

# Drug Resistant Epilepsy Among Patients Attended The Neurosciences Hospital

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## ABSTRACT

**Background:** Drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules to achieve sustained seizure freedom. Up to 30% of patients referred to clinics with a diagnosis of pharmaco-resistant epilepsy may have been misdiagnosed, and many can be helped by optimizing their treatment. Pseudoresistance, in which seizures persist because the underlying disorder has not been adequately or appropriately treated, must be ruled out or corrected before drug treatment can be considered to have failed.

**Objectives:** The objectives of this study were to determine the causes of drug failure in patients with epilepsy and to differentiate between drug resistant epilepsy and pseudoresistant epilepsy.

**Type of the study:** This is a retrospective study.

**Method:** It is conducted in Baghdad governorate at the epilepsy clinic in the neurosciences hospital during the period from the 1st of February through July 2013. Two hundred patients with refractory epilepsy were involved. These patients attended the epilepsy clinic during 2011 and 2012. The data was collected from the files of the patients including age, gender, weight, history of presenting illness, type of seizure, drugs used, duration of disease, EEG and imaging findings, compliance and follow up.

**Results:** Drug resistance epilepsy constituted a prevalence of 24% (128) as the total number of patients with epilepsy attending the hospital during the same period was 527. The mean age of patients with refractory epilepsy was 25 years. Male were 56.5% (113/200) and urban residents were

70.5% (141/200). The study revealed that 64% (128/200) of refractory epilepsy was attributed to drug resistance; while the remaining proportion was pseudoresistance 36% (72/200). The main cause of pseudoresistance was poor compliance 36.1% (26/72). The most common type of seizure in the sampled patients was generalized tonic clonic seizures in 51.5% (103/200). Compliance was found to be statistically associated with abnormal EEG finding, past medical history (hypertension, cardiac diseases, encephalitis, diabetes mellitus and any significant history) and quality of follow up. The follow-up was found to be statistically associated with the family history, past medical history (encephalitis and hypertension) and compliance of patient.

**Conclusion:** A considerable number of patients diagnosed as cases of drug resistant epilepsy had another explanation causing drug failure. The study recommends the application of consensus definition for drug resistant epilepsy and periodic evaluation of patients with drug resistant epilepsy to exclude pseudoresistance.

**Keywords:** Epilepsy, EEG, Drug.

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Drug-resistant epilepsy is failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules to achieve sustained seizure freedom. The terms "drug-resistant epilepsy" pharmaco-resistant epilepsy" and "intractable epilepsy" have been variously used to denote this condition of lack of seizure control despite antiepileptic drug (AED) therapy (1). Seizure freedom is defined as freedom from seizures for a minimum of three times the longest pre-intervention interval or 12 months, whichever is longer. (1,3) False pharmaco-resistance (pseudoresistant) is defined as seizures persist because the underlying disorder has not been adequately or appropriately treated, may not be easily recognizable, and this possibility needs to be investigated in any patient presenting with difficult-to-control seizures. Causes of false pharmaco-resistant epilepsy include:

Misdiagnosis of epilepsy (i.e. patients with psychogenic non-epileptic seizures. misdiagnosed and inappropriately treated with multiple antiepileptic drugs, or misdiagnosis of epilepsy type leading to inappropriate drug selection (i.e. Drug interactions leading to increased side effects and decreased tolerability or Inappropriate dosage and inappropriate patient behavior (i.e. poor compliance) (2).

The ILAE task force has chosen the preferred term "drug resistant" to replace the terms medically intractable, refractory, and pharmaco-resistant. We feel this term is more consistent with the intent of the definition, namely to identify patients for whom there is sufficient information to predict that they will have a substantially poorer prognosis for seizure remission with AEDs when compared with the population as a whole

Poorly controlled epilepsy degrades psychosocial functions, lowers academic performance, and limits

occupational opportunities of patients (5,6). Uncontrolled epilepsy is associated with increased mortality, including increased rates of accidental deaths and suicides. The most important predictor of medical intractability in both adults and children is when seizures are difficult to control early in the course of the epilepsy, High seizure frequency, The quantity of interictal spikes is predictive of severity in temporal lobe epilepsy. The objectives of this study are to determine the causes of drug failure in patients with epilepsy and to differentiate between true drug resistant epilepsy and pseudo-resistant epilepsy.

