Prospective Study of Intractable epilepsy – Clinical Conundrum

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Ph.D synopsis

Title: Prospective Study of Intractable epilepsy – Clinical Conundrum

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1. Introduction

1.1. Definitions

Epilepsy isa disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (International League Against Epilepsy (ILAE), International Bureau for Epilepsy (IBE) (1).

Intractable epilepsy or drug-resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. This definition can be further refined when new evidence emerges. (ILAE, 2010) (2). Epilepsy affects 3 % of the general population all over the world. People with epilepsy suffer from brain damage resulting in neurological deficit. Further, it leads to changes in social, occupational and behavioural aspects of individuals suffering from epilepsy causing devastating economical consequences. All the more it is obvious that these consequences are significant in patients with intractable epilepsy.

1.2. Prevalence and incidence of intractable epilepsy

In India, the prevalence of epilepsy is reported to be around 5.35/1000, estimated by the meta-analysis of 20 Indian published and unpublished studies (3). Prevalence estimates are reported to be more in rural areas (5.47) than urban areas (5.11) also epilepsy is more in men (5.88) than women (5.11) per 1000 population (3). Most of the studies carried out for prevalence studies were based on door-to-door survey, random survey, screening instruments, and World Health Organization protocols (4). In western countries prevalence of intractable epilepsy in adults was reported to be 5.4 per 1000 population (5) which comparable to that of our population. Despite the influx of new Antiepileptic drugs over the past 10 years the incidence of intractable epilepsy is reported to be high around 20-40% with newly diagnosed epilepsy (6).

There are several studies in western population to address the prevalence of intractable epilepsy. Due to the discrepancies in the terminologies (drug resistant epilepsy, intractable epilepsy, etc.) and criteria for subject selection, the comparison between the prevalence of intractable epilepsy across various studies was difficult. Recently the prevalence of intractable epilepsy was reported by two studies in Italy (7) and Singapore (8) using drug-resistant epilepsy criteria (ILAE, 2010).   In India, there are no such studies available using drug-resistant epilepsy criteria (ILAE, 2010), especially in adults. The prevalence of intractable epilepsy was reported to be ranging from 20 to 30% among patients with epilepsy in south India (9).

1.3. Predictors of intractable epilepsy

There are various predicators of intractable seizures in India was reported by Tripathi et al among 200 patients. On univariate analysis they observed age of onset of seizure before

fourteen years, partial seizures, presence of neurological deficits, perinatal insult, delayed milestones, history of CNS infection, febrile seizures, high initial seizure frequency of more than one per month, non-response to first Anti-Epileptic Drug and abnormal brain imaging as predictors for intractable epilepsy. On multivariate analysis significant predictors reported were radiological evidence of structural cerebral abnormality, non-response to first AED, delayed mile stones, high initial seizure frequency of more than one per month, partial seizure type, febrile seizures and age of onset before fourteen years (10). In western countries, high seizure, neonatal seizure, birth injury, epileptic encephalopathy, early breakthrough seizure, neonatal status epilepsy as a first attack, structural damage due to birth trauma, neuronal migration disorders are the predictors of intractable epilepsy (11).

1.4. Types of seizures and its clinical characteristics

International League Against Epilepsy (ILAE) has appointed a Task Force to formulate a consensus on the definition of drug resistant epilepsy and have classified into two hierarchy levels. Level 1 provides a general scheme to categorise response to each therapeutic intervention. Level 2 provides a core definition of drug resistant epilepsy using a set of essential criteria based on the categorization of response (from Level 1) to trials of antiepileptic drugs (2).

Berg et al (2010) have modified the concepts, terminologies and approaches in classification and terminology in epilepsy at International League against Epilepsy (ILAE) Commission (12). Epilepsy is classified as generalised seizures, focal seizures or Unknown as to whether focal, generalised, or depending on context. Generalised seizures are further classified as tonic-clonic, absence, myoclonic and clonic-tonic atonic (12).

1.5. Etiology of refractory seizure

Various causes have been reported in the literature. Malformations of cortical development, Head injury, Cerebrovascular disorders, CNS infection, pre and perinatal factors, CNS malformation, chronic alcoholism, encephalopathy, multiple causes, cerebral tumour, Degenerative diseases, autoimmune diseases, calcification, gliosis, cerebral atrophy, and other causes are often associated with intractable epilepsy. Epilepsy in the study group was caused by perinatal problems (48%) and sequelae of central nervous system infection (24%) and was idiopathic in 20% (13). ILAE commission recommends using terminologies Genetic, structural-metabolic, and unknown to represent and replace idiopathic, symptomatic, and cryptogenic causes of epilepsies (12).

1.6. Pathophysiology of intractable seizure

Most of the patients suffering from epilepsy of various types respond to antiepileptic drugs and they are completely free from developing attacks. But still 30 % of epileptic patients continue to develop recurring attacks of seizures in spite of adequate and appropriate antiepileptic drug therapy. The definite mechanism underlying this state is not clearly understood. Hence various hypotheses have been postulated. They are target hypothesis,

transporter hypothesis, gene variant– inherent severity hypothesis and neural network hypothesis (14).

1.7. Hypothesis for intractability

Target hypothesis

It explains how acquired structural and functional alteration at the target ion channels and neurotransmitter receptors lead to intractable seizure (15). Most of the Anti epileptic drugs (AEDs) act on targets of voltage-gated cation channels (α subunits of voltage-gated Na+ channels and T-type voltage-gated Ca+ channels) and also the influence of the gamma amino butyric acid (GABA-mediated inhibition) are very important to increase inhibitory potential.

Transporter hypothesis

Transporter hypothesis states that the distribution, metabolism and elimination of antiepileptic drugs depend on the pharmacokinetic process by which the drug reaches the appropriate target regionsand this is very important. This, pharmacokinetics of antiepileptic drug is being controlled by special proteins such as p glycoprotein, breast cancer resistance protein and multi drug resistance protein secreted at the cellular wall and are genetically determined. These are drug efflux transporters from the ATP binding cassette (ABC super family). The up-regulation of this system leads to reduced bioavailability of Anti epileptic drug at the epileptic zone leading to intractable epilepsy (16).

Intrinsic severity hypothesis

Inherent severity disorder is the determinant of the treatment outcome. For example number of attacks in the early phase of the illness/disease leads to intractable seizure which may be due to factors operating extracellular and intracellular level (intrinsic and extrinsic mechanism) genetic basis (17) has a role in this mechanism.

Network Hypothesis

Neural network hypothesis state that "seizure-induced alterations of brain plasticity including axonal sprouting, synaptic reorganization, neurogenesis and gliosis could lead to the formation of abnormal neural network, which has not only avoided the inhibitory effect of endogenous antiepileptic system but also prevented the traditional antiepileptic drugs from entering their targets, eventually leading to intractable epilepsy" (18). The above changes lead to adaptive remodelling of the neural structures after the attack of seizure may lead to permanent epileptic neural circuit causing intractable epilepsy. Brain function is a result of the activity of neural network connecting cortical and subcortical systems. Epilepsy is a dynamic disease of this neural network. When the normally functioning brain jumps to another state causes abnormal oscillation resulting in epilepsy and lasts for few seconds to minutes and returns to normal state. From the review of literature 2 systems appear to be involved in displaying epileptic behaviour:

1) Thalamocortical system is a pacemaker in generalised epilepsy
2) Mesial temporal system is involved in temporal lobe epilepsy

By studying these hypotheses, refractory epilepsy is complex and multi-factorial. Single hypothesis or multiple hypotheses may be operating in a given intractable epilepsy patient. Acquired or genetic background or both may be important in studying patient with intractable epilepsy. Understanding the above hypothesis is very important to do research in developing newer drugs and non-pharmacological ways to treat the drug-resistant epilepsy effectively.

1.8. Structural abnormalities in intractable epilepsy

1.8.1.   Computerised tomography and Magnetic resonance imaging

Computerised tomography (CT) and Magnetic Resonance imaging (MRI) are routinely used in epilepsy to identify various congenital and structural abnormalities in the brain. CT can accurately detect haemorrhage, infarctions, gross malformations, ventricular system pathologies, and lesions with underlying calcification (19). The sensitivity of CT in patients with epilepsy is not higher than 30%. CT has overall a low sensitivity and poor resolution in the temporal fossa, thus CT is not useful in detecting mesial temporal sclerosis, the most common pathology in intractable temporal lobe epilepsy (20). The sensitivity of MRI is high in detecting abnormalities in patients with epilepsy such as Mesial temporal sclerosis (MTS), small tumours, trauma and developmental malformations (21–23).

1.8.2.   Malformation of cortical development

Malformations of cortical development (MCD) are microscopic and macroscopic development abnormalities of the cerebral cortex that arise due to an interruption in cortical development during fetal development by genetic or environmental factors(24). According to Barkovich classification MCDs have classified into three groups 1) malformations due to abnormal neural proliferation, 2) malformations due to abnormal neuronal immigration, and 3) malformations due to the abnormal cortical organization (25). Due to improved technology in Magnetic Resonance Imaging (MRI) used with patients with epilepsy a forth group of Malformations of cortical development, not otherwise classified is added to Barkovich classical classification.

