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Apparent Refractory Epilepsy; Causes and Prevalence among Sudanese Patients at the National Center of Neurological Sciences, Khartoum 2018

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Abstract

Background: Refractory epilepsy is a disease that requires special care from health authorities and community. This study is a trial to lighten its aspects.

Objectives: To assess the prevalence of Apparent refractory epilepsy among Sudanese patients at the National Center of Neurological Sciences (NCNC), Khartoum and to identify its causes.

Methods: This is a prospective cohort study, 100 patients of apparent refractory epilepsy were selected out of 256 patients of epilepsy according to Berg's definition (failure of two or more drugs and occurrence of one or more seizures per month over 18 months) in the study area during the period from June 2014 to December 2018. Data was collected through pre-designed questionnaire and processed by using the Statistical Package for Social Sciences (SPSS), results was presented as tables and graphs.

Results: The prevalence of apparent refractory epilepsy was 39.1%, the mean age was 30.6 years, male to female ratio was 1.6: 1. Subtype of epilepsy showed idiopathic in 78 (78%) and secondary in 22 (22%). Within secondary epilepsy group, tumor and trauma represented 5 (22.7%) for each. Classification of epilepsy showed generalized epilepsy in 78 (78%) and partial in 22 (22%). Among generalized epilepsy 65 (83.3%) were tonic-clonic, among partial epilepsy 15 (68.2%) were partial complex. Regarding treatment, 97 (97%) of the patients used two drugs, while 3 (3%) used three drugs. In the group of patients who took two drugs combination of sodium valproate and carbamazepine were the most used (61%). Sodium valproate and carbamazepine were used by 81 (81%) for each. 55 (55%) of patients started treatment immediately, while others 45 (45%) delayed from 6 months up to 14 years. 33 (33%) of patients had family history.

Conclusion: The study concluded that, prevalence of apparent refractory epilepsy was 39.1%. The most common causes of apparent Refractory Epilepsy were uses of unsuitable combination of drugs, Family and genetic factors, wrong drug choice, and secondary etiologies of epilepsy.

Keywords: Epilepsy; Refractory; Prevalence; Sudan

Introduction

Epilepsy is characterized by a long term risk of recurrent seizures [1]. These seizures may present in a number of different ways [2]. During childhood, well-defined epilepsy syndromes are generally seen.

During adolescence and adulthood, the causes are more likely to be secondary to any CNS lesion. Further, idiopathic epilepsy is less common. Other causes associated with these age groups are stress, trauma, CNS infections, brain tumors, and illicit drug use and alcohol withdrawal. In older adults, cerebrovascular disease is a very common cause. Other causes are CNS tumors, head trauma, and other degenerative diseases that are common in the older age group, such as dementia [3].

An American study conducted by French [4] Reported that, the incidence of refractory epilepsy remains high despite the influx of many new 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. Environmental factors, such as trauma and prior drug exposure, and genetic factors that predetermine the rate of absorption, metabolism, and uptake of a drug by target tissue may also uniquely impact an individual and influence their response to AED therapy. Treatment resistance is, therefore, a multifaceted phenomenon. Since individuals with refractory epilepsy do not share a common reason for their treatment resistance, the use of targeted drug therapies may be our best option for improving treatment outcomes in this patient population. Pharmacogenetics are currently attempting to understand the genetic basis of refractory epilepsy so that they can identify subgroups of patients who share a common genetic background and then target drug therapies to meet their specific needs [4].

Justification

- Refractory epilepsy is very common condition and need to be verified.
- It is associated with increased morbidity and mortality and a significant increase in the cost of health care in the community.

Objectives

General objective

To know the prevalence of apparent refractory epilepsy among Sudanese patients in the National Centre for Neurological Science between June 2014-December 2018

Specific objectives

- To identify the causes of apparent refractory epilepsy.
- To assess occurrence of apparent refractory epilepsy, type of epilepsy and response to type (s) and number of drug (s).

Materials and Methods

Study design

Prospective Cohort study, carried out among patients with epilepsy, then apparent refractory epilepsy was assessed among the study population.

Study area and time

Neurology department at the National Center for Neurological Sciences including the wards and referred clinics and ICU. The study was carried out in the period from June 2014- December 2018.

Study population

All patients of apparent refractory epilepsy who attended the neurology department including the ward, referred clinics, and ICU.

Study sample and technique

Hundred 100 patients were included and selected out of 256 patients.

