The Egyptian Journal of Hospital Medicine (April 2024) Vol. 95, Page 1318-1322

Predictive Factors of Refractory Epilepsy

Mohamed Magdy Ezzat[*1], Mohamed El-Said Ahmed[1], Samir Mohamed Attia[2], Mohamed Abd-ElSalam Mohamed[3]
Departments of [1]Emergency Medicine, [2]Vascular Surgery, and
[3]Neurology, Faculty of Medicine, Mansoura University, Egypt
[*]**Corresponding author:** Mohamed Magdy Ezzat, **Mobile**: (+20) 01099327551, **Email:** mhmdmgdy81@gmail.com

ABSTRACT

Background: Several epileptic patients give no response to the usual line of treatment, which represents 1/5 of epileptic patients and is known as drug-resistant epilepsy (DRE). DRE is often accompanied by impaired intellectual functions, psychiatric co-morbidities, physical damage, and low quality of life (QoL).

Objective: This study aimed to assess the predictive factors for early identification of refractory seizures.

Patients and Methods: This was a cross-section study conducted during a period of one year at Emergency Department (ED), Faculty of Medicine, Mansoura University. We comprised cases with diagnosis of refractory epilepsy on a total of 80 patients with refractory seizures [at least 2 potentially effective anti-epileptic drugs (AEDs) whatever mono or combined in maximally tolerated dose].

Results: Of the studied cases, 62.5% were females. There was a significant difference in cases with refractory epilepsy as regard seizures types with higher frequency of mixed and focal seizures. There was no statistically significant difference recorded regarding the previous history of status epilepticus (SE). Mixed seizures were significantly increased among cases with refractory epilepsy. The presence of positive family history, positive history of febrile seizures, associated psychiatric disorders and younger age at disease onset increase risk of refractory epilepsy.

Conclusion: The main predictors of development of DRE were high initial seizures frequency, positive family history, febrile seizures, associated psychiatric disorders and younger age at disease onset.

Keywords: Refractory epilepsy, Neurologic disorders, AEDs, Electroencephalogram.

INTRODUCTION

Seizure has been considered as a common neurological disorder affecting approximately fifty million subjects globally, among them 90% cases are from developing nations. It is a global disease that could be occurred at any age. Genetic factors, cerebral infection, stroke, tumors and hyperthermia have been considered as the main reasons of fits. Annually, around 125000 recent seizures cases happen of which, thirty percent are below the age of eighteen at onset of diagnosis. The hallmark of seizure generation is hyperexcitability of neurons. It has been demonstrated that the main mechanism of seizure development is the impaired balance between excitatory and inhibitory neurotransmitters [1].

Based on cerebral regions are comprised, seizures might composed of disturbed conscious level with fasciculation, confusion, and sensory manifestations are noticed. Seizures could be classified according to the site as well as to the clinical presentation. Management has to be initiated with a single AEDs [1].

Although researches have demonstrated that most of subjects with seizures could be associated with relapse, fits are still refractory in at least thirty percent of cases [2].

Drug resistant seizures could be described as a failure of proper trials of two tolerated, properly selected and used AEDs schedules to reach sustained seizure freedom [3]. Pharmaco-resistant seizures remain a substantial clinical trouble. Several researches demonstrated a correlation between intractable seizures and a lot of predictors such as age at onset, neurological deficits, increased seizure frequency at onset, electroencephalographic (EEG) alterations, and abnormalities in brain image [4].

This study aimed to assess the predictive factors for early identification of refractory seizures.

PATIENTS AND METHODS

This was a cross-sectional study conducted from October 2022 to October 2023 at Emergency Department, Faculty of Medicine, Mansoura University.

Inclusion criteria: Patients above 18 years old from both genders with refractory epilepsy (at least 2 potentially effective anti-epileptic drugs whatever mono or combined in maximally tolerated dose with full compliance).

Exclusion criteria: Patients with age less than 18 years, with false refractory epilepsy (improper diagnosis, inadequate anti-epileptic drugs or none compliance) and pregnant females.

Methods:

All cases were subjected to complete history taking that included age, gender, residency, past history of previous surgeries and past history of medical diseases. Full clinical examination included general examination and full neurological examination.

The analysis of history of epilepsy included asking about family history of seizures, age of onset, etiology of seizures, type of seizures, frequency of seizures (recent and last month), duration of the attack, triggers

Received: 23/11/2023
Accepted: 22/01/2024

of the attack, seizures clusters, febrile seizures, recent anti-epileptic drugs, seizure reduction by the AEDs, number of ineffective AEDs used before and psychiatric co-morbidity. The laboratory investigations comprised complete blood count (CBC), arterial blood gases, random blood glucose, serum creatine and liver, and kidney functions tests. Radiological examinations included brain magnetic resonant imaging (MRI). Electroencephalogram (EEG) was also done.

