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Original Research Article

Evaluation of drug-resistant focal epilepsy in the western Indian adult population

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ABSTRACT

Introduction: Despite the best possible pharmacotherapy, 30% of persons with epilepsy will remain drug resistant. Drug resistant Epilepsy (DRE) has many different presentations and causes; hence evaluation may help to understand and manage appropriately.

Aim: To study a cohort of adult patients with refractory focal epilepsy, focusing on clinical semiology, risk factors, imaging and video EEG findings.

Materials and Methods: This is a prospective observational study done in adult neurology department of tertiary care hospital, from 2013 to 2016. The primary inclusion criteria were patients with drug refractory focal seizure (as per ILAE definition 2010), with age more than 12 years. Detailed clinical data, long term EEG monitoring, MRI and minimum follow up of 6 months were collected.

Results: Of 120 patients of DRE, 72% were in the age group of 12-30 yrs. Febrile seizure (26%) and head injury (17%) were the most significant antecedent history. Focal seizures with dyscognitive features were present in 87%. 16 patients had abnormal neurological examination. The most common radiological finding was mesial temporal sclerosis and gliosis. After complete evaluations, 30% of the patients were found to have pseudo-resistance. The evaluation led to modification of treatment in more than three-fourth of the patients.

Summary: Early age of onset, history of febrile seizures, past history of head injury, focal dyscognitive type of seizures and structural lesion on imaging are common factors in patients with DRE. Pseudo-resistance due to wrong diagnosis and inadequate AEDs were responsible for one third of cases.

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1. Introduction

Epilepsy is a common but serious neurological disorder, with a wide spectrum of etiology and prognosis. WHO has determined that epilepsy accounts for 1% of the global burden of disease, as measured by the number of years lost due to disability or premature death.¹ There are nearly 50 million people with epilepsy (PWE) worldwide and 80% of them reside in developing countries.^{2,3} Among them, nearly 12 million reside in India, amounting to nearly one-fifth of the global burden.⁴

Despite recent advances in neuropharmacology, around 20–30% of persons with epilepsy have drug-resistant epilepsy (DRE).^{5–7} It affects the quality of life of the patient and family adversely. Specifically for DRE patients with focal seizure onset, an appropriate evaluation may also give an option of surgery.

There is limited information available for clinical profile, predictors, and outcomes in drug-resistant epilepsy patients from India.^{8–11} In a resource-poor setting of a low "neurologist per population" ratio and a wide treatment gap for epilepsy patients, this data may help to modify treatment options.⁹ Therefore, we aimed to study a cohort of patients with drug resistant focal epilepsy, focusing on

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clinical semiology, risk factors, imaging, and video EEG findings; resulting in refractoriness in the Indian population.

2. Materials and Methods

2.1. Patients

This is a prospective observational study done in the adult neurology department of tertiary care hospital in the western part of India. Data were collected from September 2013 to September 2015 from all patients coming to neurology out patients department with history of seizures. The primary inclusion criteria were patients with drug-refractory focal seizures, with age more than 12 years. Patients with evidence of degenerative brain disease, Prion disease, and toxic or metabolic causes were excluded from the study.

2.2. Definitions

Seizures were classified based on clinical semiology, according to the International League Against Epilepsy (ILAE) classification of epileptic seizures.¹²

The drug resistance in the study was defined as ‘presence of two or more seizures in the last 1 year despite an adequate trial of two or more well-tolerated antiepileptic drugs’. ILAE defines “drug refractory seizures” as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.¹³

Seizure freedom is defined as freedom from seizures for a minimum of three times the longest pre-intervention interseizure interval (determined from seizures occurring within the past 12 months) or 12 months, whichever is longer. Studies including patients treated medically or surgically showed that absolute seizure freedom, usually taken as at least 12 months, is the only relevant outcome consistently associated with meaningful improvement in quality of life.^{14–17}

As Kwan & colleagues noted that a single seizure on any AED should be categorized as “undetermined” in defining the response,¹³ we used the term drug resistant epilepsy as “presence of two or more seizures in the last 1 year despite an adequate trial of two or more well-tolerated antiepileptic drugs” for the clinical purpose, in this study.