Inclusion criteria

All Sudanese patients who have apparent refractory epilepsy according to Berg's definition (failure of two or more drugs and occurrence of one or more seizures per month over 18 months) [5].

Exclusion criteria

Epileptic patients did not satisfied refractory epilepsy criteria.

Data collection

Personal and demographic data from all patients was collected in a designed form (questionnaire), which held through sections as follows: section (1): personal data, section (2): clinical presentation, section (3): types and classification of epilepsy, section (4): drug treatment, section (5): EEG and brain imaging and section (6): co-morbidities and complications.

Data processing and analysis

Data was processed using the computerized program; Statistical package for Social Sciences (SPSS). The data was represented in tables and graphs, and finally conclusion and recommendations were obtained.

Ethical consideration

Written consent from the head department of neurology.

Permission from the patients or their relatives was taken.

Patients informed that, their data privacy will be considered and used for purpose of the study only.

Results

Prevalence

Among 256 epileptic patients seen in the study area, 100 patients found to have apparent refractory epilepsy.

Age distribution

The mean age was 30.6 years, the age group of 16-30 years was found in 46 (46%), while age group of 31-45 years was found among 28 (28%). The age group of <15 years was found in 10 (10%).

Sex distribution

Males represented 61 (61%) of study population and female represented 39 (39%), male to female ratio was 1.6:1.

Job distribution

Thirty two (32%) were students, 25 (25%) were labourers, 16 (16%) were housewives and the same percentage found among idles.

Residence distribution

69 (69%) resides in Khartoum states and 22 (22%) in center of Sudan, while residence in other states represented 9 (9%).

Education level

Forty four (44%) of the studied group had primary education, 22 (22%) had secondary education and 19 (19%) were illiterate, while university education level was found in 15 (15%).

Clinical characteristics

Duration of epilepsy: Forty eight (48%) of study population had the apparent refractory epilepsy for 5 years or less, 21 (21%) for 6-10 years and 18 (18%) for 11-15 years. Those who had apparent refractory epilepsy for 16-20 years were 8 (8%) and those who had apparent refractory epilepsy for more than 20 years were 5 (5%) patients.

Clinical presentation: Loss of consciousness was found in 96 (96%) of the studied group, generalized convulsion was found in 68 (68%), Aura was found in 28 (28%) and frothing was found in 25 (25%), other clinical presentation were tongue bitten 13 (13%), right side convulsion 13 (13%), sphincteric disturbance 10 (10%), upward rolling of eyes 8 (8%), left side convulsions 5 (5%), electric shock-like contraction 2

(2%), while generalized spasm, single limb convulsions, lip smacking, memory loss and shaking head found in one (1%) patient for each.

Duration of attack: Attack for one minute or less was found in 17 (17%) patients, 1-5 minutes was found in 57 (57%) patients, 6-10 minutes was found in 23 (23%) patients and more than 10 minutes was found in 3 (3%) patients.

Number of attacks per month: Sixty three (63%) patients had one attack per month, 29 (29%) patients had two attacks and 8 (8%) patients had more than two attacks per month.

Clinical findings: Abnormal clinical findings were found in 11 (11%) patients, hemiparesis presented in 5 (5%) of them, aphasia was found in 3 (3%) and hemiplegia in 2 patients (2%), other findings were: slurred speech, mental retardation, bilateral optic atrophy, pill rolling tremor, rigidity, bilateral papilloedema, microcephaly and symmetrical syndactyly and they were found in one patient (1%) for each.

Subtypes of epilepsy: Idiopathic was found in 78 (78%), while secondary epilepsy was recorded in 22 (22%). In secondary refractory epilepsy causes, trauma and tumour represented 5 (22.7%) for each, encephalitis represented 3 (13.7%), A.V.M and stroke represented 2 (9.1%) for each, while other causes (e.g. meningitis, congenital and TB) represented 5 (22.7%).

Classification of epilepsy: Generalized epilepsy was found in 78 (78%) of patients and partial in 22 (22%). in partial epilepsy group 15 (68.2%) classified as complex, with secondary generalization were 4 (18.2%) and with simple partial were 3 (13.6%). Generalized epilepsy group shows 65 (83.3%) of tonic-clonic, 10 (12.8%) absence, 2 (2.6%) myoclonic and 1 (1.3%) tonic (Tables 1 and 2).

