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International Journal of Current Research
Vol. 9, Issue, 07, pp.54739-54744, July, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

A STUDY OF EFFICACY AND ADVERSE EFFECT PROFILE OF FIRST ANTI -EPILEPTIC DRUG IN CHILDREN WITH NEWLY DIAGNOSED EPILEPSY

***,[1]Dr. Nusrat Bhat, [2]Dr. Kavita Srivastava and [1]Dr. Sanjay Lalwani**

[1]Department of Paediatrics, Bharati Vidyapeeth Medical College, Pune, India
[2]Department of Paediatric Neurology, Bharati Vidyapeeth Medical College, Pune, India

ARTICLE INFO

Article History:
Received 21st April, 2017
Received in revised form
19th May, 2017
Accepted 04th June, 2017
Published online 31st July, 2017

Key words:

Epilepsy,
AED,
Oxcarbazepine.

ABSTRACT

Introduction: Limited data are available for the effectiveness of the antiepileptic drugs in children in daily clinical practice. The AED chosen for initial therapy should be one that is highly effective for the particular seizure type or syndrome and that is safe and well tolerated. The present prospective study was designed to investigate the interaction among efficacy, tolerability, and overall effectiveness of the first antiepileptic drug in children with newly diagnosed epilepsy.

Method: Out of 149 children in which (64 females and 85 males) who received valproate 56 (n = 37.6%), Oxcarbazepine 70(n = 47%), levetir-acetam 8(n = 5.4%), carbamazepine 8 (n= 5.4%), 5(n = 3.4%) received phenobarbitone monotherapy as the first-line treatment, were enrolled in the study. Seizure control and the occurrence of adverse events were assessed at 3 months and 6 months respectively. We demonstrated the outcome of epilepsy in relation to several demographic (age and gender), pharmacological and clinical aspects.

Results: Overall 110 (73.8%) were seizure free at 3 months and 130(87.2%) were seizure free at 6 months respectively. Out of which 101(67.78%) patients had focal epilepsy and 17(11.40%) had generalized epilepsy and 31(20.8%) had unclassified epilepsy. The majority of seizure free patients required only moderate daily dose of the antiepileptic drug. Valproate and Carbamazepine (the most commonly prescribed antiepileptic drugs). The reasons for treatment failures were lack of seizure control and intolerable adverse events in some patients.

Conclusion: In conclusion, the majority of patients with newly diagnosed Epilepsy become seizure free with the first line anti epileptic drugs (Oxcarbazepine/ carbamazepine) for focal epilepsy and valproate for generalised epilepsy) in our daily clinical practice. Oxcarbazepine and valproate treatment is effective, safe and well tolerable in our children with newly diagnosed epilepsy.

Citation: Dr. Nusrat Bhat, Dr. Kavita Srivastava and Dr. Sanjay Lalwani, 2017. "A study of efficacy and adverse effect profile of first anti -epileptic drug in children with newly diagnosed epilepsy", *International Journal of Current Research*, 9, (07), 54739-54744.

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by a recurrent tendency to have spontaneous, intermittent, abnormal electrical activity in a part of the brain, which manifests as seizures, and is diagnosed as the result of a patient having a second unprovoked seizure, with at least 24 hours between the first and second seizure. (Brodie and French, 2000) A seizure can be defined as" an episodic disturbance of movement, feeling, or consciousness caused by sudden synchronous, inappropriate, and excessive electrical discharges in the cerebral cortex" (Brodie and French, 2000; Brodie and Dichter, 1997) (Brodie and French, 2000). Epilepsy is a common paediatric neurological disease with an incidence rate of 5 per 1000 populations. It constitutes 70% of all paediatric neurological problems and 70 % of epilepsies have their onset in paediatric age group (Oguni, 2004) (Brodie *et al*., 1997). The most commonly used classification in clinical practice is that established by the International League against Epilepsy (ILAE) to classify epileptic seizure and epilepsy syndromes (ILAE 2017) (Scheffer *et al*., 2017). Based on the ILAE classification of epileptic seizures, these are divided into four groups based on clinical findings and electroencephalograph (EEG) readings: focal onset, (localization-related), general onset, unknown seizures and focal to bilateral seizure.

******Corresponding author:* **Dr. Nusrat Bhat,**
Department of Paediatrics, Bharati Vidyapeeth Medical College, Pune, India.