**Methods:** A retrospective study with analytic elements, conducted in Baghdad governorate. This study was conducted in epilepsy clinic at the neuroscience hospital during the period from the 1st of February 2012 through July 2012. Two hundred patients with refractory epilepsy (true drug resistance and pseudo-resistance) who attended the epilepsy clinic in neuroscience hospital from 2010 to 2012 were involved. Each patient had a file containing full information about patient including age, gender, weight, history of presenting illness, type of seizure, drugs used, duration, EEG & imaging finding, compliance & follow up. The study recorded epileptic patients with failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules to achieve sustained seizure freedom. Patients considered as a false pharmacoresistant when there are poor compliance, wrong diagnosis and therapeutic errors (wrong choice and low dose of drug). All patients with congenital anomalies, structural lesions due to major comorbidities, e.g. severe medical, sleep, or psychiatric disorders were excluded from the study. A questionnaire form had been developed and tailored by the researcher and supervisor to insure proper data collection and prevent any misunderstanding. All questionnaire forms were filled by the researcher by obtaining the data from the files of the patients in the epilepsy clinic.

**Compliance:** voluntary cooperation of patient in following prescribed regimen. This assessed by asking the patient and family members about the dose of drug and time of receiving and if there is cooperation from patients. These information kept in the file of patient every visit.

**Follow up:** the process of monitoring the progress of a patient after a period of active treatment. so by follow up the dates of visit to epilepsy clinic and if there is missing for long period of time.

**Education** was determined by numbers of years of education whether less than 12 years or more.

Data were analyzed using SPSS Statistics, (Statistical Packages for Social Sciences) version 20. Data presented in forms of numbers and percentages in tables as well as figures. Chi-square test was used to evaluate the association between compliance & each of the following variables: age, gender, age at diagnosis,

education years, duration of treatment, type of seizure, EEG findings, family history & past medical history and between follow up & the same variables. A (P value  $\leq 0.05$ ) was considered statistically significant.

**Results ;** Data were collected from the records of 200 patients with refractory epilepsy attending the neurosciences hospital in two years according to the pre-set questionnaire sheets. Drug resistance epilepsy constituted a prevalence of 24% (128) as the total number of patients with epilepsy attending the hospital during the same period was 527. The study found that the mean age of patients with refractory epilepsy was 25 years. Among them, 56.5% (113/200) were male and 70.5% (141/200) were urban residents. (Table 2). Table 3 reveals that 64% (128/200) of refractory epilepsy was attributed to drug resistance; while the remaining proportion was pseudo-resistance 36% (72/200). The main cause of pseudo-resistance was poor compliance 36.1% (26/72) followed by wrong diagnosis 29.2% (21/72), low dose of drug 19.4% (14/72) and wrong choice of drug 15.3% (11/72).

(Table 4). Most patients 74% (148/200) used two to three antiepileptic drugs and the duration of treatment till development of drug resistance was 1-2 years in 38% (76/200) as demonstrated in table 5.

Figure 2 showed that the most common type of seizure in the sampled patients was generalized tonic clonic seizures in 51.5% (103/200) followed by complex partial seizure in 28.5% (57/200) & myoclonic seizure in 9.5% (19/200). This is comparable with the EEG findings in table 6 which revealed that 62% (124/200) of patients had general spikes and waves, 21% (42/200) focal spikes and waves and 9.5% (19/200) with polyspikes. Poor follow-up was found in 59% (118/200) of patients with refractory epilepsy. (Figure 3)

The results on table 7 shows that in 28% (56/200) of patients, family history was obtained and in about equal proportion past medical history was present which include encephalitis 4% (8/200), hypertension 6.5% (13/200), diabetes 5.5% (11/200), cardiac 9.5% (19/200).

The statistical association between compliance and patients' characteristics is presented in table 8. Compliance was found to be statistically associated with abnormal EEG finding, past medical history (hypertension, cardiac diseases, encephalitis, diabetes mellitus and any significant history).

Quality of follow-up was significantly associated with the family history, past medical history (encephalitis, hypertension) and compliance of patient as demonstrated in table 9.

Table 2: The distribution of patients according to demographic characteristics.

