PROSPECTIVE STUDY OF INTRACTABLE EPILEPSY – CLINICAL CONUNDRUM

A THESIS SUBMITTED TO

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DOCTOR OF PHILOSOPHY
BY
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JULY 2017

DECLARATION BY THE CANDIDATE

This is to declare that the thesis entitled **"PROSPECTIVE STUDY OF INTRACTABLE EPILEPSY -A CLINICAL CONNENDRUM"** is based on the results of the work carried out by me for the degree of DOCTOR OF PHILOSOPHY under the supervision and guidance of Professor **Dr.A.V.Srinivasan,** Professor Emeritus, The Tamilnadu Dr.M.G.R. Medical University, Chennai. This work has not formed the basis of any associateship, fellowship, degree or diploma of any other university. This thesis was written on the basis of regulations prescribed by The Tamilnadu Dr. M.G.R.Medical University, Chennai, and Tamilnadu, India.

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Dedicated To
My Parents & Teachers

ABBREVIATIONS

ABC	-	ATP binding cassette
ADC	-	Apparent Diffusion Coefficient
BDNF	-	Brain-derived nerve growth factor
BGT	-	Bender-Gestalt Test
CE	-	Chang EF
CNS	-	Central nervous system
CPS	-	Complex partial seizures
CT	-	Computerized tomography
DTWI	-	Diffusion Tensor Weighted Imaging
FA	-	Fractional Anisotropy
FCD	-	Focal Cortical Dysplasia
FCSC	-	Focal cortical-subcortical calcifications
FLAIR	-	Fluid attenuated inversion recovery
GABA	-	Gamma aminobutyric acid
GAD	-	Glutamic acid decarboxylase
GEFS	-	Generalized Epilepsy with Febrile Seizure
HS	-	Hippocampal sclerosis
IBE	-	International Bureau for Epilepsy
IHI	-	Incomplete hippocampal Inversion
ILAE	-	International League Against Epilepsy
I.Q	-	Intelligent Quotient

M.Q	-	Memory Quotient
MAPK	-	Mitogen activated protein kinase
MCD	-	Malformations of cortical development
MDR	-	Multiple drug resistance
MRI	-	Magnetic Resonance Imaging
MTS	-	Mesial temporal sclerosis
SNPS	-	Single nucleotide polymorphisms
SPS	-	Simple partial seizures
TCA	-	Tricarboxylic acid
TLE	-	Temporal lobe epilepsy
TLR	-	T like receptors
VFO	-	Very fast oscillation
VGSC	-	Voltage-gated Sodium channel

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CERTIFICATE OF APPROVAL

To
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Professor and Head
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Dear Dr. R.M. Bhoopathy M.D.,DM

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the project entitled "The Clinical Conundrum of Intractable Epilepsy" No. 40062011.

The following members of Ethics Committee were present in the meeting held on 24.06.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. V. Kanagasabai MD Dean, Madras Medical College, Chennai-3,	-- Deputy chairman
3.	Prof. A. Sundaram, MD Vice Principal , Madras Medical College, Chennai -3	-- Member Secretary
4.	Prof R. Sathianathan MD	-- Member
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9.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	-- Layperson
10.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
11.	Tmt. Arnold Soulina	-- Social Scientist

We approve the project to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

CERTIFICATE - II

This is to certify that this dissertation work titled **"PROSPECTIVE STUDY OF INTRACTABLE EPILEPSY - A CLINICAL CONNENDRUM"** of the candidate Dr. R.M. Bhoopathy with registration number Ex.II(1) / 45099 / 2011 for the award of Ph.D. Degree in the branch of Neurology. I personally verified the urkund.com website for the purpose of Plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 7 percentage of plagiarism in the dissertation.

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1. INTRODUCTION

1.1. Definitions

Epilepsy is a 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. Epilepsy is defined as a disease with either recurrent unprovoked seizures (ie, two or more unprovoked seizures occurring atleast 24 hours apart) or a heightened tendency towards reccurent unprovoked seizures (ie, single seizure accompanied by evidence from clinical electroencephalography or neuro imaging tests that a heightened risk (at least 60%) exist for furture seizures over the next 10 years), or when an epilepsy syndrome is diagnosed. (International League AgainstEpilepsy (ILAE), 2014)[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 is reported to affect approximately 3 million Americans and 50 million people around the world[210]. People with epilepsy suffer from brain damage resulting in a neurological deficit. Further, it leads to changes in social, occupational and behavioural aspects of individuals who have epilepsy causing devastating economic consequences. All the more it is evident 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 protocol[4]. In western countries prevalence of intractable epilepsy in adults was reported to be 5.4 per 1000 population [5] which is comparable to that of the present 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 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). The prevalence of intractable epilepsy was reported to be ranging from 20 to 30% among patients with epilepsy in South India [9], but the actual studies estimating the prevalence of intractable epilepsy is unknown [10].

1.3. Predictors of intractable epilepsy

There are various predictors of intractable seizures in India as 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 antiepileptic 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 milestones, high initial seizure frequency of more than one per month, partial seizure type, febrile seizures and age of onset before fourteen years [11]. In western countries, high frequency of 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 [12].

1.4. Types of seizures and its clinical characteristics

International League Against Epilepsy (ILAE) have 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 [13]. 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 [13].

1.4.1. Focal seizure

Focal seizure or partial seizures can present with many different forms. It depends on which area of the cortex is involved and how it spreads to other areas of the brain. Focal seizures can be of Simple partial seizures or complex partial seizures [14].