Ilae classification 2017

The main three types of seizures; generalized, partial and unclassified. But based on the cause, each type is further subdivided into idiopathic, symptomatic or cryptogenic epilepsy. Partial seizures occur in one small area of the brain and can sometimes spread to other regions. Simple partial

seizures are often termed an 'aura' or warning and they can occur before a complex partial or tonic clonic seizure or on their own. There is no loss of awareness or consciousness and they usually last less than a minute and in Complex partial seizures consciousness or awareness is altered, and the person may or may not respond. Seizures are also classified on the basis of EEG findings as generalized, focal and unclassified seizures respectively.

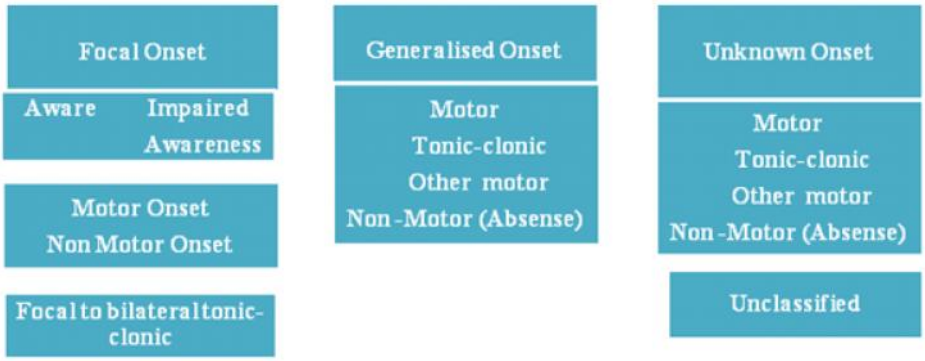

Figure 1 classification of epilepsy

Diagnosis of epilepsy

Proper diagnosis of epilepsy is an essential element for the prognosis and selection of the most appropriate treatment. Diagnosis of epilepsy can be divided into two stages: clinical evaluation and investigations. A detailed physical and neurological examination is usually performed to detect any neurological deficit that corresponds to an underlying pathology in the brain. Investigations of epilepsy to identify abnormalities in brain structure or function and support the clinical diagnosis, to aid in the identification of seizure classification and to detect any underlying brain abnormalities. Electroencephalography (EEG) is an important tool for the diagnosis of epilepsy because of its ability to identify epileptic form EEG activity in order to determine seizure classification. It is based on the recording of electrical discharge generated in the brain that in the case of epilepsy would be excessive and sometimes characteristic (Oguni, 2004). Magnetic Resonance Imaging (MRI) is another essential tool in the diagnosis of epilepsy. It is considered the most sensitive and specific structural neuro-imaging procedure for epilepsy (Bergen *et al*., 1989) (Oguni, 2004; Bergen *et al*., 1989). It is used to detect the underlying brain lesion that might be responsible for seizure development. MRI is particularly useful in symptomatic epilepsy and complex partial seizures to look for any abnormalities like temporal lobe epilepsy, leukomalacia / gliosis, grey matter lesions such as cortical dysplasia. Various other techniques used in the functional imaging of the brain have been developed and are being applied in the evaluation of epilepsy. The decision to start anti-epileptic drugs treatment based on several criteria including the likelihood of seizure recurrence, consequences, beneficial and adverse effects of the pharmalogical agents chosen. Patients with epileptiform discharges on the EEG or congenital neurological defects are at high risk of further seizure. When starting treatment, antiepileptic monotherapy is associated with better compliance and fewer side effects than combination regimens. Several factors are considered including its relative efficacy, tolerability, serious toxicity, ease of use and cost. As 60% of patients will gain control of epilepsy with the first line of antiepileptic drugs, so much attention should be given to the selection of initial drug, taking into account the efficacy of the AED for the seizure type or syndrome (Kwan and Brodie, 2000a). Effectiveness of a drug is a measure that includes both its efficacy and tolerability. Achieving complete seizure control is the main target of AED treatment and is considered as the main indicator of treatment success. The probability of achieving complete seizure freedom varies depending on the efficacy of AED applied (Di Mascio *et al*., 1986).