		N	o	%
Age (years)	< 10	10	15	57.5
	10 - 20	9	14	55.6
	20 - 30	9	14	55.6
	30 - 40	3	4	15.4
	> 40 years	2	3	11.5
	Mean±SD (Range)	25.0±12.0	(1.5 - 76)	
Gender	Male	11	17	65.4
	Female	8	12	46.2
Age at diagnosis (years)	< 10	8	12	46.2
	10 - 20	9	14	55.6
	20 - 30	3	4	15.4
	> 30 years	2	3	11.5
	Mean±SD (Range)	14.1±10.7	(40d - 45y)	
Education years	< 12 years	11	17	65.4
	> 12 years	8	12	46.2
Residence	Urban	14	21	79.2
	Rural	5	8	30.8

Table 3: The distribution of patients according to type of refractory epilepsy

	N	o	%
Drug resistant epilepsy	18	26	72.2
Pseudoresistant epilepsy	7	10	27.8

Table4: Causes of psudoresistance

	N	o	%
Poor compliance	2	3	11.5
Wrong diagnosis	2	3	11.5
Therapeutic errors			
-Wrong choice of drug	1	1	3.8
-Low dose of drug	1	1	3.8

Table5: The distribution of patients according to number of drugs used by patients and the duration of treatment.

		N	o	%
Number of drugs	One drug	-	-	-
	Two	7	10	37.0
	Three	7	10	37.0
	Four	5	7	26.0

Duration of treatment (years)	< 1	1	2	3	4	5
1	-	-	7	6	3	8
2	-	-	4	7	2	3
3	-	-	1	4	7	0
=	>	4	2	0	1	0
Mean ± SD (Range)	1.9 ± 1.7 (5 m - 11 y)					

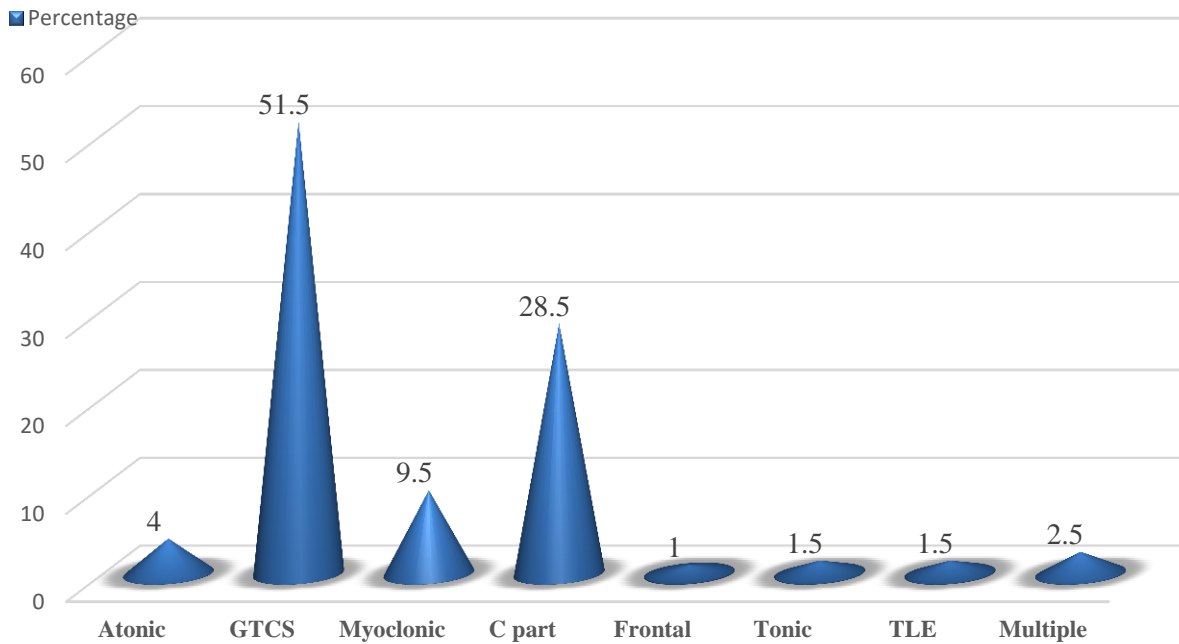


Figure 2: The distribution of patients according to type of seizure

Table 6: The distribution of patients according to EEG findings

EEG findings (S & W)	N	o	%
F o c a l *	4	2	2
G e n e r a l i z e d **	1	2	4
P o l y ***	1	9	9
T L E ****	1	5	7

\* Focal spikes and waves

\*\*Generalized spikes and waves.