1.4.1.1. Simple partial seizure

Simple partial seizures (SPS) are focal seizures without the involvement of consciousness. Clinical characteristic of SPS includes the clonic activity of one hand or leg. It can spread to the other motor areas of the motor strip. This is called as Jacksonian seizures. After the seizures, post-ictal weakness (Todd paralysis) may occur for few minutes to hours.

Clinical symptoms of SPS include:

- Epilepsia partialis continua is a continuous focal motor seizure confined to particular body part usually clonic movements present for many days without alteration in the level of consciousness.
- Motor speech arrest or vocalisation –arise from language area. Versive seizure-dorsolateral frontal cortex (frontal eye feels). Clonic seizures arise from the supplementary motor area. In addition, the asymmetric posturing of the contralateral arm, externally rotated, abducted, elevated and turning of head contralaterally could also occur.
- Simple partial seizures can also have autonomic symptoms like vomiting, sweating, piloerection, pupillary dilatation, pallor, flushing, borborygmi and incontinence of urine.
- Simple partial seizure with somatosensory symptoms – seizures arise from postcentral gyrus will present as focal paresthesias, numbness, warmth and electrical shock-like sensation. It may spread like Jacksonian presentation. It also arises from a secondary sensory area that lies above the Sylvian fissure anterior to the precentral gyrus. It is characterised by the more widespread involvement of the sensation (contralateral, ipsilateral and bilateral involvement)
- Sensory seizures-originates from the supplementary sensory area which is just

posterior to the supplementary motor area. Tingling, the desire for movement, feeling stiff, pulling, pulsing and heaviness also can occur. Sensory seizures arise from insular cortex presenting as symptoms involving nasopharyngeal, laryngeal regions such as paresthesias, warmth, tightening at throat or sense of strangulation and suffocation are also reported.

- Special sensory symptoms include visual, auditory, gustatory, olfactory and vertiginous attack can be due to simple partial seizures. Each symptom may arise from the corresponding area of the cortex. Visual symptoms from primary or association visual cortex. Auditory symptoms arise from Heschl's gyrus. Olfactory seizures originate from uncinate gyrus or medial temporal region. Gustatory sensation originates from temporal lobe insula and parietal operculum. Vertiginous symptoms originate from the lateral temporal region. A disturbance of higher cortical function in the form of psychic symptoms can present as a simple partial seizure. Dysphasic symptoms presenting as expressive or receptive language dysfunction, repetition of words or phrase is called epileptic palilalia. Dysmnesic symptoms such as memory distortion may be a form of simple partial seizure.

1.4.1.2. Complex partial seizure (temporal and extratemporal)

Complex partial seizures (CPS) are defined as partial seizures with impairment of consciousness. They may present as SPS that may be an aura, and progress to complex partial seizures with the manifestation of CPS. Patients may develop complex partial seizures from early childhood to any point of time in human life. Genetic factor and congenital anomalies cause early onset of CPS. Acquired anomalies like stroke, neurodegenerative disorders can cause CPS at an older age. Trauma, infections can give

rise to the remote onset of epilepsy [15].

Usually, CPS arises from frontal lobe or temporal lobes and rarely from occipital and parietal lobe. They can be further divided into temporal lobe epilepsy (TLE) or extratemporal lobe epilepsy. Temporal lobe epilepsy is the commonest form of focal epilepsy which may be of two types: 1) medial temporal lobe epilepsy and 2) lateral temporal (neocortical) epilepsy.

Clinical features of CPS may have different forms. It depends on which area of cerebral cortex is involved in the onset and propagation of the electrical discharge to the other areas of cerebral cortex. The patient may have motor, autonomic, somatosensory, special sensory or psychic symptoms. It may be an aura that will reveal the location of the seizure onset zone.

Following auras may be partial epilepsy or initial manifestation of CPS:

- Déjà vu - An illusion of a familiar memory
- Jamais vu - a familiar visual experience becomes unfamiliar
- Déjà entendu - an auditory illusion of something familiar
- Jamais entendu - a familiar auditory experience becomes unfamiliar
- Autoscopy - seeing oneself in external space as if the mind has left the body
- Depersonalization - a feeling of unreality in one's sense of self, feeling as if in a dream or watching oneself act.
- Macropsia/micropsia - objects appear larger or smaller than usual
- Macracusia/micracusia - sounds are louder or softer than usual

1.4.1.3. Temporal lobe epilepsy

Clinical feature of medial temporal lobe epilepsy is one of the very well known types of epilepsy described in the literature. Usually, occurs in adolescence or early adulthood. History of prolonged febrile seizures [16] may be involved in hippocampal sclerosis (HS) which is the cause for mesial temporal lobe epilepsy (TLE). Atrophy and gliosis of the hippocampus will be the marker for hippocampal sclerosis. The other causes for medial temporal lobe epilepsy are cavernous hemangiomas, gliosis and encephalomalacia secondary to past trauma/ injury, inflammation and infarction. Sometimes tumors such as Dysembryonic neuroepithelial tumors can cause medial TLE.

The temporal lobe epilepsy is divided into two:

1. lateral temporal lobe epilepsy (Neocortical)
2. Medial temporal lobe epilepsy

Familial forms of medial TLE are usually responding to the drugs, the imaging studies will be normal, exact genetic mutation is not known. Lateral or neocortical TLE-less common than Medial TLE and less well defined. The symptomatology associated with LTLE is varying and it depends on the location of the seizure onset. Medial TLE can present with auras which include psychic sensations, gastric sensation, fear or olfactory symptoms.

In Medial Temporal lobe epilepsy, loss of consciousness happens immediately after aura. The oral and manual automatisms with mild unawareness are seen in patients with dominant temporal lobe seizures, but in cases of non-dominant temporal lobe seizures, manual automatisms with intact awareness are seen. Dystonic limb posturing is the sign of seizure onset from medial temporal lobe contralateral to the dystonic limb. In non-dominant temporal lobe seizure, ictal spitting, vomiting, and urinary urge are seen.