After evaluation, an effort was made to label hemispheric and lobar localization in the patients, based on history and investigations. The etiology was classified using ILAE classification into genetic, structural/metabolic causes and unknown causes.¹² Genetic epilepsy is defined as disease in which the epilepsy is, the direct result of a known or presumed genetic defect(s) and in which seizures are the core symptom of the disorder. “Structural/metabolic” cause of epilepsy is meant to be the state in which there is distinct structural or metabolic condition or other disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy. The

term “unknown cause” was used for those patients, where clinical, EEG or imaging findings do not prove to a specific abnormality, causing the seizure. ‘Unknown’ is meant to be viewed neutrally and to designate that the nature of the underlying cause of the epilepsy is as yet unknown; it may have a fundamental genetic defect at its core or there may be a separate as yet unrecognized disorder.¹² After evaluation patients with pseudo resistance were identified and analyzed separately. In this Study, “Pseudo-resistance” was labeled in the following scenarios: 1) Diagnostic error /Wrong diagnosis; 2) Inappropriate drugs for the type of seizure/epilepsy; 3) Inadequate dosage of AEDs; and 4) Non compliance.¹⁸

2.3. Protocols

Clinical, demographic, diagnostic evaluation and treatment-related data were recorded in all patients, after a personal interview in a structured proforma, at the inclusion. Details regarding the age of onset of seizures, semiology of seizures, frequency of seizures and precipitating factors were recorded. Birth history, developmental history, psychiatric history, family history and history for febrile seizures were documented. Treatment details included were number of drugs at presentation; name of each drug, maximum tolerable dose, compliance, previously used AEDs and reason for stopping of previous AEDs. A complete neurological and systemic examination was done in all patients. Thorough blood workup including hematology, chemistry, electrolytes, sugar, calcium and thyroid function was part of the protocol. Every patient has undergone an MRI brain with epilepsy protocol on at least 1.5T machine. After admission to the epilepsy monitoring unit for long term EEG (LTEM), drug tapering was sometimes used. The duration of LTEM was decided by the requirement of capturing minimal 2 ictal events or maximum of 72 hours. We changed antiepileptic drugs when required, based on available data. The most appropriate AED regimen was selected using seizure classification and patient profile. During every follow-up visit, seizure frequency, response, and compliance were noted, for a minimum period of 6 months.

3. Results

3.1. Clinical profile

Over the 2 years period (Sep 2013-15), total 1200 patients of epilepsy attended neurology OPD at our hospital. Out of them, 120 (10%) patients met criteria for drug resistant focal seizures (68 males and 52 females) and were included in this study for further evaluation. The age ranged from 12-61 years, with a mean of 27 yrs. The commonest age group in our cohort was 12-30 years (72.5%). Febrile seizures (25.8%) and head injury (16.6%) were the most significant antecedent history. 11 patients had at least one family

member with epilepsy. (Table 1)

3.2. Seizure characteristics

The seizure frequency of more than 5 per month was present in 33% of the patients. 'Focal dyscognitive seizure' was the most common subtype, with or without secondary generalization. Epigastric aura was described by 22.9% patients; while 29.1% had a cephalic aura. Motor manifestation were prominent in 112 patients, out of which 21 had automotor and 10 had hyper-motor features. From a historical point of view, hemispheric localization of seizure was possible in 72 patients. Differentiating into the lobar origin, 40 had temporal lobe onset; 20 had extratemporal onset and undetermined onset in the rest of the patients.

3.3. Neurological deficit

Patients had an abnormality detected, on neurological examination

3.4. Long term EEG

Long term EEG monitoring was done in 100 patients and the results were normal in 24 patients.

3.5. MRI

The result of MRI Brain was available in 115 patients and the most common finding was mesial temporal sclerosis (27.8%), followed by gliosis (13.9%).

3.6. Pharmacotherapy

All patients were on more than 2 anti-epileptics when evaluated; while 36 patients were on four or more drugs. In our study group, the most common anti-epileptic drugs were Clobazam (72%) and Levetirecetam (61%). Out of 120 patients, 58.33% of the patients have had history of changing AEDs in the past and the most common reason was ineffectiveness of drugs (74.28%).

3.7. Etiology

Out of 120 patients, 84 patients were classified as true DRE, while the rest had pseudo-resistance. The most common etiology in DRE subset was structural/metabolic lesions (54.8%), followed by "unknown" (41.6%). MTLE was detected in 27.4%, while cortical malformation and other structural lesions were found in the other 27.4%. As no patient had any classical genetic epilepsy syndromic feature, no specific genetic molecular studies have been performed, for any of the patients in the present study. (Table 2)

After evaluation, 30% of the patients were found to have pseudo-resistance. The causes of pseudo-resistance were further classified (Table 3) and attempt was made to readjust the treatment regimen.

