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Original Research Article

Children with idiopathic generalized epilepsy those underwent at least two years seizure remission: a retrospective analysis

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ABSTRACT

Background: The aim of the retrospective study was to evaluate the effectiveness of the index antiepileptic drugs in children with idiopathic generalized epilepsy who underwent at least 2 years remission.
Methods: A total of 52 children with idiopathic generalized epilepsy who underwent at least 2 years remission were identified retrospectively from the records of the paediatric and neurology care clinic from April 2017 to December 2020.
Results: The seizure patterns of 52 cases were tonic-clonic seizures alone (73%), a combination of tonic-clonic seizures and absences (13.5%), and combined tonic-clonic seizures and myoclonus (13.5%). The total number of seizures at enrolment in all (age at seizure onset 7.44±5.12 years, male-female ratio (31:21) was 651 (mean 12.52±26.60). The total number of follow-up visits in all was 6.62±14.44 consisting of 1177.5±772.86 days of follow-up periods. All patients continued index antiepileptic drugs with initial target doses varies from low to moderate ranges. Add-on therapy was initiated in 43% of cases around the titration phase of index antiepileptic drugs (i.e. very early add-on). Treatment trends reveal increased use of 1st generation antiepileptic drugs than 2nd and 3rd generation. 2 years seizure remission rates were 55.77% by index antiepileptic drugs only therapy and 44.23% by very early add-on therapy. The seizure remission period was mean±SD 858.71±209.08 days.
Conclusions: Index antiepileptic drugs with low to moderate initial target doses lead to achieving 2 years or more seizure remission. Very early add-on therapy is the novelty and leads to achieving the goal.

Keywords: Idiopathic generalized epilepsy, Index antiepileptic drugs, Very early add on, 2 years seizure remission, Initial target doses

INTRODUCTION

Considering new onset epilepsy in children and adolescents 23-43% has generalized epilepsy of which 53-58% has 'Idiopathic generalized epilepsies' (IGEs).[1-3] Under the umbrella of 'Genetic generalized epilepsies' (GGE), IGEs exist as a distinct subgroup with varying response to anti-seizure medications and variation in seizure remission.[4] Considering the chronology of the clinical use, FDA approved three categories of antiepileptic drugs (AEDs) are in market such as first, second, and third generation AEDs.[5] There are limited studies in children addressing efficacy of first prescribed AEDs in newly diagnosed epilepsy.[6]

Chronologically epileptic patients enter into 3 phases such as pre-treatment, on-medication, and off-medication phases. The treatment gap still exists in developing countries due to gap in knowledge, attitude, and practices.[7] In the meantime the optimal length of treatment for IGEs is debatable on short duration of 2-3 years verses expanded duration of 5 years.[8]

The primary outcome of appropriate seizure management in epilepsy is seizure remission and subsequent lowest recurrence risk prediction. Still debate is going on in the definition of traditional seizure remission for 2 years to 5 years verses expand to 10 years remission recently longed by the International League Against Epilepsy (ILAE). The proposal to expand of 10 years seizure-free with the last 5 years off AEDs is to predict the lowest recurrence risk.[9] Considering lowest recurrence risk prediction and adverse impact Matti Sillanpaa et al critically evidences that there are no significant changes in the magnitude of the relapse rate when remission increased from 2 to 5 years and further to 10 years.[8]

There are diversities in seizure remission studies. There are limited studies in children addressing 2 years seizure remission on treatment in newly diagnosed epilepsy.[6,10] There are hardly found any study focusing 2 years seizure remission on first choice (index) AEDs without substitution in newly diagnosed epilepsy.

Additionally, it is evidenced the best response of AEDs used as monotherapy at low dosage suggesting that unnecessarily maximally tolerated AEDs doses may not be used routinely.[11]

The aim of the study was to assess the effectiveness of index AEDs in children with IGEs those underwent at least 2 years remission. The present study was a clinic based retrospective longitudinal observational study.

METHODS

The present study was designed as a retrospective longitudinal study to assess the effectiveness of first-ever AEDs in children with idiopathic generalized epilepsy (IGE). The primary endpoint of this study was at least two-year seizure remission.