Ethical approval: Our study was approved by The Ethical Committee, Mansoura University. All steps were explained to the subjects before their participation. Also, they were informed that, they have the right to leave the study without giving any reasons. Privacy and confidentiality were guaranteed. All participants signed informed consents after a thorough explanation of the goals of the study. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Data analysis was conducted by SPSS software, version 25 (PASW statistics. Chicago). Qualitative data were defined by utilizing number and percent. Quantitative data were described using median for non-normal distribution of data and mean ± SD for normal distribution of data. Chi-Square, Fischer Exact test, Monte Carlo tests were utilized for comparison of qualitative data. Mann Whitney U test was utilized for comparison between two studied groups for non-normal distribution of data. Student t test was utilized to compare two independent groups for normal distribution of data. In the context of all the previously used tests, $P \leq 0.05$.

RESULTS

Table **(1)** displayed that mean age was 36.36±13.18 years, median age of disease onset was 8 ranging from 0.6 to 23 years, median disease duration was 27.5 ranging from 3 to 58 years, 62.5% of the studied cases were females, 6.2% have delayed developmental milestones, 11.2% positive history of febrile seizures and 6.2% positive history of neonatal asphyxia. 77.5% of the studied cases had generalized tonic clonic seizures, 13.8% had focal and had 8.8% mixed seizures. 38.8% had nocturnal seizures, 6.2% catamenial seizures and 22.5% history of status epilepticus (SE). Median seizures frequency before treatment was 2 per day ranging from 1 to 5, median frequency per weeks was 1 ranging from 1 to 3 and median frequency per months was 2 ranging from 1 to 5, while median seizures frequency after treatment was 1 per day ranging from 1 to 1, median frequency per weeks was 1 ranging from 1 to 3 and median frequency per months was 1 ranging from 1 to 4.

Table (1): Demographic characteristics, history distribution and seizures characteristics of the studied cases

	n =80	**%**
Age/years		
Mean±SD	36.36±13.18	
Age of onset /years		
median (min-max)	8(0.6-23)	
(IQR)	(4-12)	
Disease duration /years		
median (min-max)	27.5(3-58)	
(IQR)	(17.25-38)	
Sex		
Male	30	37.5
Female	50	62.5
Family History		
-ve	70	87.5
+ve	10	12.5
Delayed Developmental Milestones	75	93.8
-ve	5	6.2
+ve		
History of Febrile Seizures		
-ve	71	88.8
+ve	9	11.2
History of Neonatal Asphyxia		
-ve	75	93.8
+ve	5	6.2
Seizure Types		
GTCS	62	77.4
Focal	11	13.8
Mixed	7	8.8
Nocturnal Seizures		
-VE	49	61.2
+VE	31	38.8
Catamenial Seizures		
-VE	75	93.8
+VE	5	6.2
History of Status Epilepticus		
-VE	62	77.5
+VE	18	22.5
Seizures frequency before treatment	Median (min-max)	
(Days)	2(1-5)	
(Weeks)	1(1-3)	
(Months)	2(1-5)	
Seizure frequency after treatment	Median (min-max)	
(Days)	1(1-1)	
(Weeks)	1(1-3)	
(Months)	1(1-4)	

IQR: interquartile range

Table **(2)** illustrated that 7.5% of the studied cases have symptomatic seizures and 92.5% idiopathic seizures. Of the studied cases, 82.5% were on Levitracetam, 57.5% on Valproic, 43.8% on Carbamazepine, 18.8% on Lamotrigine, 11.2% on Phenytoin, 6.2% on Zonisamide, 2.5% on Clonazem & Topiramate and 1.2% on Andovimpamide. Of the studied cases, 42.5% were on single drug, 37.5% on two drugs, 13.8% on three drugs and 6.2% on four drugs. The median duration before treatment start was ranging from 1 to 4 years, 82.5% of the studied cases had no associated psychiatric comorbidities, 11.2% had mental sub-normality, 2.5% had Depression and anxiety and 1.2% had cerebral palsy.

