PREDICTORS OF DRUG RESISTANT EPILEPSY IN CHILDREN: A CLINICAL , ELECTROENCEPHALOGRAPHIC AND NEUROIMAGING STUDY

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ABSTRACT

Background and aim of the study: Refractory epilepsy is usually defined as failure to achieve seizure freedom for 12 months or more, for whatever reason .This study aims to determine various epidemiologic and clinical factors, electroencephalographic changes, and neuroimaging abnormalities associated with medically intractable seizures in children . **Subjects and methods:** 150 epileptic patients were included in the study aged 18 months to 13 years; sixty patients were considered to be intractable to treatment while the remaining ninty patients were controlled epileptic children. The collected data from patients included personal history, presence of neurological deficits, age of seizure onset, number of seizure attacks before initiation of therapy, previous occurrence of status epilepticus, type of seizures ,presence of infantile spasms and developmental state. All the patients had performed EEG.All patients had performed magnetic resonant brain imaging either as a part of the study or due to any cause within their routine care. **Results:** There was a significant intractability to therapy in patients with developmental delay, associated neurological deficits, early onset of seizures, partial seizure type, infantile spasms , microcephaly , MRI abnormality and focal EEG abnormality. MRI revealed brain atrophic changes to be the most common lesion associated with intractable seizures. EEG revealed that focal epileptogenic activity was the most common abnormality associated with intractable seizures .**Conclusion:** Neurological deficits, early onset seizures , microcephaly , developmental delay ,infantile spasm , abnormal MRI and focal EEG abnormalities are important predictors of intractable epilepsy.

INTRODUCTION

Some experts define a patient as having refractory seizures if treatment fails to achieve seizure freedom for 12 months or more, for whatever reason[1]. Another definition of refractory seizures was proposed by Berg: failure of two or more drugs and occurrence of one or more seizures per month over 18 month[2].

The incidence of refractory epilepsy remains high despite the influx of antiepileptic drugs (AEDs) over the past 10 years. Epidemiological data indicate that 20-40% of the patients with newly diagnosed epilepsy will become refractory to treatment. Factors that may be used to predict whether or not a patient will respond favorably to AED therapy include the type of epilepsy, underlying syndrome, etiology, and the patient's history of seizure frequency, density, and clustering[3].

The two prevailing hypotheses proposed to explain multidrug resistance in epilepsy are: 1) the transporter hypothesis, which posits that there is inadequate access of AEDs to epileptic tissue because they are removed by multidrug transporters that are pathologically overexpressed, and 2) the target hypothesis, that proposes inherited or acquired alterations in the molecular targets of AEDs, leading to pharmacodynamic effects of the drugs[4].

These hypotheses posit that drug refractoriness is a condition separate from the underlying epilepsy. Inadequacies in both hypotheses mandate a fresh approach to the problem.[5].

The inherent severity model of epilepsy proposes that there is a continuum in severity of the disease, which determines its relative response to medication. Increased frequency of seizures at the time of diagnosis is a signal of' increased severity and future drug refractoriness. However, clinical and experimental studies in epilepsy have generally ignored the concept of disease severity that is fundamental in the description of disease in other areas of medicine. The development of measures of epilepsy severity is urgently needed to enable clinical studies mining the prognostic implications of severity and its relationship to drug responsiveness[5].

Patients with intractable epilepsy may benefit from epilepsy surgery especially if they have a radiologically demonstrable cerebral lesion; so, patients with refractory epilepsy should be referred to an MRI unit with epileptological experience at an early point[6].

There are many risk factors of refractoriness to treatment. These factors include: remote symptomatic etiology, seizures onset in infancy, occurrence of 10 seizures before starting treatment, myoclonic seizures, neonatal seizures, abnormal EEG, abnormal brain imaging results and head trauma[7,8].

Aim of the work:

This study aims to determine various epidemiologic and clinical factors, electroencephalographic changes, and neuroimaging abnormalities associated with medically intractable seizures in children .

METHODS

This study is a case control study that carried out at Zagazig University Hospitals, Pediatric Department inpatient and regular attendants of Pediatric Neurology Clinic during the period from June 2009 to December 2010.