There are very few studies in the literature regarding the prevalence of MCD in drug-resistant epilepsy. The prevalence of MCD reported being high in children with drug-resistant childhood epilepsy ranging from 25% to 40% (21,23,26). In adults, the prevalence of intractability among patients with MCD is reported to be 84.8% (27) in a large series of patients with epilepsy (N=3000). With recent advancement in radiological imaging techniques, the identification of MCD has increased significantly (24,28–31). Studies carried out among MCD population revealed several developmental anomalies like focal cortical dysplasia, Polymicrogyria, Lissencephaly, heterotopias, dysembryonicneuroepithelialtumour, Hemimegalencephaly and others (28,30,32). Clinical features of MCDs are often heterogeneous. MCD exhibit seizures majorly complex partial seizure, to any other form of seizures (27,30),

family history (27,30), usually drug resistant and intractable(27,28), change in semiology (29), associated with febrile seizures (30), present with delayed motor or mental milestones (30,32), cognitive defects and learning disability (27,32). About a third of patients with MCD had hippocampal abnormalities like the hypoplastic hippocampus, hippocampal sclerosis, malrotated hippocampus, and enlarged hippocampus(32). Febrile seizures with Focal Cortical Dysplasia (FCD) are reported to have dual pathology (FCD with hippocampal sclerosis) (29).

1.8.3. Incomplete-hippocampal inversion

Incomplete hippocampal Inversion (IHI) is a failure of hippocampal inversion that occurs during normal fetal developmentand can be diagnosed with MRI and often reported to be pathological in patients with seizures (33). Recent studies on patients with temporal lobe epilepsy (TLE) and MCD have reported that IHI can be found in a similar proportion of MCD and TLE (34). An excellent study by Bajic et al, have shown that IHI is observed in 30% of patients with epilepsy mostly on the left side followed by bilateral and right sided IHI(35). The presence of IHI has been reported to be a marker of a more extensive disorder of brain development (34,35). With the evidence of having IHI as a malformation of brain development, it would be a possible abnormality causing intractable epilepsy.

1.8.4. Mesial temporal sclerosis

The most common pathology seen in patients with intractable temporal lobe epilepsy is Mesial Temporal Sclerosis (MTS). MTS is pathologically characterised by the presence of atrophic hippocampus, increased signal on T2-weighted images or FLAIR (fluid-attenuated inversion recovery) and decreased signal on inversion recovery sequences (36–38). Brain abnormalities especially MTS, either alone or in association with another lesion are major predictors of intractable epilepsy (39). MTS is classified histopathologically into three types namely, type 1a (classic hippocampal sclerosis involving severe cell loss in CA1 and moderate loss in other subfields except CA2), type 1b (severe hippocampal sclerosis involving severe cell loss in all hippocampal subfields), type 2 (atypical hippocampal sclerosis involving severe neuronal loss restricted to CA1) and type 3 (atypical hippocampal sclerosis involving severe neuronal loss restricted to hilar region)(40). Early brain insult (trauma, febrile seizures) is called as initial precipitating injury could lead to hippocampal damage resulting in type 1A, 1B pathology. In type 2 and type 3 the initial precipitating injury is reported to as result of late insult to the hippocampus(40). After initial precipitating injury, most of the damaged cells in the hippocampus (inhibitory function) remain silent, but the dentate gyrus granule cell layer and its axons (mossy fibres) sprout into the molecular layer andis excitatory in function. After sprouting there is an excitation and inhibition mismatch leading to increased excitation resulting in recurrence of seizure with a change in seimiology(41). The observation supports the concept that extensive bilateral hippocampal circuit rewiring leads to intractability in temporal lobe epilepsy patients (42).

T1 and T2 weighted images less than 3mm cuts will help us to evaluate hippocampus. The Smaller size of the hippocampus in intractable epilepsy is suggestive of hippocampus sclerosis on the affected side. Increase T2 signal in the hippocampus suggestive of gliosis. Gradient echoes help to identify vascular lesions. Flurodeoxy glucose positron emission tomography (FDG –PET) is a useful test in pre-surgical evaluation of patients suffering from temporal lobe epilepsy. Hypo metabolism in the temporal lobe ipsilateral to the seizures focus is a positive predictor for good outcome after epilepsy surgery. Hence it is useful only in people who are subjected to epilepsy surgery. In the genetic form of temporal epilepsy, images studies will be normal. In lateral or neo cortical epilepsy, Lesions like malformation of the cortical development, vascular malformation, encephalomalacia secondary to trauma, inflammation, ischemia, haemorrhage and tumour are seen.

1.8.5. Vascular lesions

Most frequently encountered vascular causes of intractable epilepsy is arteriovenous malformations (AVMs) and cavernomas(43). In a large sample, 30% of AVMs are reported to be associated with a seizure. Most of the AVMs were reported to be located in temporal and rolandic region presenting with partial epilepsy, where as frontal or Sylvian region AVMs were presenting with generalised seizures. 24.7% of patients with partial epilepsy were reported to be intractable.(44). The severity of the seizure depends on the size of AV malformation, haemorrhage and fronto temporal location (45). Delay in the intervention leads to structural abnormalities of the brain, namely hemi-atrophy of the brain.

1.8.6. Tumors

Intractable epilepsy associated with tumours often present with focal epilepsies. Glioneuraltumours most commonly arise from the temporal lobe. Studies on a large sample (N= 207) of patients underwent surgical resection of tumour associated with intractable epilepsy showed 154 patients with classic epilepsy-associated tumours (dysembryoplasticneuroepithelialtumour, ganglioglioma, and pilocyticastrocytomas) and 53 others tumors (astrocytomas and oligodendrogliomas) (46). Also, cortical dysplasia and other neuronal migration disorders often coexist with these tumours. These are all drug resistant epilepsy and amenable to surgical therapy(47).

1.8.7. Post-traumatic epilepsy

Several studies have reported the incidence of post-traumatic epilepsy from 7-31.9% following brain injury (48,49). Closed traumatic brain injuries often cause brain parenchymal haemorrhage, necrosis, oedema and white matter lesions (50). Injury to neurons causes cellular loss with gliosis, changes in neuronal plasma membrane, sodium and potassium ionic channels leading to increased excitation of cells resulting in epilepsy (51,52).

1.8.8. Infections and epilepsy

Brain infections are reported to be the significant contributors of epilepsy by crossing blood brain barrier and causing neuronal loss. Recent studies suggest that subjects with chronic infections are susceptible to epileptogenesis and intractability of seizures. Due to epilepsy, evidence for inflammation of nerve cells are demonstrated by post-surgical studies (53) , hippocampal sclerosis (TLE)(54), Rasmussen's encephalitis (55), tuberous sclerosis(56) and antiepileptic effect of anti-inflammatory drugs in west, Landau Kleffner syndromes, Lennox–Gastau syndromes(57).

1.8.9. Post-stroke epilepsy

Stroke is the one of the common neurological disorder that can be often associated with epilepsy and adds on to the disability and increase complexity for treatment. Several studies have reported that seizures may occur approximately up to 10% of patients following stroke (58,59). Individuals with stroke may present with early seizure or late seizures following stroke (ILAE, 1993). Seizures are reported to be often associated with hemorrhagic strokes than ischemic stroke. Complex partial seizures are often reported to be present with early seizures whereas generalised tonic-clonic seizures are reported to be associated with late seizures after 2 weeks (59,60). Acute Metabolic dearrangementsassociated with stroke cause early seizures that can be reversed. In contrast Late seizures cause structural changes like gliosis or meningocerebral scar tissue (61). Changes in the cell membrane, neuronal loss and collateral sprouting are reported to cause excitation in epilepsy (62). Cortical infarction is most often reported to be resulting in seizure rather than subcortical involvement (63). Large cortical infarction (64) especially the involvement of temporal lobe are often reported to be a high-risk factor for developing post-stroke seizures.

1.8.10. Calcification

Calcification occurs in the brain due to various factors like infections (toxoplasmosis, rubella, cytomegalovirus, cysticercosis, AIDS), calcium metabolism disorders, genetic(Cockayne syndrome, tuberous sclerosis, Fahr's disease, down syndrome, and neurocutaneous syndrome like storage weber's syndrome) or autoimmune disorders (autoimmune encephalitis) and persistent inflammation. Focal cortical – subcortical calcifications are reported to be associated with focal or generalised epilepsy especially in India. 77.5% of patients with calcifications are reported to have focal epilepsy(65). Basal ganglia calcifications are often associated with hypoparathyroidism and pseudohypoparathyroidism. Intracranial calcifications are also considered as incidental in 0.3 to 1.5% of the patients (66). Calcification due to infections may be associated with perilesionaloedema. These patients have the tendency to develop seizures intermittently. The pathophysiology of the perilesionaloedema is not clearly understood but it may be due to post ictaloedema or release of ionic calcium (67). Focal cerebral calcifications in CT scan are reported to be associated with gliosis around the calcified lesion on T1 weighted

MRI images. 33.3% of patients with perilesionalgliosis is reported to be have increased seizure frequency and they were drug resistant (68).