Age (year)		Sex		Job		Residence		Educational level	
15	10	Males	61	Student	32	Khartoum	69	Primary	44
16-30	46	Females	39	Labourer	25	Center	22	Secondary	22
31-45	28			House Wife	16	North	4	Illiterate	19
46-60	12			Employee	6	West	3	University	15
>60	4			Others	21	EAST	2		

Table 1: Demoghrahpic data of patients with apparent refractory epilepsy.

Duration of Epilepsy (year)		Duration of the attack (minute)		Number of attacks per month	
≤5	48	<1	17	1 ATTACK	63
6-10	21	01-May	57	2 ATTACKS	29
11-15	18	06-Oct	23	>2 ATTACKS	8
16-20	8	>10	3		
>20	5				

Table 2: Related information about patients with apparent refractory epilepsy.

Medical treatment: Ninety eight (97%) of the patients used two drugs, while 3 (3%) used three drugs. Out of the group who used two drugs, 61 (61%) took (sodium valproate+carbamazepine), 9 (9%) took (sodium valproate+phenytoin), 8 (8%) took (sodium valproate +lamotrigine), 8 (8%) took (carbamazepine+lamotrigine), 5 (5%) took (carbamazepine+phenytoin), 2 (2%) took (carbamazepine +topiramate), 2 (2%) took (carbamazepine+phenobarbitone), 1 (1%) took (Sodium valproate+topiramate) and 1 (1%) took (phenytoin +phenobarbitone). In patients who took three drugs, 2 (2%) used (carbamazepine+lamotrigine+sodium valproate) and 1 (1%) used (carbamazepine+lamotrigine+phenytoin). Sodium valproate and carbamazepine were used by 81 (81%) for each, lamotrigine used by 18 (18%) and phenytoin by 16 (16%), 3 (3%) patients used phenobarbitone and the same number used topiramate.

Duration of treatment: Fifty eight (58%) had treatment for five years or less, 16 (16%) had treatment for 6-10 years, 15 (15%) had treatment for 11-15 years, 7 (7%) had treatment for 16-20 years and 4 (4) had treatment for more than 20 years.

Delay of treatment: Fifty five (55%) of patients had immediately started treatment, 34 (34%) started treatment after 6-36 months, 4 (4%) patients started after 3.5-6 years, 4 (4%) patients started treatment after 6.5-9 years, 3 (3%) patients started treatment after 9.5-14 years.

Family history: Thirty three (33%) patients had family history of epilepsy.

Seventy seven (77%) patients were compliant to drug, while 23 (23%) had unsuitable drug combination. drug side effects was found in 17 (17%), unavailability of drug was found in 17 (17%) and no response was found in 13 (13%).

EEG findings: Normal result was found in 56 (56%) patients, 32 (32%) had generalized epileptic activity, 7 (7%) had focal epileptic activity, 2 (2%) had atypical absence of seizure, the same number showed focal with secondary generalization and one patient had juvenile myoclonic epilepsy.

MRI findings: Eighty five (85%) patients subjected to MRI, 62 (62%) were normal, 6 (6%) had infarction, tumour and mesial temporal sclerosis was found in 5 (5%) for each, other different findings were found in 7 (7%) patients.

Co-morbidities and association: Hypertension was found in 6 (6%) patients, diabetes mellitus was found in 5 (5%) patients, skeletal deformity and skin manifestation were found in 2 patients (2%) for each, cardiac arrhythmia was found in one patient as well as electrical abnormality, other co-morbidities were found in 8 (8%) patients.

Complications and disability: Forty five patients (45%) had complications; 18 (18%) lost their jobs, 11 (11%) had trauma, 10 (10%) had brain insult, 2 (2%) had drug side effects and 4 (4%) had other complications (Figures 1-4).
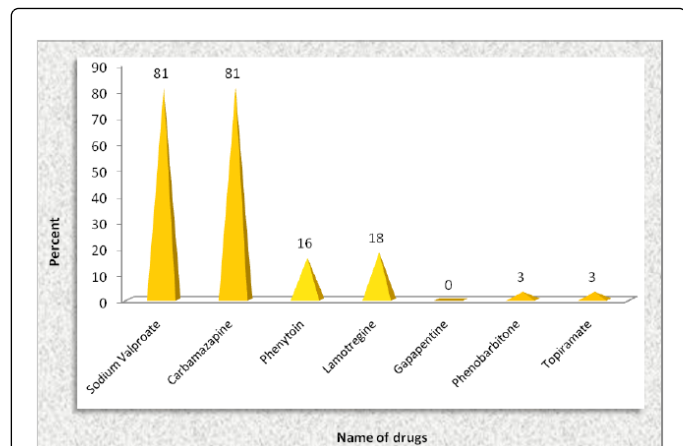

Figure 1: Type of drugs taken by 100 patients with apparent refractory epilepsy.