\*\*\*Polyspikes

\*\*\*\*Temporal lobe epilepsy



Figure 3: The distribution of patients according to quality of follow-up

**Table 7: The distribution of patients according to family and past medical history**

	N	o	%
F a m i l y H i s t o r y	5	6	28.0
P a s t m e d i c a l h i s t o r y	5	8	29.0
- E n c e p h a l i t i s	8	4	.0
- H y p e r t e n s i o n	1	3	.5
- D i a b e t e s	1	1	.5
- C a r d i a c	1	9	.5
- O t h e r s	7	3	.5

**Table 8: Statistical association of compliance and patients' characteristics**

	C o m p l i a n c e						P value
	Y e s			N o			
	N	o	%	N	o	%	
Age (years)	< 10	8	53.3	7	46.7	0.227	
	10 - 19	2	47.9	2	52.1		
	20 - 29	2	35.6	4	64.4		
	30 - 39	1	64.0	2	59.0		
	> 40 years	1	50.0	1	40.0		
Gender	Male	5	48.7	5	51.3	0.129	
	Female	3	37.9	5	62.1		
Age at diagnosis (years)	< 10	3	37.5	5	62.5	0.142	
	10 - 19	2	64.3	3	58.7		
	20 - 29	2	59.5	1	40.5		
Education years	> 30 years	1	50.0	1	50.0	0.206	
	< 12 years	2	40.3	7	59.7		
	= 12 years	4	49.4	4	50.6		
Residence	Urban	6	43.3	8	56.7	0.745	
	Rural	2	45.8	3	54.2		
Drugs number	One drug	-	-	-	-	0.671	
	Two	3	41.1	4	58.9		
	Three	3	48.0	3	52.0		
	Four	2	42.3	3	57.7		
Duration of treatment (years)	< 1 year	1	44.2	2	55.8	0.100	
	1 - 2	3	44.7	4	55.3		
	2 - 3	1	34.0	3	66.0		
	3 - 4	5	35.7	9	64.3		
	> 4	1	70.0	6	30.0		
Type of seizure	Atonic	3	37.5	5	62.5	-	
	GTCS	3	35.0	6	65.0		
	Myoclonic	1	78.9	4	21.1		
	Copart	2	49.1	2	50.9		
	Frontal	-	-	2	100.0		
	Tonic	2	66.7	1	33.3		
EEG findings (S&W)	TLE	3	100.0	-	-	0.002*	
	Multiple	1	20.0	4	80.0		
	Focal	1	40.5	2	59.5		
	General	4	37.1	7	62.9		
	Polyl	1	78.9	4	21.1		
Family History	TLE	1	66.7	5	33.3	0.141	
	Yes	2	35.7	3	64.3		
	No	6	47.2	7	52.8		
Past medical history	Yes	3	61.2	2	38.8	0.005*	
	No	5	38.4	9	61.6		
Encephalitis	Yes	6	75.0	2	25.0	0.071	
	No	8	42.7	1	57.3		
Hypertension	Yes	1	92.3	1	7.7	0.0001*	
	No	7	40.6	1	59.4		
Diabetes	Yes	6	54.5	5	45.5	0.469	
	No	6	40.6	1	59.4		

C a r d i a c	N	o	8	2	43.4	1	0	7	56.6	0 . 8 6 1	
	Y	e	s	8	42.1	1	1	57.9			
O t h e r s	N	o	8	0	44.2	1	0	1	55.8	0 . 1 3 7	
	Y	e	s	5	71.4	2	28.6				
F o l l o w u p	N	o	8	3	43.0	1	1	0	57.0	0.0001*	
	G	o	o	d	7	8	95.1	4	4.9		
	P	o	o	r	1	0	8.5	1	0	8	91.5

\*Significant using Pearson Chi-square test at 0.05 level.

