



# A Retrospective Analysis of the Long-Term Outcome of Drug-Resistant Epilepsy in Children Treated in Urban India

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## Abstract

**Objective:** To study the outcome of childhood-onset drug-resistant epilepsy. **Methods:** Fifty-five patients with drug-resistant epilepsy, meeting inclusion criteria, were identified from the Pediatric Neurology Clinic database with seizure onset less than age 13 years and a minimum follow-up of 5 years. Seizure remission was defined as no more than 1 seizure/year. Kaplan-Meier analysis was used to calculate the annual probability of seizure remission. Chi-square/Kruskal-Wallis tests were used to detect differences in predictors between those with seizure remission,  $\geq 75\%$  improvement and  $< 75\%$  improvement based on caregiver reports. **Results:** Median follow-up was 11 years. Of 55, 22 (40%) were in seizure remission at last contact; 14 (25.4%) improved by  $\geq 75\%$ ; 19 (34.5%) experienced  $< 75\%$  improvement. Annual remission probability was 3% in IQ  $\geq 70$  group and 2.48% in IQ  $< 70$  group ( $P = .126$ ). **Conclusion:** This study shows patients with drug-resistant epilepsy treated in urban India can expect an overall remission rate of 2% per year starting from the third year of follow-up.

## Keywords

antiepileptic drugs, children, epilepsy, outcome, pediatric, drug-resistant, risk factors

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Epilepsy is a common neurological condition in children. Over time, most epileptic children achieve seizure remission with or without medication. However, about 10% to 30%<sup>1-3</sup> continue to have seizures despite treatment. Prognosticating long-term outcomes is difficult in drug-resistant epilepsy where surgery is either not possible or refused. Drug-resistant epilepsy adversely affects the quality of life of the patient/family, and accurate prognostication of outcome in such children helps parents in treatment planning and other life decisions especially in a developing country where government-funded community support systems are virtually nonexistent. Although studies have investigated seizure remission in children with epilepsy,<sup>4-6</sup> information available for outcomes in drug-resistant epilepsy is limited.<sup>7,8</sup> Questions remain over natural or spontaneous resolution of epileptogenic processes over time leading to seizure remission even in the most refractory drug-resistant epilepsy.

The primary aim of this study was to determine the probability of seizure remission in children with drug-resistant epilepsy in the long term in a developing country where newer antiepileptic drugs have been in use for several years.

The study also attempts to analyze risk factors that may predict probability of seizure remission in the developing country scenario.

## Materials and Methods

This retrospective observational study was carried out in a hospital-based tertiary care child neurology clinic in Mumbai, India. Demographic details along with information related to epilepsy (eg, etiology, semiology, investigations done, treatment received, and clinical status at last contact) were obtained from the clinical records maintained with Vrajesh Udani. Attempts were made to contact the patients telephonically if available data were incomplete and/or to collect information about the most recent clinical condition. International League Against Epilepsy definitions were used for epilepsy

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and epilepsy syndromes.<sup>9</sup> Frequency of seizures at last contact was estimated from parents/caregiver observations and/or their seizure diaries. Consent was implied for use of anonymized data from hospital records for research purposes. Additional verbal consent was gained from those patients or caregivers with whom personal/telephonic contact was possible during the study.

## Participants

Children had to meet the following criteria to be included in the study:

1. Age of onset of seizures younger than 13 years.
2. An elapsed time period of at least 5 years from the onset of seizures.
3. Average frequency of one seizure per month for a period of at least 2 years despite the use of medical therapy with at least 2 appropriately chosen and tolerated anti-epileptic agents at adequate doses, either singly or in combination at any point during their follow-up.<sup>10</sup>

Patients with the following conditions were excluded:

1. Progressive brain diseases.
2. Known or suspected genetic (idiopathic) epilepsy syndromes where natural remission over time is the rule (eg: benign epilepsy with centrotemporal spikes).
3. Those who had undergone surgical treatment for their epilepsy.