1.8.11. Metabolicdisorder

Intractable epilepsy due to metabolic disorder is not rare in adults. The metabolic disorders may be due to small and large molecule disorders. Small molecule disorders include defective molecule or mechanisms related to amino and organic acids, fatty acids, neurotransmitters, urea cycle, vitamin cofactors, and mitochondria. Large molecule disorders include defective molecules and mechanisms related to lysosomal storage disorders, peroxisomal disorders, glycosylation disorders, and leukodystrophies. Epileptic encephalopathies are inborn metabolic defects that present with intractable epilepsy. They may present with intractable neonatal seizures, early myoclonic encephalopathy, early infantile epileptic encephalopathy, infantile spasms, and generalised epilepsies and in particular include myoclonic seizures (69). These disorders are reported to be rare in the adult population.

1.9. *Diffusion Tensor weighted imaging*

Diffusion Tensor Weighted Imaging (DTWI) is a recently developed MRI technique, which has gained importance over time to assess abnormalities with focal epilepsy (70–72). DTWI measures the molecular motion of water in tissue in various directions in every voxel, providing information regarding the microstructure of the white matter & grey matter, cellular packing, cellular loss or regional oedema in focal status epilepticus (73). In DTWI, Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) are the commonly recorded tensor measured in structural MRI (74,75). Diffusion tensor weighted images have been studied well on a small group of individuals with temporal lobe epilepsy (TLE) and extra-temporal lobe epilepsy (ETLE). Interictal DTWI imaging studies are reported to be more sensitive in identifying hippocampal involvement rather than conventional MRI in TLE (76). Interictal imaging studies in patients with medial temporal lobe epilepsy associated with hippocampal sclerosis showed diffusion abnormalities involve a pathologic hippocampus and larger network involvement (77). Diffusion tensor imaging in patients with epilepsy and MCD have shown changes in tissues beyond the areas of MCDs and appeared normal on conventional MRI (78). Patients with partial seizures and normal MRI findings showed various areas with abnormal anisotropy or diffusion, which were normal in conventional MRI (79). The Interictal study of patients with normal structural MRI and TLE shows bilateral and extratemporal lobe involvement (72). In TLE, lateralization of the epileptogenic region using DTWI studies highly correlates with the presence of unilateral hippocampal sclerosis on conventional MRI (80). In patients with non-lateralizing conventional MRI findings, the interictal DTWI studies will not provide lateralizing information (76). From the review of the literature, there is ample evidence of DTWI image abnormalities unilaterally or bilaterally when MRI studies of the brain are normal or abnormal.

1.10. *Volumetric studies of hippocampus*

Incomplete hippocampal Inversion (IHI) is a failure of hippocampal inversion that occurs during normal fetal development, which can be diagnosed with MRI and often reported to be pathological in patients with seizures (33). Recent studies on patients with temporal lobe epilepsy (TLE) and MCD have reported that IHI can be found in a similar proportion of MCD and TLE (34). An excellent study by Bajic et al, have shown that IHI is observed in 30% of patients with epilepsy mostly on the left side followed by bilateral and right sided IHI(35). The presence of IHI has been reported to be a marker of a more extensive disorder of brain development (34, 35). With the evidence of having IHI as a malformation of brain development, it would be a possible abnormality causing intractable epilepsy.

1.11. *Neuropsychological manifestations in epilepsy*

The psychiatric manifestations of psychosis, depression, anxiety and other behavioural disturbances can coexist with intractable epilepsy but sometimes they may manifest as a part of seizure or they may be due to drugs (81–84). The psychiatric manifestations may worsen the existing epileptic condition. Gross impairment of cognition may be due to continuous seizure and drugs (83–86). Mood disorders, personality change, Attention deficit hyperactive disorders, language disorders are also associated with epilepsy (83, 84, 87, 88)

Anxiety and depression often coexist in individuals suffering from epilepsy (81,88–92). The prevalence of anxiety ranges from 11 to 25% and depression range from 9 to 40% in persons with epilepsy across various studies when compared to individuals without epilepsy. The prevalence of anxiety and depression is often reported to be higher in individuals with drug resistant epilepsy and temporal lobe epilepsy (82, 87, 93–96). Depression and anxiety have been also reported to be often associated with suicide, suicidal ideation and suicidal attempt (97–99). Altogether anxiety and depression in patients with epilepsy affect quality of life (100–102).

Most important cognitive deficit in Temporal lobe epilepsy (TLE) patients, especially in patients with mesial temporal sclerosis, is memory impairment (103,104). Weschler's memory scale -III and Weschler's adult intelligent scale –Revised can differentiate patients with refractory temporal lobe epilepsy from normal subjects but they cannot differentiate between the right and the left TLE (104). Also, other factors including long-term antiepileptic drugs, the age of onset, duration of epilepsy, types of seizure also contribute to cognitive defects over the years (105,106).

1.12. *Electroencephalography*

Interictal Electroencephalography (EEG) in patients with intractable seizure shows generalised abnormality in 75% of the cases rest of the EEG show focal epileptiform activities, which correlate with their clinical conditions (107). In Focal cortical dysplasia, interictal routine video EEG were reported to show regional epileptic activity in 89% of patients (108). When compared to routine EEG, intensive EEG monitoring was reported to be useful in detecting epileptic activity in patients with intractable epilepsy (109).

Interictal electroencephalography (EEG) findings in MTLS – spike and sharp waves are seen over the anterior temporal region. Sleep deprivation sometimes activates focal epileptic form of discharges. Therefore EEG with sleep recordings is recommended during diagnostic workup. The presence of mid and posterior temporal lobe spikes in EEG may suggest a widespread involvement of epileptic network. Even in the presence of normal medial temporal lobe, ictal EEG may reveal rhythmic, alpha or beta activity and evolve to rhythmic delta or theta activity. The seizure discharge may be limited to a medial temporal lobe or it may spread to ipsilateral hemisphere and contralateral temporal lobe. Unilateral temporal lobe slowing in EEG is suggestive of ipsilateral seizure onset. Interictal EEG pattern was almost same in neocortical epilepsy as seen in medial temporal epilepsy. But abnormal waves like spikes or sharp waves are seen over T4, T3 and T6, T5and rapidly propagates to other lobes and quickly spread to opposite side. Polymorphic delta pattern is also seen over above-said areas. Dorsolateral and frontopolar epilepsies will be associated with focal epileptiform activity because the electrodes placement will be very easy. Foci arising from inter-hemispheric, orbitofrontal cortex and frontal opercular cortex cannot be recordable because of the difficulty in placing electrodes. The frontal lobe is very near to temporal lobe, so epileptic form of activity can also recorded in the anterior temporal electrodes. Bilateral secondary hyper-synchrony has also described in patients with frontal lobe epilepsy. The epileptic form discharges appear as generalised spikes, polyspikes or spike and wave. It is always differentiated from frontal lobe epilepsy by locating unilateral epileptic form discharges before the generalised discharges.

Need for the study and hypothesis

From the review of the literature, studies using drug-resistant epilepsy criteria (ILAE, 2010) to identify its prevalence and clinical characteristics are sparse, especially in Indian context. There are few studies in India regarding the prevalence of intractable epilepsy (13,107) and its risk factors (10). They report various risk factors that contribute for intractability in the epileptic population. Identification of various risk factors responsible for intractability is reported to be associated with significant therapeutic implications. Several studies in western countries and in India identify various structural abnormalities like mesial temporal sclerosis, malformations of cortical development, vascular lesions, stroke, traumatic brain injury, calcification and infections as a cause for intractability and accounts for 60-70% of the population. 30-40% of them do not show any lesions/ malformations still they exhibit intractable epilepsy. With the advancement of technology especially DTWI, volumetric studies it would be possible to identify microstructural abnormalities and asymmetries that would contribute to intractable epilepsy. Identifying structural abnormalities or multiple lesions using various investigations would help up in tracing the neural network responsible for epilepsy.

In developing countries like India, where accessibility to neuroimaging facilities are not easily accessible the prevalence of intractable epilepsy and various structural lesion associated with them is largely unknown. There are few preliminary studies carried out in India to document frequency and clinical characteristics of MCD among children (30,110) and adults

(30). Their studies are carried out retrospectively especially from the case records of the epileptic population (30). Also little is known about the prevalence of Mesial temporal sclerosis and incomplete hippocampal inversion in the Indian context. Studies in Indiausing Diffusion tensor weighted images (111) were reported to be useful in identifying white matter structural abnormality among extratemporal epilepsy patients. DTWI is also reported to be helpful in predicting the postoperative neurological outcome, surgical decision-making and preoperative counselling of patients.