Table 1: Clinical profile of patients

Age (years)	12-30	72.5% (87)
	31-50	23.3% (28)
	>50	4.2% (5)
Gender	Male	56.7% (68)
	Female	43.3% (52)
Seizure type	Focal with dyscognitive	46.6% (56)
	Focal without dyscognitive	13.3% (16)
	Focal with sec. general	40% (48)
Aura	Sensory	34.2% (41)
	Experiential	5.8% (7)
	None	60% (72)
Seizure frequency (per month)	<1	35% (42)
	2-5	31.6% (38)
	6-10	9.2% (11)
	>10	24.2% (29)
H/o febrile seizure		25.83% (31)
Positive F/H		9.16% (11)
H/O abnormal neurological examination		13.3% (16)
H/O abnormal perinatal history	9.16% (11)	
	Normal	43.5% (50)
	MTS	27.8% (32)
	Gliosis	13.9% (16)
	Other	14.2% (17)
	Not done	4.2% (5)
MRI	Normal	24% (24)
	Temporal localization	26% (26)
	Extra temporal localization	16% (16)
	Non-localizing (abnormal)	23% (23)
	No EEG changes during ictus	11% (11)
Not done		No. :20

Abbreviations: H/O: history of; F/H: family history; MRI: Magnetic Resonance Imaging; MTS: Mesial temporal sclerosis; EEG: Electroencephalograph; LTEM: Long term EEG monitoring.

Table 2: Etiology of DRE(after complete evaluation; no: 84)

Cause	No. of patients	Percentage
Genetic*		
Structural/Metabolic	49	58.3
Hippocampal sclerosis	23	27.4
Malformation of cortical development	3	3.6
Other Acquired brain abnormality	16	19
Stroke	1	1.2
Focal cortical dysplasia	2	2.4
Tumour	1	1.2
Infection	2	2.4
Immune	1	1.2
Unknown	35	41.7

Table 3: Pseudo-resistance

Causes	No. of patients (%)
Wrong Diagnosis (Epilepsy Imitators)	11(30.55%)
PNES	10
PKD	1
Inappropriate drug	3 (8.33%)
Inadequate dose (according to DDD)	16 (44.44%)
Poor drug compliance	6 (16.66%)

Abbreviations: PNES:Paroxysmal nonepileptic seizures; PKD: paroxysmal Kinesogenic dyskinesia; DDD:Defined Daily Doses.

With all the data, it was possible to change the etiology of epilepsy as well as a cause of drug resistance in 25.83% of patients. LTEM was helpful in 19.16% of patients to localize the focus. With the help of LTEM and/or detailed epilepsy protocol imaging, structural etiology yield increased from 45.83% to 54.76% and reduce the "unknown" etiology subset from 52.5% to 41.66%. This evaluation helped us to modify treatment in 77.5% of patients. On follow up for six months, 66 patients reported benefit; while 26 patients were seizure-free for six months.

4. Discussion

In this prospective study, we evaluated adult patients with refractory focal seizures in a tertiary care hospital for clinical features and etiology with emphasis on factors contributing to drug resistance and response to medical treatment.

There was a slight male predominance (M: F ratio 1.3: 1) and the maximum number of patients (72.5%) were in the group of 12 - 30 years. Similar observations of high male preponderance have been noted in studies by Ramos et al and Tripathi et al.^{9,19} Mukherjee et al considered it to be due to higher family care for male patients in eastern India population.¹⁰

The age of epilepsy onset had been suggested to be a major predictor of DRE. We found a significantly higher number of patients of DRE in the 2nd and 3rd decade. Similar findings were also seen in other studies from other geographical distributions.^{9,19} Even in the Kolkata study (2014-15), most of the patients of DRE were presented in their first decade of life.¹⁰ In a study by Chawla et al, the age at onset of seizure less than 1 year was an independent predictor of intractability in a multivariate analysis.¹¹ Berg et al. also noted that the predictive value of age in drug resistance appeared not only in neonates but also for the whole age range in their study population.²⁰ Conversely, patients with late age of onset (>60 %) had fewer chances of developing drug resistance.²¹

More than half of the patients had a significant past neurological event, the most common being febrile convulsions and head injury. Camfield et al observed that

prolonged febrile seizures were associated with intractable epilepsy.²²

Abnormal birth or developmental history and family history of epilepsy were also significant in this subset of DRE. The other Indian studies also noted similar high incidence of history of hypoxia and family history of seizures; to be high in DRE patients.^{9,11} In the early postnatal phase, there lies a critical window of development for enhanced learning, synaptogenesis, and neuronal plasticity compared to the adult population. So, one hypothesis states that the heightened state of excitability and plasticity during the maturation phase promotes excitatory network activity and thereby causes pathological changes in the network that may persist for life. This may explain the younger age of onset and significant neurological past history, as a contributor to refractoriness in drug resistance epilepsy subset.^{23,24}

The most common type of seizure was focal dyscognitive seizure with or without secondary generalization. Similar result was recorded by Sinhgvi et al in 74% of patients with DRE.⁸ Focal with dyscognitive and focal seizure evolving into secondary generalization have more chances of developing DRE, compared to pure focal seizure with preserved awareness. From lobar distribution, temporal lobe epilepsy was most common in our group of refractory seizures. The concept of "network inhibition hypothesis", as proposed by Norden and Blumfeld states that focal seizure arising in temporal lobe spreads to subcortical structures (medial diencephalon and Ponto-mesencephalic reticular formation) and disrupts their activating function. This, in turn, leads to inhibition of the frontoparietal network, resulting in an impaired level of consciousness.^{25–27} Intracranial EEG monitoring and functional studies also support that temporal lobe focal seizure without loss of consciousness were associated with limited changes, sparing the frontoparietal association cortices.²⁸ Thus the more common prevalence of focal dyscognitive and temporal lobe seizures in the DRE series indicates that more widespread network involvement may be the responsible factor for drug resistance.