The seizure lasts for 60-90 seconds followed by confusion or disorientation, especially in dominant temporal lobe seizures. Postictally language dysfunctions are also seen in dominant temporal lobe seizures. Medial temporal lobe seizures rarely end in secondary generalization, but it is common in the neocortical temporal lobe or extratemporal lobe epilepsy. There are several clinical features helps to localize the temporal lobe focus irrespective of the dominance. They are post-ictal nose wiping, ictal unilateral eye blinking and piloerection. The hand that wipes the nose first after the seizure is typically ipsilateral to the seizure focus. Preserved awareness and minimal post-ictal symptoms always delay the clinicians to make a diagnosis of non-dominant temporal lobe seizures. The patient may not be aware of the seizures because the symptoms are trivial.

The onset of a seizure in these areas will give rise to the specific aura, ictal manifestations, and post-ictal automatism. The latent and silent periods implies the progressive course of temporal lobe epilepsy which involves the cognitive functions of the brain, such as memory and intelligence impairment [17,18]. The clinical features of temporal lobe epilepsy can be categorized into subjective and objective type.

Subjective features of TLE & stages of presentation

1. Aura - 9% of patients with temporal lobe epilepsy will have an aura. Aura may be of the psychic, perceptual and dysmnesic phenomena. Epigastric rising sensation, fear, anxiety, and other emotional sensations suggestive of the involvement of amygdala are the common auras seen in TLE.
2. Pseudo-absence – motor arrest, impairment of awareness and responsiveness.
3. Automatisms – Oro alimentary, manual (fidgeting), ipsilateral upper limbs automatism, the contralateral posturing of upper extremities, ictal speech arrest (non-dominant), ictal anomia, post-ictal dysphasia (dominant), unilateral eye

blinking, spitting.

In the genetic form of neocortical epilepsy, there are two forms of genetic epilepsy. Autosomal dominant lateral temporal lobe epilepsy or autosomal dominant partial epilepsy with auditory symptoms, Sporadic form of lateral temporal lobe epilepsy with auditory symptoms. They will be presenting with auditory aura and other sensory auras frequently going for secondary generalization. The above forms of epilepsy have a good prognosis and they will very well respond to drug treatment.

1.4.1.4. Frontal lobe epilepsy

It is the second most common type of focal epilepsy. The symptoms of frontal lobe epilepsy depend upon seizure onset zone at the frontal lobe. Seizures are often short, usually presenting with motor symptoms during sleep.Postictally, the patients with frontal lobe seizures, recover quickly with normal cognition. Patients may be presenting with paresis or paralysis of the limbs. Frontal lobe seizures are brief and bizarre. They may be misdiagnosed with psychogenic nonepileptic seizures. It is always confused with temporal lobe epilepsy because these patients with frontal lobe epilepsy often present with symptomatology of staring, unresponsiveness and late motor manifestation, versive head or eye movements and complex automatism.

The ictal clinical manifestation of frontal lobe seizures depends on the region of the frontal lobe where it arises [15,19,20]. In areas of Prerolandic or primary motor cortex, the ictal manifestations may be focal motor seizures, with or without the Jacksonian march, speech arrest, dysphasia, and vocalisation. If epilepsy arises from Supplementary sensorimotor area located on the Brodmann area 6, medial or dorsal aspect of the frontal lobe, patient will have bilateral sensorimotor symptoms because of its bilateral

representation. Ictal manifestations may present with focal asymmetric tonic posturing, versive movements of head and eye, speech arrest, vocalisation and fencing seizures, bilateral asymmetric tonic seizure (tonic flexion of one arm and extension of the other with or without tonic leg involvement). These type of seizures are always partial even though there are bilateral motor manifestations with retained awareness. In patients with involvement of Dorsolateral prefrontal lobe, they may present with focal tonic-clonic activity, versive movements of head and eye, speech arrest or dysphasia. Patients with epilepsy involving orbitofrontal regions, ictal manifestations present with complex motor automatism, olfactory hallucination, illusion, autonomic features, bicycling movements involving the legs or windmilling movements in the arms.

Patients with epilepsy involving anterior frontopolar regions may present with the versive movement of head and eyes, forced thinking, initial loss of contact and absence like attack or motor arrest, bicycling in the legs or windmilling movements in the arms. Patients with epilepsy involving opercular region can have ictal presentations with Mastication, salivation, swallowing, laryngeal symptoms, speech arrest, aphasia, epigastric aura, fear, autonomic features, facial clonic activity or gustatory hallucination. If the cingulate area is involved, they may present with fear, vocalisation, emotional or mood changes, complex motor automatism and autonomic features. If negative motor cortex (posterior aspect of the inferior frontal gyrus or near the supplementary sensorimotor area)is involved, they may present with an inability to move a limb or a body part. Clinical characters of frontal lobe epilepsy are brief motor seizures, stereotyped movements occur multiple times at night, normal intelligence and normal neurological examination between the attacks. Family history also reported being positive.

1.4.1.5. Parietal lobe epilepsy and occipital lobe epilepsy

Occipital or parietal lobe seizures are difficult to diagnose with specific clinical symptoms because of the extensive and complex connection between the two lobes. Usually, visual symptoms are elementary visual auras and are more common in occipital lobe epilepsy. Ictal blindness, blinking and ocular movements are also experienced. Visual scenes or objects during ictus suggest spreading of discharge from the temporo occipital region. Seizure generating from temporal lobe below the calcarine sulcus are reported to spread to the temporal region with complex partial symptomatology. Foci above the calcarine sulcus are reported to spread to the parietal and frontal lobe. Parietal lobe seizures present with somatosensory auras contralateral to the seizures focus. Sometimes it may be bilateral also. This will spread to the premotor and temporo-occipital region [20–22].

