

## ORIGINAL ARTICLE

# DRUG DISCONTINUATION IN EPILEPTIC CHILDREN: PREDICTIVE VALUE OF THE EEG

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**Background**– Electroencephalography (EEG) is capable of determining the foci and intensity of epileptic discharges. The long-term use of antiepileptic drugs (AEDs) in children may be accompanied by side effects in 50% of cases; hence, drug therapy should be discontinued as early as possible. Before a decision is made to discontinue a drug, the recurrence of seizures could be predicted by interpreting the characteristics of the EEG.

**Methods**– This study was conducted on 106 children who were without recurrent seizures for at least 1 year. They had been under AED therapy continuously. An EEG was taken while the child was awake, and the trace was assessed by a single neurologist with respect to background activity, focal slowing of waves, focal spike waves and generalized sharp spike waves. The children were monitored for signs of recurrent seizures every 3 months for at least 1 year. The results were assessed according to Kaplan-Meier survival analysis and the Log-Rank test.

**Results**– The probability of recurrent seizures was 24.8 % (95% CI, 22.5–28.5 %) after 1 year of follow-up. A significant relationship existed between the state of the present EEG and previous EEGs ( $p < 0.05$ ). Among the children with abnormal EEG results on drug discontinuation, seizure recurrence was more frequent in boys ( $p = 0.045$ ). Comparing present and previous EEGs, the relative risk was calculated to be about 1.98 (95 % CI, 1.01–3.91,  $p < 0.05$ ).

**Conclusion**– The risk of seizure recurrence was quite similar to the findings of other studies. Overall, there was no significant relationship between the presence of abnormal EEG findings and recurrence of the seizures. An important result of our study was the importance of comparing EEGs prior to drug withdrawal with primary EEGs ( $p < 0.05$ ). Estimation of the probability of recurrent epileptic seizures must be only one part of the process of the physician's decision. Attention must be paid to other factors such as the physical, social and economical consequences as well as the estimation of AED side effects.

**Keywords** • antiepileptic drug • EEG • prognosis • seizure

### Introduction

Electroencephalography (EEG) although inexpensive, safe and applicable in outpatient settings, has limited sensitivity. Electrical artifacts and physiologic derangements can affect the results, and its utility is limited in conditions of abnormal metabolic functioning such as hypoglycemia, subconscious states and the concomitant use of some drugs.<sup>1</sup>

Long-term use of antiepileptic drugs (AEDs) in children may be accompanied by side effects in 50% of the cases, some remaining dormant for long periods.<sup>2</sup> On the other hand, long-term pharmacologic treatment of epilepsy does not guarantee permanent remission.<sup>3</sup> Therefore, it is recommended to discontinue AEDs as early as possible, especially in children.<sup>2,4-24</sup> When making the decision to discontinue AEDs, the possibility of seizure recurrence should be considered and premature termination of therapy should be avoided. Prior to drug withdrawal, probable risk of recurrence should be contrasted with the risk of

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**Table 1.** Analysis of electroencephalographic (EEG) variables in children in order to forecast the occurrence of recurrent seizures (Log-Rank test).

	Remission (%)	Without remission (%)	Total (% of all patients)
Normal EEG	55 (73)	20 (27)	75 (70.8)
Abnormal baseline EEG	22 (71)	9 (29)	31 (29.2)
Focal slowing	53 (74.5)	18 (25.5)	71 (67)
Generalized spike	15 (88)	2 (12)	17 (16)
Focal spike	27 (67.5)	13 (32.5)	40 (37.7)

drug side effects, psychosocial disorders and economic status of the patient.<sup>3,5-7</sup> The parents of epileptic children should be informed about probable side effects and should be provided with clear estimates of recurrence.<sup>25</sup>

At present, many studies have been conducted to evaluate the efficacy of EEG in predicting the recurrence of seizures after drug discontinuation in epileptic children and adults.<sup>2,3,8,11-24,26,27</sup> It seems that abnormal EEG findings prior to drug withdrawal are associated with higher risk of recurrence of seizures in epileptic children.<sup>19</sup> In the present study, correlation between EEG report and recurrence after drug discontinuation is addressed.

### Materials and Methods

This study was conducted on a group of children who were free of seizures for at least 1 year and who had incessantly received antiepileptic drug therapy. The subjects were selected from a population of children below 12 years of age who attended the private clinic or the Epilepsy Clinic of Al-Zahra Hospital in Isfahan from 1996 to 1999.

A total of 106 children met the inclusion criteria and were enrolled in the study. First, a complete history was taken and physical examination was performed. The parent's written

consent was obtained. An EEG was taken while the child was awake. Each EEG trace was assessed by a single neurologist in both wakefulness and activation (e.g., hyperventilation) with respect to the presence or absence of variables such as background activity, focal slowing of waves, focal spike waves and generalized sharp spike waves.

The final report was categorized as normal, mildly abnormal or severely abnormal. In addition, comparison of the whole EEG obtained with that of the primary EEG was defined in the checklist as no change, worsened or better. The drug dose was gradually tapered. The children were followed up for signs of recurrent seizures every 3 months for at least 1 year. The results were assessed according to Kaplan-Meier survival analysis. The Log-Rank test was used to analyze each variable in the EEG and its relation with recurrence of epileptic seizures. SPSS 7.5 software was used to analyze the data.

### Results

Of the 106 children, 62 (58 %) were boys and 44 (42 %) were girls. The mean duration of follow-up from the time that AEDs were discontinued was 26 months. The probability of recurrent seizures was 24.8 % (95 % CI, 28.5-22.5%) after 1 year of

**Table 2.** The relation between assessment of children's electroencephalographic (EEG) findings at the onset of drug withdrawal according to gender and forecasting of seizure recurrence (Log-Rank test).