The following outcomes were evaluated: (a) *seizure remission*: No more than 1 seizure per year for a period of 12 months prior to last contact. We used this definition of seizure remission based on a similar previous long-term outcome study by Huttenlocher and Hapke<sup>7</sup> in Chicago. This definition was considered more pragmatic as sustained seizure freedom was presumed to be uncommon in drug-resistant epilepsy. This category therefore included children who were either completely seizure free, that is, had zero seizures per year or had only 1 seizure per year for the 1 year prior to last contact. (b) *Improved*: If parents/caregivers reported  $\geq 75\%$  reduction in seizure frequency over at least a year prior to last contact. (c) *Not improved*: If parents or caregivers reported no change/increase in seizure frequency or  $< 75\%$  improvement in seizure frequency over at least a year prior to last contact. A cutoff of 75% was chosen as seizure improvements of this magnitude would be easily observed by the caregivers (as all did not maintain meticulous seizure diaries) rather than the usual 50% cutoff used in drug efficacy short-term studies.

The institution's ethical board reviewed our study design and determined it was exempt from ethical approval as it was a retrospective observational study and patient data was kept anonymous.

## Statistical Analysis

The Kaplan-Meier analysis was used to calculate the annual remission probability. For children who underwent a formal IQ assessment (Binet Kamat Test of Intelligence or Malin's Intelligence Scale for Indian Children), remission probabilities based on a cutoff IQ of 70 were calculated separately. Log-rank test was used to determine differences in time to remission between those with IQ  $< 70$  and those with IQ  $\geq 70$ . IQ was not available in a significant minority. This was either because of young age or the patients being severely intellectually or physically challenged making an accurate assessment

impossible. Information of present school placement—whether in a normal school or in one for children with special needs was also used to assess functioning. However, only those children with available standard IQ score were used in the calculation of remission rate based on IQ.

Chi-square (for categorical variables) and Kruskal-Wallis tests (for continuous variables) were used to detect differences in clinical factors between those with seizure remission, those labeled as improved and those labeled as not improved at last contact. Cox proportional hazard ratios with 95% confidence intervals were calculated to determine association between various clinical factors/potential predictors and remission. All significance tests were 2-tailed with  $\alpha = .05$ . Data were analyzed using SAS University Edition (SAS Institute Inc, Cary, North Carolina).

## Results

Sixty-two patients fit the inclusion criteria. Follow-up information was insufficient in 3 patients, 2 patients were excluded as they underwent surgery, and 2 patients were reclassified as having progressive disorders in the follow-up period. Therefore, data from 55 (88%) patients were used for analysis. Median age of the patients at last contact was 16 years (range: 6-33 years). Median duration of follow-up from onset of seizures to the time of last contact was 11 years (range: 5-26 years).

At last contact, 22 (40%) patients had no more than 1 seizure per year, that is, were in *seizure remission*, 14 of whom were seizure free (zero seizures per year). Fourteen (25.4%) reported  $\geq 75\%$  improvement (*improved*) while 19 (34.5%) reported  $< 75\%$  improvement (*not improved*).

Table 1 shows details of demographic and clinical characteristics of the study population. A majority of our patients were diagnosed with structural/metabolic (symptomatic) epilepsies (69.1%). Perinatal brain injury was the commonest etiology (47.2%). Most patients (72.7%) had a trial of 5 or more antiepileptic drugs.

Figure 1 shows the Kaplan-Meier curve for predicting overall seizure remission in our study population. The annual remission probability in our patients was 2.03%.

A formal IQ result was available for 44 (80%) of 55 patients—30 (68%) had an IQ  $< 70$  and 14 had an IQ  $\geq 70$ . The annual remission probability was 2.48% in the low IQ group and 3% in the group with normal to borderline intelligence. However, the log-rank test did not show statistically significant difference in time to remission between those with IQ  $< 70$  and those with IQ  $\geq 70$  ( $P = .05$ ; Figure 2).