Table (2): Seizures characteristics, treatment lines and associated psychiatric disorders among studied cases.

	n =80	%
Seizures Causes		
Idiopathic	74	92.5
Symptomatic	6	7.5
Andovimpamide	1	1.2
Topiramate	2	2.5
Zonisamide	5	6.2
Valproic	46	57.5
Clonazepam	2	2.5
Carbamazepine	35	43.8
Levitracetam	66	82.5
Phenytoin	9	11.2
Lamotrigine	15	18.8
Number of AEDS		
1	34	42.5
2	30	37.5
3	11	13.8
4	5	6.2
Duration before treatment /years median (min-max)	1 (1-4)	
Co-morbid Psychiatric Disorders		
No	66	82.5
Mental sub-normality	9	11.2
Depression	2	2.5
Cerebral palsy	1	1.2
Anxiety	2	2.5

Table **(3)** illustrated that 13.4% had encephalomalacia and 7.5% had brain atrophy by brain imaging. Regarding EEG imaging, 2.5% of the studied cases showed normal interictal EEG, 5% showed left anterior temporal epileptogenic dysfunction, 51.2% showed poly-spike slow wave, 33.8% showed centrencephalic epileptogenic dysfunction and 7.5 showed bitemporal epileptogenic dysfunction.

Table (3): Brain and EEG imaging among studied cases

Brain imaging	**n=80**	**%**
Brain Atrophy	5	7.5
Encephalomalacia	9	13.4
Normal	53	79.1
EEG Imaging		
Normal Interictal EEG	2	2.5
Left Anterior Temporal	4	5.0
Epileptogenic Dysfunction	41	51.2
Poly-Spike Slow Wave	27	33.8
Centrencephalic Epileptogenic Dysfunction	6	7.5
Bitemporal Epileptogenic Dysfunction		

DISCUSSION

Several epileptic patients give no response to the usual line of treatment, which represents 1/5 of epileptic patients and is known as DRE. DRE is often accompanied by impaired intellectual functions, psychiatric co-morbidities, physical damage, and low QoL. Early determination and prediction of DRE are important in determination of the patient's most appropriate therapeutic modality [5]. Thus, the aim of the current study was to assess the predictive factors for early identification of refractory seizures.

Regarding demographic data, our study displayed that the mean age of the studied cases was 36.36 ± 13.18 years, median age of disease onset was 8 ranging from 0.6 to 23 years, median disease duration was 27.5 ranging from 3 to 58 years. Of the studied cases, 62.5% were females. Our study displayed that there was a statistically significant difference between cases with refractory epilepsy as regard family history, positive history of febrile seizures and age at onset of disease. Like in the current study, in the majority of researches, first onset seizure frequency was recognized as a predisposing factor for DRE [6, 7]. Recurrent fits are demonstrated to be accompanied by neuronal loss especially in the hippocampal area, that could ultimately ends in recurrent excitatory circuits [8]. Likewise, **El-Deen *et al.*** [9] displayed that past history of febrile seizures were significantly increased among cases with DRE than those with responsive epilepsy. In contrast, **Ohtsuka *et al.*** [10] recorded no correlation between febrile seizures and DRE. In addition, **Berg *et al.*** [11] reported a relatively protective correlation between febrile seizures and intractability.

In regard to seizure frequency, the current study demonstrated higher frequency of seizures per weeks before start of treatment (p=0.03). Likewise, **El-Deen *et al.*** [9] recorded that high initial seizure frequency was a significant predisposing factor of DRE.

As regards seizures etiology, our study displayed that there was no significant difference between both groups concerning etiology (either idiopathic or symptomatic). In contrast, a lot of researches have

documented that symptomatic cause is recorded as a significant predisposing factor for DRE [6, 12].

The anatomical and physiological changes in the brain have been demonstrated to be associated with hyperexcitability as the etiology of epilepsy. Cerebral lesions are often accompanied by neuronal loss and astrogliosis. The most frequently reported mechanism of DRE was the transporter theory. Based on this theory, the structural alterations affect the capillary endothelial cells, which ultimately ends in the overexpression of efflux transports and drug resistances [13]. In addition **Karaoğlu *et al.*** [5] have displayed that, eighty six percent of cases with DRE had symptomatic cause, significantly greater than DRE free ones.

