 years (25), 3–5 years (32), 6–10 years (17). Idiopathic (14), Cryptogenic (77), Symptomatic (57) 3 months (122), 6 months (26) 12 (8.1%), 8 had recurrence 41 (27%) 31 (20.9%). 18 did not have cerebral palsy – 4 had recurrence. 13 had cerebral palsy – out of which 8 had recurrence. 26 (17.57%) Normal (22) – 8 had recurrence, Focal discharges (63), multifocal discharges (21), generalized spike/polyspike wave discharges (15) Normal (45) – 9 had recurrence. Abnormal (33) – 9 had recurrence Normal (42) – 12 had recurrence. Abnormal (25) – 13 had recurrence 2.4 years to 19.6 years. 2–3 years (10) – 2 had relapse, 3–5 years (32) – 10 had relapse 5–7 years (26) – 11 had relapse, 7–10 years (28) – 10 had relapse 10–15 years (41) – 10 had relapse, More than 15 years (11) – 4 had relapse Range: 6 months to 13 years (Mean 2.06 years). Follow up was available for 1 year (56), 1–2 years (43), 2–3 years (31), 3–5 years (12), 6–8 years (3), 10 (1) and 13 (1). Time to recurrence: 1 month to 10 years (Mean 1.189 years) During withdrawal (7), Within 2 months (16), 3–6 months (11), 6 months to 1 year (5), 1–2 years (10), 3 years (2), 5 years (91), 10 years (2) Total recurrence within 1 year of withdrawal: 32 (68%), Within 2 years: 89%. After 2 years: 11%.
Number of AED used	
Seizures before start of AED	
Seizures after start of AED	
Total number of seizures	
Duration of AED therapy	
Etiology:	
Duration of tapering	
History of perinatal insult	
History of febrile seizures	
History of developmental delay	
Family history of seizures	
EEG at onset (123)	
EEG at withdrawal (78)	
MRI findings (67)	
Age at AED withdrawal	
Follow up period (no. of patients)	
Timing of seizure recurrence on follow up in 47 out of 148 patients (31.76%)	

3.2. Risk factors for recurrence

3.2.1. Univariate analysis (Table 2)

The following factors were found to be **significantly associated** with higher risk of recurrence – duration of active epilepsy (if more than 2 years), symptomatic etiology, prior history of neonatal seizures, concomitant cerebral palsy, response time after starting AED of more than 1 year, more than 2 seizures after start of AED therapy, total duration of AED given was more than 3 years.

The risk factors **not found significant** were gender, type of epilepsy, total number of seizures, past history of febrile seizures, family history of epilepsy, prior developmental delay alone (without associated cerebral palsy), EEG at onset of AED therapy as well as before withdrawal, abnormal neuro-imaging, number of AED required to control seizures, number of seizures before the start of AED, type of AED used, duration of AED withdrawal and age of AED withdrawal.

3.2.2. Multivariate analysis: (Table 3)

Cox proportional hazard model was used and three factors acquired significance for increased risk of seizures: duration of epilepsy more than 2 years, age of AED withdrawal if more than 10 years and total duration of AED more than 3 years.

4. Discussion: comparison with other studies

The literature search included adult and pediatric studies that looked at recurrence on follow up after AED withdrawal including a meta-analysis (Berg and Shinnar¹⁴) and a literature review (Britton¹⁵).

Rate of recurrence: Most studies found a recurrence rate between 14% and 41%^{3–5,12–23,25–27} Patients with JME reported a higher relapse rate, up to 80% while only 6.2% in CAE.²¹ Ohta et al.¹² reported a low recurrence rate of 9.2% in cryptogenic focal epilepsies with normal pre-withdrawal EEG. Hitiris et al.,³⁰ found 1 year seizure remission in upto 75% after treatment for 2–4 years. A prospective population based study (Cockerell et al.,³²) found 3 and 5 years remission in 86% and 54% respectively, but they included single unprovoked seizures.

Timing of recurrence: In our study, 14% of relapses occurred during withdrawal, 68% within 1 year and 89% within 2 years of AED withdrawal. In other studies, 20–50% of relapses were noted during withdrawal itself.^{5,21,25} The percentage of relapses happening within 1 year of withdrawal ranged from (30–40%)^{5,13} in some studies to (60–70%)^{14,16,19,21,23,27} up to more than 70%.²⁵ The percentage of relapses that happened within 2 years of AED withdrawal were (10–20%),^{3,17} (20–30%),²⁰ 30–40%,⁴ (40–50%),¹³ (70–80%),³ and 95%.²¹ Thus, maximum

Table 2

Univariate analysis: Relation of different risk factors to rate of recurrence.