The study was retrospectively evaluated the follow-up medical records of consecutive patients compatible with the diagnosis of IGE during the period April 2017 to December 2020. The study was done in the author's private paediatric and neurology care clinic in the city of Agartala of North-East India. Patients meeting the following criteria were included: (1) diagnosis of IGE according to the ILAE 2017 criteria; (2) diagnosis of IGE in the setting of convincing clinical evidence; (3) less than 18 years of age at onset of epilepsy; (4) established clinical remission of at least two years.[4]

A combination, of generalized seizure types compatible with the diagnosis of IGE was also inclusive in the study. The exclusion criteria were patients who do not neatly fit into recognized IGE, had less than two follow-up visits after medication, and any comorbidity other than IGE.

A combination of another AED compatible with the index AED (the first-ever AED initiated) was not excluded from the analytic study.

A retrospective chart review using a standard preformat to capture demographic data, family history of epilepsy, history of febrile seizures, number of follow-up visits, follow-up periods, age at last data collection, age at the seizure onset, number of seizures at enrolment, seizure patterns, last attack of seizures, seizure remission period, first choice of AED and dosage, concomitant AEDs, efficacy and any troublesome adverse effects of drugs was recorded. Follow-up period was calculated from the first day of enrolment in the clinic to the date at last data collection. Seizure remission period was calculated from the last attack of seizures to the date at last data collection.

The choices of the index AED regimen and target dosage level was made according to author's experiences and preferences and not according to any formal protocol. The initiated target doses (ITD) was the calculated doses that were planned to titrate and maintain during follow-up period. AEDs were grouped into three categories according to the chronology of the clinical use such as first-generation AEDs, second-generation AEDs, and third-generation AEDs. Considering combination therapy AEDs were also categorized as index AED category and add-on category. The recorded brain imaging (MRI or CT) and electroencephalography (EEG) results were retrieved carefully.

Descriptive statistics were used to demonstrate baseline characteristics of the patients expressed as means±SD. The online quick standard deviation and variance calculator was used to analyse the data. Categorical variables are expressed as numbers and percentages. The distribution of drug doses was represented by the box and whisker plot.

Medians, and interquartile ranges were calculated. The box and whisker plot was created using Microsoft office 2019 excel.

RESULTS

The study population was comprised of 52 patients with IGE (Table 1). The mean age was 12.42±5.05 years (2.9-18 years) at last data collection, whereas the mean age of seizure onset was 7.42±5.08 years (range, 0.9-16 years). The study population was 59.6% male (31 patients) and 40.4% female (21 patients). The basic findings of the study cohort were depicted in Table 2. Cumulatively 651 seizures manifested at enrolment in all patients before treatment initiation.

The mean seizure manifestation at enrolment was 12.52±26.60 (range: 2-120). Considering seizure patterns 73% of cases fulfilled the criteria for generalized tonic-clonic seizures alone (GTCA). The remaining 27% of cases had a combination of generalized seizure types such as a combination of tonic-clonic seizures and absences in 13.5%, and combined tonic-clonic seizures and myoclonus in 13.5%. Only 7.69% of cases had a family history of epilepsy. A history of febrile seizures was found in 11.5% of cases.

The total number of follow-up visits in all patients was 6.62±14.44 (range: 2-18). Cumulatively all follow-up visits constituted 1177.5±772.86 days of follow-up periods. Electroencephalography (EEG) results were retrieved in 80.77% of cases of which abnormality was found in 71.43%. The EEG showed the classical finding of generalized spike-wave discharges. Normal routine EEG was found in 28.57% cases in the setting of convincing clinical evidence of IGE. Brain imaging (MRI or CT) was done in 36.54% of cases in which abnormality was found in one case only that consisted of left parietal oedema after a recent seizure manifestation. 63.46% of cases did not undergo neuroimaging.

Categorically 78% of patients received 1st and 2nd generation groups of AEDs, whereas 22% of cases received 3rd generation AEDs (Figure 1A). Comparatively most (45%) of the cases received 1st generation AEDs. The AEDs used under the umbrella of 1st generation AEDs were phenytoin (PHT), valproate (VPA), clobazam (CLB), and clonazepam (CZP). Next was 2nd generation AEDs such as lamotrigine (LTG), topiramate (TPM), and oxcarbazepine (OXC). Among the prescribed AEDs two were 3rd generation AEDs such as levetiracetam (LEV) and lacosamide (LAC).