EEG investigations may show interictal spikes and focal slow waves not only at parietal or occipital region but also seen at temporo-frontal regions because of increased synaptic connections. False localizing EEG findings are reported to be observed at the midline with parietal and occipital foci. Malformation of the cortical development and tumors are the common pathology seen in parieto-occipital lobe epilepsy.

1.4.1.6. Insular lobe epilepsy and cingulate lobe epilepsy

Focal epilepsy arising from insular cortex is uncommon, but symptoms involving insular region are a contraction or choking sensation at the oropharynx and the larynx .Painful sensory aura in the throat may be due to seizure originating from cingulate or insular cortex. In these patients,invasive EEG may confirm the diagnosis. MRI of this region may help us to find out the structural pathology in this area [23].

1.4.2. Generalized seizure

Generalized seizures are a group of seizures that present with various clinical manifestations and loss of consciousness [14]. There are different types of generalized seizures as follows:

1.4.2.1. Absence seizure

Absence seizures are characterized by sudden behavioral arrest, stare and unresponsiveness and brief rotation of the eyes upward for few seconds to half a minute with abrupt cessation of symptoms. The patient will be fully conscious and continue his/her activity what he/she was doing prior to the seizure onset.

There are five subtypes of absence seizures reported in literature

1. with impairment of consciousness only.
2. with mild clonic components.
3. with atonic components.
4. with tonic components.
5. with automatism.

Absence seizures may present with mild clonic components and clonic movements of the eyelids, corner of the mouth and the upper extremities at the frequency of 3 Hz which causes the head to drop, trunk to slump forward, the arms to drop or the grip to relax and falls are rare. Tonic muscle contraction of the neck extensor and the trunk muscles leads head to extend and trunk to arch causing retropulsion. Absence with automatism includes lips licking, chewing, lips smacking, swallowing, grimacing, smiling, yawning, fumbling with the hands, picking, scratching, rubbing or aimless walking. Absence seizures with autonomic phenomena are another subtype with signs of

tachycardia, pallor, flushing, piloerection, salivation or urinary incontinence. Complex absence seizures are a mixture of clonic, atonic, tonic, automatic and autonomic symptoms with absence features. Usually, the clinical events may be induced by hyperventilation and less commonly with photic stimulation in the laboratory. EEG may show 3 Hz generalized monomorphic spike and wave discharges with abrupt onset and termination [24].

1.4.2.2. Generalized tonic-clonic seizure

Also known as grand mal seizures characterized by abrupt loss of consciousness followed by tonic contractions of the muscles and leads to ictal cry. The ictal cry is due to the forceful expiration of air against closed glottis. The mouth is tightly closed leads to tongue bite, pupils are dilated, eyes are deviated upwards. Upper limbs are abducted and flexed at the elbow. Lower limbs are briefly flexed and then extended and later abducted with toes pointed. Clonic activity are initially rapid and then slows. Gasping respiration occurs if the respiratory muscles are involved in the clonic activity. Sometimes the patient may become cyanotic. Incontinence of urine may occur. The patient may become unconscious for a brief period.

A tonic-clonic seizure may be manifested as focal seizure, may arise from other generalized seizures or occur during secondary generalization of a partial onset seizure. Primary generalized epilepsy may be bilaterally symmetric or involve a forced head deviation to either side. In secondary generalized partial onset seizures, the contralateral arm extends and the ipsilateral arm flexes at the elbow and it occurs with the legs also. Tonic-clonic seizures may lead to injuries such as burns, head injuries, vertebral compression, fractures, shoulder dislocations, tongue and cheek lacerations [25].

1.4.2.3. Myoclonic seizure

Myoclonic seizures are generalized seizures characterized by brief, irregular, shock-like jerks of the head, trunk or limbs. They can be symmetric or asymmetric and involve the whole body, regions of the body or focal areas. Myoclonic seizures can be sometimes idiopathic generalized epilepsies, symptomatic generalized epilepsies, progressive myoclonic epilepsies and infantile spasms. Myoclonus may be positive or negative. Negative myoclonus refers to the brief loss of postural tone when the body part is held against gravity. Consciousness is not impaired and no postictal confusion occurs after single myoclonic jerks. Myoclonic seizures can occur in clusters and evolve into clonic-tonic-clonic seizures with resultant loss of consciousness and postictal confusion. The ictal EEG pattern is characterized by brief generalized poly spike or polyspike and wave discharges that correspond to the myoclonic jerk [25,26].

1.4.2.4. Tonic seizures

Tonic seizures involve tonic contraction of the face, neck, axial or appendicular musculature lasting from 10 sec to 1 min involving extension or flexion of the muscles and often lead to falls and head injuries, upward eye deviation. Usually seen in patients with symptomatic generalised epilepsy, Lennox-Gastaut syndrome, and myoclonic-astatic seizures. The ictal EEG usually shows a brief generalised attenuation of cerebral activity followed by generalised paroxysmal fast activity at a beta frequency range [26].

1.4.2.5. Clonic seizures

Clonic seizures are generalised seizures characterised by repetitive rhythmic clonic jerks (1Hz to 2Hz) with impairment of consciousness and a short postictal phase. They can lead to a clonic-tonic–clonic seizure. Repetitive discharges are due to rhythmic excitatory discharges from the cortex. The ictal EEG shows polyspike and wave

discharges or generalised fast activity [26].

