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ly identification of Risk Factors for Development of Refractory Epilepsy

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Abstract

Background Epilepsy is the most common neurological disorder, Epilepsy result from diverse etiologies, including structural brain lesions, as well as monogenic and polygenic variation. The importance of timely identification of refractoriness, it is crucial to prioritize the detection of this condition before considering alternative treatments like surgery **.Objective:** To determine risk factors for development of refractory epilepsy among children and adolescents with epilepsy in Pediatric Neurology Clinic of Benha University Hospitals. **Methods:** This study was prospective cohort study. We studied 125 children aged 1 day-18 years who were diagnosed with epilepsy. For each patient, age, gender, full clinical examination were noted. Study sample included 125 patients ,patients were divided into two groups .Patients who were responsive nominated as control (48 patients) , patients were considered to be seizure-free if they had not had any seizures for at least one year**.** While patients who were resistant nominated as cases (77 patients) who failed adequate trials of 2 tolerated and appropriately chosen and used anti-epileptic drugs schedule . **Results:** History of developmental delay and age of onset of seizure below one year were significantly higher among patients with refractory epilepsy than those with responsive epilepsy. Structural brain changes and abnormal neuroimaging were more prevalent in refractory epilepsy group than responsive group. **Conclusion:** Our study revealed the most important independent predictors of refractoriness were: age of onset below one year, presence of structural brain changes, abnormal neuroimaging and history of developmental delay

Keywords: Epilepsy**,** Risk factors, Drug resistance epilepsy, Refractory epilepsy.

Introduction

Epilepsy is the most common neurological disorder, affecting 50 million people worldwide, with approximately 80% living in developing countries with limited resources. The incidence of epilepsy is the highest in childhood [1] .

Epilepsies result from diverse etiologies, including structural brain lesions, as well as monogenic and polygenic variation. Recent advances in both neuroimaging and genetic testing have resulted in a significant increase in the proportion of epilepsies that can be etiologically resolved, particularly among epilepsies that begin in early childhood [2] .

children with anti epileptic drugs (AEDs) resistance based on International League Against Epilepsy (ILAE) definition which is the failure to achieve sustained seizure freedom after administration of two or more appropriately chosen and used AEDs schedules [3] .

Previous studies have shown that resistance to AEDs can be predicted early after diagnosis. Several clinical characteristics were found to be indicative of a higher risk for resistance to AEDs. Symptomatic etiology, history of perinatal insults, earlier age of onset, history of febrile seizure, presence of multiple types of seizure, complex partial seizure, abnormalities on EEG or brain imaging, and poor response to first drug have been associated with drug resistant epilepsy [4] .

The aim of this study was early identification of risk factors for development of refractory epilepsy among Egyptian children and adolescents with epilepsy

Methods

This study was prospective cohort study. We studied 125 children aged 1 day-18 years who were diagnosed with epilepsy. For each patient, age, gender, full clinical examination were noted. Study sample included 125 patients were collected from the Pediatric Neurology Clinic at Pediatric Department, Benha University Hospitals over 2 years from June 2022 to June 2024.

Inclusion criteria: Patients who were given a diagnosis of epilepsy , epilepsy was classified according to epilepsy type as (focal, generalized and combined) and etiological type as (structural, genetic, infectious, immune, metabolic and unknown).

Exclusion criteria: Patients whose epilepsy was the result of a possibly remediable lesion, such as mesial temporal sclerosis, a tumor, or arteriovenous malformation, patients with low compliance to treatment were excluded from study

All children underwent the following:

A thorough history taking process that included their personal history (age and sex), a history of any current illnesses, and a prior history of any

significant medical events. All patients were divided into two groups for purposes of comparison according to whether or not they were seizure-free during follow-up. during follow-up patients who were responsive nominated as control while patients who were resistant nominated as cases. All children were subjected to the following, during the first visit, we used a structured questionnaire to collect demographic and clinical information from the patients and any witnesses to the seizures and performed a general physical and neurologic examination to asses tone, power and reflexes and to asses presence of signs suggestive of neurocutaneous syndromes eg, café au lait patches in neurofibromatosis and dysmorphic features which may suggest underlying genetic disease. For all patients who were given a diagnosis of epilepsy, the appropriate antiepileptic drug was chosen . At each follow-up visit, clinical information and the response to antiseizure medication therapy were recorded. Compliance was monitored at the clinic. Investigations done included, Routine EEG, MRI brain and metabolic workup if inborn errors of metabolism were suspected. Baseline investigations were done, including CBC, kidney functions tests, liver functions tests and electrolytes' measurement.