All patients continued index AEDs such as VPA (50%), LEV (19.23%), LTG (9.61 %), OXC (9.61%), and 3.85% each of TPM, PHT, and CLB throughout the course of therapy. Therefore, VPA was the most frequently used AED regimen in this study cohort. Only 3 index AEDs such as VPA (71.42%), LEV (14.29%), and LTG (14.29%) was used in 14 patients with a combination of generalized seizure types. The top 7 index AEDs to which patients were exposed are shown in the pie chart (Figure 1B). Among 52 patients who followed up, no one received substitution or polytherapy. Only 23 patients exposed to add-on AED manifested seizures around 24 to 48 hours of titration phase of index AED. This group of patients was categorized as a very early add-on group. Therefore, there were two categories of patients based on treatment such as the index AED exposure group and very early add-on AED group. The top 3 AEDs to which patients were exposed as add-on therapy is shown in the pie chart (Figure 1C). Among three drugs used as add-on therapy in combination with the index AEDs, most of the cases (91.3%) received CLB than CZP (4.35%) and LAC (4.35%). The add-on AEDs were limited to 7 patients with a combination of generalized seizure types of which 5 (71.42%) patients were exposed to CLB, 1 (14.29%) case exposed to CZP, and 1 (14.29%) case exposed to LAC.

The dosage patterns to which patients were exposed daily are shown in box and whisker plots (Figure 2). The median was 500 (range: 200-1250), 1000 (range: 500-2000), 600 (range: 300-900), 200 (200-200), 300 (range: 200-300), 112.5 (range: 75-150), and 10 (range: 5-20) in VPA, LEV, OXC, TPM, PHT, LTG, and CLB. Accordingly, Inter-quartile ranges (IQR) were 480, 0, 0, 0, 50, 112.5, and 5 respectively. Only one case received LAC with 75 mg daily dosage as add-on therapy and another one received CZP with 0.5 mg daily dosage. These combined data demonstrated that patients exposed to lower to moderate dose ranges both in monotherapy and very early add-on therapy appeared to have at least 2 years seizure remission.

Fortunately, no troublesome adverse drug reactions were recorded among all of those with index AED only and add-on therapy. Two years seizure remission rates were 55.77% by index AEDs only therapy and 44.23% by very early add-on therapy with the index AEDs respectively (Figure 1D). The seizure remission period was 858.71±209.08 days (range: 730-1782 days).

Table 1: The demographic characteristics of study cohort.

Variables	Characteristics
Patients (N)	52
Male: female ratio (%)	31: 21(59.6: 40.4)
Age in years (mean±SD)	12.42±5.05
Age of seizure onset in years (mean±SD)	7.42±5.08

Table 2: Baseline findings of the study cohort.

Variables	Characteristics
Number of follow-up visits (mean±SD)	6.62±14.44
Follow up visit period in days (mean±SD)	1177.5±772.86
Number of seizures at enrolment in all patients (mean±SD)	651 (12.52±26.60)
Seizure patterns: tonic-clonic seizures alone (%)	38 (73)
Combined tonic-clonic seizures and absences (%)	7 (13.5)
Combined tonic-clonic seizures and myoclonus (%)	7 (13.5)
Seizure remission period in days (mean±SD)	858.71±209.08
History of febrile convulsion (%)	6 (11.54)
Positive family history for epilepsy (%)	4 (7.69)
Imaging (MRI or CT result, N=19) (%): normal	18 (94.74)
Abnormal*	1 (5.26)

Continued.

Variables	Characteristics
Imaging not done (%)	33 (63.46)
Interictal EEG findings, N=42 (%): normal	12 (28.57)
Abnormal	30 (71.43)
Failed to retrieve	10 (19.23)

Note: *Left parietal oedema after a seizure manifestation.