1.4.2.6. Atonic seizures

Atonic seizures are characterised by sudden loss of muscle tone, head drop, limb drop or a drop of the whole body, loss of consciousness and injuries occur particularly to face. Tonic seizures last less than 5 seconds and are followed by minimal postictal confusion. The criteria distinguishing between negative myoclonus, atonic seizures, and some atypical absences need to be developed. Atonic seizures are usually seen in symptomatic generalised epilepsies, such as Lennox-Gastaut syndrome. The ictal EEG typically shows a generalised high voltage spike and wave or slow wave followed by a generalised attenuation of cerebral activity or low voltage paroxysmal fast activity [26].

1.4.2.7. Unclassified epileptic seizures

Those seizures that will not come under classification because of incomplete data are classified as Unclassified epileptic seizures. For example, during infancy chewing, swimming movements, eye movements, jittering and apneic spells are not typed under specific forms of seizures. These phenomena with epileptic seizures are yet to be classified [26].

1.5. Aetiology of refractory epilepsy

Various causes have been reported in the literature. Malformations of cortical development, head injury, cerebrovascular disorders, central nervous system (CNS) infection, pre and perinatal factors, CNS malformation, chronic alcoholism, encephalopathy, cerebral tumor, degenerative diseases, autoimmune diseases, calcification, gliosis, cerebral atrophy, and other causes are often associated with intractable epilepsy. Epilepsy is reported to be due to perinatal problems (48%) and sequelae of central nervous system infection (24%) and was idiopathic in 20% [27]. ILAE

Commission recommends using terminologies genetic, structural-metabolic, and unknown causes to represent and replace symptomatic, and cryptogenic causes of epilepsies [13].

1.6. Pathophysiology of intractable epilepsy

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 understood. Hence various hypotheses have been postulated. They are target hypothesis, transporter hypothesis, gene variant hypothesis and neural network hypothesis [28].

1.6.1. Hypothesis for intractability

1.6.1.1. Target hypothesis

Acquired alterations to the structure and functionality of target ion channels including neurotransmitter receptors. It explains how acquired structural and functional change at the target ion channels and neurotransmitter receptors lead to intractable seizure [29]. Most of the antiepileptic 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-aminobutyric acid (GABA-mediated inhibition) are very important to increase the inhibitory potential.

T –type Ca2+ channels are expressed at the postsynaptic region, not present at the presynaptic regions are acted on by the particular AED and inhibit postsynaptic excitatory influence, thus preventing the depolarization of the epileptic neuron. Any modification in these receptors either due to genetic or acquired causes reduces the

efficacy of given AED at the target level due to the following factors:

1. Down-regulation of the voltage-gated Na+ channels, β subunits,
2. altered α subunits expression,
3. induction of neonatal Na+ channels II and III α isoform mRNAs,
4. Changes in GABA-A receptors decrease in α 1 subunits and increase of α 4subunits,resulting in reducing GABA and benzodiazepines affinity for their receptors.

Thus modification of specific targets occurs and this results in seizure activity.

Mechanism of excitotoxic neuronal cell death and development of intractable epilepsy.

The GABA and Glutamate are the two important biochemical markers involved in epilepsy. It is very well known how GABA and glutamate are produced. Glutamate is a neuroexcitatory and GABA is a neuroinhibitor. The dynamic balance between these two neurotransmitters leads to the normal function of the brain. The imbalance between these two neurotransmitters results in seizures. The increase of excitatory neurotransmitter (glutamate) at the extracellular level of the receptors results in over-excitation of neurons. Thus these excited neurons unable to recover from the tonic excitation and results in death of the neurons .The neuronal death leads to permanent injury and it paves the way for seizure activity resulting in intractable epilepsy.

The C junction N –terminal kinases (JNKs) are members of mitogen activated protein kinases (MAPKs) family. It is activated by neurotoxins such as kainic acid, beta amyloid, and nitropropionic acid.Thus activation of JNKs results in increased neuronal excitation and cell death. Experimental evidence confirms drugs blocking the access of

the enzyme C JNKs to their substrate C JUNCTION may offer neuroprotection and prevent cell death. Thereby AED may be developed in future targeting the JNKs activity over the C junctions.

Genes and intractable epilepsy

Alterations of Sodium Channel

Genetic, epigenetic and exogenous factors lead to alterations at the site of action of the drugs. The genetic drug resistance is due to mutations in genes encoding the specific receptors. For example, voltage-gated Sodium channel (VGSC) subunits. They are SCN1A gene located at chromosome 2q24.3 linked to myoclonic epilepsy of infancy or Dravet Syndrome and Generalized Epilepsy with Febrile Seizure Plus (GEFS+). In SCN1A gene exon 5 encodes for one of the four voltage-sensitive channel, the 1-S4 domain. There are two versions. One is neonatal (N) and another one is an adult (A) which differ in three amino acid components. Polymorphism of SCN2A gene encodes for alpha 2 subunit of the neuronal sodium channel. Mutations in the gene encoding for beta1 subunit has been linked to GEFS+.

Alteration of Voltage-Dependent Calcium (Ca+) Channels

Repeated seizures promote transcriptional or post-transcriptional changes leads to structural changes in Voltage-Dependent Calcium (Ca+) Channels (VGSC). Voltage-gated calcium channel VGCC are excitatory. The T- type calcium channels are low threshold Ca^{2+} channel involved in thalamocortical discharges and also involved in the pathophysiology of absence seizures. The alpha 1G subunit of the T-type calcium channel is related to the generation of spike and wave discharges, whereas the alpha1 subunit has no physiological property. The imbalance in the distribution of alpha1 and alpha 1G subunit in the T calcium channel reduces the responses to anti absence AEDs.