Moreover, it has been reported that structural abnormalities would give rise to focal seizures and may be the temporal or extratemporal type. Correlating the type of epilepsy, the age of onset, duration of seizure, status epilepsy, clustering and Electroencephalography finding with structural lesions of the brain would guide us in predicting the possible clinical manifestations of those lesions. Also, intractable epilepsy associated with various structural lesions may present with various profiles of neuropsychological manifestation. Identifying the neuropsychological profile for each structural lesion would help us to approach clinically for further investigations and treatment planning. Intractable epilepsy being one of the important disorders causing disability, correlating structural abnormalities with demographic data and quality of life would reveal the psychosocial aspects of the patients

To obtain seizure freedom from the recurring and debilitating seizures understanding the mechanism involved in epilepsy, identify neural networks and its clinical manifestation is essential. Surgical, medical management and rehabilitation measures are important to control seizures and improve the quality of life. This can have a great impact not only on psychosocial aspects of patients and their family but also reflect on the country's economy. So the present study was carried out to identify various structural lesions using different radio imaging techniques including CT scan, MRI, DTWI and volumetric studies and correlate with demographic data, medical history, seizure examination, neurocognitive profiles and EEG.

2. AIMS AND OBJECTIVES

2.1. Aims

To investigate the prevalence, demographics, clinical characteristics, psychological status, radio imaging findings and EEG in patients with intractable epilepsy

2.2. Objectives

1. To estimate the prevalence of intractable epilepsy in an adult who attend epilepsy clinic, Institute of neurology, Rajiv Gandhi Government General Hospital.
2. To assess the educational, occupational status, clinical characteristics, psychological status, EEG and structural abnormalities in patients with intractable epilepsy

3.   To compare type of seizure (generalized and partial seizures) in adult intractable epilepsy patients with demographic (age, gender, occupational status, educational level), clinical characteristics (developmental history, natal history, postnatal history, family history, age of onset, duration of seizure, seizure frequency, clustering, precipitating factors, status epilepsy, neuro examination, comorbid conditions and Drug), psychological assessment (Intelligent quotient (IQ), Mental quotient (MQ), Bender-Gestalt test (BGT), depression and anxiety scores), radio imaging findings (Computerized tomography (CT) scan, Magnetic Resonance Imaging (MRI), Diffusion Tensor Weighted Imaging (DTWI)) and Electroencephalography

4.   To associate the type of structural lesions in MRI with the demographics, clinical characteristics, psychological assessment and EEG findings.

5.   To associate side of abnormality across various neuroimaging investigation (CT, MRI, DTWI) and EEG with the type of seizure.

6.   To assess the sensitivity of each radio imaging techniques (CT, MRI and DTWI) or in combination (CT &MRI, MRI and DTWI) to identifying structural lesions.

3.   METHOD

A prospective study was carried out to investigate prevalence, demographics, clinical characteristics, psychological status, radioimaging structural abnormalities and EEG in subjects with intractable epilepsy. Subjects who fulfilled the Drug resistant epilepsy criteria defined by ILAE were considered for the present study. A cohort of 600 patients with intractable epilepsy was considered for data collection over a period of 3 years from 21-09-11 to 20-09-14. Prior to the study ethical committee clearance was obtained from the local ethical committee in Madras Medical College, Letter No. 40062011 dated 24-06-201. Collection of data was carried out after getting informed written consent (Tamil) from all participants.

The present study was carried out in four phases. 1) Screening for intractable epilepsy using Drug-resistant epilepsy criteria (ILAE, 2010), 2) Data collection from the previous medical records, case history and Neurological examination, 3) follow-up and review of a patient after radio imaging investigations and interictal EEG recordings 4) follow-up and review of patients after neuropsychological assessment.

Phase 1: During the period of 3 years (from 21-09-11 to 20-09-14) at the epilepsy clinic, Department of Neurology, Institute of Neurology, Rajiv Gandhi Government Hospital, Chennai a total of 2850 patients were screened to identify patients with intractable epilepsy. Among the patients who fulfilled the inclusive and exclusion criteria's, 600 patients were randomly selected for data collection.

Phase 2: All the participants underwent detailed data collection from previous medical records, case history and Neurological examination. Medical records seen over the period ranging from 5 to 20years were obtained from the patient. Case histories were obtained from the patient or

caregivers with the procedure as mentioned in the methodology. Also, all patients underwent neurological examination under the direct supervision f the researcher himself. All the data collected were entered into a personalcomputer using software designed for entering data.

Phase 3: Following neurological examination the intractable epilepsy patients were referred to the radiology department for neuroimaging studies (CT, MRI and DTWI). The protocols used for each test were described in methodology. Interictal EEG recording was done after neuroimaging investigations at our department. All the tests in phase 3 were carried out within 3 to 6 months after enrolment of each patient. All the patients were reviewed and neuroimaging findings were entered into the computer.

Phase 4: Neuropsychological evaluations like (Intelligent quotient (IQ), the mental quotient (MQ), Bender-Gestalt test (BGT), anxiety and depression scales) was carried out by experienced clinical neuropsychologist within 2- 3 months of radiological investigation. All the patients were reviewed with neuropsychological reports and data collected were entered into the computer and all statistical analyses were carried out using the well known statistical package IBM SPSS (version 21) software.

3.1. Participants

600 intractable epilepsy patients with the following inclusion and exclusion criteria were considered as a cohort group for the present study.

Inclusion criteria:
1.   Patients who fulfilled the criteria of Drug-resistant epilepsy defined by ILAE (2) were considered for the present study.
2.   Patients in the age range of 10years to 70 years were considered for the study
Exclusion criteria:
1.   Patients with poor drug compliance were excluded from the present study.
2.   Patients with Alcohol addiction and substance abuse were not considered
3.   Patients should not have a pseudo seizure.

3.2. Material and Procedure

3.2.1. Case history
Detailed Case history evaluation was done using direct one to one clinical interview and questionnaire. The questionnaire contained set of questions to collect information regarding demographic data, family history, prenatal, perinatal and postnatal history. The questionnaire was administered by the clinician to the patients or caregivers at the outpatient department in epilepsy clinic. If the patients have severe cognitive impairment the questionnaire was

administered to the caregivers. Demographic data included Patient record number, Name, Age, gender, address, contact number, educational status and occupational status. Following details were collected under Medical history, prenatal history, natal, post natal history, developmental history, family history, patient habits (alcohol, smoking, and substance abuse), sleep disturbance, behavioural changes, cognitive impairment and neuropsychological manifestation.

3.2.2. Neurological examination

Neurological examination included collecting information about seizure from previous medical records, description of seizure by patients or caregivers and direct observation of patients. The information collected include data about Seizure type, Onset of seizure, Duration of seizure, Seizure semiology and changes, Neurocutaneous markers, Frequency of seizure, Clustering, Precipitating factors, Status epilepsies, Hemiplegia, Migraine headache and Trauma

3.2.3. Neuroradiological investigations

Neuroradiological investigations included CT scan, MRI scan, diffusion tensor weighted imaging (DTWI) and hippocampal volumetric studies. All the neuroradiological investigations were carried out by an experienced neuroradiologist and identified structural abnormalities in the brain. All CT, MRI, DTWI, volumetric studies images and reports were collected and the information's were entered for the corresponding patients. Following protocols were used to collect data from each radiological investigation.

3.2.3.1. CT scan protocol

All the subjects underwent conventional CT scan assessment using 16 slices CT scanner system (Seimens, Germany). Axial sections were taken using the following protocol: 1. Scout: Lat (Length 350) Breath Hold: None 2. Axial: 5mm x 5mm Recon: 5mm x 5mm Bone 3. FOV: 250 4. Scan Length: angled to the base of the skull through the top of the skull.

3.2.3.2. MRI protocol

All the subjects underwent conventional MRI and DTWI imaging on a 1.5T, 48 channel System (SeimensAera, Germany) using a head coil (40 elements), Gradient strength of 45mT & flow rate of 200 Mt/sec. MRI protocol consisted of axial T1 weighted sequence (T1), axial T2 weighted sequence (T2) and volumetric T1 weighted MRI (3D – SPGR) sequence. These images were analysed by experienced neuroradiologists who detected the MCDs and hippocampal malformations.

3.2.3.3. DTWI and hippocampal volumetric study Protocol

DTWI was performed in the axial plane by using single-shot echoplanar imaging with the following parameters: TR/TE, 3500/83 ms; diffusion-gradient encoding in 20 directions; b0, 1000 s/mm2; FOV, 230 X 100 mm; matrix size, 128 X 128; section thickness, 5 mm; bandwidth- 1500, EPI factor- 128 average - 3 and number of signals were acquired. Standard DWI acquires data in three orthogonal planes (typically X, Y, and Z axis).

The acquisition was repeated with gradients oriented in each of the 3 directions in space. With 2 acquisitions with different b-factors (typically b = 0 and 1000 s/mm2), it becomes possible to calculate the apparent diffusion coefficient (ADC) without the T2. While ADC maps reveal the tendency of the water molecules to diffuse within a voxel, directional variation is also required to image 3D anisotropic diffusion. The complex mathematical equation used to model 3D anisotropy is called tensor.