For the purposes of this project, efficacy of AED is measured based on the percentage of patients achieving seizure freedom for a minimum period of 6 months at last recorded follow up. The other important aspect in the effectiveness of any drug is its tolerability. Tolerability is a factor directly related to the side effects exerted by the drug. It is assessed based on the incidence, severity and impact of side effects of a particular agent on the patients. The main difficulty associated with the evaluation of side effects is that it is often based on spontaneous reporting by the patients. Although spontaneous reporting highlights the clinically there is variability in the accuracy of detection of side effects (Mattson and Cramer, 1993). It is difficult to assess the severity of these side effects quantitatively (Cereghino, 1992). In addition, most clinical trials have allowed a limited flexibility for dose adjustment or dosage escalation (Perucca, 1996). The main difficulty associated with the evaluation of side effects is that it is often based on spontaneous reporting by the patients. Further problems include the difficulty to assess the severity of these side effects quantitatively and to differentiate the side effects of an added AED from those resulting from concomitant medications or drug interactions. The main purpose of this study is to know the efficacy and tolerability of first line anti-epileptic drugs in children in newly diagnosed epilepsy as none of the studies had been done for India that's why we want to do this study. There are relatively fewer studies examining the tolerability and the treatment failure of antiepileptic drugs in children compared with adults. We provide a comphrensive and current literature review of the AEDs, focusing on tolerability and efficacy data in children.

MATERIALS AND METHODS

Study design: Prospective observational hospital based study. It includes, detailed history from patients and witnesses including demographic data, risk factors of epilepsy, medical condition, detailed description and frequency of episodes that have already occurred. This is followed by electroencephalography (EEG) and magnetic resonance imaging (MRI) that are carried out as clinically indicated in order to confirm the diagnosis of epilepsy and to help in

identifying the seizure type or syndrome which will subsequently help in selection of antiepileptic drugs appropriate for that specific seizure type. All children aged 3 months to 18 years attending pediatric OPD or admitted in wards as well as patients in status epileptics, PICU who had more than 2 unprovoked seizures. A child referred for seizures was screened; those who are newly diagnosed with epilepsy and started on AED will be studied. These children followed up at 3 months and 6 months to look for seizure control and side effects. Exclusion criteria: Children with febrile convulsion, acute symptomatic seizures and who was already on anti-epileptic drugs. Antiepileptic drugs were selected by the pediatric neurologist according to International league against epilepsy recommendations in which carbamazepine/ Oxcarbazepine was first choice for partial onset and valproate for generalized onset seizures. Children were monitored and followed after 3 month and 6 month respectively. At each visit seizure response, adverse effects, medication dose were recorded. Efficacy of Anti-epileptic drugs was measured based on the percentage of patients achieving seizure freedom at 3 months and 6 months of follow up. Adverse events were assessed by history given by parents or the children. Analysis of data was obtained from the excel sheet by using SPSS (Statistical Package for Social Sciences) Version 20:0. Qualitative data variables expressed by using frequency and Percentage (%). Quantitative data variables by using mean and SD etc. Chi –square test or Fischer exact used to find the association between seizures free with various qualitative data variables.

RESULTS

Demography:

Out of 160 patients that were initially included in our study, 11 patients were lost to follow up and were excluded from the study.

The data of 149 children with newly diagnosed epilepsy who received anti-epileptic drug monotherapy for at least 6-month, with follow up periods at 3 months and 6 months respectively were analyzed at Bharati Vidyapeeth hospital in pediatric department. We demonstrated the outcome of epilepsy in relation to several demographic (age and gender), pharmacological and clinical aspects. Patients were demonstrated for better understanding of the natural history of treated epilepsy, an informational aid for the future prescription choice of drug. Of 149 children, 56 (37.6%) received valproate, 70(47%) received Oxcarbazepine, 8(5.4%) received levetir-acetam, 8 (5.4%) received carbamazepine, 5 (3.4%) received phenobarbitone monotherapy. 110 (73.8%) were seizure free at 3 months and 130(87.2) were seizure free at 6 months. Overall 101(67.78%) patients had focal epilepsy and 17(11.40%) had generalized epilepsy and 31(20.8%) had unclassified epilepsy. Partial epilepsy was significantly more prevalent among patients received carbamazepine, Oxcarbazepine and levetir-acetam as compared to those treated with valproate and phenobarbitone. Demographic characteristics of subjects are presented in table 1. Gender distribution was as follows: 64 (43%) female and 85 (57%) male in table 2a and age of onset with seizure control at 3 month and 6 month respectively presented in table 2b as:

Distribution of patients according to Age of onset of seizure

Patients were divided in 3 age groups as: less than 1 year, 2-5 years and > 10 years, table 2 b and fig 2 shows the age of onset of first epileptic seizure along with seizure control at 3 month and 6 month respectively. In our study we found 29 patients in age group of less than 1 year out of which 23(79%) patients were seizure free at 3 months and 27(93%) at 6 months respectively. Patients in age group of 1- 5 years was found to be 63 patients out of which 48(76%) were seizure free at 3 months and 59(93%) at 6 months respectively. In age group of more than 5 years up to 16 years, total patients were 57 in

Table 2a. Gender distribution

Gender	Patients	Percent
Male	85	57.0
Female	64	43.0
Total	149	100

Characteristics of the patients treated with the first antiepileptic drug monotherapy

Characteristic	Total	Seizure free	
		3month	6month
Patient enrolled n= (%)	149	110 (73.8)	130(87.2)
Gender n= (%)			
Male	85(57)	67(11.9)	77(51.7)
Female	64(43)	46(30.8)	54(36.2)
Age group			
< 1 year	29(19.5)		
1year-2 years	26(17.4)		
2 years-5 years	37(24.8)		
5years-10 years	39(26.2)		
>10 years	18(12.1)		
Seizure type n= (%)			
Generalized	17(11.4)	10(58.82)	15(88.2)
Focal	101(67.8)	63(62.3)	85(84.15)
Unclassified	31(20.8)	27(81.09)	30(96.77)
Epilepsy syndrome			
BECTS	7(4.7)	5(71.4)	6(85.71)
None	142 (95.3)	103(72.50	122(85.91)
AEDs used			
Valproate	56(37.6)	41(73.21)	48(85.71)
Oxcarbazepine	70(47)	47(57.14)	55 (78.57)
Carbamazepine	8(5.4)	7(87.5)	7(87.5)
Phenobarbitone	5(3.4)	5(100)	4(80)
Leveraicetam	8(5.4)	7(87.5)	7(87.5)

number out of which 41(71%) were seizure free at 3 month and 44(77%) at 6 month respectively. Age of onset of seizures is considered to be significant factor for the seizure control. In our study, we found less percentage of patients with seizure control in age group > 10 years at the onset of seizure as compared to other age groups.. According to shinnar *et al*. (1985) in their study 40% children with epilepsy reported cumulative risk of seizures reoccurrence of 29%, 37% and 42% at 1 year, 2 years and 5 years interval respectively. In our study there were somewhat statistical significant differences in the seizure free rates between onsets of age (p value- 0.015)

Table 2 b. Age of onset with respectively seizure control at 3 and 6 months

Age of onset	Patients	Seizure free at 3 months	Seizure free at 6 months
≤ 1 years	29 (19.5)	23(79.31))	27(93.1)
1 – 5 years	3(42.28)	48(76.19)	59(93.6)
>5 years	7(38.25)	41(71.9)	44(77.19)
P value		0.404	0.015

History of Perinatal insult and seizure freedom

In our study we found 26 patients with history of Perinatal insult and 123 patients had normal Perinatal history, out of which 16(61.53%) patients were seizure free at 3 month and 22(84.61%) at 6 month respectively. In our study seizure free rate is higher in patients had normal Perinatal history as compared to the patients had abnormal Perinatal history as in Table 3. There is high risk of recurrence of seizure for patients with Perinatal insult resulting in neurological abnormalities. This result is similar as compared to other studies [14](Shinnar *et al*, Devilat *et al* Engl. J. Med 1985 313). Those patients with severe insult were still on antiepileptic drugs and not controlled. But statistical, there was no significant difference between the patients had normal perinatal difference as compared to patient who had normal Perinatal history.

Perinatal history	Patients	Percent	Seizure free 3 month	6 month
Normal	123	82.55	90(73.17)	108 (87.8)
Abnormal	26	17.44	16(61.53%	22(84.6%)
p-value			0.260	0.667

Family History of Epilepsy and seizure freedom

In our study 10 patients had positive family history of epilepsy. Out of 10 patients only 3 patients had seizure recurrence (30%) at 3 month and 1 patient (10%) had seizure recurrence at 6 month. On the contrary there were 139(71.2) with no family history of epilepsy out of which 26 % seizure recurrence at 3 months and 10.19% had seizure recurrence at 6 months. There was no significant difference found between family history of seizure and recurrence and also statistical no significant difference were found (p value-0.865). No other previous studies had found family history of epilepsy as significant risk factor for prediction of seizure recurrence.