	EEG interpretation before drug withdrawal	Remission (%)	Without remission (%)	Total
Boys	Normal	15 (79)	4 (21)	19
	Slightly abnormal	11(78.5)	3 (22.5)	14
	Severely abnormal	16 (61.5)	10 (38.5)	26
	(Total)	42 (71)	17 (29)	59
Girls	Normal	7 (100)	0	7
	Slightly abnormal	6(85.5)	1(14.5)	7
	Severely abnormal	21 (70)	9 (30)	30
	(Total)	34 (77)	10 (23)	44

**Table 3.** Comparison of present and previous electroencephalography (EEG) and EEG assessment prior to drug withdrawal and forecasting of seizure recurrence

EEG interpretation before drug withdrawal	Current EEG compared with previous ones	Remission (%)	Without remission (%)	Total
Normal	Improved	21 (91.5)	2 (8.5)	23
	Unchanged	1 (50)	1 (50)	2
Slightly abnormal	Improved	5 (71.5)	2 (28.5)	7
	Unchanged	12 (86)	2 (14)	14
Severely abnormal	Improved	9 (75)	3 (25)	12
	Unchanged	23 (64)	13 (36)	36
	Deteriorated	5 (62.5)	3 (37.5)	8

follow-up. No significant relationship was present between background EEG characteristics prior to drug withdrawal with those of recurrent epileptic seizures (Table 1). A significant relationship existed between the state of the present EEG and previous EEGs performed ( $p < 0.05$ ). Among the children with abnormal EEG findings on drug withdrawal, recurrence of seizures was more frequent in boys ( $p = 0.045$ ). Comparing present and previous EEGs, the relative risk was calculated to be about 1.98 (95 %CI, 1.01–3.91,  $p < 0.05$ ).

The mean age of the children at the start of epilepsy was 3.4 years (SD,  $\pm 0.3$ ) and the mean age at the time of drug withdrawal was 8.3 years (SD,  $\pm 3$ ).

The children whose EEG findings had worsened as compared to previous findings, had a 14.5% higher risk of developing recurrent seizures.

On the whole, a significant relationship was not found between the final EEG report of these children at the time of drug withdrawal and recurrence of seizures. However, when gender was taken into account, a significant relationship was found to exist between the final EEG report at the time of drug withdrawal and recurrence of seizures (Table 2).

As seen in Table 3, there was only a 9 % change in recurrent seizures occurring in a child whose present EEG was normal, and which had shown improvement from previous EEGs. On the other hand, an approximately 38 % chance of recurrence was found for a child whose present EEG was abnormal compared to previous EEGs. A significant relationship was however not found to be present between them by the Log-Rank test.

In the analysis of a few variables, and by use of the Cox proportional hazard, the relative risk of the childrens' present EEG reports with those of previous reports were calculated to be around 1.98

(95 % CI, 1.01–3.91;  $p < 0.05$ ).

## Discussion

The risk of seizure recurrence 1 year after drug withdrawal was 24.8 %. This result is quite similar to the findings of other researchers who reported the mean recurrence percentage to be between 20–30%.<sup>2,3,5,7,9,14,28</sup> Considering these low recurrence values, the researchers suggest that AEDs in children should be gradually tapered as early as possible.<sup>2,4,24,28</sup>

The value of EEG during the periods between the seizures (interic EEG) is unknown, and varying results have been reported. In the meta-analysis performed by Shinner and colleagues, a significant relation was present between abnormal EEG findings and seizure recurrence (RR –1.45,  $p = 0.03$ ).<sup>9</sup>

A study on 136 patients with at least 1 year of follow-up showed abnormal EEG findings prior to drug withdrawal, which had no value in predicting recurrence of seizures. The patients who had progressive EEG changes on drug withdrawal however, had a higher seizure recurrence as compared to other patients. These were statistically significant.<sup>20</sup> In a similar study, Forster and Schmidberger reported comparable findings.<sup>21</sup>

In another study conducted in Ireland, patients who had abnormal EEG findings prior to drug withdrawal and who had no trace changes on tapering of the drug, were found to have the worst prognosis.<sup>17</sup> Matricardi et al reached the conclusion that the presence of continuous abnormal EEG findings during the disease and prior to drug withdrawal could be considered as a forecasting factor.<sup>11</sup> In yet another study, the forecasting value of EEG during AED withdrawal was evaluated in partial seizures. In that study, it was observed that

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the recurrence rate was higher among patients whose condition was worse at the time of drug withdrawal.

It has also been highlighted that EEG has a prognostic value during drug withdrawal, but not at the onset of drug withdrawal.<sup>22</sup> A study conducted in Holland showed that there was no relationship between the EEG status prior to drug withdrawal with seizure recurrence.<sup>23</sup> Andersson et al pointed to the fact that only the presence of epileptic waves, such as generalized spike waves, had no effect on the prognosis of epilepsy after drug discontinuation.<sup>24</sup>

The most important result of our study was the importance of comparing the child's EEG prior to drug withdrawal with the primary EEG ( $p < 0.05$ ). Only a few researchers have pointed to the importance of this factor.<sup>11,16,24</sup> It seems that this is important for cases where tapering had taken a long time.<sup>17,20,22</sup>

It has been reported that the focal slowing of waves as well as the presence of abnormal photoconvulsive response and focal spike waves could forecast the recurrence of seizures.<sup>8,14,26</sup> In our study, none of these had a statistically significant importance.

We conclude that the risk of recurrence inferred by the status of a child's EEG is one of the many factors that the neurologist should consider before discontinuing AEDs. Other factors include psychologic and socioeconomic, and the probability of the development of drug side effects.<sup>2-7,9,19,25,28</sup>

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