Alteration of GABA channels

GABA is an inhibitory neurotransmitter in the adult brain. There are two GABA receptors. GABA A and GABA B. GABA-A is the binding sites for benzodiazepines and barbiturates. GABA-A channels have seven different subfamilies (α, β, γ, δ, π, θ and ρ).

Changes in the composition of the channel may lead to its role and sensitive to AEDs. Molecular and functional studies reveal the transcriptional changes occur in the alpha subunit of the GABA-A receptor which decreases in the alpha1 subunit expression and increases in the alpha 4. Pathogenic alteration or mutation in genes and structural abnormalities in chromosomes (insertions and deletions) result in varieties of epilepsies most of them are drug-resistant.

GABA system abnormalities in intractable epilepsy:

GABA system is a ubiquitous system, and some different genes regularise the genesis of various receptors subunits, interacting proteins, transporters, synthesis and metabolism of enzymes. GABA is synthesised by decarboxylation of glutamate by glutamic acid decarboxylase (GAD). GAD exists in two forms; GAD65 and GAD67. Degradation of GABA requires GABA-transaminase (GABA-T) to convert GABA to succinic semialdehyde (SSA) by transamination with the co-substrates glutamate and alpha-ketoglutarate (alpha-KG). SSA is subsequently oxidised by SSA dehydrogenase (SSADH) to succinate, a constituent of the tricarboxylic acid cycle (TCA). Inhibition of GAD, the GABA-synthesizing enzyme, is known to produce seizures [30].

Since glutamic acid decarboxylase is dependent on pyridoxal phosphate as the coenzyme, carbonyl trapping agents like derivatives of hydrazine are convulsant in

nature (Tapia and Pasantes, 1971). At the nerve terminal, GABA can be released into the synaptic cleft by two different pathways. 1. Calcium-dependent vascular release or calcium-independent release via transporter reversal. The release of GABA at the synaptic cleft mediates its action via two classes of receptors, ionotropic GABAa receptors and GABAc receptors and metabotropic GABAb receptors. Unlike GABAa and GABAb which form chloride channel and are involved in fast synaptic inhibition. The $GABA_b$ Receptors are guanine nucleotide binding (G) protein-coupled receptor that modulates calcium and potassium channels and elicits both presynaptic and slow postsynaptic inhibition. After dissociation from the receptors complex, GABA is transported back into presynaptic nerve terminal or surrounding astrocytes via the GABA transporter system thereby terminating the GABA's inhibitory action. Neuronal GABA transport system is more efficient than astrocytic GABA transport system. The deregulation of GABA is by the enzymes GABA transaminase and succinic semialdehyde dehydrogenase yielding succinate. GABA transaminase is located in both neurons and astrocytes with the highest activity in the neuron. GABAa receptors are pentameric complexes of subunits form an integral anion channel permeable to chloride and bicarbonate ions.

GABAa receptors are composed of two alpha subunits which in turn are presented in 6 isoforms (α1 to α6) that contribute to the binding site of GABA [31,32] and β subunits with 3 isoforms, i.e., β1, β2S, β2L and β3 and one γ subunits (γ1,γ2S,γ2L and γ3). This different combination of isoforms and their assembly determines the properties of GABAa receptors, i.e., affinity for gamma-aminobutyric acid (GABA), allosteric modulation, interactions with intracellular proteins, the probability of channel opening, kinetics and conductance. Hence changes in the composition of the receptors subunits appear to affect the function of GABAergic neurotransmission. GABAergic system

modulating synaptic excitability and plasticity in the cerebral cortex generating rhythmic activity in cortico-thalamic circuits relying on primary afferent input to the spinal cord and brain stem and modulating the activity of dopaminergic and other monoaminergic neurons. These Receptors have been implicated in neurologic and psychiatric disorders. For example - Absence seizure and autoimmune limbic encephalitis fast synaptic GABAergic transmission rely essentially on chloride- fluxes through GABAa receptors for which the maintenance of electrochemical chloride gradient is crucial to determine a GABA-mediated neuronal effect. Changes in neuronal Chloride homoeostasis affect GABAa receptors mediated transmission and may contribute to epileptic activities.

The cation chloride transporters (CCCs) regulates cellular volume and play a crucial role in the cellular electrochemical Cl- gradient. Functionally CCCs are grouped into three types:

1. NKCC1, NKCC2 (cotransport Na+/ K+/2Cl-) towards the inside of the cell.
2. KCC-14(K+/Cl-) towards outside of the cell.
3. NCC (Na+/Cl-) towards inside of the cell.

All CCCs are expressed in neurons or glial cells or both.

NKCC2 exclusively expressed in neurons and responsible for maintaining neuronal electrochemical chloride gradient. In an immature neuron, the level of NKCC1 is higher than KCC2, and thus the intracellular chloride concentration is higher than the extracellular chloride. GABAa receptors activation induces membrane depolarization and neuronal excitation throughout chloride efflux. The opposite reaction occurs in the mature neuron. The level of KCC2 is higher than NKCC1. Thereby GABAa Receptors activation leads to neuronal inhibition.

In temporal lobe epilepsy, alteration in subunits architecture of GABA receptors noted in hippocampal tissues resected from TLE and non-TLE patients compared with controlled tissues at autopsy. These findings are also found in cortical dysplasia with intractable seizures. Changes in relative expression of NKCC1 and KCC2 may be the contributing factor for epileptiform activity in the subicular region adjacent to sclerotic areas of the hippocampus.

