Zagazig University Medical Journal
www.zumj.journals.ekb.eg

https://dx.doi.org/10.21608/zumj.2020.18233.1590 Volume 28, Issue 5, September 2022(1041-1047)

**Manuscript ID** ZUMJ-1910-1590 (R3)
**DOI** **10.21608/zumj.2020.18233.1590**

**ORIGINAL ARTICLE**

# Predictors of Drug Treatment Failure in Childhood Epilepsy

***Wael Mahmoud Elsayed, Adham M. M. Ismail, *Shaimaa Wagih Abd El Salam and Mohamed Hamdy Ismail.***
Neurology departments Faculty of Medicine, Zagazig University, Egypt.

***Corresponding author:**
Shaimaa Wagih Abd El Salam
**Email**:
shimaawagih480@gmail.com

| | |
|---|---|
| **Submit Date** | 2019-11-25 |
| **Revise Date** | 2020-02-06 |
| **Accept Date** | 2020-02-06 |

## ABSTRACT

***Background:*** Epilepsy is considered as one of the most common serious neurological conditions. The prevalence of childhood epilepsy is approximately 3.5 to 7 per thousand children. Drug resistance is one of the major problems facing the treatment of epilepsy even with the new drugs and medical science progress. Assessment of the risk factors of epilepsy drug treatment failure in epileptic children may be determine the (risk factor or cause) of drug resistance epilepsy.

***Objectives:*** This study aimed to identify the most important factors of drug treatment failure of epilepsy in children.

**Patients and Methods**: A total of 120 epileptic children were recruited from Outpatient Clinics, Zagazig University Hospitals. All patients were subjected to Full history taking, thorough general and neurological examination. Then they were classified according to the response of treatment into controlled and uncontrolled groups.

***Results:*** Their ages ranged between 2 and 18 years including 74 males **(**61.7**%**) and 46 females (38.3%). About 44.2% of patients were on polytherapy while 55.8% were on monotherapy. There was 47 patients(39.2 %) controlled on treatment while 73 patients (60.8 %) were uncontrolled. There was significant association between focal seizures, generalized tonic colonic seizures, abnormal EEG, polytherapy and bad combination of drugs on one hand and poor control of seizures on the other hand .

***Conclusion:*** Accurate diagnosis, good choice of antiepileptics with appropriate dose and combinations (when indicated) can help better control of epilepsy.

***Keywords:*** Childhood epilepsy, Predictors, Drug, Treatment Failure

## INTRODUCTION

Epilepsy is one of the oldest recorded diseases. It is a brain disorder in which clusters of nerve cells in the brain sometimes signal abnormally, causing recurrent seizures [1]. It is considered as one of the most common neurological disorders and represents a major health problem, affecting 1- 2% of the world population [2].The prevalence of childhood epilepsy is approximately 3.5 to 7.2 per thousand children [3].

Despite of this, Its the incidence and prevalence figures varied considerably in different studies and countries. This is mainly due to differences in inclusion criteria, classification, diagnosis and case ascertainment methods [4].

Drug resistance is one of the major problems facing the treatment of epilepsy even with the new drugs and medical science progress and lefted unexplained [2].So assessment of the risk factors and causes of epilepsy drug treatment failure in children is important to be determined [5].So , if these risk factors are detected at onset, those children who might benefit from vigorous invasive treatment options [2].

**Site of the study**: This observational prospective study was carried out on 120 epileptic patients selected from Zagazig University Neurology Out-patient Clinic and Inpatient ward over the period from December 2017 till november 2018 .

All patients were diagnosed and classified according to classification and terminology of the International League Against Epilepsy (Commission on classification and terminology of the (ILAE) International League Against Epilepsy,1989). The diagnosis was based on history, description of seizures, and results of interictal electroencephalography (EEG). Clinical informations were obtained by interviewing the

patient and at least one witness for description of the seizures.The patients were 74 males and 46 females. Their age ranged between 2 to 18 years.

The following were used as tools in patients' selection and their acceptance to be included in the study:-

**Inclusion criteria:**

Patients with non-symptomatic epilepsy, ages range between 2 to18 years, all types of seizures and patient sex: patients of both sexes.

**Exclusion criteria:**

Duration of epilepsy diagnosis is less than 2 years, febrile seizures, associated general medical illness and concurrent use of regular medication known to interfere with AEDs.

**Ethical consideration:**

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to the code of ethics of the World Medical Association (declaration of Helsinki) for studies involving humans.

**All patients were subjected to the following**: Detailed general and neurological history taking from patient and/or eyewitness(es).