Table 9: Statistical association of follow-up with patients' characteristics

		F o l l o w u p				P v a l u e				
		G o o d		P o o r						
		N o	%	N o	%					
A g e ( y e a r s )	< 1 0	1	0	8	53.3	7	46.7	0 . 4 5 7		
	1 0 - 2 0	1	9	2	1	43.8	2		7	56.3
	2 0 - 3 0	2	9	2	6	35.6	4		7	64.4
	= > 3 0 y e a r s	1	3	9	1	4	35.9		2	5
G e n d e r	M a l e	5	3	46.9	6	0	53.1	0 . 0 5 3		
	F e m a l e	2	9	33.3	5	8	66.7			
A g e a t d i a g n o s i s ( y e a r s )	< 1 0	1	0	3	0	37.5	5	0	62.5	0 . 6 7 4
	1 0 - 2 0	2	8	44.4	3	5	55.6			
	2 0 - 3 0	1	4	37.8	2	3	62.2			
	= > 3 0 y e a r s	1	0	50.0	1	0	50.0			
E d u c a t i o n y e a r s	< 1 2	2	4	3	36.1	7	6	63.9	0 . 0 9 0	
	= > 1 2 y e a r s	3	9	48.1	4	2	51.9			
R e s i d e n c e	U r b a n	5	8	41.1	8	3	58.9	0 . 9 5 2		
	R u r a l	2	4	40.7	3	5	59.3			
D r u g s n u m b e r	O n e d r u g	-	-	-	-	-	-	0 . 9 3 1		
	T w o	2	9	39.7	4	4	60.3			
	T h r e e	3	2	42.7	4	3	57.3			
	F o u r	2	1	40.4	3	1	59.6			
D u r a t i o n o f t r e a t m e n t ( y e a r s )	< 1	1	9	44.2	2	4	55.8	0 . 7 3 7		
	1 - 2	3	2	42.1	4	4	57.9			
	2 - 3	1	6	34.0	3	1	66.0			
	= > 3	5	0	50.0	1	0	50.0			
T y p e o f s e i z e r	A t o n i c	3	7	37.5	5	6	62.5	0 . 1 8 1		
	M T C S	3	0	35.9	6	6	64.1			
	M y o c l o n i c	1	0	52.6	9	4	47.4			
	C o p a r t	2	6	45.6	3	1	54.4			
	F r o n t a l	-	-	-	2	1	100.0			
	T o n i c	2	3	66.7	1	3	33.3			
E E G f i n d i n g s ( S & W )	M u l t i p l e	1	5	20.0	4	7	80.0	0 . 1 0 6		
	F o c a l	4	7	35.7	2	7	64.3			
	G e n e r a l	1	0	52.6	9	7	62.1			
	P o l y	1	0	66.7	5	4	47.4			
C o m p l i a n c e	Y e s	7	8	88.6	1	0	11.4	0.0001*		
	N o n	4	3	3.6	1	0	96.4			
F a m i l y H i s t o r y	Y e s	1	2	21.4	4	4	78.6	0.0001*		
	N o	7	0	48.6	7	4	51.4			
P a s t m e d i c a l h i s t o r y	Y e s	3	0	55.1	2	7	44.9	0 . 0 2 1 *		
	N o	5	5	36.4	9	6	63.6			
E n c e p h a l i t i s	Y e s	6	7	75.0	2	2	25.0	0 . 0 4 6 *		
	N o	7	6	39.6	1	1	60.4			
H y p e r t e n s i o n	Y e s	1	0	76.9	3	3	23.1	0 . 0 0 6 *		
	N o	7	2	38.5	1	1	61.5			
D i a b e t e s	Y e s	4	7	36.4	7	6	63.6	0 . 7 4 8		
	N o	7	8	41.3	1	1	58.7			
C a r d i a c	Y e s	9	7	47.4	1	0	52.6	0 . 5 5 3		
	N o	7	3	40.3	1	0	59.7			
O t h e r s	Y e s	4	7	57.1	3	3	42.9	0 . 3 7 7		
	N o	7	8	40.4	1	1	59.6			

\*Significant using Pearson Chi-square test at 0.05 level.

**Discussion** :Drug-resistant epilepsy is associated with a range of deleterious consequences, including higher mortality and morbidity, restriction on social activities, and stress on the patient's family members and

caregivers. It is also a great economic burden for the society through expenditures in healthcare and unemployment (3). The prevalence of intractable epilepsy in the present study was 24.3% which is very