All patients were diagnosed as epilepsy (A child was considered epileptic if he had 2 or more unprovoked seizures). on optimal dose of antiepileptic drugs appropriate for their conditions The type of seizures was classified according to the guidelines of the International League Against Epilepsy (ILAE).

Selection of cases and controls:

All epileptic children admitted to pediatric hospital or regularly attending Pediatric outpatient neurology clinic were included in the study then they were divided into cases; children with refractory epilepsy who experienced more than one attack of seizures per month despite being on full dose of two or more appropriate antiepileptic drugs (60 patients), and controls who were free of seizures of any type for a minimum of one year while receiving one or two antiepileptic drugs or while not taken any medications (90 patients).

Exclusion criteria:

All patients with intracranial space occupying lesions and patients with obscure history were excluded from the study.

The following data were collected by interviewing the caregivers, examining the patients and reviewing their hospital records:

- Personal data including date of birth, gender, residence, parent educational level and occupation, crowdness index, income of the family and number of siblings.
- Age of onset of seizures either neonatal (first month of life), infantile(the first year of life after the first month), early childhood (from two to five years) or late childhood (from six to twelve years).
- Number of seizure attacks before initiation of therapy (few attacks < 10 & frequent attacks ≥ 10).
- Type of seizures either partial, generalized or mixed.
- Previous occurrence of status epilepticus.
- Number of drugs used in therapy.

Electroencephalograph (EEG):

EEG was done for all patients at the Neurology Department, Zagazig University Hospitals using 21-channel Nicolet, Biomedical EEG machine .Electrodes were arranged according to the 10-20 International System of electrode placement using mono and bipolar montages. All EEGs were carried out under normal standard conditions .Photic stimulation were done for all patients while hyperventilation for 3 minutes were done for some patients as a provocative techniques.

Brain magnetic resonant imaging:

All the 152 patients were subjected to MRI study in Radio-diagnosis department, Zagazig University Hospitals, using standardized protocol of any epilepsy patient.

Patients with refractory epilepsy (n = 72) had already underwent MRI brain as a part of their epilepsy work up; mean

while, 43 out of 80 patients with controlled epilepsy had performed MRI brain due to various causes as suspected intra-cranial lesion, associated developmental delay, acutely provoked seizures or partial unexplained seizures . The remaining cases (n= 37) had been subjected to MRI using the same standard protocol used for epilepsy patients, after written consent from their care givers.

The study was conducted using 1.5-T Philips (Achieva, class II a) scanner using a quadrature head coil.

Standard MRI epilepsy protocol: FLAIR for screening, T2-weighted imaging for confirmation, T1-weighted for anatomical reference.

- Sagittal T1-weighted images, 5-mm slice thickness (for anatomical reference, especially to allow orientation of the coronal images perpendicular to the long axis of the hippocampus, and for inspection of perisylvian/ midline/ cerebellar areas)
- Axial FLAIR and T2-weighted images ≤ 5-mm slice thickness (for screening and confirmation of extratemporal, mainly frontal lobe pathology)
- Coronal FLAIR, ≤ 5-mm slices (for screening of temporal lobe pathology)
- Coronal double-echo sequence (T1 & T2) with 5-mm slices (for confirmation and also for T2 relaxometry)
- Axial or coronal T2* gradient echo images (screening for hemosiderin and calcification..., if present)

T1- and T2-weighted images are used to visualize the gray-white matter interface during different stages of myelination.

All images were obtained with a 2D half-Fourier transformation technique, and data were collected on a 256.256 matrix, with 22-25 field of view, 8 mm slice thickness on the axial plane and 4-5 mm on the coronal plane, with no interslice gap.

Ethical consideration:

Permission was taken from the head of Pediatric department Zagazig University Hospitals to do this work also an informed written consent from caregivers after explaining the objectives of the study and ensuring confidentiality of the results.

Data management was done by using SPSS version 12, classification of the social class was done according to Elsherbini and Fahmy, 1983 classification score.

RESULTS

We studied 150 patients, their age range from 18 months to 13 years . Sixty patients of them were cases and the remaining (ninty patients) were control.

Table (1) This table shows Gender distribution of the studied groups and revealed no significant statistical difference (P>0.05).

Table (2) shows that the percentage of those suffering from early onset seizures, develop delay, partial seizures and infantile spasms are significantly higher among cases when compared with controls.