Table 2 shows differences in clinical factors between those with seizure remission, those who had improved, and those who had not improved at last contact. Children who had received a trial of  $\geq 5$  antiepileptic drugs during the course of treatment were less likely to have seizure remission or show improvement at last contact as compared to those who received  $< 5$  antiepileptic drugs ( $P = .008$ ). Differences in other factors between the 3 groups were not statistically significant.

Table 3 shows results of Cox proportional hazards analysis for associations between clinical factors/potential predictors

**Table 1.** Demographic and Clinical Characteristics of Study Participants (n = 55).

Characteristics	n (%)
Age at onset of seizures	
<2 years	31 (56.3)
≥2 years	24 (43.6)
Male	42 (76.3)
Age in years at last contact, median (range)	16 (6-33)
Epilepsy syndrome	
Structural/metabolic epilepsy	38 (69.1)
Genetic	3 (5.4)
Unknown	14 (25.5)
Structural–Metabolic	
Perinatal brain injury-related epilepsy	26 (47.2)
Postencephalitic epilepsy	4 (7.2)
Malformations of cortical development	1 (1.8)
Mesial temporal sclerosis	3 (5.4)
Neurocutaneous syndromes	3 (5.4)
Chemotherapy-related leukoencephalopathy	1 (1.8)
Adverse birth history	30 (54.5)
Developmental delay	35 (63.6)
Positive family history of epilepsy	9 (16.3)
IQ (n = 44)	
<70	30 (68.2)
≥70	14 (31.8)
School placement	
Special needs	43 (78.2)
Normal	12 (21.8)
Status epilepticus	20 (36.3)
MRI/CT findings	49 (89)
Focal	16 (29.1)
Diffuse	24 (49)
Normal	9 (18.4)
Daily seizures during follow up	24 (43.6)
No. of AEDs used	
<5	15 (27.2)
≥5	40 (72.7)

Abbreviations: AED, antiepileptic drug; CT, computed tomography; MRI, magnetic resonance imaging.

and seizure remission. Factors with  $P < .1$  in bivariate analysis were included in the multivariate model. Only trial of  $\geq 5$  antiepileptic drugs was seen to predict remission, with children on trial of  $\geq 5$  antiepileptic drugs less likely to have remission than those on  $< 5$  antiepileptic drugs (Cox hazard ratio [95% confidence interval] = 0.319 [0.114-0.894];  $P = .029$ ), when adjusted for sex and IQ. This is not surprising and would reflect the severity of their condition.

## Discussion

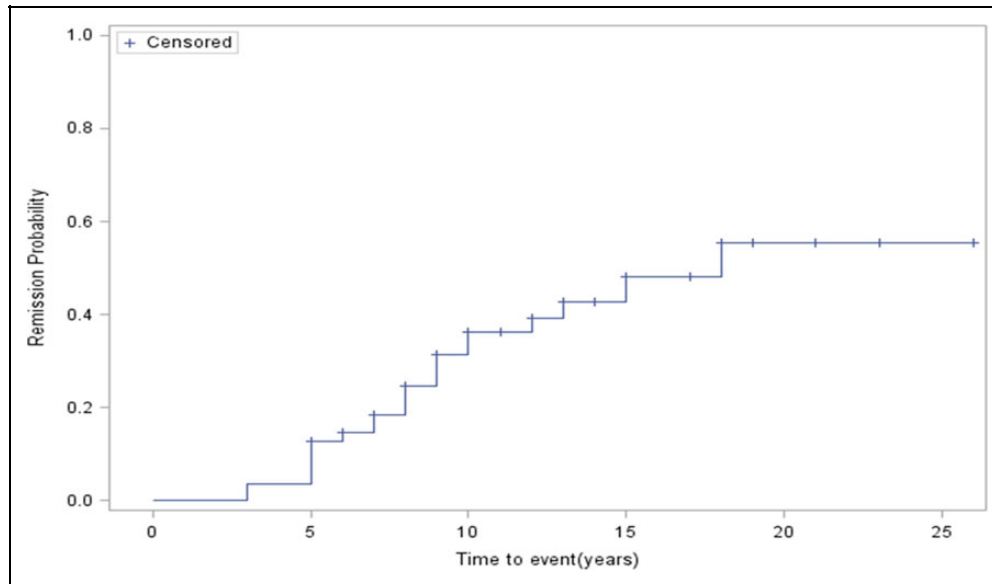
The results from our study imply that around 2 patients of every 100 with drug-resistant epilepsy will undergo remission every year starting from around the third year of follow-up. They also predict that 13%, 37%, 40%, and 48% would enter remission by 5, 10, 12, and 15 years of follow-up, respectively (Figure 1). Using a similar definition for seizure remission, that is, no more than 1 seizure per year at last contact, an earlier long-term study in children with medically treated drug-resistant epilepsy