Seizure history: Age at onset of the first seizure and duration of epilepsy diagnosis. Past and current seizure frequency. Longest seizure-free period. Data of last seizure. Previous history of status epilepticus. Time of occurrence of seizures: diurnal, nocturnal or both; during sleep, on awakening from sleep. Precipitating factors of seizures: fever, fatigue, hyperventilation, sleep deprivation, emotional upset, GIT upset, menstruation, or sensory stimuli. Current seizure pattern. Anti-epileptic drugs (AEDs): types, compliance, and dosage regime for: Current AEDs. Past AEDs. Detailed history was taken from patients and/or their relatives about compliance to treatment in the recommended doses.

- Based on detailed AEDs' history taken from our patients and/or their relatives, a patient was considered to be on" good or bad AEDs combination" according to the evidence provided by some authors [6].

**Investigations:**

Interictal electroencephalography (EEG). Radiological investigation using brain computed tomography (CT) and/or Magnetic Resonance Imaging (MRI). Laboratory Investigation: CBC, liver, kidney function tests, ESR and serum level of AEDs(when applicable).

Study design patients were divided into the following groups based on the control of their seizures by AED(S):

**Controlled seizures group:** This group included 47 patients, who patients were considered controlled if they remain seizures free for at least two consecutive years on AEDs [7].

**Uncontrolled seizures group:** This group included 73 patients. Drug-resistant epilepsy had defined as the failure of adequate trials of two tolerated, appropriately chosen and used anti-epileptic drug schedules (whether as monotherapy or in combination) for two consecutive years [8].

**Satistical analysis**

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) **(**Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test ($X^2$) . Differences between quantitative independent groups by t test or Mann Whitney, P value was set at <0.05 for significant results & <0.001 for high significant result [9].

## RESULTS

The study included 120 patients, females represented 46 (38.3% ) ,and 74 (61.7%) were males [Table1] .The majority of patients were having GTC seizures as it represented (66.7%),then focal seizures with secondary generalization as it represented(14.2%),then focal seizures as it represented(7.5%),then tonic seizures as it represented(6.7%) ,and least common was absence as it represented(5%) [Table3] .We found statistically significant association between the GTC and focal seizures and uncontrolled epilepsy [Table 3] . There was significant relation between abnormal EEG activity and uncontrolled seizures, as (72.3%) of patients with abnormal EEG had uncontrolled seizures [Table4].Our study showed that there were 53 patients on polytherapy AEDs (77.4%) of these patients were not controlled [Table5].Thirty patients of the poly therapy group (56.6%) were on good combination but 23 of patients of this group (43.4%) were on bad AEDs combination There was significant relation between

bad combination of AEDs and un control of seizures as ( 87%) of patients on bad combination were not controlled [Table 6].

**Table 1:** Relation between sex of patients and seizure control

| Patient sex | | | Control of seizures | | Total | $X^2$ | P |
|---|---|---|---|---|---|---|---|
| | | | controlled | Uncontrolled | | | |
| Sex | Female | N | **18** | **28** | **46** | **0.0** | **0.99** |
| | | % | **39.1%** | **60.9%** | **38.3%** | | |
| | Male | N | **29** | **45** | **74** | | |
| | | % | **39.2%** | **60.8%** | **61.7%** | | |
| Total | | N | **47** | **73** | **120** | | |
| | | % | **100.0%** | **100.0%** | **100.0%** | | |

$X^2$**:**qui square

**Table 2:** Relation between Type of seizure distribution between studied groups and Seizure control

| Type of seizure | | Control of seizures | | Total | $X^2$ | P |
|---|---|---|---|---|---|---|
| | | Controlled n=47 | Uncontrolled n=73 | | | |
| Absence | N | **4** | **2** | **6** | **5.41** | **0.004*** |
| | % | **66.7%** | **33.3%** | **5.0%** | | |
| Focal | N | **3** | **6** | **9** | | |
| | % | **33.3%** | **66.7%** | **7.5%** | | |
| GTC | N | **29** | **51** | **80** | | |
| | % | **36.25%** | **63.75%** | **66.7%** | | |
| Tonic | N | **4** | **4** | **8** | | **0.14** |
| | % | **50%** | **50%** | **6.7%** | | |
| Focal with 2ry Generalization | N | **7** | **10** | **17** | Non-significant | |
| | % | **41.2%** | **58.8%** | **14.2%** | | |