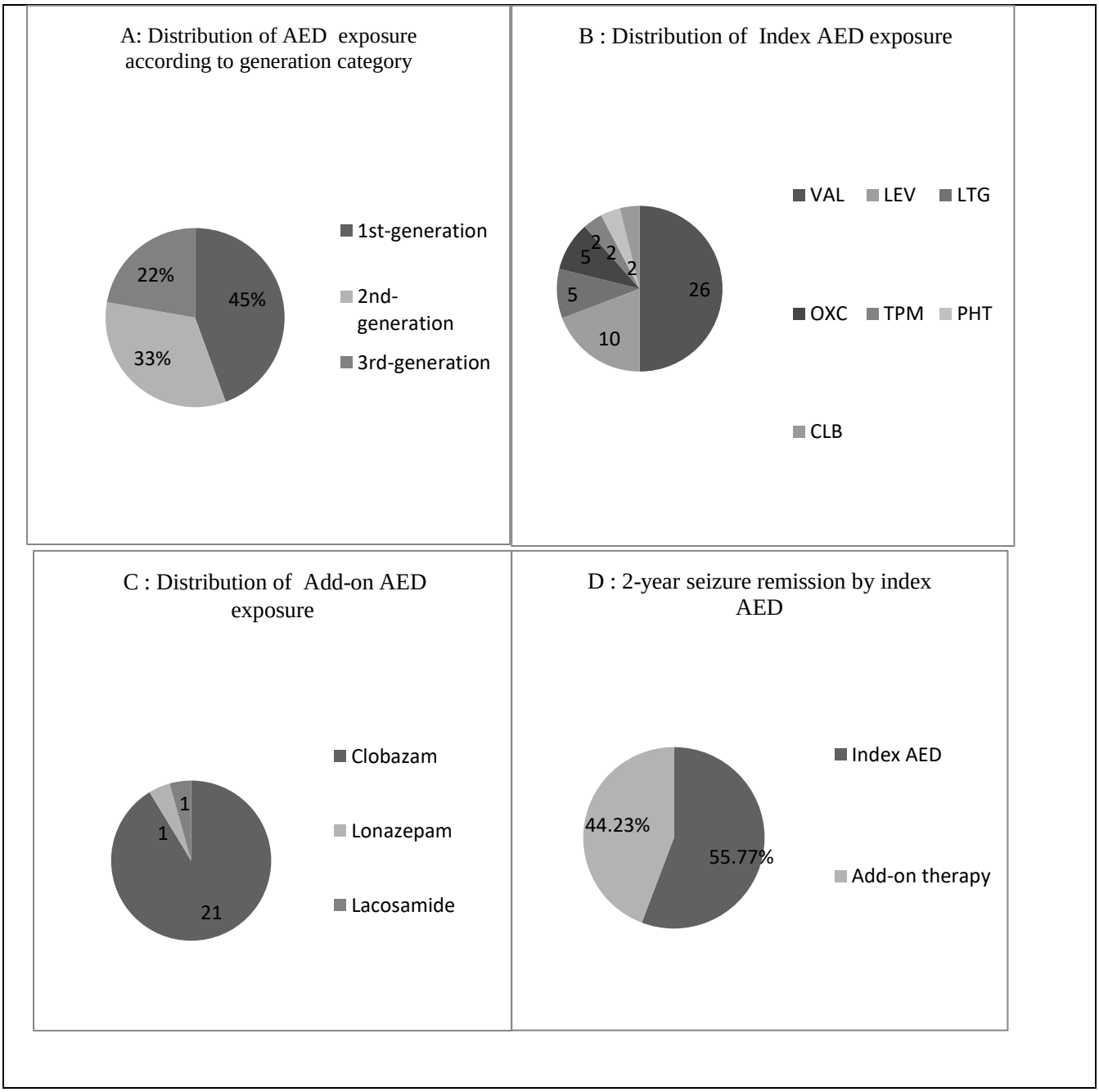

Figure 1: Distribution of AED exposure and 2-year seizure remission by index AED
(A) distribution of AED exposure according to a category of generation in all patients in percentages; (B) distribution of index AED exposure in all patients in numbers. This group included 14 patients with a combination of generalized seizure types out of which 10 patients exposed to VPA, 2 cases exposed to LEV, and 2 cases exposed to LTG; (C) distribution of early add-on AED exposure in 23 patients in numbers. This group included 7 patients with a combination of generalized seizure types out of which 5 patients exposed CLB, 1 case exposed to CZP, and 1 case exposed to LAC; and (D) 2 years seizure remission by index AED. 2 years seizure remission for index AED and very early add-on among patients was 56% (29 patients) and 44% (23 patients) respectively.