Patients were treated with a single drug when possible, as was recommended practice. Treatment was changed to another drug if seizures remained uncontrolled or if the patient had an idiosyncratic reaction or intolerable side effects. A combination of drugs was used in patients whose epilepsy remained uncontrolled despite treatment . Study sample included 125 patients, patients were divided into two groups .Patients who were responsive nominated as control (48 patients) , while patients who were resistant nominated as cases (77 patients).

Ethical approval: Benha Medical Ethics Committee of the Benha Faculty of Medicine gave its approval to this study with approval code MD 7-6-2022. All participants gave written consents after receiving all information.

Statistical analysis: The data were coded, handled, and analysed using version 24 for Windows®. To evaluate if the data had a normal distribution, Shapiro Walk test was used. Frequencies and relative percentages were used to represent qualitative data. The Chi square test (X^2) was used to compare the differences between two or more sets of qualitative variables. The mean ± SD of quantitative data was used. The Mann-Whitney test is a non-parametric test that was used to compare two non-parametric quantitative variables. To compare two independent groups of regularly distributed variables (parametric data), the independent samples t-test was employed. Significant was defined as $P \leq 0.05$.

Results

Revealed that the mean age was 7.34 years and median age of studied group

was 6 years, males and female of equal percentage in studied sample.

There was no statistically significant difference between refractory epilepsy and the control group regarding age and sex (table 1).

There was highly statistically significant difference between refractory epilepsy and the control group regarding presenting symptom. Increased incidence of convulsions with global developmental delay (GDD) in refractory epilepsy group(53%) compared to (25%) in the control group . Increased incidence of convulsions with normal development in (64.6%) in the control group compared to refractory epilepsy group (41.6%) (Fig 1)

There was highly statistically significant difference between refractory epilepsy and the control group regarding age of onset of seizure below one year age. Increased incidence of age of onset below one year in patients with refractory epilepsy (50.6%) than control patients (16.6%),while there was no statistically significant difference between refractory epilepsy and the control group regarding duration of attack and postictal duration (table 2)

There was no statistically significant difference between refractory epilepsy and the control group regarding urinary organic acid (UOA) and tandem mass spectrometry (TMS) (table 3)

There was highly statistically significant difference between refractory epilepsy and the control group regarding structural brain changes. Increased incidence of structural brain changes in patients with refractory epilepsy (38.9%) than control group (10.4%)

There was statistically significant difference between refractory epilepsy and the control group regarding neuroimaging. Increased incidence of abnormal neuroimaging in case group (44.2%) than control group (23%).Increased incidence of brain atrophy in case group (22.1%) than control group (14.6%). Increased incidence of Subependymal calcification in case group (6.5%) than control group (0.0 %) (table 4)

There is highly statistically significant difference between refractory epilepsy and the control group regarding EEG. It show the most common abnormal finding was focal spike-slow wave complex (41%) in case group and (64%) in control group so there was statistically significant difference between them. Increased incidence of generalized slowing in patients with refractory epilepsy than control group (table 5)

Binary logistic regression analysis showed the most predictable risk factors of refractory epilepsy were age of onset of seizure below one year and history of developmental delay (table 6)