By sampling a minimum of 6 or more diffusion directions and establishing a relationship between the acquired data and applied diffusion gradients in the pulse sequence, the directional variation in the tendency of water molecules to diffuse within a voxel was imaged. FA- fractional anisotropy, geometric tensor metrics (linear anisometry-Cl, planar anisometryCp, and spherical anisometry- Cs), and ADC- apparent diffusion coefficient, RA- relative anisometry , GA-Geodesic anisometry were calculated by using the standard algorithms respectively. Images were transferred to a separate multi-modality workstation (Siemens MMWP) - Neuro 3D software for post processing.

In addition to the above, MR data was also obtained on a separate cohort of controls and patients on a 3T Siemens Spectra scanner: a T1 weighted structural axial MPRAGE sequence was performed to obtain high resolution structural data. The voxel dimensions were 0.98 mm x 0.98 mm x 1mm. DWI images with an isotorphic voxel dimension of 2mm x 2mm x 2 mm was obtained with 64 gradient directions at a B value of 1000. Reference volumes with B = 0 were also obtained.

Maps of FA and ADC were calculated at the various region of interest especially in Frontotemporal fasciculus, frontoparietal fasciculus, temporoparietal fasciculus, temporooccipital fasciculus, parietooccipital fasciculus, uncinate fasciculus, hippocampal and parahippocampal region, fornix and fimbrae, cingulate gyrus to identify various tracts or regions which are involved in maintenance of normal brain function.

3.2.4. EEG investigations

Routine Scalp EEG recording was performed using Nicolet EEG system (Natus, USA) during the interictal period. Electrodes were placed on the scalp using 10-20 classification systems. EEG was recorded using 25 channels. Waves were amplified and filtered with low pass filter with a high cutoff of 70Hz and high pass filter with a low cutoff of 1Hz. Sensitivity used were 70micorvolt/ cm with a time base of 30mm/sec. EEG was recorded during awake time, eye opening and eye closure, Photic stimulation, sleep deprivation and hyperventilation.

3.2.5. Neuropsychological Assessment

After neuroradiological investigations, the clinical neuropsychologist assessed the patients for psychological functions. Neuropsychologist was blinded to the type of structural abnormalities in the brain. All of the neuropsychological assessments were carried out in a quiet room and well-lit room. Initially, Bender Gestalt test (BGT) was administered. If patients were able to perform the task in BGT, the Intelligent quotient (I.Q) and Memory quotient (M.Q) assessment were carried out. If the I.Q were greater than 70, scales to evaluate anxiety,

depression and quality of life were administered. Whenever patients were not able to perform BGT or could not perform any task, or low IQ less than 70, scales to evaluate anxiety and depression and quality of life scale were not administered. The following neuropsychological tools were used to assess each patient 1) Bender Gestalt test to assess visuoperceptual gestalt functions, 2) Weschler's children or adult intelligence scale to assess intelligence quotient, 3) Weschler memory quotient to assess memory quotient 4) Multiphasic personality questionnaire to assess anxiety and depression and 5) WHO quality of life Brief (WHOQOL – BREF) questionnaire to assess quality of life scores in all four domains namely physical health, psychological, social relationship and environment. World health organisation quality of life scale was used in the present study to estimate the quality of life in 4 domains (physical health, psychological health, social relationship and the environment. Scores in each domain ranged from 0 to 100. 147 patients who had mental retardation were considered as having a poor quality of life. Scores less than or equal to 50 were considered as a poor quality of life and scores greater than 50 were considered as a good quality of life. Total quality of life scores ranged from 0 to 120. Scores were classified into 4 categories 1) very poor (mentally retarded group), 2) poor scores less than or equal to 60, 3) scores between 61 and 90 & 4) scores between 91- 120.

3.3.   Statistical Analysis

Out of 600 patients with fulfilled the criteria for drug-resistant epilepsy (ILAE, 2010) only 506 patient returned back with complete information regarding the medical history, neuro radio imaging reports, interictal EEG findings and neuropsychological assessment reports. Thus 506 patients with a complete set of data were included in the study for further analysis. The data collected from intractable epileptic patients were carefully coded and entered into a personal computer. All statistical analyses were carried out using the specially designed statistical software package, IBM SPSS (Version 21). Some of the statistical analyses carried out for the present study include formation of frequency tables – one way, two way and multiway - with percentages; summary statistics such as mean, standard deviation etc. For qualitative data analyses, non-parametric tests and for quantitative data analysis parametric was used. In all the tests, the significance level was kept at, $\alpha = 0.05$.

4.   Observation

4.1.   Prevalence of intractable epilepsy

The present study estimated prevalence of intractable epilepsy using drug-resistant epilepsy criteria (ILAE, 2010). Out of 2850 patients (1523 males and 1327 females) seen at our epilepsy clinic, 600 (21.05%) patients fulfilled the criteria for drug-resistant epilepsy. Patients who completed all the investigation were 506 patients - 294 (58.1%) males and 212 (41.9%) females. From the present study at out epilepsy clinic, the prevalence of intractable epilepsy is reported to be 21.05% that approximates 1 in 5 patients with epilepsy.

4.2. Demographics of patients with intractable epilepsy

Demographic details collected from patients with intractable epilepsy showed the distribution of patients across the age, gender, education and occupation. Most of the patients with intractable epilepsy were observed commonly in the age range of 16-20 years (24.11%), followed by 26-30 years age range (16.60%). Decreased prevalence was observed in the age range >60 years (1.38%).

Educational status of patients with intractable epilepsy shows most of the patient's literacy is high school level (38.54%) and elementary school level (32.21%). 16.8% of them were illiterate and had no school education. Though major literacy level of patients with intractable epilepsy was high school and elementary level, high frequency of unemployment (36.96%) was observed in patients with intractable epilepsy. Only a few proportion of the population were skilled workers (13.24%), in clerical jobs (3.36) and professional jobs (1.58%). A significant proportion of patients (13.64%) were underemployed who were working as daily labour. 34.9% of females in the intractable epilepsy group were housewives. 33.81% of patients with intractable epilepsy less than 25 years of age were graduates and high school students.

4.3. Clinical characteristics of patients with intractable epilepsy
4.3.1. Type of seizure

The major type of seizure that caused intractability is partial seizures (n = 369, 72.92 %,) followed by generalized seizures (n=137, 27.08%). In partial epilepsy 312 patients had complex partial seizures, 50 patients had a simple partial seizure and 7 had mixed type of seizures and constitute 63.04%, 9.88% and 1.38% of the total patients with intractable epilepsy respectively. In generalised epilepsy, 121 patients had generalised tonic clonic seizures and 16 patients had myoclonic epilepsy whichconstitutes 23.91% and 3.16% of the total patients with intractable epilepsy. In our series of 506 patient's absence seizures was not observed.

4.3.2. Duration seizure

Most of the patients (77.07%) in our study had seizure duration ranging from 1-20years. Seizure duration (greater than 21years) was observed in less proportion of patients (22.92%) with intractable epilepsy.

4.3.3. Onset of seizure

From the present study, it was observed that most of the patients who had intractable epilepsy had early onset of seizure i.e. less than 5 years of age (30.24%, n=153). The age of onset of seizure decreased with increase in age range. The number of patients slightly decreased as the age of seizure onset increased from 21-25years. Later the percentage of patients with intractable epilepsy decreased with increasing age range.

4.3.4. Seizure frequency

Most of the patients with intractable epilepsy had seizure frequency of 1-4 times per month (54.35%, n=275), followed by 1-6 times per week (29.84%,n=151) and daily seizure occurrence (15.81%, n=80).

4.3.5. Seizure semiology

Seizure semiology change was observed from the clinical records. Majorly seizure semiology changed from generalised to complex partial seizure and also from simple partial to complex partial seizures in 329 patients (65.02%). These changes in seizure semiology occurred 1-5years after the onset of an initial seizure.

4.3.6. Clustering

Clustering of seizure was not observed in 296 patients (58.5%) with intractable epilepsy. Clustering was reported to be present for 1-2 times in 145 patients (28.66%), 2-3 times in 44 patients (8.70%) and greater than three times in 21 patients (4.15%).

4.3.7. Precipitating factors

Many patients in our study population had sleep deprivation as precipitating factor (15.42%, n=78), followed by other factors (4.15%,n=21), sleep (3.16%, n=16) and febrile illness (1.98%, n=10). The patients or caregivers did not report any precipitating factors for their illness is 75.30% of the population (n=381). Other precipitating factors include loud sounds and light (cinema, watching TV and working as a welder).

4.3.8. History of Status epilepsy

History of Status epilepsy was reported in 42 patients (8.30%) of the population.

4.3.9. Drugs

Most of the patients with intractable epilepsy were under polytherapy (84.78%, n=429). 15.22% (n=77) of them were under monotherapy. All the patients were treated with one or more of the following drugs (carbamazepine, sodium valproate, phenobarbitone, and phenytoin sodium).

4.3.10. Co-morbid conditions

The major comorbidity of epilepsy in the present study is a migraine and accounts for 14.03% (n=71), followed by stroke (3.36%, n=17), head injury (2.37%, n=12) and smoking (<1%).