Figure 2: Family history in 100 patients with apparent refractory epilepsy.

showed that, among 350 referred patients of uncontrolled seizure 55% were male and 45% were female.

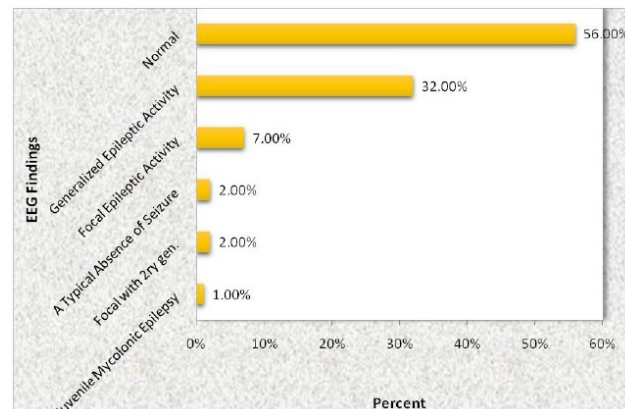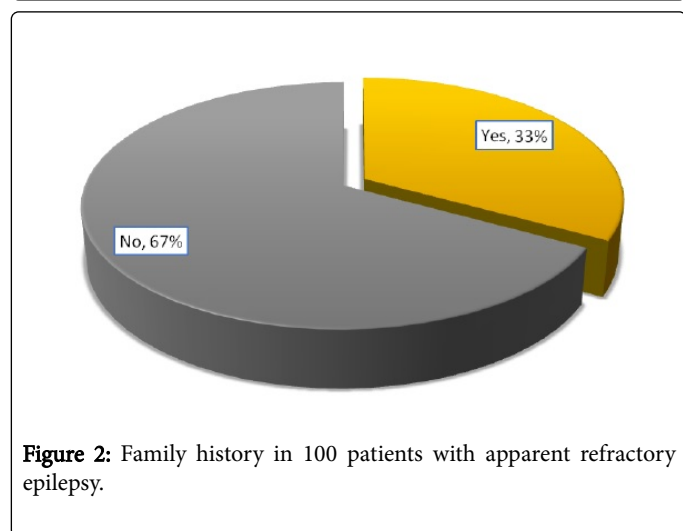**Figure 3:** EEG findings in 100 patients with apparent refractory epilepsy.
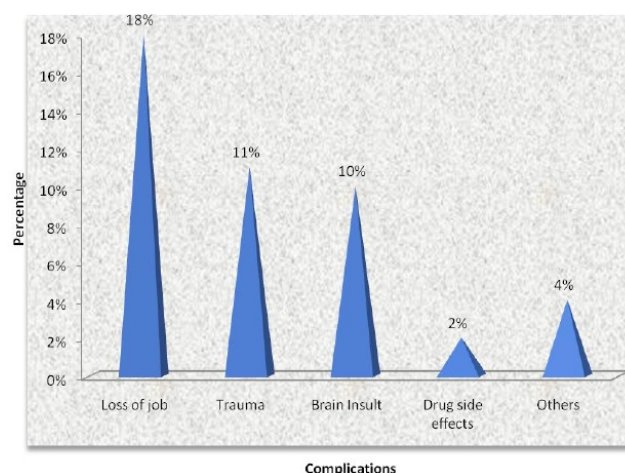

Figure 4: Complications in 100 patients with apparent refractory epilepsy, (n=45).

Discussion

Refractory epilepsy is a distressing health problem for patient and doctor. Therefore, great efforts should be done to solve this problem. The current study faced a problem in finding enough cases that fulfilled the criteria of true medically refractory epilepsy. Thus, detected cases were titled as "apparent refractory epilepsy". The study found that, the prevalence of refractory epilepsy was (39.1%), which is compatible with the literature of French [4] who reported that, 20%-40% of epilepsy patients develop refractory epilepsy and also compatible with findings of the Iranian study which showed that, 40% had indeed medically-refractory epilepsy [6].

The most common age group is 16-30 years (46%), followed by 31-45 years (28%), which reflects that the reproductive age is affected more. Incidence of refractory epilepsy in males predominated (61%), this was a little more than findings of the Iranian study [6] which

Financial burden of treatment and social stigma are highly affected by job type of the patient, as well as the education level will determine the response and attitude towards the diseases. The current study found that, students were most common than others; (32%) followed by labourers who represented (25%) and (16%) were housewives. On the other hand, the percentage of patients with limited education (illiterate and primary) was very high (63%); primary education represented the most common (44%) followed by illiterate who represented (19%).