by Huttenlocher and Hapke<sup>7</sup> reported a comparable remission rate of slightly less than 10% at the 5-year follow-up. There were some key differences between the two studies. We probably had patients with more severe epilepsy in our sample as almost 70% of cases had structural/metabolic etiology of epilepsy vis-à-vis the Chicago study which had predominantly epilepsies of unknown (cryptogenic) etiology. However, considering the older generation imaging available in the 1980s/early 1990s, it is likely that many subtle lesions like gliosis or cortical dysplasia were missed thereby leading to an underestimation of the true number of structural/metabolic cases in the Chicago study. The etiology of the structural epilepsies in our study was often perinatal brain injury, a known important precedent of drug-resistant epilepsy.<sup>11</sup> This is an important etiology to target with preventive measures to help reduce the burden of drug-resistant epilepsy in developing countries. To limit our patients to pure drug-resistant epilepsy, we had deliberately excluded suspected genetic epilepsies that may at times masquerade as drug-resistant epilepsy for a while, before spontaneous remission in the teenage years. This, not being an exclusionary criterion in the Chicago study, raises the possibility that a few such children with atypically evolving benign epilepsies were inadvertently included. Also, our nonlesional epilepsies had a significant number of well-characterized epileptic encephalopathies like Dravet syndrome, Lennox-Gastaut syndrome, and so on, conditions known to have poor seizure control and intellectual outcome. Despite these differences, the remission rate at 5-year follow-up of 13% in our study is close to the 10% in the Chicago study. The use of several new anti-epileptic drugs in our more contemporary study could have contributed to improving seizure remission rates.

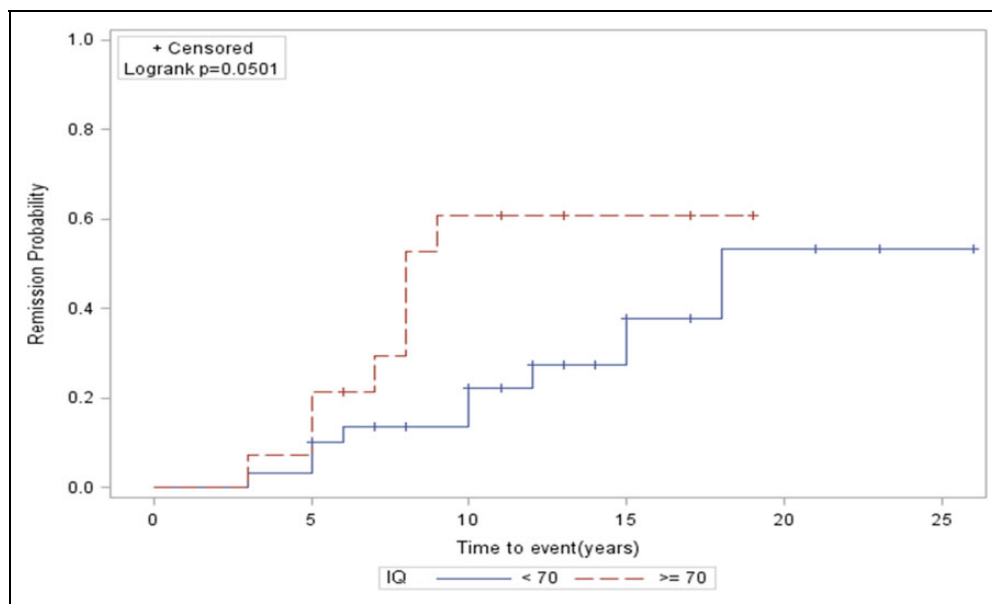
In 2009, another study<sup>8</sup> reported outcomes in children with epilepsy after 2 drug failures. When defined as seizure freedom for at least 1 year at last contact, their remission rates at 5, 10, and 12 years were 18%, 40%, and 47%, respectively. Having fewer cases with structural/metabolic etiology (25% vs 69.1%), poor IQ (31% vs 68.2%), and daily seizures at the start of the study (26% vs 43.6%) when compared to our sample may explain their better remission rate.