S.n.	Risk Factors	Categories	Numbers (%)	Recurrence seen in	Relative risk	95% C.I.	P value
1.	Age of onset of epilepsy	1 year or less	44 (29.7)	18 (40.9)	1.467	0.916–2.349	0.127
		More than 1 year	104 (70.2)	29 (27.8)			
2.	Sex	Male	97 (65.5)	32 (32.9)	1.123	0.672–1.869	0.713
		Female	51 (34.5)	15 (29.4)			
3.	Duration of active epilepsy	2 years or less	106 (71.6)	25 (23.5)	0.450	0.287–0.704	0.001
		More than 2 years	42 (28.4)	22 (52.3)			
4.	Number of AED used	One	112 (75.6)	31 (27.6)	0.623	0.338–0.998	0.067
		More than 1	36 (24.3)	16 (44.4)			
5.	Type of epilepsy	Generalized	38 (25)	13 (35.1)	1.1	0.656–1.865	0.706
		Focal	110 (74.5)	34 (30.9)			
6.	Etiology	Idiopathic/cryptogenic	91 (61.5)	20 (21.9)	0.464	0.288–0.7454	0.001
		Symptomatic	57 (38.5)	27 (47.3)			
7.	No. of seizures before starting AED	Two	61 (41.2)	24 (39.3)	1.488	0.931–2.378	0.097
		More than two	87 (58.8)	23 (26.4)			
8.	No. of seizures after starting AED	0–2	97 (65.5)	25 (25.7)	0.597	0.376–0.948	0.031
		More than 2	51 (34.5)	22 (43.1)			
9.	Time to control seizures	0–12 months	108 (73)	3 (2.7)	0.05	0.016–0.159	<0.001
		More than 12 months	40 (27)	22 (55)			
10.	Total duration of AED	3 or less years	99 (66.8)	20 (20.2)	0.367	0.230–0.584	<0.001
		More than 3 years	49 (33.1)	27 (55.1)			
11.	H/o seizures in neonatal period	Yes	11 (7.4)	8 (72.7)	2.555	1.63–4.00	0.005
		No	137 (92.6)	39 (28.5)			
12.	Past h/o febrile seizures	Yes	41 (27.7)	18 (43.9)	1.619	1.01–2.57	0.075
		No	107 (72.3)	29 (27.1)			
13.	Family h/o seizures	Yes	26 (17.5)	5 (19.2)	0.559	0.244–1.274	0.166
		No	122 (82.4)	42 (34.4)			
14.	H/o perinatal insult	Yes	12 (8.9)	7 (58.3)	1.983	1.15–3.41	0.053
		No	136 (91.8)	40 (29.4)			
15.	H/o developmental delay	Yes	31 (21.1)	12 (38.7)	1.283	0.76–2.16	0.391
		No	116 (78.9)	35 (30.2)			
16.	EEG at onset of AED (123 patients)	Normal	22 (17.2)	8 (38.1)	0.598	0.311–1.148	0.170
		Abnormal	101 (82.7)	33 (22.7)			
17.	EEG at withdrawal of AED (78)	Normal	45 (57.7)	9 (20)	1.364	0.604–3.057	0.588
		Abnormal	33 (42.3)	9 (27.2)			
18.	MRI findings (67 patients)	Normal	42 (62.3)	12 (28.6)	1.820	0.999–3.345	0.070
		Abnormal	25 (37.3)	13 (52)			
19.	Concomitant cerebral palsy	Yes	17 (11.5)	12 (70.6)	2.642	1.73–4.01	0.001
		No	131 (88.5)	35 (26.7)			
20.	Age of AED withdrawal	Less than 10 years	104 (70.2)	35 (33.6)	1.23	0.709–2.14	0.563
		More than 10 years	44 (29.7)	12 (27.3)			
21.	Duration of AED withdrawal	3 or less months	122 (82.4)	37 (30.3)	0.789	0.452–1.374	0.488
		More than 3 months	26 (17.57)	10 (38.46)			

Table 3

Multivariate analysis for risk factors causing recurrence after AED withdrawal.