Close residence to health facilities facilitates easy access and encourage patient to follow treatment. 69% of patients were found to reside in Khartoum State, those who came from the center of Sudan were 22%, and from other states were 9%.

Nearly half of the studied population had the refractory epilepsy for five years or less (48%), those whose disease duration more than five years represented 52% and they expected to have a varying degrees of

compliance, resistance to treatment and probability of developing complications. Longer duration of epilepsy might expose patients to refractory epilepsy, this is supported by the two studies of Luciano [7] and Schiller [8] who reported that, longer duration of epilepsy is associated with the risk of DRE.

The vast majority of patients showed the commonest symptoms of epilepsy; loss of consciousness (96%), followed by generalized convulsions (68%), Aura was found in 28% of patients.

Attack duration for 1-5 minutes predominated (57%), nearly quarter of the study population had attack for 6-10 minutes (23%).

The vast majority of patients had one or two attack per month; 63% and 29% respectively, while 8% had more than two attacks per months. Brain insult, social and psychological impacts increase proportionally with increase of attacks per month.

Hemiparesis was the most frequent clinical finding (5%), followed by aphasia (3%) and hemiplegia (2%).

Idiopathic refractory epilepsy predominated against secondary refractory epilepsy (78% vs 22%). This does not go with Scotland study [9] where the prevalence of symptomatic epilepsy was higher than the idiopathic epilepsy (40% vs 26%).

The generalized refractory epilepsy is found more common than partial refractory epilepsy (78% vs 22%). Tonic-clonic predominated in generalized epilepsy patients (83%) out of 78 patients followed by absence seizure (12.8%), myoclonic (2.6%) and tonic (1.3%). Complex predominated in partial refractor epilepsy (68.2%) out of 22 patients, followed by partial with secondary generalization (18.2%) and simple partial (13.6%).

Drugs are a palliative treatment preventing the clinical expression of seizures but cannot affect the underlying pathological state.

In our study, the vast majority (97%) of patients took two drugs, while only a few (3%) took three drugs. In the group of patients who took two drugs combination of sodium valproate and carbamazepine were the most used (61%). Sodium valproate and carbamazepine were the most common drug used (81%) for each. Lamotrigine, phenytoin, phenobarbitone and topiramate has less usage; (18%, 16%, 3% and 3%) respectively. Sodium valproate and carbamazepine are the first line of treatment for generalized and partial refractory epilepsy respectively [10], also availability of these two drugs might be second cause of being more used in Sudan.

In patients who used sodium valproate the maximum dose was reached 2000 mg. In patient who used carbamazepine, 31 out of 81 received 800 mg, 27 received 1200 mg and 17 received 1000 mg. Patients who used phenytoin all of them received 300 mg.

Taking 800 mg or less by 57 patients of sodium valproate and 78 patients of carbamazepine might be indicator of receiving suboptimal dose. Presence of suboptimal dose is supported by the Iranian study which showed that, 18% were taking suboptimal doses of AEDs [3].

The most common dose used in patients who used lamotrigine is 200 mg/day; (7 out of 18 patients), followed by 150 mg/ day (4 patients). One patient used high dose (225 mg/ day). A UK study [11] revealed that lamotrigine is effective in generalized tonic clonic refractory epilepsy, putting in mind that (83.3%) of generalized epilepsy in the current study were tonic-clonic and lamotrigine was used by only 18%, this might be due to the unavailability of lamotirigine all the times in Sudan.

More than half of patients had treatment for five years or less (58%), while remainders had 6 years of treatment or more (42%). Long period of treatment might expose patients to more risks, adverse effect of drug.

In our study, third of the patients found to have family history of epilepsy (33%). Family history and genetics has its influence on inheriting the epilepsy as well as it has a contribution on management. This is supported by the American study [4] which reported that, pharmacogeneticists are currently attempting to understand the genetic basis of refractory epilepsy so that they can identify subgroups of patients who share a common genetic background and then target drug therapies to meet their specific needs [4].

Nearly quarter of patients were using unsuitable combination of drugs. This is very much higher than that provided by the Iranian study [6] which showed that, 1% was not compliant.