Regarding seizures characteristics, our study demonstrated that high frequency of mixed and focal seizures was detected among cases with refractory epilepsy, presence of nocturnal seizures and higher frequency of seizures per weeks before start of AEDs. In the context of status epilepticus (SE) related refractory seizure, the present study illustrated that there was no significant difference regarding previous history of SE. In agreement **Ko and Holmes** [14] have demonstrated that SE isn't accompanied by refractoriness. In addition, **Moinuddin *et al.*** [15] reported that previous history of SE wasn't demonstrated as a predictor of bad prognosis and negative consequences. In contrast, **Karaoğlu *et al.*** [5] and **Yilmaz *et al.*** [7] are in disagreement with the current study as regards history of SE as they have demonstrated that there was a significant correlation between previous history of SE and the development of refractory seizures. Also, **El-Deen *et al.*** [9] have demonstrated that history of SE and existence of epileptic syndromes recorded among 43% and 26.9% correspondingly of children with DRE, with significant difference. The actual discrepancies of debated outcomes could be because SE might develop owing to and a reason of DRE [16].

Regarding mixed seizures the current study demonstrated that mixed seizures were significantly increased among cases with refractory epilepsy compared to refractory free ones. In accordance, several studies have demonstrated that mixed seizure types were recognized as a predisposing factor for DRE in the majority of researches [7, 16, 17]. In addition, preceding researches concluded that seizure types have an important role in terms of the overall prognosis, and children with multiple seizure types could develop worse outcomes [7, 17]. In the same line, **Karaoğlu *et al.*** [5] have illustrated that, mixed seizure types could be considered as an independent predisposing factor for DRE development.

Regarding refractory seizure related psychiatric disorders, the current study demonstrated that high frequency of associated psychiatric disorders among cases with refractory epilepsy. Likewise, **Kedare and Baliga** [18] have demonstrated that cases with DRE are especially observed to have a greater risk of psychiatric and behavioral side effects. Another recent study conducted by **Elbeh *et al.*** [19] demonstrated that there was a correlation between personality traits and the degree of seizure as those patients are likely to have a significant need for control.

Regarding neonatal asphyxia, our study displayed that there was no statistically significant difference regarding neonatal asphyxia. In contrast, **El-Deen *et al.*** [9] demonstrated that history of birth hypoxemia, cyanosis, neonatal seizures and NICU admission were significantly increased among cases with DRE in comparison with DRE free ones.

Concerning brain imaging findings, our study displayed that there was statistically significant difference in studied group in terms of brain imaging findings with 76.9% of the cases with refractory epilepsy had normal image, 15.4% had encephalomalacia and 7.7.% had brain atrophy. On the contrary, it has been demonstrated that epileptic cases with structural cerebral changes have a minimal possibility of entering remission in comparison with cases with normal cerebral structures [8]. Also, **Karaoğlu *et al.*** [5] have displayed that abnormal MRI images were significantly increased among children with DRE.

In terms of the predictors of refractory epilepsy among studied cases, our study demonstrated that presence of positive family history increases risk for refractory epilepsy, presence of positive history of febrile seizures increases risk for refractory epilepsy, younger age at disease onset. Presence of associated psychiatric disorders increase risk of refractory epilepsy. Likewise, **Sporiš *et al.*** [4] divided their patients into two groups according to frequency of seizures, responses to AEDs and seizure duration. One group consisted of DRE cases and the other group of responsive cases. They have demonstrated that there was a statistically significantly earlier development of 1st epileptic seizure among cases with DRE. The group of DRE cases had a statistically significantly higher ratio of secondary generalization of complex partial seizures and a greater ratio of cases with focal changes in EEG. Also, **Karaoğlu *et al.*** [5] conducted their study on 177 cases diagnosed with DRE who were compared with 281 responsive cases. They have displayed in their univariate analysis that age at seizure onset, mixed seizure types, history of SE, history of neonatal seizures, daily seizures at the onset, abnormality on the 1st EEG, epileptic abnormalities on EEG, abnormalities in neurodevelopmental condition, abnormal neuroimaging, and having symptomatic etiology were significant predisposing factors for DRE development ($p<0.05$). With regard to multivariable analysis, having mixed seizure types, history of SE, having multiple seizures in a day, impaired intellectual functions, symptomatic cause, and presence of radiological abnormalities remained significant predictors for DRE development. Moreover, **Saygi *et al.*** [6] have reported in their univariate analysis that age at onset, infantile

spasm, previous history of neonatal fits, abnormal neurodevelopmental condition, neurologic changes, mental retardation, remote symptomatic cause, and abnormalities in MRI image were significant predisposing factors for the development of intractable epilepsy. In addition, multivariate regression analysis displayed that high initial seizure frequency and remote symptomatic cause were significant and independent risk factors for DRE. Also, **Akhoundian *et al.*** [20] have demonstrated that factors interfering with the development of DRE comprised age less than one year, multiple seizures prior to beginning the therapy, male sex, myoclonic fits, neurologic deficits, neonatal and daily seizures, and first abnormal EEG and brain CT.