4.3.11. Medical history

In the birth, history asphyxia was reported to be present in 4.15% (n= 21) of the population. Postnatal febrile seizures were observed in 1.98% (n=10), followed by 6 patients (1.19%) with infections, 5 patients (.99%) with the head injury, and 4 patients (.79%) with hypothyroidism and 3 patients (n=3) with infantile stroke. Delayed motor developmental milestones were reported to be present in 73 patients that constitute 14.43% of the population.

4.3.12. Family history

Positive family history for seizure was reported to be present in 34 patients (6.72%) of the population studied.

4.3.13. Neurocutaneous markers

Neurocutaneous markers like adenomasebaceum, hypomelanosis of Ito, neurofibromatosis and Sturge-weber syndrome were observed in our case series. A total 10 patients with intractable epilepsy (1.98%) had neurocutaneous markers and associated structural abnormalities in the brain. 6 patients with adenomasebaceum, 2 patients with neurofibromatosis, one patient with hypomelanosis of Ito, and one with Sturge-weber syndrome.

4.3.14. Neurological examination

Headache (19.96%, n=101) and hemiparesis (3.36%, n=17) were often present in patients with intractable epilepsy during neurological examination.

4.3.15. Electroencephalography findings

Interictal EEG showed generalisedepileptiform discharges in 40.71% (n=206) of the total population. Focal epileptiform discharges were observed in 80 patients (15.81%) with intractable epilepsy. Out of 80 patients with focal EEG activity, 25 patients were from the right hemisphere and 55 patients from the left hemisphere. 220 patients (43.48%) in spite of their seizure intractability showed normal interictal EEG.

4.4. Neuroimaging results in patients with intractable epilepsy
4.4.1. CT scan findings

In the present study, several investigations were carried out systematically to evaluate lesions in the brain among patients with intractable epilepsy. 388 (76.68%) patients with intractable epilepsy did not show significant abnormalities of the brain in CT scan. The lesions most commonly observed in participants with intractable epilepsy were calcification (10.47%, n=53), followed by atrophy (5.34%, n=27), gliosis (4.15%, n=21) and infarction (1.98%, n=10). Non-neoplastic cysts, neoplastic and lissencephaly were rarely observed in patients with intractable epilepsy us CT investigations. The majority of lesions were bilateral (12.06%, n=61) especially calcifications. Following bilateral lesions left sided lesion were common than right-sided lesions.

4.4.2. MRI findings

Most common abnormality (32.02%, n=162) that was observed in patients with intractable epilepsy wasMesial temporal sclerosis (MTS). Following MTS, non-specific lesions that include cortical atrophy, periventricular white matter calcifications were commonly observed in 15.61% (n=79) of the population. Neoplastic and nonneoplastic lesions including gliosis, cyst, vascular malformations, Hemorrhage and infective lesions were observed in 12.06% (n=61%). Malformations of cortical development were observed in 9.88% (n=50) of patients with intractable epilepsy. Incomplete hippocampal inversion was observed in 35 patients with intractable epilepsy that constitute 6.92% of the total population studied. Commonly, lesions were observed on left side (35.57%, n=180), compared to bilateral (23.52%, n=119) and right-sided lesions (17.39, n=88). 119 (23.52%) patients with intractable epilepsy did not show any abnormalities in 1.5Tesla MRI.

4.4.2.1. Mesial temporal lobe sclerosis

Mesial temporal sclerosis was most commonly observed in the left side (18.37%, n=93) compared to the right side (8.30%, n=42). Bilateral MTS was observed in 27 patients (5.33%). Also, MTS were associated with malformation of cortical development, gliosis, non-specific cystic lesions, infarction, and incomplete hippocampal inversion in 28 patients (5.53%). These lesions were categorised under multiple lesions.

4.4.2.2. Incomplete hippocampal Inversion

Hippocampal malrotation or incomplete hippocampal inversion (IHI) were identified in a small proportion of patients with intractable epilepsy using hippocampal volumetric studies. Out of 509 patients, 35 patients had incomplete hippocampal inversion and constitutes 6.92% of the total population. IHI was commonly observed in left hippocampus (n=30) compared to the right hippocampus (n=5). Three patients who had IHI also presented with FCD were categorised under multiple pathologies.

4.4.2.3. Malformations of cortical development

Several malformations of cortical development were observed in 506 patients with intractable epilepsy. MCD were grouped into the following categories as summarised in table 1.

4.4.2.4. Neoplastic and non-neoplastic lesions

Neoplastic lesions were observed in two patients. One patient with glioma and another patient with gliomatosisceribri. Inflammation and Infections like herpes simplex encephalitis with granuloma (1 patient), tuberculousmeningoencephalitis (2 patients), neurocysticercosis (1patient) and Hashimoto's autoimmune encephalitis (1 patient) were observed in 5 patients with intractable epilepsy. Gliosis at various regions of the brain especially peritoocipetal and orbitofrontal regions was observed in 29 (5.70%) with intractable epilepsy signifying nonspecific lesion secondary to trauma, ischemia and inflammation. Intractable epilepsy associated with

Infarctions was observed in 12 patients (2.37%). Most of the patients had infarction at the left hemisphere, especially in the parietooccipital region. Arteriovenous malformations (AVM) were associated with focal intractable epilepsy with secondary generalisation in 6 patients (1.18%). All of them had AVM at the parietotemporal region. 2 patients with intractable epilepsy presented with haemorrhage in the brain (.39%).

4.4.2.5. Non-specific lesions

Idiopathic focal cortical atrophy was observed in 11 patients (2.2%). Calcification (focal calcification, multiple calcifications (small and large)), calcification with gliosis and calcifications with perilesionaloedema were observed in 68 patients (13.43%).

Table 1: Various malformation of cortical development observed in 506 patients with intractable epilepsy

Various Malformation of cortical development		Frequency (n=50)	Percentage
Focal cortical dysplasia			
Frontal lobe	Right	26	5.13
	Left	3	
		5	
Bilateral		1	
Temporal lobe	Right	1	
	Left	4	
		2	
Bilateral		-	
Parietal lobe	Right	1	
	Left	1	
		1	
Bilateral		1	
Occipital lobe	Right	-	
	Left	5	
Bilateral			
Multiple FCD			
Pachygyria		1	.19
Polymicrogyria		2	.39
Dysembryonicneuroepithelial tumor		2	.39
Heterotopia		4	.79
Lissencephaly		2	.39
Schizencephaly		2	.39

4.4.3. DTWI findings

Diffusion tensor weighted images (DTWI) showed increased FA (fractional anisotropy) values and decreased ADC (apparent diffusion coefficient) values in one or several regions in the brain among the various regions interest considered for the present study. DTWI were significantly abnormal in 406 (80.23%) intractable epilepsy patients. 158 (31.23%) patients showed left sided abnormality followed by bilateral (30.24%) and right-sided (17.39%) abnormality. The areas of interest considered for the present study were Frontotemporal fasciculus, frontoparietal fasciculus, temporoparietal fasciculus, temporooccipital fasciculus, parietooccipital fasciculus, uncinate fasciculus, hippocampal and parahippocampal region, thalamus, corpus callosum, fornix and fimbriae and cingulate gyrus. 217 patients especially patients with MTS showed abnormal DTWI values in hippocampal and parahippocampal regions. Also, abnormal ADC and FA values were observed in higher frequencies at middle cerebellar peduncle, uncinate fasciculus, temporooccipital fasciculus, temporoparietal fasciculus, fimbriae, fornix, thalamus and corpus callosum. Also, the involvement of cingulate gyrus, parietooccipital fasciculus, frontoparietal fasciculus were less commonly observed in the patient with intractable epilepsy.

4.5.   Neuropsychological assessment findings in patients with intractable epilepsy

Out of 506 patients with intractable epilepsy, 147 patients (29.05%) had mental retardation (<69) score in Weschler intelligence scale. 20% (n=104) of them had dull normal intelligence. 255 patients (50%) of them had adequate intelligence. Weschler's memory quotient scores were low (<70) in 194 patients (38.34%). Bender Gestalt test revealed abnormal visuoperceptual gestalt functions in 218 patients (43.08%). Multiphasic personality questionnaire to assess anxiety and depression could not be administered in 147 patients who had mental retardation. Multiphasic personality questionnaire administered to patients without mental retardation showed anxiety in 161 patients (31.82%), depression in 142 patients (28.06%) and mixed anxiety and depression in 126 patients (24.90%). A Higher proportion of intractable epilepsy patients had a poor quality of life in a social relationship (36.17%) followed by psychological health, environment and physical health domains. Most of the patients with intractable epilepsy had the poor and very poor quality of life scores in all the four domains.

4.6.   Comparison of type of seizure with demographics, clinical characteristics, structural imaging and neuropsychological assessment findings of intractable epilepsy

Pearson's Chi-square test was applied to the data to find the association between the type of seizures with the demographics, clinical characteristics, structural imaging and neuropsychological findings. Pearson's chi-square test revealed a significant association between the patient age group and type of seizure. Generalised seizures were significantly ($p<0.05$) associated with 16-20 years, 26-30 years and 31-35 years age groups. The partial type of seizures had the strong association ($p<0.05$) with the age ranges between 16 years to 40 years.