Although direct comparisons with the abovementioned studies may not be possible due to differences in their inclusion criteria and definitions of seizure remission, our findings support the general conclusion of other such studies, that is, the natural history of drug-resistant epilepsy shows a slow linear improvement for several years after onset.

This conclusion is contrary to the widely held belief that if remission is not achieved in 2 years (early remission) then the epilepsy is unlikely to remit. Schmidt and Loscher<sup>12</sup> in a critical review in 2005 suggest that "... in most patients, drug resistance seems to be continuous and occurs de novo" and that "current AEDs have only a modest short-term effect on seizure frequency." However, 2 recent large studies,<sup>6,13</sup> one in childhood-onset epilepsy followed for a median of 40 years and the other in adult drug-resistant epilepsy followed for a median of 7 years, report a substantial number of patients with remission after several years of follow-up (late remission), very



**Figure 1.** Kaplan-Meier estimate for probability of seizure remission in study participants (n = 55).



**Figure 2.** Kaplan-Meier estimate for probability of seizure remission in the study participants with formal IQ assessment (n = 44).

similar to our study where also patients were followed up for a median of 11 years. Late remission even after the use of 6 anti-epileptic drugs has been reported in about a quarter of patients.<sup>13</sup> All these extended long-term studies suggest a much improved seizure outcome if patients are followed long enough. It appears that the period of highly active seizure propensity wanes over time, even in drug-resistant epilepsy, leading to seizure freedom or significant improvement in seizure frequency.

Whether there is any effect of the newer antiepileptic drugs on long-term seizure propensity is also unknown at this point. In our study, patients were prescribed escalating doses of monotherapy followed by polytherapy with the aim to then wean off the drugs that were thought to be least effective. Therapeutic

drug monitoring was used where needed prior to dosing changes. Ketogenic diet was tried in 14 patients. Specific therapies such as Diamox, steroids, vitamin B6, biotin, and aspirin were also tried in a few patients. The drugs prescribed included a mixture of old (phenytoin, phenobarbitone, carbamazepine, clobazam, valproate, and ethosuximide) and new drugs (levetiracetam, lamotrigine, topiramate, felbamate, and oxcarbazepine).

Another recognized pattern in the natural history of drug-resistant epilepsy is the relapsing-remitting pattern, identified in 27% of our patients having a seizure remission period of at least 12 months at some point during their follow-up. This has been described previously in 25% to 32% of adults with drug-resistant epilepsy.<sup>13,14</sup> In a long-term natural history study of