Genetic abnormalities in GABA Receptors in intractable epilepsy:

Changes in GABAa receptors subunit genes have been linked to different types of idiopathic and cryptogenic epilepsies that are drug resistant. The following genetic alteration of GABA receptors has been studied that is

1. Coding sequence missense mutations
2. Coding sequence nonsense mutations
3. Coding sequence frameshift mutations
4. Non-coding sequence mutations (intronic or 5 upstream)

GABA receptors mutations associated with changes in receptor function (impaired channel gating) imparting receptors biogenesis, (impaired subunit messenger RNA transcription, and stability subunit holding, stability or receptors trafficking. The following genes have genetic alterations which are associated with human refractory epilepsy.

1. GABA aminobutyric acid A receptor alpha1 gene
2. GABA aminobutyric acid A receptor delta gene
3. GABA aminobutyric acid A receptor gamma2 gene
4. GABA aminobutyric acid receptor beta 3 gene
5. GABA aminobutyric acid B receptor 2 gene

Modulation of the GABAergic function is very important in epilepsy treatment. It gives rise to changes in sensitivity of recognition of the binding site and alterations in the GABA binding and thereby agonist activity is established. It is very important to understand the biomolecular physiology of the neuronal GABA system to develop newer drugs in future.

1.6.1.2. Transporter hypothesis

Transport hypothesis states that intractability of seizure occurs due to an inadequate entry of AEDs across the blood brain barrier. It explains how the distribution, metabolism, and elimination of antiepileptic drugs depend on the pharmacokinetic process by which the drug reaches the appropriate target regions which are very crucial for the seizure control. This pharmacokinetics of antiepileptic drug is being affected by special proteins such as p glycoprotein, breast cancer resistance protein and multidrug resistance protein secreted at the cellular wall which is genetically determined. These are drug efflux transporters from the ATP binding cassette (ABC superfamily). The upregulation of this system leads to reduced bioavailability of antiepileptic drug at the epileptic zone leading to intractable epilepsy [33].

Molecular mechanism in intractable epilepsy

Several hypotheses have been proposed to describe molecular mechanisms in intractable epilepsy. Transport and target hypothesis as described above explain the pharmacodynamics in intractable epilepsy. Target hypothesis can explain possible mechanisms related to channels that lead to morphological changes of the same. Drugs may not be able to act due to changes in the morphology of the ion channels. Molecular alteration at the drug receptor sites may lead to a reduction in drug effectiveness and drug action. Transporter hypothesis suggests increased secretion of the efflux proteins

(p-glycoprotein) at the cellular wall which prevents the entry of AEDs from crossing the blood brain barrier and acting to stabilise the cell membrane. This may be due to increased expression of multiple drug resistance (MDR -1) genes. Overexpression of MDR protein either due to genetic causes or AEDs themselves induces the cells to secrete more drug efflux proteins. The above-said mechanisms are classical biological reactions involved in the brain during drug treatment in epilepsy. The pharmacodynamic response (PD) refers to the effects caused by drugs on individuals. The pharmacokinetic response (PK) refers to the concentration of active ingredients of the drugs administered (AED) in different body tissues or fluids, and it is the result of action exerted by the body on the administered molecules. The PK and PD play a major role in serum drug level and the clinical response of the individual to that particular drug. In intractable epilepsy overexpression of multidrug transporters not only caused by genetics and also by the administered antiepileptic drugs and sometimes spontaneously due to seizure activity itself. The resistance to multiple drugs could not be explained using single mechanism or hypothesis. A multidrug drug-resistant epilepsy model as adapted in cancer chemotherapy are reported to use in understanding the molecular mechanisms behind intractable epilepsy [36].

1.6.1.3. Gene variant hypothesis

An inherent resistance maintained by genetic variants of proteins involved in the pharmacokinetics and pharmacodynamics of AEDs action. The unpredictability in the efficiency of controlling seizures, adverse drug reactions and optimal doses required in individual patients when treating epilepsy with AED may be a consequence of genetic variation. The AED pharmacokinetics and pharmacodynamics are clearly due to genetic polymorphism. Single nucleotide polymorphisms (SNPs) and variations at a single site in the DNA are the most frequent forms of sequence variations in the human genome,and

it may affect the efficacy, tolerability and duration of action of AEDs. In both target and transporter hypotheses, the genetic variants pave the way for abnormal drug transport and alteration in the drug targets. Inherent severity disorder is the determinant of the treatment outcome. For example, a number of attacks in the early phase of the illness/disease leads to intractable seizure which may be due to factors operating at extracellular and intracellular level (intrinsic and extrinsic mechanism). The genetic basis [34] has a role in this mechanism.

1.6.1.4. 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 preventing the traditional antiepileptic drugs from entering their targets, eventually leading to intractable epilepsy"[35]. 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.

This hypothesis reveals that refractory epilepsy is a complex and multifactorial disease. 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 nonpharmacological ways to treat drug-resistant epilepsy effectively.

Role of neural network in 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 which lasts for few seconds to minutes and returns to normal state. From the review of literature two 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

Increased up-regulation and decreased down-regulation of the ionic channel and synaptic strength is the causes for the genesis of seizure. The homeostatic mechanisms possessed by neuronal network operate over different temporal and spatial scales. This is observed not only in neocortical cells but also in hippocampal pyramidal neurons. The synaptic strength is often balanced by long term potentiation and long term depression. The homeostatic mechanism of regulation of neuronal excitability is maintained by regulation of synaptic strength and ionic channels that translate changes in membrane potential into a pattern of action potential firing. Three main processes have been implicated in signalling pathways for synaptic scaling: a) brain-derived nerve growth factor (BDNF), tumor necrosis factor α (TNF α), and intracellular Ca^{2+}. Administration of BDNF can prevent the upscaling synaptic strength in vitro suggest a role of BDNF as a possible signalling molecule. The cytokine TNF α once released from the glial cells can also upscale the synaptic strength in neurons which was decreased by tetrodotoxin. Ca^{2+} that modulates the synaptic strength is disturbed in epilepsy leading to shifting in synaptic scaling involving both presynaptic and postsynaptic process.