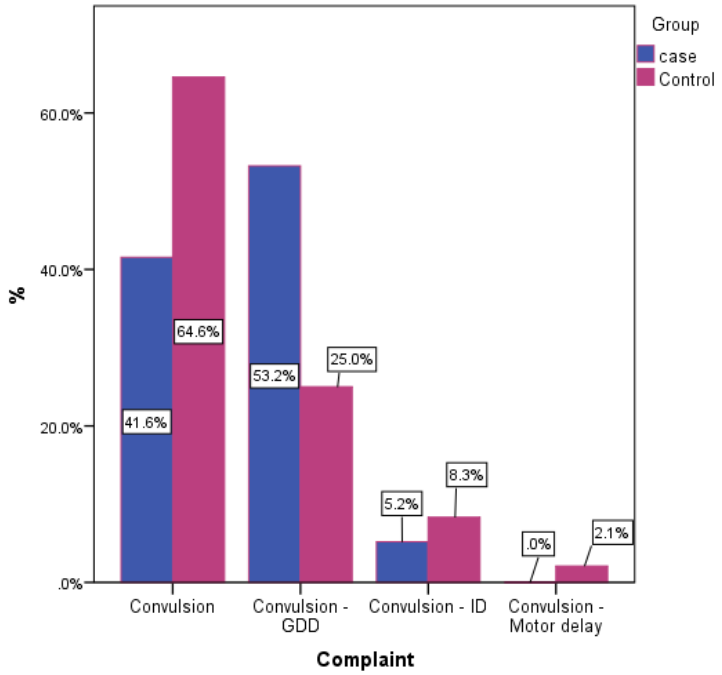

Figure 1. Differences between the studied groups according to their presenting symptom

Global developmental delay(GDD)[Both motor and mental retardation]

Intellectual disability (ID) [Neurodevelopmental disorder that affect both cognitive and adaptive function]

Table 1: difference between the studied groups regarding their age and sex

Variable		Cases	Control	Chi-Square test	P value
Age (years)	**≤6**	40 51.9%	31 64.6%	1.96	.165
	>6	37 48.1%	17 35.4%		
Sex	**Female**	42 54.5%	22 45.8%	.88	.34
	Male	35 45.5%	26 54.2%		

P values less than 0.05 were considered significant. P values less than 0.01 were considered highly significant

Table (2): Differences between the studied groups according to their age of onset, attack duration and postictal state duration

Variable		Cases N.=77 N. %	Control N.=48 N. %	P value
Age of onset (years)	≤1 year	39 50.6%	8 16.6 %	.000
	>1 year	38 49.4%	40 83.3 %	
Variable		**Cases Median (IQR)**	**Control Median (IQR)**	**P value**
Duration of attack (min)		10.0 5.0-10.0	10.0 3.0-15.0	.611
Postictal state duration (hour)		2.0 1.0-2.0	1.5 1.0-2.5	.682

P values less than 0.05 were considered significant. P values less than 0.01 were considered highly significant.

Table 3: Differences between the studied groups according to their TMS and UOA disorders

Variable		Cases N.=77 N. %	Control N.=48 N. %	FET	P value
TMS	Normal	75 98.7%	48 100.0%	1.9	.52
	Elevated phenylalanine	1 1.3%	0 0.0%		
UOA	Normal	73 94.8%	48 100.0%	3.2	.51
	Elevated glutaric acid, 3 hydroxy glutaic acid & glutaconic acid	2 2.6%	0 0.0%		
	elevated 3- hydroxyisovaleric, 3-methylcrotonylglycine methylcitrate 3 hydroxy propionic acid	1 1.3%	0 0.0%		
	elevated Methyl malonic acid	1 1.3%	0 0.0%		

FET: Fisher's exact test

P values less than 0.05 were considered significant. P values less than 0.01 were considered highly significant.

Table 4: Differences between the studied groups according to their neuroimaging

Neuroimaging (CT&MRI)	Cases N.=77 N. %	Control N.=48 N. %	FET	P value
Normal	43 55.8%	37 77 %	15.1	(.04)
Area of encephalomalacia	2 2.6%	1 2.1%		
Area of infarction	2 2.6%	1 2.1 %		
Brain atrophy	17 22.1%	7 14.6%		
Brain malformation	6 7.8 %	1 2.1 %		
Hydrocephalic changes	0 0.0%	1 2.1%		
Altered signals of basal ganglia	2 2.6%	0 0.0%		
Subependymal calcification	5 6.5%	0 0.0%		

FET: Fisher's exact test

P values less than 0.05 were considered significant. P values less than 0.01 were considered highly significant.