Table (3) shows that the percentage of those suffering from neurologic deficit microcephaly are significantly higher among cases when compared with controls.

Table (4) shows that the percentage of those having MRI brain defects is significantly higher among cases when compared with controls.

Table (5a): MRI finding among cases. Brain atrophy and structural brain defect were the most common findings. Table (5b): MRI finding among controls.

Table (6) shows that the percentage of those having EEG abnormalities is significantly higher among cases when compared with controls

Table (7a): shows EEG findings among cases and revealed that focal epileptogenic activity was the most common finding. Table (7b): shows EEG findings among control.

Table (1): Gender distribution of the studied groups

	Cases No= 60		Control No=90		X^2	p
	No	%	No	%		
Gender						
Male	32	53.3	42	46.7	0.64	0.42
Female	28	46.7	48	53.3		

Table (2): History findings of the studied groups

	Cases No=60		Controls No=90		X^2	p
	No	%	No	%		
Family history						
-ve	54	90	82	91.1	0.054	>0.2
+ve	6	10	8	8.9		
seizure onset						
< 1 year	40	66.7	79	87.8	9.79	0.0017*
>1 year	20	33.3	11	12.2		
No.of attack						
< 10 attacks	45	75.0	77	85.6	2.64	0.1
>10 attacks	15	25.0	13	14.4		
Status epilepticus						
-ve	43	71.7	76	84.4	3.58	0.053
+ve	17	28.3	14	15.6		
Type of seizures						
Partial	32	53.3	29	32.2		
Generalized	20	33.3	42	46.7	6.7	0.03*
Mixed	8	13.3	19	21.1		
Developmental delay						
-ve	40	66.7	74	82.2	4.78	0.029*
+ve	20	33.3	16	17.8		
Infantile spasms						
Absent	51	85	89	98.9	8.39	0.004*
Present	9	15	1	1.1		

Table (3): Clinical examination findings of the studied groups

	Cases No=60		Controls No=90		X^2	p
	NO	%	NO	%		
Neurological deficit						
-ve	33	55.0	71	71.9	9.66	0.0018*
+ve	27	45.0	19	21.1		
Microcephaly						
-ve	43	71.6%	79	87.7	6.15	0.014*
+ve	17	28.4%	11	12.3		

Table (4): MRI defect

	Cases No=60		Controls No=90		x	p
MRI	No	%	No	%		
-ve	39	65.0	78	86.7	9.85	0.001*
+ve	21	35.0	12	13.3		

OR(95% C.I)=3.5 (1.46-8.5)

Table (5a): MRI finding among cases.

	N (21)	%
Temporal lobe lesions	5	23.8
Structural brain defects	8	38.1
Brain atrophy	8	38.1

Table (5b): MRI finding among controls.

	N (12)	%
Mesial temporal sclerosis	2	16.67
Structural brain defects	3	25
Brain atrophy	7	58.33

Table (6) EEG Abnormality

	Cases No=60		Controls No=90		x	p
EEG	No	%	No	%		
-ve	13	21.7	51	56.7	18.03	0.001*
+ve	47	78.3	39	43.3		

Table (7a): EEG findings among cases

EEG pattern	No	%
Focal epileptic activity (excluding rolandic)	20	42.55
Generalized epileptogenic activity (Excluding absence)	13	27.66
Hypsarrhythmia	7	14.89
Burst suppression	3	6.38
Other patterns (Including rolandic and absence epilepsy)	4	8.51

Table (7b): EEG among control

EEG pattern	no	%
Focal epileptic activity (excluding rolandic)	9	23.07
Generalized epileptogenic activity (Excluding absence)	18	46.15
Hypsarrhythmia	0	0
Burst suppression	0	0
Other patterns (Including rolandic and absence epilepsy)	12	30.77

DISCUSSION

Unfavourable outcome or intractability is a burning concern for both patients and personnel dealing with epilepsy. This study was done to search the factors that were associated with unfavourable outcome or intractability.

Early identification of these factors would help in planning early intervention.

Out of 150 epileptic children included in our study 60 were intractable to treatment with appropriate antiepileptic drugs (cases) and 90 were controlled epileptics (control). A patient was defined as having refractory seizures if treatment fails to achieve seizure freedom for 12 months or more, for whatever reason[1].