$X^2$**:**qui square
P>0.005

**Table (3):** Relation between types of EEG epileptiform activity distribution between group

| Type of epileptiform activity | | Control of seizure | | Total | X2 | P |
|---|---|---|---|---|---|---|
| | | Controlled | uncontrolled | | | |
| Focal | N | **3** | **6** | **9** | **3.61** | **0.006** |
| | % | **33.3%** | **66.7%** | **7.5%** | | |
| Free | N | **28** | **27** | **55** | | |
| | % | **51%** | **49%** | **45.8m%** | | |
| Generalized | N | **10** | **26** | **36** | | |
| | % | **27.8%** | **72.2%** | **30%** | | |
| Focal with 2ry generalization | N | **5** | **15** | **20** | | |
| | % | **25%** | **75%** | **16.7%** | | |

$X^2$**:**qui square
P>0.005

**Table 4:** Relation between mono- and poly- therapy regimes and seizure control

| Type of treatment | | Seizure Control | | Total | $X^2$ | P |
|---|---|---|---|---|---|---|
| | | Controlled n=47 | Uncontrolled n=73 | | | |
| Mono therapy n=67 | N | **35** | **32** | **67** | **7.67** | **0.005*** |
| | % | **52.2%** | **47.8%** | **55.8%** | | |
| poly therapy n=53 | N | **12** | **41** | **53** | | |
| | % | **22.6%** | **77.4%** | **44.2%** | | |

$X^2$**:**qui square P>0.005

**Table 5:** Relation between AEDs combination and seizure control

| Response to drugs | | | Control | | Total | $X^2$ | P |
|---|---|---|---|---|---|---|---|
| | | | Controlled n=26 | Uncontrolled n=27 | | | |
| **Combination** | Good n=30 | N | **23** | **7** | **30** | **5.07** | **0.01*** |
| | | % | **76.7%** | **23.3%** | **56.6%** | | |
| | Bad n=23 | N | **3** | **20** | **23** | | |
| | | % | **13%** | **87%** | **43.4%** | | |

$X^2$**:**qui square
P>0.005

**Table 6:** A multivariate analysis was performed using logistic regression model for predicting prognostic factors of childhood epilepsy drug treatment failure in early stages the disease.

| | Adjusted OR (95% CI) * | Pv |
|---|---|---|
| Age of onset | | |
| late | Reference | |
| **early** | **2.31(1.51–4.65)** | **<0.001** |
| Sex | | |
| **M**ale | 0.85( 0.52–1.35) | 0.731 |
| female | Reference | |
| epilepsy type | | |
| controlled | Reference | |
| uncontrolled | 2.62 ( 1.13–3. 06) | o.03 |
| seizure type | | |
| Focal | Reference | |
| generalized | 1.05( 0.721–1.72 | o.751 |