Table 5: Differences between the studied groups according to their EEG findings

EEG	Cases N.=77 N. %	Control N.=48 N. %	FET	P value
Normal	21 27.3%	14 29.2%	13.5	.004
Focal spike, slow wave complex	32 41.6%	31 64.6%		
Generalized Slowing	11 14.3%	0 0.0%		
Generalized Slowing and focal spike, slow wave complex	11 14.3%	3 6.2%		
Generalized spike, slow wave complex	2 2.6%	0 0.0%		

HS:highly significant ;p<.01; FET: Fisher's exact test

Table (6): Binary logistic regression analysis of factors associated with refractory epilepsy

Variable	P- value	Odds ratio	95% C.I.
Age of onset of seizures ≤ 1year	.003	10.397	2.230-48.474
History of developmental delay	.028	11.303	1.300-98.267
Neuroimaging	.072	.227	.045-1.138
Neurological examination	.219	1.301	.855-1.979
Abnormal EEG	.134	1.466	.889-2.417
Type of seizure			
Generalized Type of seizures	.000	.006	.000-.100
Multiple seizure types	.005	.135	.033-.554

Discussion

Epilepsy is the most common neurological disorder, epilepsies result from diverse etiologies, including structural brain lesions, as well as monogenic and polygenic variation. Recent advances in both neuroimaging and genetic testing have resulted in a significant increase in the proportion of epilepsies that can be etiologically resolved, particularly among epilepsies that begin in early childhood [2] .

Early identification risk factors of drug resistance epilepsy is essential before considering alternative treatments like surgery. Early surgical intervention, when successful, has the potential to prevent or reverse the emotional and cognitive impacts of uncontrolled seizures, especially during critical developmental periods [5] .

Our study showed that there was no statistically significant difference between refractory epilepsy and the control group regarding age and sex, our results are in agreement with **Sree and Belavadi** [6] who carried out a prospective case-control study to find out the prevalence and clinical features of intractable epilepsy in a tertiary referral center on 60 childrens, they reported no significance difference regarding age and sex.

In our study large proportion of patients (62%) was found with uncontrolled epilepsy over study time, whereas the proportion with controlled epilepsy was relatively small (38%). These findings are in agreement as observed by **Yilmaz et al**., [7]

In contrast to those of, **Kong et al .,** [8] **and Jovel et al**., [9] who reported the prevalence of DRE was 21.5% and 27.1%, respectively (both used ILAE DRE definition) .

This higher prevalence of intractability in our study may be due to high prevalence of complicated cases referral to tertiary center.

Our study revealed that global developmental delay (GDD) were significantly higher among patients with refractory epilepsy (53.2%) than those with control group (25%) . This result is in agreement with **Patil et al., [10] Sree and Belavadi et al., [6]** .

In our study , the early onset of seizures before the age of one year was statistically higher among refractory epilepsy group (50%) than the control group (16%) . This finding is in agreement with **El-Deen et al., [11]** . Age of epilepsy onset has been suggested to be a major predictor of pharmacoresistance. Multiple studies showed that drug resistance epilepsy (DRE) was associated with younger age at the onset especially in the first year of life **[12]** .

Our study revealed that there is highly statistically significant difference between refractory epilepsy.

(38.9%) and the control group (10.4) regarding structural brain changes this in agreement with **Farghaly and colleagues [13]** .Our study show Increased incidence of abnormal neuroimaging in case group (44.2%) than control group (23%), and the most common finding was brain atrohy (19.2%) this in agreement with **Xue-Ping et al., [14]** .

Our study revealed there was increased incidence of generalized slowing as EEG finding in 11 patients in refractory epilepsy group and no patients in control group in agreement with **Yildiz et al., [15]** .

Binary logistic regression analysis of factors associated with refractory epilepsy revealed that the most important independent predictors of refractoriness were age of onset of epilepsy below one year age history of developmental delay.

our study revealed that age of onset of epilepsy below one year is independent risk factor this is in agreement with **Wirrell et al., [16] .**

Also our study revealed that history of developmental delay is independent risk factor this is in agreement with **El-Deen et al., [11]** .

Conclusion

Our study revealed the most important independent predictors of refractoriness were: age of onset below one year and history of developmental delay

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