Tripathi et al. while searching for predictors of drug resistant epilepsy in North India in a case-control study, found that abnormal brain imaging was seen in 79% of the patients in intractable group and only 39% of the patients in well-controlled group.⁹ Our findings of a structural lesion on imaging in DRE patients are comparable with other studies depicting the importance of a detailed neuroimaging study;⁸ as they may be surgically treated and subsequent control may improve significantly. Among structural lesions, hippocampal sclerosis and other acquired brain abnormality were most frequently encountered. Temporal lobe epilepsy (TLE) with MTS is one of the most common types of medically refractory epilepsy but responds favorably to surgery.²⁹ Focal epilepsies related

to structural brain abnormalities are less likely to enter remission, compared to that occurring in patients with structurally normal brains.^{30,31}

Long-term video EEG monitoring helped us to identify pseudoseizures in 11% and localize the focus in 42% of the cases. We did not find any significant difference in type and location of EEG abnormalities correlation with refractoriness. The usefulness of video-EEG in making the change in diagnosis &/or management following is very significant and valuable.³² Long-term monitoring does improve EEG yield and so it is important in improving treatment choices, which in turn is impactful for quality of life.

In our study group, Clobazam and Levetiracetam were the most commonly used drugs. Mukherjee et al mentioned that Carbamazepine was the most commonly used drug, to be followed by clobazam and levetiracetam.¹¹ Clobazam as the first add-on is very commonly prescribed; because it has good efficacy, high retention rate and is easily available at low cost. There exists good data for efficaciousness and tolerability for Clobazam.^{33,34} Levetiracetam was found to be the second most commonly used drug, probably because of its better side effect and interaction profile. One study showed that Levetiracetam demonstrates the best combination rate for long-term efficacy and tolerability of DRE patients.³⁵

In the analysis of pseudo-resistance, inappropriate or inadequate drug & dose was found in 52.7% (19/36) of cases; while poor drug compliance was the reason in 6 out of 36 patients (16.6 %). PNES forms 11% of our DRE patient cohort.

DRE and PNES are not mutually exclusive and can be seen together in 10-30% of the patients. Frontal lobe epilepsy is a common denominator. A few cases of PNES after successful epilepsy treatment have revoked interest in understanding the pathophysiology. It has been proposed that 'burden of normalization' appear to arise out of a general process of adjustment, following relief of chronic illness.³⁶

A comprehensive evaluation of the focal drug resistance epilepsy patients improves our diagnostic yield of the etiology of epilepsy and the etiology of drug resistance in 26 % of the patients. LTEM and/or detailed epilepsy protocol imaging improves focal structural etiology yield to increase up to 10 % from baseline and to reduce the "unknown" etiology subset. That turned into better management decisions for more than 77% of the patients. On follow up for six months, 66 patients reported benefit; while 26 patients were seizure-free for six months.

In the present study, we found that few of the factors are commoner in drug-resistant patients; i.e.; early age of onset, febrile seizures, past history of head injury, focal dyscognitive type of seizures (with or without secondary generalization) and structural lesion on imaging. To an extent, the risk of developing intractable epilepsy may be

predicted, if properly analyzed, early in the course. This will eventually result in selecting patients for intensive investigations early in their clinical course for a possible surgical treatable cause; proper family counseling and choosing the right drug for the individual, in a country like India where a large treatment gap exists.

To summarize, we understood that uncontrolled epilepsy is not necessarily the same as drug-resistant epilepsy. Pseudo-resistance due to wrong diagnosis and inadequate AEDS were responsible for about one-third of cases. Following other research studies, we also found structural causes, especially mesial temporal lobe epilepsy as the major cause of DRE. Despite our efforts, "unknown" causes account for the second-largest group of DRE. The evaluation process enabled us to change the course of management in more than three fourth of DRE patients, with positive outcomes during the study period. We conclude that specialized tertiary care epilepsy center with protocol-based epilepsy evaluation is mandatory for the evaluation of all patients with DRE.

5. Conflict of Interest

The authors declare that there are no conflicts of interest in this paper.

6. Source of Funding

None.

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