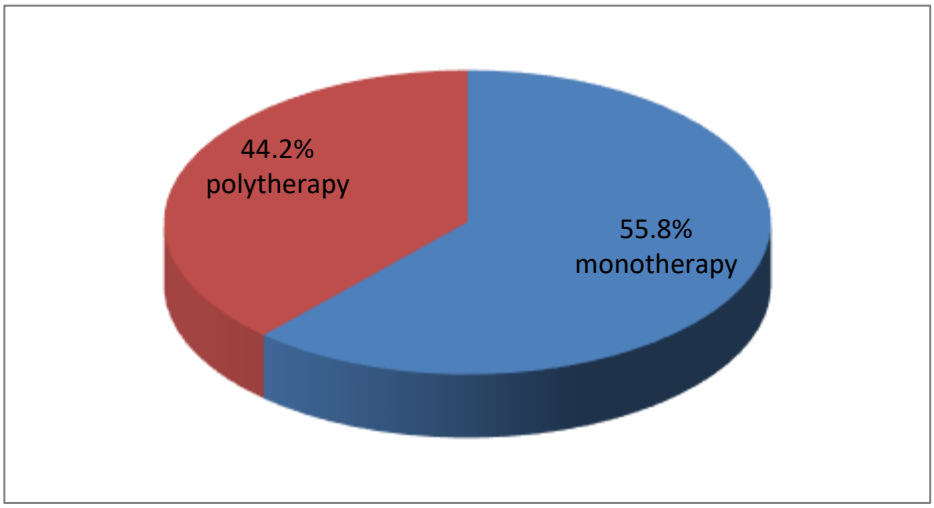


**Figure (1):** Monotherapy and polytherapy distribution

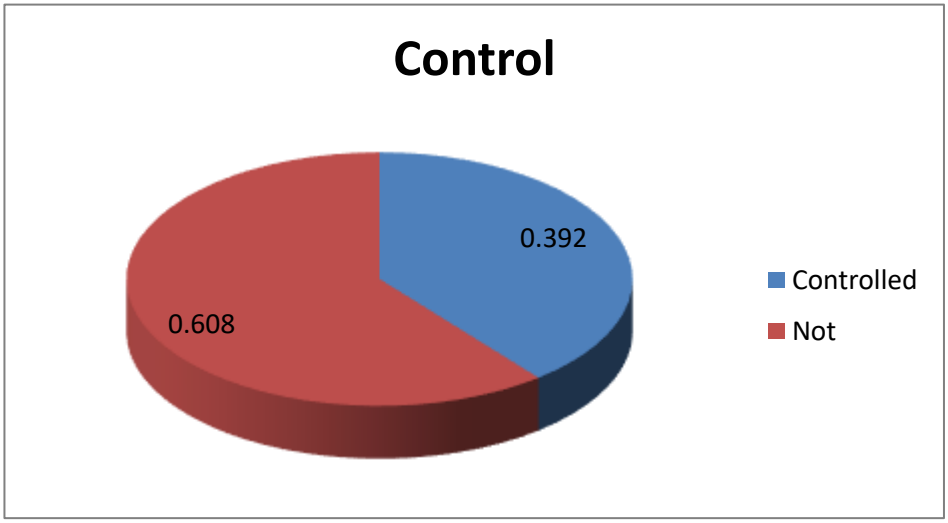


**Figure (2):** Association with treatment and control

## DISCUSSION

Epilepsy is the commonest neurological disorder in childhood and often confused with other frequently occurring childhood non-epileptic paroxysmal disorders [10]. Drug resistance is one of the major problems facing the treatment of epilepsy, even with the new AEDs and medical science progress. Treatment failure in childhood epilepsy had not been fully explained, for long time with many challenging data [11]. The present study had been conducted on 120 patients, 46 of them (38.3%) were females, and 74 of them (61.7%) were males. Contrary to our results a study with a much bigger number of patients (4288 child), 2104 were females (49.1%), and 2184 were males (50.9%). This may be due to the large, included number of patients in this study [12]. Our results showed that both sexes had no relation with the control of seizures and this is in agreement with Helen and Neil [ 13]. In epidemiological study, Aziz et al [14] do not found difference in the incidence between males and females. Most of our patients were suffering from generalized tonic-colonic seizures (66.7%), and focal seizures with secondary generalization (14.1%), while the least number of patients were suffering from absence (5%). These results are

similar to those of earlier studies which showed higher prevalence of generalized seizures in comparison to focal seizures Aziz et al [14] , David [15]. In contrast to our finding , Camfield [16] found focal seizures to be the most common (30.3%).This may be due to the large number of studied patients of different races ,and including all epileptic patients ,not only idiopathic as in our study. This study showed that there was statistically significant relation between the GTC and focal seizures and uncontrolled seizures, while Jull et al [ 17] Marinas et al[18] found the significant relation only was between the GTC and uncontrolled seizures. In our study there was a significant relation was found between abnormal findings in EEG and poor control of seizures as (72.3 %) of patients with abnormal EEG were not controlled on treatment (p 0.006). Similar to our findings Sakir et al [19] found 53.5% of their patients with abnormal EEG to have AEDs treatment failure. Lukman et al [20] found that 40% of patients with abnormal EEG had difficult-to-control seizure. Akm et al [21] also found that 67.7% of the controlled epileptic patients had normal EEG, and 80.9% of the uncontrolled patients had abnormal EEG (P <.001). In our study it was found that multiple drug therapy is a risk factor for uncontrolled epilepsy with high significant association (p 0.005), where out of 53 patients on multiple drug therapy, 41 patients (77.4 %) were uncontrolled. Similarly, [ 20] found that 62% of epileptic children on multiple drug therapy had sub-optimal seizure control (p = 0.003). While in Louis and Truly [22] study only (42.2%) were on poly therapy and poor seizure control (p .0002). our study demonstrated that" AEDs bad combinations" were found to be a major risk factor for uncontrolled seizures as out of 53 patients on poly therapy,30 of them (56.6%) were on good combination, (76.7 %) of these patients had controlled seizures, and 23(43.4%) were on bad combination, (87%) of them had uncontrolled seizures. Similarly, Louis [22] found that patients having drug resistant epilepsy are commonly on bad combination AEDS. Concerning to our study, early disease onset and type of seizures were found to be most statistically significant variables associated with treatment failure. Similarly, Assadi et al [23] showed agreement with our results.

## CONCLUSION

Accurate diagnosis, good choice of antiepileptics with appropriate dose and combinations (when indicated) and follow up of patients using estimation of serum level of AEDs (if available and indicated) can help better control of epilepsy.