No significant association (p>0.05) was observed between the type of seizure and other demographic variables like gender, occupational status and educational level. Clinical characteristics (developmental history, natal history, postnatal history, family history, the age of onset, duration of seizure, seizure frequency, precipitating factors, status epilepsy, comorbid conditions and Drugs) did not show any association with the type of seizure in our population. The majority of patients with intractable epilepsy type of seizure were not associated with clustering (p<0.05). But a few proportion of patients (34.42%, n=127) in partial seizure group had a significant association with the clustering of 1-2 times. In the neurological examination, none of the comorbid conditions except a postictal headache had an association with the type of seizures. Partial type of seizures had a strong association with a headache in 23.31% of the population (p<0.05). Seizure semiology change was observed significantly in a high proportion (68.02%) of patients with partial seizures followed by generalised seizure (56.93%).

CT scan findings did not reveal significant results with the both type of seizures (p<0.05). Both the type of seizures showed strong association with MTS, Neoplastic and Non-neoplastic lesions (gliosis, cyst, vascular malformed, infectious) and non-specific lesions (p<0.05). 39.02% of patients with partial seizure were significantly associated with MTS when compared to generalise seizure (13.14%). 19.71% of patients with generalised seizures had non-specific lesions when compared to 14.09% of patients with partial seizures. Neoplastic and non-neoplastic lesions were observed almost in equal proportion among patients with generalised (13.87%) and partial seizures (11.38%). 38.69% patients with generalised seizure had statistically significant normal MRI findings. DTWI findings showed a significantly higher proportion of abnormalities in 85.09% of patients with complex partial seizures followed by 67.15% of patients with generalised seizures. DTWI findings were significantly normal in 32.85% of patients with generalised seizures.

Interictal EEG findings were significantly normal in both the type of seizures (p<0.05). 49.64% patients with generalised seizures and 41.19% with partial seizures had normal EEG results. Focal epileptiform discharges in 20.05% of patients with partial seizures. Focal epileptiform discharges were rarely observed (4.38%) in patients with generalised seizures. 45.99% of patients with generalised epilepsy had bilateral epileptiformgeneralised discharges followed by 38.75% of patients with partial seizures.

Neuropsychiatry findings and type of seizures were compared using Pearsons Chi- Square test. A comparatively similar proportion of patients with the generalised seizure and partial seizure had low IQ and mentally retarded, reduced MQ, abnormalities in BGT, anxiety and depression and quality of life. Pearsons Chi-Square test did not reveal any significant difference between the IQ, MQ, BGT, anxiety, depression and quality of life scores between the generalised and partial seizure.

4.7. Association of type of structural lesion with demographics, clinical characteristics, neuro radio imaging and neuropsychological findings

4.7.1. Structural abnormalities and their demographics in intractable epilepsy

Patients with structural abnormalities and without structural abnormalities were compared to find the association with demographic details. There was no association observed between the type of structural lesion and the demographics such as age, education level and occupational status except gender (p>0.05) as seen in the table. Male being more in our study population showed a significant increase in the frequency of structural lesions.

4.7.2. Association of Clinical characteristics with structural abnormalities in intractable epilepsy

There was no significant association between the structural abnormalities and the clinical characteristics (medical history and seizure characteristics) of intractable epilepsy patients. The clinical characteristics associated with structural lesions were natal history and postnatal history, developmental history, family history, Seizure type, Onset of seizure, Duration of seizure, Seizure semiology changes, Neurocutaneous markers, Frequency of seizure, Clustering, Precipitating factors, Status epilepsies, neurological examination, comorbid conditions and drugs. Even though there were significant p values in neurocutaneous marker, family history, the age of onset of a seizure, clustering, neurological examination and comorbid condition using chi-square test, many of the cells had frequencies less than 5, thus they were not considered as significant measures.

4.7.3. Association of structural abnormalities with radio imaging findings

The side of the lesion in CT, MRI, DTWI and EEG were associated with various structural lesions using chi-square test. The side of the lesion in MRI was significantly associated with MTS (right and left lesions) and bilateral nonspecific lesions. The side of the lesion in DTWI was significantly associated with MTS (right, left and bilateral lesions). CT scan findings were associated with neoplastic- non-neoplastic lesion (right and left) and nonspecific lesions (right, left and bilateral) but the results were not considered significant due to 10% of cells has expected frequencies less than 5. The side of the lesion in EEG was associated with MTS (right and left), but the results were not considered significant due to 10% of cells has expected frequencies less than 5.

4.7.4. Neuropsychological manifestations of structural abnormalities in intractable epilepsy

Abnormal IQ scores (below average), MQ scores, BGT results were strongly associated (p<0.01) with MTS. The significant proportion of patients with intractable epilepsy who had no

structural abnormalities had normal I.Q scores, M.Q scores and BGT results. The significant proportion of patients with MTS had anxiety and depression. Also, a significant proportion of patients without any structural abnormalities did not show any signs of anxiety or depression. Another significant proportion of patients with MTS had combined symptoms of anxiety and depression ($P<0.05$).

Total quality of life was very poor in MCD, MTS, neoplastic and non-neoplastic, nonspecific lesions and patients without any structural abnormalities. For these patients, IQ and MQ were severely impaired. 16.33% of MCD patients fell into the very poor quality of life and rest of them did not show a significant association of other categories of quality of life. IHI patients did not show any association between quality of life. Other individuals with MTS, Neoplastic and Non-neoplastic lesions, Nonspecific lesion and patients without any structural abnormalities showed heterogeneity in the quality of life scores. A significant proportion of patients with the above-mentioned lesion fell into very poor, poor, average and good quality of life scores.

4.8.   Association of side of lesion across neuroimaging investigation (CT, MRI, DTWI) and EEG

4.8.1.   Association of side of lesion in CT vs MRI investigations

Out of 506 cases, 115 cases were found to be normal without any structural lesions in both CT and MRI. Out of 388 patients who had normal CT results 273 patients had abnormal results in MRI (right-sided lesion (66), left sided lesion (139) and bilateral lesions (68). Out 95 patients who had an abnormality in both CT and MRI, 18 of them were found to have a lesion on the right, 29 of them were found to have a lesion on the left, and 48 of them were found to have a bilateral lesion.   Hence the consistency of CT and MRI results in our study is (115+18+29+48)/506 (*100) = 41.5%. If CT and MRI results of patients were combined ignoring patients without structural abnormalities, then the consistency is (18 +29+48)/115 (*100) = 82.6% or nearly 83 %. In other words, both CT and MRI imaging showed the same side of a lesion in more than 80% of patients.

4.8.2.   Association of side of lesion on MRI and DTWI

From the present study, it was observed that a significant proportion of patients who have normal MRI showed significant DTWI abnormalities (left and bilateral hemispheres of the brain). A significant proportion of patient with right hemisphere MRI lesions showed right and bilateral hemispheric abnormalities in DTWI as seen in table 21. Similarly, a significant proportion of patients with left hemispheric lesions in MRI showed left or bilateral hemispheric lesions. Also, a significant proportion of patients who showed bilateral lesions in MRI showed bilateral abnormalities in DTWI. The consistency of MRI and DTWI results in our study is [(54 + 103 +68)/ (79 +129+125)] * 100 = 67.57%

4.8.3.   Association of side of lesion between MRI and EEG

A significant proportion of patients without Structural lesion in MRI (61.3%), right (43.2%) or left (37.8%) or bilateral (34.5%) abnormalities in MRI did not reveal any abnormalities in EEG. Also, one third of patients (34.5%) without structural abnormalities in MRI did show bilateral epileptiform discharges from both hemispheres. Patients with right-sided abnormalities in MRI showed significant EEG abnormalities in the right hemisphere (25%) and bilateral hemispheres (28.4%). Similarly, patients with left hemispheric lesions in MRI showed a significant amount of EEG abnormalities in left (25%) and bilateral hemispheres (36.7%). Bilateral lesion often showed significant bilateral EEG abnormalities in 62.2% of the population. The consistency of MRI and EEG results in our study is [(22+45+74)/ (23+52+165)] * 100 = 58.75%.

4.8.4.   Association of side of lesion between DTWI and EEG

Patients who had normal DTWI finding, 24% showed significant bilateral EEG abnormalities and 64% of them did not show any EEG abnormalities. The significant proportion of patients who had right or left or bilateral hemispheric abnormalities in DTWI significantly showed bilateral EEG abnormalities as seen in table 23. The consistency of DTWI and EEG results in our study is [(19+34+95)/ (22+46+182)] * 100 = 59.2%.

4.9.   *Role of Neuroimaging results (CT, MRI and DTWI) and EEG in identifying structural lesions*

CT scan results have a greater chance in identifying non-specific lesions (40.7%) and neoplastic - nonneoplastic lesions (29.7%). Altogether CT scan has 70% chance to identify neoplastic - nonneoplastic lesions or non-specific lesions. MRI results have a higher chance (41.9%) identifying MTS. Similar to MRI, DTWI also has a greater chance of detecting an abnormality in MTS (36.7%). EEG revealed abnormal result in MTS and is a form of focal lesion associated with CPS. Among MCD, MRI had higher sensitivity when compared to CT scan.