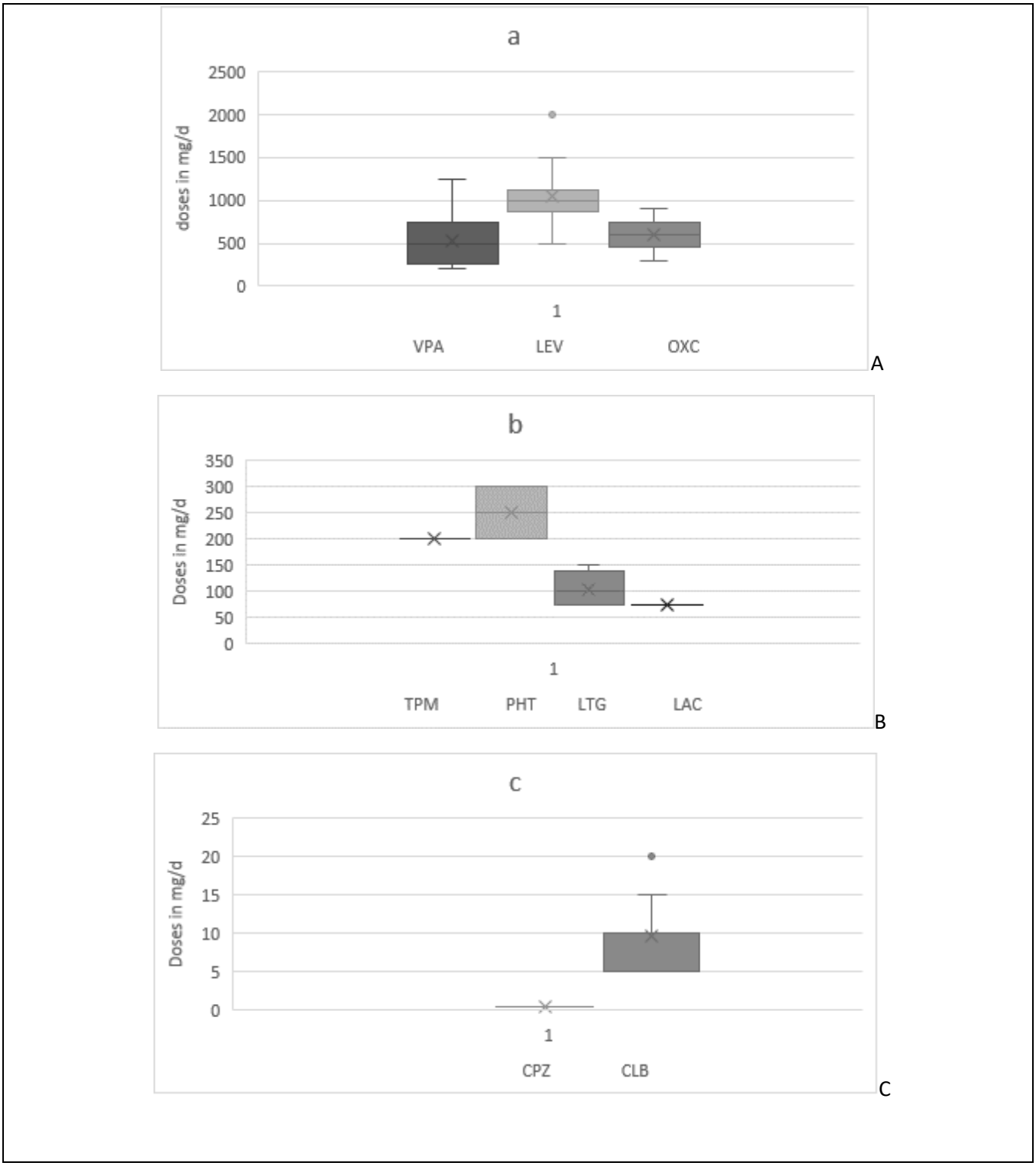

Figure 2: Box and whisker plots of daily AED doses in mg of 52 patients. The ends of the whiskers represent the maximum and minimum values (A) the median was 500 (range: 200-1250) in VPA, 1st quartile, 3rd quartile, and IQR were 257,737, and 480 respectively. For LEV it was 1000 (range: 500-2000), 1000, 1000, and 0 respectively. For OXC it was 600 (range: 300-900), 600, 600, and 0 respectively; (B) the median was 200 (range: 200-200) in TPM, 1st quartile, 3rd quartile, and IQR were 200,200, and 0 respectively. For PHT it was 300 (range: 200-300), 225, 275, and 50 respectively. For LTG it was 112.5 (range: 75-150), 75, 125, and 50 respectively. For LAC it was 75 (range, 75-75), 75, 75, and 0 respectively; and (C) only 1 patient received CZP 0.5 mg daily as an add-on. The median was 10 (range 5-20) in CLB, 1st quartile, 3rd quartile, and IQR were 5, 10, and 5 respectively.
IQR is inter-quartile range.