**Conflict of interest:** The authors declare no conflict of interest

**Funding sources**: The authors have no funding to report

**Acknowledgement**

The authers are grateful for the patients without whom this study would not have been done.

## REFERENCES

1- Benbadis S. The differential diagnosis of epilepsy. A critical review. Epilepsy Behav 2009; 15: 15-21.
2- Berg A, Berkovic S, Brodie M, Buchhalter J. Revised terminology and concepts for organization of seizures and epilepsies. report of the ILAE Commission on Classification and Terminology. Epilepsia 2010;4: 676-685.
3- Gregg H R, Ian B, Markus R .Predictors of health-related quality of life in patients with epilepsy and psychogenic nonepileptic seizures.Epilepsy Behav 2017; (68):153-158.
4- Bell G, Sander J. The epidemiology of epilepsy: the size of the problem. Seizure 2011; 10(4):306-316.
5- Fisher R S ,Cross J H, French J A, Higaurashi N, Hirsch E, Jansen FE, et al.Operational classification of seizure types by international league against epilepsy:Positional Paper of ILAE commission of classification and terminology. Epilepsia 2017 ;58(4):522-530.
6- Ehsan M S, Mattew C W, Caroline S .Evidence for Efficacy of Combination of Antiepileptic Drugs in Treatment of Epilepsy. J Neurol Researc 2015;56:267-276.
7- David J .Childhood epilepsy; prognostic factors in predicting the treatment failure.J child Neurol2009;11:898-911.
8- Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen H W, Mathern G, etal. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2009;51: 1069-1077 .
9- IBM Crop.released .IBM SPSS statistics for windows ,version 22.0 Armonc,NY:IBM crop 2013.
10-Luef G.Hormonal alterations following seizures. Epilepsy and behavior 2010; 19(2):130- 131.
11-Berg A. Identification of Pharmacoresistant Epilepsy. Neurol Clin 2009;4: 1003-1013.
12-Jousif I, Serven M D, Patrigia O. Prevelance of epilepsy and seizures as a comorbidity of neurologic disorder in nursing homes. Epilepsy foundation 2017;88:751-757.

13- Helen E , Neil J .Sex differences in the neurobiology of epilepsy: a preclinical perspective .Neurobiol Dis 2015;72: 180–192.
14- Aziz H, Ali SM, France B. Epilepsy in Pakistan: Apopulation – based epidemiological study. Epilepsia 2009;5: 950-958.
15- David Y.Tonic–Clonic Seizures. E Medicine 2007;2: 237-249 .
16- Camfield P, Camfield C.Incidence, prevalence and aetiology of seizures and epilepsy in children. Epileptic Disord 2015;2:117-123.
17- Jull B E, Virta LJ , Kalvianin R , Keranen T.Choice of the first antiepileptic drug in elderly patients with newly diagnosed epilepsy.Seizure 2015;31:27-32.
18- Marinas A, Villanueva V, Giráldez BG, Molins A, Salas-Puig J, Serratosa JM. Efficacy and tolerability of zonisamide in idiopathic generalized epilepsy. Epileptic Disord 2009 ; 11(1):61-66.
19- Sakir D, Gulcin B S , Derya Y D, Naz Y .The role of sleep electroencephalography in patients with new onset epilepsy. Seizure2015;31: 80-83.
20- Lukman FO, Shehu S, Shakirah D, Aisha N, Muhammad U, Aminu AT. Electroencephalography Abnormalities in Generalized Epilepsy and Their Predictors: A Multicenter Experience.Ann Afr Med 2018;17(2): 64–69.
21- Akm M, Mizanur R, Shaheen A, Syeda T, Alam K.Risk Factors of Poorly Controlled Childhood Epilepsy - A Study in A Tertiary Care Hospital. Bangladesh J Child Health 2010;2: 44-50.
22- Louis St,Truly EK.Rational polytherapy: maximizing efficacy and minimizing drug interactions, drug load, and adverse effects. Curr Neuropharmacol 2009;2:96-105.
23- Assadi PA, Emami M, Ashzadizeh M, Necksresht A.Reasons of uncontrolled seizures in adults; the impact of pseuduintractability.Seizure;22(4):271-274.

To Cite:
El Sayed, W., Ismaeil, A., Abd Elsalam, S., Ismail, M. Predictors of Drug Treatment Failure In Childhood Epilepsy. *Zagazig University Medical Journal*, 2022; (1041-1047): -. doi: 10.21608/zumj.2020.18233.1590