All patients of the study subjected to EEG, 56% of them found to be normal, generalized epileptic activity was the main finding by EEG (32%), 7% had focal epileptic activity and 2% had atypical absence of seizure, and the same percentage had focal secondary generalizations.

Association of abnormal EEG findings with DRE is supported by the studies of Berg et al. [12] and Brodie et al. [13].

The vast majority of our patients were subjected to MRI (85%), while others (15%) had CT scan in which two patients showed underlying pathology, Preferring MRI might be due to the high sensitivity. This was supported by Bronen et al. [14] who concluded that sensitivity of MRI was (95%) while CT scan sensitivity (32%), MRI was also demonstrated to be significantly better than CT scanning for the localization of mesial temporal sclerosis (98% vs 2%) [14].

Most of our patients (62%) had normal MRI. MRI detected infarction in (6%), tumour and mesial temporal sclerosis in (5%) for each.

The commonest co-morbidities were hypertension (6%), diabetes mellitus (5%) and skeletal deformity (2%).

It is hard for patients of epilepsy to survive without complications, especially those with long duration of epilepsy. In the current study, (45%) found to have complications, 18% lost their jobs, 11% had trauma, 10% had different brain insult and disabilities and 2% had drug side effect.

Delaying to start treatment is varied between 6 months up to 14 years in the current study, and they represented nearly half of patients (45%). This means delay in treatment can contribute to develop the refractory epilepsy. This is compatible with Kwan and Brodie study which concluded that, patients who have many seizures before therapy or who have an inadequate response to initial treatment with antiepileptic drugs are likely to have refractory epilepsy [9].

Mental illness is believed to be caused by sprit possession, so some patients prefer seeking help from traditional spiritual healers before coming to doctor, even in lesional type of epilepsy (tumour).

Conclusion

The prevalence of apparent refractory epilepsy in our study was high (39.1%). It is found more common in males than females. More than half of the studied population found to have epilepsy for six years or more. There was a delay in starting treatment by nearly half of the studied patients. Most of our patients used carbamazepine and sodium

valproate. Causes of apparent refractory epilepsy in our study were: unsuitable combination of the drugs, family and genetic factors, wrong drugs selection, delay in starting treatment from the onset of the epilepsy and secondary etiologies of epilepsy.

Conflicts of Interest

We have participated sufficiently in the intellectual content conception and design of this work, the analysis and interpretation of the data, as well as the writing of the manuscript.

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References

1. Oby E, Janigro D (2006) The blood-brain barrier and epilepsy. Epilepsia 47: 1761-1774.
2. Patient Fact Sheet: Epilepsy (2012) American Academy of Neurology. Retrieved January 5.
3. Browne TR, Holmes GL (2008) Handbook of epilepsy (4th ed.). Philadelphia: Lippincott Williams & Wilkins.
4. French JA (2007) Refractory epilepsy: clinical overview. Epilepsia 48: 3-7.
5. Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, et al. (2006) How long does it take for epilepsy to become intractable? A prospective investigation. Ann Neurol 60: 73-9.
6. Asadi-Pooya AA, Emami M, Ashjazadeh N, Nikseresht A, Shariat A, et al. (2013) Reasons for uncontrolled seizures in adults; the impact of pseudointractability. Seizure 22: 271-274.
7. Luciano AL, Shorvon SD (2007) Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. Ann Neurol 62: 375-381.
8. Schiller Y, Najjar Y (2008) Quantifying the response to antiepileptic drugs: effect of past treatment history. Neurology 70: 54-65.
9. Kwan P, Brodie MJ (2000) Early identification of refractory epilepsy. N Engl J Med 342: 314-319.
10. Fauci AS, Kasper DL, Longo DL, Braunwald E, Hauser SL, et al. (2008) Harrison Principles of Internal Medicine; Selection of Antiepileptic Drugs 17: 363.
11. Tjia-Leong E, Leong K, Marson AG (2010) Lamotrigine adjunctive therapy for refractory generalized tonic-clonic seizures. Cochrane Database Syst Rev 8: CD007783.
12. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, et al. (2001) Early development of intractable epilepsy in children: a prospective study. Neurology 56: 1445-1452.
13. Brodie MJ, Kwan P (2002) Staged approach to epilepsy management. Neurology 58: 2-8.
14. Capizzano AA, Vermathen P, Laxer KD, Ende GR, Norman D, et al. (1996) Temporal lobe epilepsy: qualitative reading of 1H MR spectroscopic images for presurgical evaluation. Radiology 218: 144-151.