close to that reported by Viteva et al, and Hyunmi et al . (7,8,9) .Among 200 patients with refractory epilepsy, the prevalence of drug resistant epilepsy was 64% & that of pseudo-resistance was 36%. The pseudo-resistance was higher than that reported in a study conducted by Viteva et al and this may be due to lack of advance facilities in diagnosis of epilepsy like availability of video EEG monitoring , PET scan, SPECT, MEG , MRS & intracranial EEG. (7) The main cause that determined pseudo-resistance was poor compliance 36.1% which is higher than what was reported in studies conducted by Viteva et al and Gelisse et al which is due to lack of knowledge of our people about the complications of epilepsy and the importance of compliance in controlling of seizures and may be due to unavailability of antiepileptic drugs or economic purposes (7,10) . Therapeutic errors were demonstrated in 15.3% of patients with pseudo-resistance due to wrong choice of drugs and in 19.4% due to low dose of drugs while pseudo-resistance in 29.1% was due to wrong diagnosis which is lower than that documented by Viteva et al but higher than that reported by Hyunmi et al & this can be explained by that the epileptic patients in our country seen by many doctors before referral to a neurologist or specialized center of neurology. (7,9) Refractoriness was higher in male than in female which is different from the findings of Vitava et al, Gelisse et al & Hyunmi et al. This may be due to that epilepsy is considered a stigma in our society especially for female patient so the visit to the epilepsy clinic & follow up become less than what is expected for every epileptic patients. (7,9,10) When considering the age at diagnosis, intractable epilepsy was highest in those who aged less than ten years at the time of diagnosis. Refractory epilepsy was found to be less in patients with more years of education which can be explained by that patients with higher level of education may have good knowledge about epilepsy and its complications making them more compliant and more care about follow up. The proportion of refractory epilepsy was higher in urban than rural residing patients & this can be attributed to the cultural beliefs of rural people forcing them to neglect seeking medical care as alternative faulty methods for treating epilepsy patients are common among such people.

There was little difference in refractoriness between those using two antiepileptic drugs and those using more than two drugs. This finding is comparable with that found by Kwan and Brodie. Who documented that the likelihood of patients with intractable partial epilepsy becoming seizure free with the third or additional antiepileptic drug is approximately 4%. (4) The generalized type of seizure was more than the other types including partial seizure while other studies conducted by Viteva et al, Gelisse et al, Hyunmi et al and Mari picot et al revealed that partial seizure was the most common. This can be explained by the fact that partial seizure is mostly lesional and can be treated surgically and not need referral to the epilepsy clinic. (7,9,10) The follow up was poor in 59% which is higher

than that reported by Hyunmi et al. this may be due to poor security situation causing difficulty in access of patients to the health facilities. (9) The family history of epilepsy was found in 28% of patients with refractory epilepsy while it was 9.5% in a study conducted by Viteva et al. (7) About one quarter of patients with refractory epilepsy had past medical history with cardiac problems was the most common. This finding differs from the result documented by Hui et al who showed that patients with mesial temporal sclerosis & mental retardation were more likely to develop drug resistant epilepsy. (11)

A statistical significant association was revealed between compliance and EEG findings; focal and generalized spikes and waves were associated with non-compliance. The relation between compliance and past medical history was found to be statistically significant. Those having past medical history were more compliant and this can be attributed to the previous experience of those patients making them more aware about the benefit that can be gained when becoming compliant with the advices of the health professionals in regard to the treatment of the disease. The quality of follow up was another determinant of the compliance; good follow up most likely associated with more compliance. Possible explanation of such relation is the personal characteristics; the patient who is devoted to follow up his/her condition is expected to comply with the treatment lines to obtain control of the disease he/she suffers from.

A statistical significant impact was demonstrated between the quality of follow up and family history where patients with family history of epilepsy appeared to had poor follow up. Past medical history was one of the factors influencing the quality of follow up; about two thirds of patients with such a history reported to have good follow up. This can be explained by that patients with past medical history might become informed about the importance of follow up in the disease control from their experience with their previous morbidities. The generalized ability of the study findings is limited due to the use of convenience sampling. Any conclusions that were reached may be applicable only to patients who share the characteristics of this sample. This is a hospital-based study and its results may not reflect the real picture in the general population. Another point of weakness is the use of patients' records which may contain incorrect information or inadequate details in contrast to directly taking the data from the patients.

**Conclusions:** Large number of patients diagnosed as cases of drug resistant epilepsy had another explanation causing drug failure like therapeutic errors, poor compliance and wrong diagnosis. Drug resistance epilepsy constituted a prevalence of 24%. The mean age of patients with refractory epilepsy was found to be 25years. The highest percentages of patients with refractory epilepsy were male and urban residents.

Small percentage of patients with refractory epilepsy had family history of epilepsy and past medical history. The most common cause of pseudo-resistance was poor compliance. The most common seizure type in patients with drug resistant epilepsy was generalized tonic clonic seizure.

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