The study revealed non significant statistical difference between both groups regarding gender (Table 1). This finding was in agreement with many reported studies[7,9,10,11]

However, one study performed by Malik et al.[8] suggested more risk of resistance of epilepsy among males. This single study was not agreed by formerly reported studies.

A positive family history was not a predictor of intractability in this study (Table 2). This finding is in agreement with Patil et al[12].

Indeed positive family history is more commonly found in benign conditions like Idiopathic generalized tonic-clonic epilepsy. On the other hand malignant syndromes like early myoclonic encephalopathy, severe myoclonic epilepsy of infancy etc., which also has got family history, but are less in incidence [13].

Our study also revealed that early onset of seizures is usually associated with refractoriness to treatment (Table 2), which is the same finding of most studies[7,11,12,14].

Seizures in the immature brain of a child may result in nonpruning of neurons and contribute to high numbers of gap junctions, which leads to abnormal connectivity, the hyperconnected cortex [15]

Epilepsy due to structural malformation like, microcephaly and macrocephaly, tuberous sclerosis, neuronal migration disorders likelissencephally, pachygyria, etc. present in early life. These epilepsies are difficult to control [16].

Epilepsy associated with various inborn errors of metabolism present early in the life are difficult to control. Severe brain damage caused by severe perinatal insult manifest early in the life[17].

Number of attacks before initiation of therapy either frequent (≥ 10 attacks) or infrequent (<10 attacks) was not associated with intractability of epilepsy (Table 2). This finding was in agreement with multiple studies[14,18,19].

On the other hand, some studies had reported the occurrence of 10 or more seizure attacks before treatment to be a risk factor of later drug failure[1,7,8].

This difference may be attributed to many aspects. First, some attacks may no be witnessed by the parents. A second factor is the number of caregivers as when it is increased precise history is less likely. A third factor is that the number of attack may be related to the reluctance of caregiver to ask for medical care not to the disease nature. Lastly, the number of (10) attacks itself is doubtful and has no scientific bases to be a measure for frequent or infrequent attacks, it is just a tradition; even some studies used other number rather than 10 e.g. **Arts et al. ,1999** who consider 25 attacks as the number sufficient for epileptic seizures to be frequent[10].

Although status epilepticus was more common in cases but no significant statistical difference were revealed between the two groups (Table 2). This result is opposite to that found by some studies[7,14].

Moinuddin et al. concluded that history of status epilepticus was not found as apredictor of unfavourable outcome or intractability[20].

It has been seen that subsequent episodes of status epilepticus occurred at various times during the seizure disorder, generally after a pattern of intractability has been established. This suggests that status epilepticus is a marker rather than a cause of intractability[21].

Neurologic deficit was more common in cases group and so was a strong predictor of intractability (Table 3). This result was in agreement with many studies[7,8,14,20].

Presence of underlying neurologic deficit points to either the intrinsic severity of epilepsy or to the severity of underlying etiology. These two factors may account for the revealed pharmacoresistance[12].

Another factor that supports our finding is that many well-known refractory epilepsy syndromes are characterized by neurologic deficit like West syndrome, Lennox-Gastaut syndrome, epilepsia partialis continua and progressive myoclonic epilepsies.

Developmental delay was statistically more significant among cases (Table 2). This result is in agreement with many reported studies [7,12,22]

Microcephaly was a predictor for refractoriness being statistically more prevalent among cases. This finding is in agreement with many studies (Table 3).

Moinuddin et al. ,2009 found that ninety three percent of patients with microcephaly developed intractable epilepsy. It was found as an independent predictor of intractable epilepsy[20].

Chawla et al. 2002 found 58% of intractable group compared to 2% of well-controlled group had microcephaly (P<0.001)[23]. **Berg et al. 1996** found 23.7% cases of intractable group compared to only 3.1% of well-controlled group had microcephaly (P<0.001)[24].

Partial seizures constituted the most common form of seizures among refractory patients (53.3%), whereas generalized epilepsy constituted the most common form among controlled patients (46.7%).

Partial seizures were statistically more common among cases (Table 2). This finding is concordant with those found by multiple studies[7,14,22]

This finding may reflect an underlying structural problem that accounts for the focal nature of the lesion .