In the context of CP, **Abdel-Maksoud *et al.*** [21] have demonstrated that additive effect of a poor Apgar score at 5 minutes, the existence of neonatal seizures and focal epilepsy could be used as essential predisposing factors for DRE prediction. In brief, there are a lot of factors, which could predict the development of uncontrolled seizures. Knowledge of such factors helps us to distinguish our cases and give more care to cases at risks of developing uncontrolled seizures.

CONCLUSION

The main predictors of development of refractory epilepsy were high initial seizures frequency, positive family history, febrile seizures, associated psychiatric disorders and younger age at disease onset.

Conflict of interest: None.
Sources of funding: Nil.

REFERENCES

1. **Mayuri B, Kumar D, Kishore P (2019):** A review on epilepsy. Journal of Medical Science and Clinical Research, 7 (3): 1362-1369.
2. **Kwan P, Brodie M (2000):** Early identification of refractory epilepsy. N Engl J Med., 342 (5): 314-319.
3. **Kwan P, Arzimanoglou A, Berg A *et al.* (2010):** Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies, Epilepsia, 51 (6): 1069-77.
4. **Sporiš D, Bašić S, Šušak I *et al.* (2013):** Predictive factors for early identification of pharmacoresistant epilepsy. Acta Clinica Croatica, 52 (1): 11-15.
5. **Karaoğlu P, YİŞ U, Polat A *et al.* (2021):** Clinical predictors of drug-resistant epilepsy in children. Turkish Journal of Medical Sciences, 51 (3): 1249-1252.
6. **Saygi S, Erol I, Alehan F (2014):** Early clinical predictors of intractable epilepsy in childhood. Turk J Med Sci., 44 (3): 490-95.
7. **Yilmaz B, Okuyaz C, Komur M (2013):** Predictors of intractable childhood epilepsy. Pediatric Neurology, 48 (1): 52-55.
8. **Mohanraj R, Brodie M (2013):** Early predictors of outcome in newly diagnosed epilepsy. Seizure, 22 (5): 333-44.
9. **El-Deen M, Taghreed A, Metwally K *et al.* (2018):** Risk Factors and Predictors of Refractory Childhood Epilepsy: Case Control Study. Med J Cairo Univ., 86: 1891-1899.
10. **Ohtsuka Y, Yoshinaga H, Kobayashi K (2000):** Refractory childhood epilepsy and factors related to refractoriness. Epilepsia, 41: 14-17.
11. **Berg A, Shinnar S, Levy S *et al.* (2001):** Two-year remission and subsequent relapse in children with newly diagnosed epilepsy. Epilepsia, 42 (12): 1553-1562.
12. **Chawla S, Aneja S, Kashyap R *et al.* (2002):** Etiology and clinical predictors of intractable epilepsy. Pediatric Neurology, 27 (3): 186-191.
13. **Kwan P, Schachter S, Brodie M (2011):** Drug-resistant epilepsy. New England Journal of Medicine, 365 (10): 919-926.
14. **Ko T, Holmes G (1999):** EEG and clinical predictors of medically intractable childhood epilepsy. Clinical Neurophysiology, 110 (7): 1245-1251.
15. **Moinuddin A, Rahman M, Akhter S *et al.* (2009):** Predictors of childhood intractable epilepsy-A retrospective study in a tertiary care hospital. Bangladesh Journal of Child Health, 33 (1): 6-15.
16. **Altunbasak S, Herguner O, Burgut H (2007):** Risk factors predicting refractoriness in epileptic children with partial seizures. Journal of Child Neurology, 22 (2): 195-199.
17. **Oskoui M, Webster R, Zhang X *et al.* (2005):** Factors predictive of outcome in childhood epilepsy. Journal of Child Neurology, 20 (11): 898-904.
18. **Kedare J, Baliga S (2022):** Management of Psychiatric Disorders in Patients of Epilepsy. Indian Journal of Psychiatry, 64 (2): 319-323.
19. **Elbeh K, Elserogy Y, Hamid M *et al.* (2021):** Personality traits in patients with refractory versus non-refractory epilepsy. Middle East Current Psychiatry, 28: 1-8.
20. **Akhoundian J, Heydarian F, Jafari S (2006):** Predictive factors of pediatric intractable seizures. Arch Iran Med., 9 (3): 236-9.
21. **Abdel Maksoud Y, Suliman H, Elsayed Abdulsamea S *et al.* (2021):** Risk Factors of Intractable Epilepsy in Children with Cerebral Palsy. Iranian Journal of Child Neurology, 15 (4): 75–87.