Risk factor	P-value	Hazard ratio	Confidence interval	
			Lower	Upper
Male sex	0.253	0.451	0.115	1.768
Age of onset of seizures less than 1 year	0.103	0.253	0.049	1.318
Duration of active epilepsy more than 2 years	0.008	0.065	0.009	0.495
Time to control seizures more than 1 year	0.930	1.102	0.127	9.591
More than 1 AED required to control seizures	0.580	1.682	0.267	10.586
Symptomatic etiology	0.724	0.595	0.033	10.641
More than 2 seizures before starting of AED therapy	0.986	0.988	0.250	3.907
More than 2 seizures after starting AED therapy	0.097	5.509	0.734	41.376
Previous history of febrile seizures	0.388	1.798	0.475	6.809
Family history of epilepsy	0.789	1.332	0.163	10.859
Prior history of perinatal insult	0.306	0.293	0.028	3.074
History of delayed development	0.186	0.228	0.026	2.037
Concomitant cerebral palsy	0.222	3.298	0.485	22.430
Abnormal EEG at onset of AED	0.804	0.604	0.011	32.752
Age of withdrawal of AED more than 10 years	0.013	10.384	1.647	65.464
Total duration of AED more than 3 years	0.036	0.101	0.012	0.860
History of seizures in neonatal period	0.306	0.293	0.028	3.074
Abnormal EEG at withdrawal of AED	0.241	2.381	0.559	10.150
Abnormal MRI	0.753	0.647	0.043	9.705
Generalized epilepsy	0.704	1.426	0.228	8.913

Table 4
Risk factors for recurrence: comparison of our results with existing literature.

Risk factor for recurrence	Our study result	Studies that found the factor significant	Studies that found the factor not significant	Comments on the basis of existing literature
Age of onset of epilepsy	Not significant (less or more than 1 year)	Older age of onset – more than 10 years ^{8,14,15,17,21,26,31} More than 5 years ⁶ More than 6 years ¹²	3–5, ^{13,19,23}	Epilepsies with onset in adolescent age may have more recurrence.
Sex	Not significant	Female ^{3,7,21,22,33,40}	4–6, ^{13,17,19,23,27}	Female sex may act as additional risk factor in IGE
Duration of active epilepsy more than 2 years	Significant	3,6,12,16,17,29,33,40	30,23,27,34	Surrogate marker for difficult to control epilepsy
Number of AED used more than one	Not significant	More than 1 drug ^{4,12,15,18,19,25–27}	3,5,6,16,17	Surrogate marker for difficult to control epilepsy
Type of epilepsy – focal or generalized	Not significant	Focal ^{4,13} Generalized ^{21,22,25,26} Multiple seizure types ^{4,17,20,21}	3,5,16,19,23,27	Equivocal effect of type of seizures but multiple seizure types confer higher risk of recurrence
Etiology – symptomatic versus idiopathic	Significant	Remote symptomatic ^{6,8,13–15,18,20,24,26,31,35–37,40} Idiopathic ^{2,14,15,17,21,26}	3,7,33	Adolescent onset IGE may have equal risk as Symptomatic
More than 2 seizures before starting AED	Not significant	12,17,34,44	30,4,6,16,27,43	Equivocal
More than 2 seizures after starting AED	Significant	12,13,16,17,25,26,29,33,34	30,6,27	Surrogate marker for difficult to control epilepsy
Time taken to control seizures was more than 1 year after start of AED	Significant	Poor initial response ^{3,6,12,13,15,38}		Surrogate marker for difficult to control epilepsy
Total duration of AED if more than 3 years	Significant	Shorter duration ^{3,6,8,18,25,26,39,40,42} Prolonged AED ^{13,24,29,33}	5,16,17,19,41	Equivocal
History of seizures in neonatal period	Significant	17,20		Not studied adequately
Past history of febrile seizures	Not significant	Febrile seizures ^{4,20,27}	3,6	Not studied adequately
Family history of seizures	Not significant	Positive family history ^{15,17}	3,5,16,27	Family history of seizures may not confer an additional risk for recurrence
History of perinatal insult (asphyxia/hypoglycemia/seizures)	Significant	17	27	Not studied adequately
History of prior developmental delay	Not significant	Delayed development ^{6,8,14,15,27,44}	3,4,35	Associated developmental delay has higher risk of recurrence
EEG at onset of AED (123 patients)	Not significant	Abnormal EEG ^{5,8,14,15,17,24,26,27}	3,4,6,7,23	Abnormal EEG at onset of AED may have a higher risk of recurrence
EEG at withdrawal of AED (78)	Not significant	Abnormal EEG ^{3–5,14,15,17,21,22,46}	3	Abnormal EEG at withdrawal of AED may have a higher risk of recurrence
MRI findings (67 patients)	Not significant	Abnormal ¹⁷	3,23,27	Not adequately studied
Concomitant cerebral palsy	Significant	Motor deficits ^{14,15,17,18,23} More risk in hemiplegia ⁴⁵	19	Associated Cerebral palsy has higher risk of recurrence
Age of AED withdrawal more than 10 years	Not significant	12,21,22	30,20,23,50	Late onset epilepsies may have a higher risk of recurrence.
Duration of AED withdrawal over 3 or more than 3 months	Not significant	Less than 3 months ^{5,15,24}	3,15,20,23,41,48,49	May not be significant