Infantile spasms are statistically more significant among cases(Table 2). In fact our control group had only one case of primary infantile spasms that was well controlled .All refractory cases were associated with developmental delay.

Many studies consider infantile spasm as a strong predictor for refractoriness in treatment of epilepsy. **Berg et al., 1996** found infantile spasm in 19.7% cases of intractable epilepsy compared to 1% cases of well-controlled group(P=0.003)[24].

Moinuddin et al. 2009 found that Infantile spasm was significantly associated with intractibility in their study (P=0.007)[20].

MRI defect was noticed in 21 cases (35 % of cases), while it was present in only 12 controlled patients (13.3% of controls) (Table 4). This difference proved to be of a high statistical significance. This result is in agreement with many other studies.

Sameh and Ryvlin, 2005 stated that the presence of a brain lesion demonstrated by neuroimaging or suggested by a neurological deficit or a developmental delay are the main predictors of intractability of epilpesy[11]. similar findings are suggested by **other studies[7,14,25]**

The most common MRI abnormality in refractory cases was brain atrophic changes, followed by structural anomalies and temporal lobe anomalies (Table 5a).

Patil et al., 2009 utilized MRI as imaging modality in most of patients for better characterization of epilepsy early in course. It revealed that in 71% children with IE had neuroimaging abnormality with major share of findings suggestive of perinatal asphyxia (50%) followed by neuronal migration disorders[12].

Magnetic resonance imaging with a specified epilepsy protocol is the imaging study of choice and is mandatory as the primary imaging modality according to the International League Against Epilepsy guidelines[26].

Subtle structural abnormalities are better visualized on MR imaging compared with CT, although CT may be indicated in special circumstances, such as when looking for intracranial calcifications [27].

MRI findings of intractable epilepsy may be the picture of other risk factors

rather than a separate entity as children with partial epilepsy which is significant factor for intractability is commonly associated with the temporal lobe lesion in MRI; also, children with developmental delay are commonly presented with atrophy or congenital malformations in MRI[14].

An EEG abnormality was found in 78.3 % of cases while it was present in 43.3 % of controls. This difference was of highly significant statistical difference (Table 6).

Among cases focal epileptogenic activity was the most common EEG abnormality followed by Generalized epileptogenic activity, then hypsarrhythmia followed by burst suppression and lastly other patterns.

In contrast generalized epiletogenic activity was the most common finding among control. These EEG findings are consistent with the clinical findings.

Hypsarryhthmia and burst suppression patterns were exclusively present among cases. These findings can reflect that these EEG abnormalities are mirrors of the intrinsic severity of underlying epilepsy. These findings are consistent with **Moinuddin et al,2009[20].**

Patil et al. (2009) found that Abnormal EEG was present in 84% of children with intractable epilepsy as compared to 50% in well-controlled seizures[12].

Patil et al. (2009) found that abnormal findings on EEG among refractory cases ranged from focal epileptic activity ,multifocal epileptic activity, generalizedepileptic activity to hypsarrhythmia[12].

Moinuddin et al. ,2009 found that The risk of developing unfavourable outcome in patients with EEG abnormality was calculated to be 3-fold higher (95% CI = 1.78-6.18) than those without EEG abnormality ($p < 0.05$)[20].

Many benign syndromes like idiopathic generalized tonic-clonic epilepsy may present epileptiform discharges on EEG, absence seizure got generalized 3Hz spike-wave discharges, rolandic epilepsy got temporal epileptiform discharges[20]

On the other hand, malignant syndromes like epileptic encephalopathies got background slowing. Encephalitis and hypoxia-ischaemic encephalopathy may have burst suppression, infantile spasm presents hypsarrhythmia on EEG. So, it is more precise to search for specific EEG finding as a predictor rather than the mere presence of an abnormality[20].

CONCLUSION

On the light of this study we conclude that multiple risk factor can predict epilepsy to be refractory to treatment .These factors include:

- Early onset
- Neurological deficit
- Developmental delay
- Microcephaly
- Abnormal MRI brain
- Partial seizures
- Infantile spasms
- Focal EEG abnormalities

Presence of these predictors must be a guide of general pediatrician for early referral to specialized center and specialized Pediatric Neurology consultants as early as possible. Those children may be of need of early visits, further investigations and probably referred to surgical opinion.