DISCUSSION

To achieve targeted seizure remission for 2 years or more the present study reveals that for IGEs, all patients maintain index AEDs with ITD without escalation and substitution. Of note, 56% of patients achieve the goal with index AEDs only treatment and 44% achieve the goal with add-on therapy accounting for similar efficacy. This result dictates responsiveness to appropriate antiseizure medications in IGEs.[12,13] The add-on therapy in this study is not due to adverse drug effect or due to failed index AEDs. It is a very early add-on due to seizure manifestation around the titration phase and maintains the same dosage with ITD of index AED throughout the course of therapy. Here is the novelty of our study. It is worthy to mention sub-therapeutic dosing during AED titration may result in seizures.[14]

Treatment trends reveal increased use of 1st generation AEDS followed by 2nd generation AEDs without shifting towards 3rd generation AEDs. VPA and CLB are the most commonly prescribed AEDs in this study cohort. This surprising finding contradicts the trends in to use of newer AEDS in other studies.[15,16] There is substantial evidence that old and new AEDs account for similar efficacy and tolerability profiles.[6]

The majority of the patients achieving the goal of 2 years seizure remission or more maintain their AEDs in the low to moderate dose ranges. With this dosage ranges possibility of intolerance and troublesome side effects may be less. Interestingly no one in the present study experiences troublesome side effects. In contrast to the expectation of higher AED dosages incremental responsiveness accepting the possibility of side effects, our result is focusing on a lower dosage regimen for long time seizure remission in IGEs. This is in favour of a recent study highlighting better efficacy of lower quartile dosage regimen to control seizures in epilepsy compared to higher quartile ranges.[11]

Presumed to have genetic aetiology IGEs recognize as a distinct subgroup of the GGEs.[17,18] The term genetic and hereditary is not synonymous.[4] A family history of epilepsy in the present cohort is limited to 8% of cases only. This is in favour of other study showing the association of a first-degree family history of epilepsy in approximately 10-12% of cases.[19-21] This association is supportive of generalized seizures. However, considering the genetic basis of aetiology a family history of epilepsy is not mandatory for the diagnosis of IGEs.[4]

A history of febrile seizures in the present cohort was limited to 11.5%. Of note typical febrile seizures manifest approximately in 5% of all children under the age of 6 years.[22] Again generalized epilepsy with febrile seizures plus (GEFS+) which is familial epilepsy may resemble IGEs.[23] However, this association is not fit in our cases. Considering IGEs this association may be incidental.

Although there are no atypical features, neuroimaging is done in 36.5% of cases of which all except one are normal. The abnormality in one case is minor delineating left parietal oedema immediately after a seizure manifestation. Although normal neuroimaging is a criterion for diagnosis of IGEs, neuroimaging is not required if the clinical presentation is convincing for IGES and the patient is not presenting with atypical features.[24,25]

Considering the sensitivity of routine EEG is around 50% for the initial EEG, a normal routine EEG finding in this study is 28.6% cases limits within the expectation.[26] This result does not exclude a diagnosis of IGEs in the setting of convincing clinical evidence. Abnormal interictal EEG finding is supportive for IGEs.

To achieve the goal of 2 years or more seizure remission in this study, consistency in follow-up and consistency in compliance to treatment play a critical role together with appropriate antiseizure medications.

Being a retrospective-study, the author was constrained by the dataset without a priori assumptions. The author could not deny the possibility of biases in the selection of AEDs and ITDs because the selection strategy was dependent on the experience of the doctor. Another limitation of the study was the small sample size.

CONCLUSION

Our findings highlighted that appropriate index AED with fixed ITD leads to achieving seizure remission for 2 years or more. Very early add-on therapy is the novelty. Add-on in seizure manifestation around titration phase of index AED leads to achieving seizure remission for 2 years or more. No escalation, substitution and polytherapy are required to achieve seizure remission for 2 years or more. Low to moderate doses of AEDs are effective to achieve the goal in most cases. Treatment trends reveal increased use of 1st generation AEDS such as VPA and CLB. Above all consistency in follow-up and consistency in compliance to treatment play a critical role together with appropriate antiseizure medications to achieve the goal.

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