number of relapses is reported to occur within 2 years of withdrawal.

Risk factors for recurrence: Table 4 shows an overview of different risk factors found significant/not significant in our study and their status in the literature. We did not consider specific AEDs or post withdrawal EEG to look for worsening. History of neonatal seizures and perinatal insult (HIE, hypoglycemia) was not studied in most of the other existing literature.

Britton¹⁵ asserted that abnormal EEG prior to withdrawal has limited predictive value, as some medications like Valproate may have EEG normalizing effects. They pointed out that relapse rates were up to 83% in patients whose EEG worsened on dose reduction, compared to 54% in patients whose EEG remained unchanged, suggesting that post withdrawal EEGs may be useful. Berg¹⁴ showed that slowing on EEG may be as important as presence of epileptiform abnormalities, as also photo-paroxysmal response which may be predict a higher risk of relapse.

4.1. Multivariate analysis

We found only three factors achieved significance-duration of epilepsy of more than 2 years, age at AED withdrawal if more than 10 years and duration of AED therapy if more than 3 years

conferred a higher risk of recurrence. Different studies found various combinations of risk factors to be significant for recurrence: e.g. female sex,^{3,22} higher age of onset of seizures,^{12,25} time to control seizures more than 5 years,¹² high initial seizure frequency,¹³ seizures after start of AED,²⁵ remote symptomatic etiology,¹³ abnormal EEG at onset or withdrawal,^{22,25,27} abnormal neurological examination,²³ generalized seizures (primary or secondary),²⁵ polytherapy,²⁷ etc.

Elson⁵⁰ concluded that the most consistent factor is the ease of controlling seizures – how soon seizures are controlled on AED, frequency of seizures after AED initiation and the number of AED required to control seizures. Camfield and Camfield⁵¹ found the following factors to predict remission in children (Class I evidence): normal neurologic/mental abilities, seizure onset below the age of 12 years and infrequent or easily controlled seizures. The remission rate was 80% if all three factors were present versus 20% if none were present.

4.2. Limitations of our study

There were several limitations in our study. 22% (45 out of 202) patients who completed 2 years of AED therapy did not follow up with us. Most patients were included retrospectively and the

remaining patients were included over a period of 5 years from the onset of the study. Patients were treated for 2 or 3 years as per physician's discretion. It is possible that those patients who had difficult to control epilepsy and those who had florid abnormalities on pre withdrawal EEG were given prolonged therapy. We did not study type of EEG abnormalities, degree of mental retardation, etc. to stratify the risk of relapse. MRI was not available in many patients.

5. Conclusion

This is the first study to look at rate of recurrence and its risk factors amongst children treated for epilepsy in India. In general, older age of onset in a previously normal child points to Idiopathic generalized epilepsies (IGE) like JME which carry a greater risk of relapse even if easily controlled. Among the symptomatic group, mostly due to perinatal brain injury (asphyxia, hypoglycemia) – the presence of co-morbidities like motor deficits, difficult to control seizures along with an abnormal EEG at withdrawal is associated with a higher rate of recurrence. There is no consensus in the world literature regarding the combination of prognostic factors to predict recurrence.

6. Areas for further research

Larger prospective studies with longer follow up to generate survival curves and to find out the factors affecting the rate of recurrence are needed to address this important issue with impact on future physical, economic and social well being of these children.

Conflicts of interest

The authors have none to declare.

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