None of the imaging techniques used could identify any abnormalities in 6.13% (n=31) of patients with intractable epilepsy. Interestingly, DTWI could identify an abnormality in 7.91% (n=40) of patients with intractable epilepsy apart from all other investigations. If MRI and DTWI were combined for investigating intractable epilepsy patients, the frequency of identifying structural abnormalities increased to 18.58% (n= 94). If MRI, DTWI and interictal EEG were combined it could identify abnormalities in 30.24% (n=153). If all the four investigations showed consistent abnormality in 12.85% (n=65)

4.10.   *Association education and occupation in intractable epilepsy*

Chi square test was applied to associate education and occupational levels in intractable epilepsy. Occupational status were grouped into 1) unemployed (unemployed + housewife), 2) Employed (daily labour, skilled, clerical, professional) and 3) Students for analysis. Intractable

epilepsy being a heterogeneous group (cognitive functions, structural abnormalities) showed varied level of educational status and occupation. Patients without any school education (63.53%), elementary level of education (65.64%) and high school level of education (46.67%) were significantly associated with unemployment. Also 31.28% of population with high school education and 42.86% of populationwith a graduate level of education were significantly associated with employment.

4.10.1.   Factors contributing to education in patients with intractable epilepsy

Chi-square test was applied to find out the association of demographic variables, structural abnormalities and psychological variables that contribute to education and unemployment in patients with intractable epilepsy. A significant proportion of patients (41.18%) who had a younger age of onset of seizure had no school education followed by 29.45% of them having an elementary level of education. Also, longer duration seizures (16-20 years) had a significant proportion of association with no schooling (30.59%) and elementary level of education (20.25%). The equal proportion of patients with longer duration of seizure had significant association across all the education level. 91.76% of them who were under polytherapy had no schooling and 88.96% of them who were under polytherapy had education up to elementary level. The various structural lesion, radio imaging techniques, side of lesion across various radio imaging techniques and EEG did not associate significantly with any category of education being considered for the study. 48.24% and 12.94% of the population who had low IQ scores had no school education. High IQ scores were associated with the graduate level of education in 73.02% of the population. 85.71% and 65.64% of them who had normal MQ scores fall undergraduate and high school education category. 55.29% and 43.56% of patients who had low MQ scores have not undergone any school education and studied the only elementary level of education respectively. 71.43% of the population with normal BGT results significantly correlated with the graduate level of education. 58.82% and 48.47% of the population who had abnormal BGT scores were uneducated and had the only elementary level of education. An equal proportion of patients with anxiety, depression, and mixed anxiety depression symptoms fall in elementary, high school and gradual level of education.

4.10.2.   Factors contributing to occupation in patients with intractable epilepsy

Among clinical characteristics duration of seizure (longer than 16-20years) was significantly associated with unemployment. Patients who had a younger age of onset (6-10years) had a significant association with employment. Almost equal proportion of patients with intractable epilepsy for who did not have an episode of status epilepsy were unemployed, employed and student which indication no association of status epilepsy with unemployment. Drugs (polytherapy) were significantly associated with unemployment, employment and students in equal proportion. None of the other clinical characteristics significantly associate with employment status (p>0.05).

Among structural imaging techniques, none of them had an association with employment. Structural abnormalities like MTS had a significant association with unemployment (37.09%). Also, patients who did not show any structural abnormalities had 20.36% chance of unemployment. The side of lesion and EEG finding did not associate with employment. A Higher proportion of patients with mental retardation (40%) and MQ scores (48.36%) were significantly associated with unemployment. Patients with normal IQ scores (65.22%) and MQ scores (75.16%) were significantly associated with employment (65.22%). Normal BGT scores were significantly associated with employment (62.73%). The absence of anxiety (46.58%), depression (55.28%) and anxiety- depression (57.76%) was significantly associated with employment.

5.   Inferences summary

5.1.   *Prevalence of intractable epilepsy*

The prevalence of intractable epilepsy in the adult population (21.05%) of the present study were comparable to the western studies (8,112), that considered Drug-resistant epilepsy (ILAE, 2010) criteria. Despite differences in definition, the prevalence of intractable epilepsy in this study was congruent to that of the western studies(5,7,112) in which the prevalence ranged from 15.6% to 22.5%. Higher frequency of patients with intractable epilepsy was observed in the age range of 16-20 years followed 26-30 years age range, which was similar to the results of a study that showed increased prevalence in 20-29 years (85), a hospital-based study in Singapore. Our results were not in congruence with results of a population-based study in north Italy (112) and shows increased prevalence in the age range of 35 to 54years.   Decreased prevalence was observed in the age range >60 years (1.38%) were similar to both the studies (85,112) that showed the reduced prevalence of intractable epilepsy (> 55 years of age). There are no studies in India regarding the prevalence of intractable epilepsy especially using drug resistance epilepsy (ILAE, 2010) criteria.

5.2.   *Association of type of seizure with demographics, clinical characteristics and neuropsychological findings*

From the present study, it was observed the type of seizure (a partial seizure) has a strong association with seizure semiology changes, MTS, DTWI abnormalities and low IQ scores. The type of seizure was not associated with any other variable considered for the study. These findings were consistent with several invitro and invivo research studies (40,85,113,114).

5.3.   *Association of Structural lesions with demographics, clinical characteristics and neuropsychological findings*

Among structural abnormalities, MTS was associated with a side of the lesion in MRI and DTWI(8,10). Neoplastic and nonneoplastic lesions were significantly associated with CT

results. MTS was associated with low IQ scores and anxiety and depression(115). Structural lesion in patients with intractable epilepsy did not show any significant association with other demographic and clinical characteristics. The quality of life is invariably poor in patients with intractable epilepsy (structural lesions).

5.4. Association of education and occupation with demographics, clinical characteristics, structural lesions and neuropsychological findings

Early age seizure onset, longer duration of seizure, polytherapy, low IQ and MQ scores were significantly associated with low education levels. Similar to education unemployment was significantly associated with early age of seizure onset, polytherapy, MTS, low IQ scores and MQ scores. Patients without any schooling, elementary or high school level of education were associated with unemployment. Recurrent attacks of seizure from childhood and polytherapy lead to permanent damage to the brain structures particularly memory, language and emotional neural network. This would result in impaired cognitive function, learning disability and behavioural disturbances leading to a reduced level of education and employment in intractable epilepsy patients (89,116–119).

5.5. Localizing side of abnormality across various radio imaging techniques and EEG

CT and MRI could identify the same side of the lesion in more than 80% of patients. Even though MRI was abnormal in patients with intractable epilepsy, DTWI could reveal microstructural white matter abnormalities in a significant proportion of patients(71,72,76,79). Moreover, patients showing a localised lesion in one hemisphere using MRI showed the same side or bilateral white matter abnormalities in DTWI indicating large neural network involvement (71,72,75,77,78,80). Less proportion of patients with a focal lesion in right or left hemisphere in MRI showed similar hemispherical lateralization in interictal EEG. A significant association was observed in bilateral lesions in MRI with bilateral abnormalities in EEG(107). A significant proportion of patients with bilateral microstructural changes in DTWI showed bilateral EEG abnormalities.

5.6. Sensitivity of radio imaging techniques and EEG

From our study, it was observed that CT scan is more sensitive in identifying non-specific lesion, neoplastic – non-neoplastic lesions. MRI results were more associated MTS and MCDs. Interestingly it was observed that a small group of patients who did not have any lesions in CT and MRI but showed microstructural abnormalities in DTWI (71,72). Any one of the neuroimaging techniques is not sufficient to reveal the neural network involved in epilepsy. The combination of tests or a test battery approach including CT, MRI, DTWI and EEG could help us to trace out the neural network in intractable epilepsy. Our study showed 6.13% of intractable epilepsy patients without any structural abnormalities in the brain using conventional CT, MRI, DTWI and EEG. Among patients who did not show any structural lesion, few of them had metabolic encephalopathy (Mitochondrial cytopathy, glute1 deficiency disorder). Patients whose

conventional radio imaging including DTWI could not demonstrate any structural abnormalities; higher Tesla MRI may help in identifying neural network or tissue pathology.

6.   Conclusion

➢ From the present study it was found that the prevalence of intractable epilepsy in our population is 21.05 % using ILAE criteria.

➢ Intractable epilepsy being a heterogeneous group with varying clinical characteristics, neuropsychological manifestations affecting their education, employment and quality of life.

➢ It was observed that wide range patients with various structural abnormalities present with intractable epilepsy were noted from this research.

➢ Conventional CT and MRI could identify the structural lesion in 80% of patients. Patients who do not show any lesion in CT, MRI may show microstructural white matter abnormalities in DTWI. In patients whom conventional radio imaging including DTWI could not demonstrate any structural abnormalities, higher Tesla MRI may help in identifying neural network or tissue pathology.

➢ Also a small percentageof patients (6.13%) without any structural abnormalities in the investigation carried out do present with intractable epilepsy is still a clinical conundrum.

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