**Table 2.** Characteristics of Study Participants by Outcomes (n = 55).

Characteristics	Outcomes at Last Contact			P Value
	Seizure Remission, n (%)	Improved, n (%)	Not Improved, n (%)	
Total	22 (40)	14 (25.4)	19 (34.5)	
Age in years at last contact, median (range)	17.5 (6-32)	15 (7-33)	14 (6-24)	.27
Age at onset of seizures <2 years	12 (54.5)	9 (64.2)	10 (52.6)	.78
Males	14 (63.6)	12 (85.7)	16 (84.2)	.22
Structural/metabolic epilepsy	17 (77.2)	7 (50)	14 (73.6)	.19
Genetic/unknown	5 (22.7)	7 (50)	5 (26.3)	-
Adverse birth history	12 (54.5)	7 (50)	11 (36.6)	.9
Developmental delay	11 (50)	10 (71.4)	14 (73.6)	.22
Positive family history	5 (22.7)	1 (7.1)	3 (15.7)	.52
IQ < 70 (total n = 44)	9 (52.9)	11 (84.6)	10 (71.4)	.18
Special needs school	16 (72.7)	11 (78.5)	16 (84.2)	.71
Focal seizures	11 (50)	8 (57.1)	7 (36.8)	.48
Status epilepticus	6 (27.2)	4 (28.5)	10 (52.6)	.18
Daily seizures at any point	8 (36.3)	7 (50)	9 (47.3)	.66
Trial of ≥ 5 AEDs	11 (50)	12 (85.7)	17 (89.4)	.008

Abbreviation: AED, antiepileptic drug.

**Table 3.** Association Between Characteristics of Study Participants and Seizure Remission at Last Contact.

Characteristics	Cox HR	95% CI	P Value
Bivariate analysis (n = 55)			
Age in years at last contact	0.993	0.922-1.07	.86
Age at onset (>2 years)	1.001	0.431-2.324	.99
Sex (females)	2.361	0.975-5.713	.056
Structural/metabolic epilepsy	0.511	0.179-1.46	.21
Adverse birth history	1.093	0.471-2.535	.835
Developmental delay	0.585	0.253-1.355	.211
Positive family history	1.659	0.608-4.528	.323
IQ ≥ 70 (n = 44)	2.488	0.952-6.502	.063
Special needs school	0.513	0.186-1.414	.196
Focal seizures	1.514	0.574-3.996	.402
Status epilepticus	0.601	0.21-1.722	.343
Daily seizures at any point	0.542	0.199-1.476	.23
Trial of ≥ 5 AEDs	0.293	0.108-0.794	.015
Multivariate analysis (n = 44)			
Trial of ≥ 5 AEDs	0.319	0.114-0.894	.029
Sex (females)	1.749	0.615-4.977	.294
IQ ≥ 70	2.184	0.803-5.941	.126

Abbreviations: AED, antiepileptic drug; CI, confidence interval; HR, hazard ratio.

all epilepsy beginning in childhood by Sillanpää and Schmidt,<sup>6</sup> about 14% of 144 patients did not enter re-remission after an early/late prolonged remission. In another 19%, there never was any significant period of remission from onset suggesting that these were inherently pharmacoresistant and many of these were symptomatic epilepsies.

The Chicago study<sup>7</sup> had predicted higher remission rates in children with normal IQ (4% per year) vis-à-vis those with a low IQ (1.5% per year). In our study (Figure 2), remission rates in those with normal IQ and low IQ were 3% per year and 2.48% per year, respectively. Looked at another way, 50% of patients with normal/near-normal IQ would enter remission in 8 years,

while in patients with low IQ this would take 18 years. However, this difference was not statistically significant. Cognitive change is common in drug-resistant epilepsy not only because of an underlying abnormal neurological substrate but also due to the effects of certain seizure-related risk factors like early age of onset, high seizure frequency, prolonged epilepsy duration,<sup>15</sup> and so on. We had a relatively small cohort with an even smaller number of patients with a normal/borderline IQ (only 14 patients). Also, baseline seizure-related risk factors were similar in both groups making it difficult to find a link between IQ and seizure remission. As discussed above, our patients probably had more severe epileptic conditions than the patients in the Chicago study probably leading to cognitive changes in most patients due to seizure-related factors. It is of interest to note that more of our nonlesional epilepsies of unknown etiology (76%) had IQs < 70 as compared to those with lesional structural/metabolic epilepsy (63%) suggesting that epilepsy effects on cognition are as important as an abnormal neuropathological substrate. A larger sample size may help verify the strength of the association between IQ and seizure remission in drug-resistant epilepsy.