Abnormal EEG and seizure freedom

In our study we found 118 (79.19%) patients had abnormal EEG and 31 (20.80%) had normal EEG in which we found patients had abnormal finding on EEG showed 82 (69.49%) were seizure free at 3 months and 101 (85.59%) were seizure free at 6 months and patients had normal findings on EEG showed 28(90.32%) and 29(93.54%) were seizure free at 3 and 6 months respectively. Some researchers have not found EEG to be of predicative importance (Holowach *et al*, Broson *et al*, Oller *et al*) while others found its predictive significance (Matricardi *et al*, Shinner *et al*). We also compared EEG findings of focal epilepsy and generalized epilepsy, there were no significant difference between EEG outcome and seizure freedom.

EEG Findings (Focal Vs Generalized)

EEG	Abnormal EEG	Percent	Seizure free 3 month	6 month
Focal (n=101)	97	96.05	67(69.07)	82(84.53)
Generalised(n=17)	17	100	12(70.58)	15(88.23)

Abnormal Neuro-imaging and seizure freedom

In our study, we found MRI Brain was done in 32 patients in which 16 patients had abnormal MRI findings and 16 patients had normal findings. Out of 16 patients had abnormal findings, 8(50%) patients were seizure free at 3 months and 12 (75%) patients were seizure free at 6 months respectively. 16 patients with normal MRI findings, 14 (87.5%) patients were seizure free at 3 months and 16 (100%) were seizure free at 6 months. Patients with abnormal neuro-imaging had higher risk of seizure recurrence as compared to patients with normal neuro-imaging but statistically we didn't found any significant difference (p value -0.999).

Milestones and seizure freedom

In our study, we found 30(20.38 %) patients with delayed milestones and 119(79.86%) patients with normal milestones. Out of which 15 (50%) were seizure free at 3 months and 24(85%) patients were seizure free at 6 months respectively. Out 119 patients, 94(78.99) were seizure free at 3 months and 106 (89.07) patients at 6 months respectively. There was significantly high rate of seizure free in patients with normal mile stones at 3 months and 6 months respectively but statistically no significant difference were found (p value-0.999).

Milestones	Patients	Percent	Seizure free 3 month	6 month
Normal	119	79.86	94(78.9)	106(89.0)
Abnormal	30	20.38	15(50)	24(85)
p-value			0.419	0.999

Efficacy, tolerability and Drug response

Success rate in terms of reduction in seizure frequency were good in newly diagnosed epilepsy with first line anti-epileptic drugs. The majority of seizure-free patients required only a moderate daily antiepileptic drug dose (valproate 20.21 ±7.20 mg/kg) and Oxcarbazepine/ carbamazepine (12 ± 3mg/kg). Of the 149 patients recruited, 110 (73.8%) reached a state of seizure freedom at 3 month and 130 (87.2%) at 6 month respectively. In the first line anti-epileptic treatment, drugs with the highest prescription rate were Oxcarbazepine (n=70) followed by sodium valproate (n= 56) and carbamazepine (n= 8) with similar rates of response (47%, 37.6% and 5.4%, respectively). Overall, 17 (11.4%) patients had generalized epilepsy and 101 (67.8%) had partial epilepsy (focal) and 31 (20.8%) had unclassified epilepsy. When classified in regard to electro clinical syndromes, 7 (4.7%) patients had benign

epilepsy with Centro temporal spikes, 142 (95.3%) patients; no specific electro clinical syndrome could be diagnosed. In our study we found in focal epilepsy, out of 101 patients, 66 patients received Oxcarbazepine and 34 received other drugs and there is somehow significant difference of seizure free rate with Oxcarbazepine (p value-0.07) and it showed fairly higher success rate were achieved also in subgroup of patients given Oxcarbazepine to replace another anti-epileptic drugs. The difference between success rates in patients treated for less than 6 months and those treated for 6 months or more was approx. statistically significant (p value 0.07). In our study we found in focal epilepsy, the seizure free rate is higher as compared to other drugs and in case of generalized and unclassified epilepsy (p value- 0.148) as shown in Table 3 and 4.