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المتنبئات بالصرع المقاوم للعقاقير في الأطفال:
دراسة سريرية وبرسم المخ وبالأشعة التشخيصية للجهاز العصبي

تعد التشنجات الصرعية مستعصية على العلاج إذا ما كانت غير مستجيبة للعلاج لمدة عام كامل لأي سبب كان أو إذا كانت متكررة الحدوث بمعدل مرة على الأقل شهريا بالرغم من استعمال عقارين فعالين بجرعات كافية وذلك على مدى ثمانية عشر شهرا. ولا تزال نسبة كبيرة من التشنجات الصرعية مستعصية على العلاج رغم اندراج العديد من العقاقير العلاجية في العشر سنوات الأخيرة. وتشير الإحصاءات إلى أن قرابة عشرين إلى أربعين بالمائة من التشنجات الصرعية تكون مستعصية على العلاج. وهناك أكثر من نظرية تفسر حدوث الاستعصاء على العلاج منها نظرية الناقل الذي قد يقوم بضخ العقار إلى خارج الخلية أو نظرية تحور مستقبلات العقاقير التي تحيل دون قيام العقار بوظيفته. وهذه النظريات مقبولة إلى حد كبير بيد أنها تغفل طبيعة ونوع التشنجات الصرعية نفسها والعوامل المرتبطة بها .ويعتبر تكرار التشنجات بشكل مكثف عند بدء تشخيصها والتعامل معها علامة على استعصاء التشنجات على العلاج وكذلك على مدى شدتها. وهناك العديد من العوامل التي قد ترتبط بمقاومة الصرع للعلاج منها مسببات الصرع و تاريخ بدايته و نوعه و حدوث التشنجات الوليدية والتشنج الطفولي وعدد التشنجات وقت التشخيص هذا بالإضافة إلى نتائج رسم المخ والفحص بأشعة الرنين المغناطيسي.

الهدف من الرسالة: تهدف الرسالة إلى دراسة العوامل السريرية واختلال رسم المخ الكهربي و نتائج الفحص بالرنين المغناطيسي على المخ ومدى ارتباطهم بمقاومة التشنجات الصرعية للعلاج.

المرضى وطرق البحث: تم إجراء هذه الدراسة في مستشفيات جامعة الزقازيق بقسم الأطفال بوحدة الأمراض العصبية

تم تقسيم المجموعات المشتملة إلى مجموعتين:

المجموعة الأولى : وقد اشتملت على ستين مريضا بالصرع المستعصي على العلاج

المجموعة الثانية: وهي مجموعة ضابطة وقد اشتملت على تسعين مريضا بصرع مستجيب للعلاج

وخضعت المجموعتان لما يلي:

١- التاريخ المرضي:وقد تم أخذه كاملا مع التركيز على: تاريخ مرضي لحدوث التشنجات في أفراد العائلة الاخرين، تاريخ مرضي لحدوث التشنج الطفولي، تاريخ بدئ التشنجات وعددها وشدتها، تاريخ تطور الطفل العقلي والحركي، الاستجابة للعلاج وطرق العلاج المختلفة
٢- فحص سريري كامل
٣- الفحص بأشعة الرنين المغناطيسي على المخ
٤- رسم مخ كهربائي

وقد تم تجميع البيانات وتحليلها إحصائيا

النتائج : أظهرت الدراسة أن هناك عدة عوامل مرتبطة بكون الصرع مستعص على العلاج وهذه العناصر التي أفرزتها الدراسة تتألف من عوامل قد يتسنى معرفتها من خلال التاريخ المرضي مثل السن المبكر لبداية النوبات الصرعية و ووجود تأخر بالتطور العقلي والحركي للطفل هذا بالإضافة لوجود التشنج الطفولي . وقد أظهر الفحص السريري للحالات بان صغر محيط الرأس ووجود خلل عصبي من المتنبئات باستعصاء الصرع على العلاج . ويعد فحص المخ بموجات الرنين المغناطيسي من أهم الفحوصات الواجبة لمرضى الصرع المستعصي حيث أنه يظهر أي عيوب تركيبية لا سيما الصغير منها. ويساهم رسم المخ في تحديد وجود بؤرة صرعية ويقوم بدور محوري في تقييم الصرع عموما والمستعصي منه على وجه خاص .