Studies looking at predictors for intractability at epilepsy onset in children<sup>3,16</sup> have identified symptomatic (structural–metabolic) epilepsy, high initial seizure frequency, mental retardation, difficulty in initial control, seizure onset in infancy, and status epilepticus as some risk factors. These factors have been examined for their role as predictors for remission in intractable epilepsy as well. Idiopathic (genetic) etiology, seizure frequency, shorter epilepsy duration, and fewer antiepileptic drugs used were some of the factors found to be associated with seizure remission in children and adults.<sup>8,15</sup> We found only the use of ≥ 5 antiepileptic drugs as a negative risk factor for remission. Other risk factors studied did not reach significance, at least partly due to the small sample size.

It is not surprising that antiepileptic drugs are rarely weaned off these patients even in those with seizure freedom for several

years. Although the number of antiepileptic drugs and the dosage used was lower, all the patients in the Chicago study<sup>7</sup> continued their medication. We had only a single child weaned off all antiepileptic drugs with terminal remission at the 2-year follow-up, while another 4 are on monotherapy.

Although the long-term seizure outcome appears favorable, the price these families pay in terms of cognitive/behavioral difficulties, learning disabilities, future employability, and other social issues is high. Psychiatric/cognitive comorbidity is increased in all epilepsies, especially if drug resistant.<sup>15</sup> Early age of onset of drug-resistant epilepsy, which was the case in most of our patients, appears to have a larger comorbidity burden. Hence, there is a need to explore all possible surgical therapies which could be potentially curative.

Limitations of this study include its retrospective nature and the small number of patients. The probability of remission may differ if a larger sample size is analyzed. The recruited patients who continued to follow-up with VU for so many years may have done so as they had improved while those who had not improved may have dropped out from follow-up. Accurate seizure diaries were not maintained continuously and meticulously for some patients during this prolonged follow-up and we had to rely on parental/caregiver reports. We used a high cutoff of >75% to estimate improvement for this very reason to try and reduce possible inaccuracy.

## Conclusions

This long-term follow-up study of childhood drug-resistant epilepsy suggests that a significant improvement in seizure control occurs over time. The remission rates were not found to be significantly different between those with and without intellectual impairment.

Those receiving a trial  $\geq 5$  antiepileptic drugs were more likely to have a poor outcome in our setting. Perinatal brain injury is an important preventable cause of drug-resistant epilepsy in developing countries.

Future prospective cohort studies of incident cases of childhood-onset drug-resistant epilepsy are needed to examine long-term outcomes of seizure frequency and other comorbidities.

### What is already known on this topic-

- Children with drug resistant epilepsy have a gradual decline in seizure frequency with time (around 3-4% per year in a developed country).
- Annual remission rate in developed countries is lower in children with lower IQ.
- No evidence is currently available on a cohort of DRE children treated in a developing country starting to gain access to newer anti-epileptic drugs.

### What this study adds-

- Annual remission probability for childhood onset drug resistant epilepsy is 2% in children treated in a developing country.
- No significant difference seen in remission rates between children with low and normal intelligence.
- Trial of  $\geq$  five AEDs is the only risk factor associated with a poor outcome.
- Perinatal Brain Injury is an important preventable cause of DRE in developing countries.

### Authors' Note

Toranj Raimalwalla is now with the Paediatrics Department, Royal Berkshire Hospital, Reading, United Kingdom.

### Author Contribution

TYR: Collection and analysis of data; preliminary draft  
VU: study concept; source of patient data; writing of final manuscript  
DM: reviewing results; statistical analysis statement for ethical approval in text.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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