Table 3. Focal n= 101

Drugs used	Control at 3 month	P value	Control at 6 month	P value
Oxcarbazepine/ Carbamazepine N=66	44(66.8)	0.702	57(86.36)	0.074
Others: Leveraicetam/ N=35	22(62.8)		24(68.5)	

Table 4. Generalized n=48

Drugs used	Control at 3 month	P value	Control at 6 month	P value
Valproate N=29	22(75.51)	0.237	26(89.7)	0.148
Others- N=19 phenobarbitone /Oxcarbazepine	17(89.4)		19(100)	

Comparison of Adverse events of Antiepileptic Drugs

The most common adverse effect was weight gain which developed with valproate as patients become obese because of increase in appetite, and headache which developed more often with Oxcarbazepine but most of the patients can tolerate this side effects and the second most common adverse event was gastrointestinal problems in our studies. Rash was developed with carbamazepine than with valproate and necessitated carbamazepine discontinuation. The majority of seizure-free patients required only a moderate daily antiepileptic drug dose (valproate 20.21 ±7.20 mg/kg) and Oxcarbazepine/ carbamazepine (12 ± 3mg/kg). Dosage was also compared for children with treatment in terms of adverse effects, lack of efficacy or combinations of both factors. There was no significant difference in the doses between seizure free patients using valproate, Oxcarbazepine and carbamazepine and those who had to change treatment because of intolerable adverse events in all these antiepileptic drugs. Although the difference didn't reach significance, patient who became seizure free took slightly lower doses than those with the treatment failures because of adverse events for all antiepileptic drugs. However 4(2.68) patients withdrew drugs of valproate because of significant major side effects like weight gain and 6(8.57) patients withdrew drugs of Oxcarbazepine because of major adverse events like rash with fever with dizziness.

Drugs Dosage (Oxc) n=77No. of Patients

10-20mg/kg/day	59 (76.6%)
20-30mg/kg/day	16 (20.77%)
30-40mg/kg/day	2 (0.02%)

Drugs Dosage (Val) n=56 No. of Patients

10-20mg/kg/day	45 (80.3%)
20-30mg/kg/day	13 (23.21%)
30-40mg/kg/day	nil (0.0%)

Table 5. Comparison of adverse events between OXC vs. VAL vs. other drugs

Drugs	Adverse effects at 3 months	P value	Adverse effects at 6 months	P value
Oxcarbazepine/ Carbamazepine N= 78	54 (69.23)	0.975	20 (25.64)	0.692
Valproate acid N= 56	39(69.42)		15(26.74)	
Others like Leveraicetam etc N= 15	10(66.66)		4(26.66)	

Table 5. Adverse events of first antiepileptic drug in children

Adverse Events Sample size	Valproate n= 56	Oxcarbazepine n=70
Headache	5	8
GIT problems	5	4
Weight gain	7	3
Scholastic performance	3	5
Dizziness	1	6
Rash	0	3
Alopecia	2	0
Nocturnal Enuresis	2	0
Excessive sleep	5	2
Constipation	1	1
Abdominal pain	3	5

P-value for occurrence of adverse effect in Valproate vs Oxcarbazepine is 0.228 (> 0.05).

Conclusion

In conclusion, the majority of patients (73.8% at 3 months) and (87.2%) at 6 month of follow up) with newly diagnosed Epilepsy become seizure free with the first line anti-epileptic drugs (Oxcarbazepine/carbamazepine for focal epilepsy and valproate for generalized epilepsy) in our daily clinical practice. Oxcarbazepine and valproate treatment is effective, safe and well tolerable in our children with newly diagnosed epilepsy with partial seizures and generalized seizures at 3 and 6 months of follow up. In addition to seizure control, the overall effectiveness is also determined by adverse effects and children with epilepsy have a good prognosis after treatment with first anti-epileptic drugs. Overall all adverse events –as major and minor adverse events only 2 patients with drew drug due to major side effect on valproate medication and 6 patients withdrew drug due to major side effect of Oxcarbazepine. There are certain factors associated with seizure freedom which we found in our study: Age of onset > 10 years having somehow low seizure control as compared to other age group while other factors like perinatal history, milestones, EEG and MRI finding were not significant in our study.

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