Post deafferentation epileptogenesis plays a major role in post-traumatic epileptogenesis. The upregulation of excitatory synapses between pyramidal cells mediated by AMPA receptors, either with or without a concurrent downregulation of inhibitory synapses and upregulation of excitatory synapses. Deregulations of excitatory input due to ion accumulation, osmotic changes and cell swelling are sufficient to initiate the process of seizure.

All the mechanisms finally lead to form a seizure network, that is initiated by high-frequency firing in the pyramidal cell and axon plexus resulting in very fast oscillation (VFO).VFO is initiating factor for seizure activity.This depends upon the special extracellular condition such as alkaline state at the extracellular space, lowering of calcium, elevation of extracellular potassium to open the gap junction**.** It iswell-demonstrated in-vivo and in-vitro experimental studies. The activity of VFO in epileptic patients being recorded by using MRI [1, 17] in addition to EEG or electrocortical graphic recordings. The above information helps us to approach and treat intractable epilepsy prevention and effective management [3, 31].

Proteomics

Proteomics is a science that deals with proteome. A number of proteins expressed in a cell or in a tissue or in an organism which is determined by genes. It may be altered by cell or tissue or organism due to internal status, external stimulations or developmental changes [37]. The proteins are modified by phosphorylation, ubiquitination, palmitoylation, oxidation and post-translational modification. Proteomics is used to search for biomarkers associated with the disease. It is also used in agronomy researchers (sugarcane and wheat). In Neurology proteomics technology is applied to understand the cell mechanism is called as neuroproteomics or neuromics. The neuroproteomics helps

us to study proteome of brain fragments or single cell to determine the dynamics of subproteome under different conditions. Proteomics is a multi-disciplinary method which is based on principle, biochemical, biophysical and bioinformatics. Proteomics analysis has four basic stages: extraction, purification, separation and identification of proteins. This can be done by mass spectroscopy by using either digested peptide or intact proteins [38–40].

In epilepsy, the study of proteomics is used to identify biomarkers associated with epileptogenesis. There are several biomarkers such as Isoform 1 ofa serum albumin ALB, Heat shock-related 70 kDa protein -2(HSPA2), Dihydrolipoyllysine – residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial – dihydrolipoyl acetyltransferase etc, identified as potential proteins expressed in the hippocampus of patients with intractable epilepsy.

Autoantibodies

The central nervous system is protected from the infection by the blood-brain barrier and it is not equipped with the immune systems that are represented in most other organs. When the blood-brain barrier breaks down, immune cells from the vessels supplying the brain seep into the brain causing an inflammatory reaction. Lack of histocompatibility also is a factor which is unique to the brain cells. Microglial cells are considered as the macrophages of central nervous system. These cells participate in the expression of T like receptors cells (TLRs). TLRs will produce cytokines (interleukin 1,6,12, interferon type 1, and TNF-alpha). Microglial cells invade the brain forming a protective network of the potential effector cells throughout the CNS. Astrocytes are other CNS cells which are also involved in the immunological functions by suppressing T helper 1 and 2 cells activation, proliferation and effector functions of the activated T

cells. All these mechanisms lead to apoptosis of CNS cells. Astrocytes have a crucial role in formation and maintenance of the blood-brain barrier.

Inflammation of the CNS occurs in autoimmune reaction, epilepsy, trauma, infection and ischemia. The above-mentioned cells particularly the inflammatory cells are released in the CNS after the breakage of the blood-brain barrier. The TLRs are transmembrane proteins expressed by immunocompetent cells (APC cells- antigen presenting cells) are activated. The cells will release cytokines and chemokines, proteins of the complement system cyclooxygenase-2 and nitric-oxide synthase. An immune response in the CNS may be triggered by endogenous ligands that stimulate TLR.

The immune system is involved in the pathogenesis of certain type of epilepsy. Example the limbic encephalitis is a form of autoimmune encephalitis where the patient will be presenting with intractable epilepsy. This is evidenced by detection of elevated levels of the proinflammatory mediators in CSF and serum in patients with autoimmune encephalitis and some types of febrile seizures. The inflammatory activity is affected in different ways by an intractable seizure. When the seizure is intractable, increase in levels of interleukin 1,6,12, interferon type 1, and TNF-alpha is observed. In the case of Rasmussen encephalitis in addition to cell death due to CD8 and T cell mediated attack, the autoantibodies also found at the site of inflamed regions signifying various immunological mechanisms in addition to cell mediated destruction.

1.7. Structural abnormalities in intractable epilepsy

1.7.1. 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 [41]. 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 [42]. 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 [43–45].

1.7.1.1. Malformation of cortical development

Malformations of cortical development (MCD) are microscopic and macroscopic developmental abnormalities of the cerebral cortex that arise due to an interruption in cortical development during fetal development by genetic or environmental factors [46]. According to Barkovich classification, MCDs are 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 organisation [47]. Due to recent advances in Magnetic Resonance Imaging (MRI) used in patients with epilepsy, the fourth group of malformations of cortical development is added to Barkovich classical classification as "not otherwise classified".

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% [43,45,48]. In adults, the prevalence of intractability among patients with MCD is reported to be 84.8% [49] in a large series of patients with epilepsy (N=3000). With recent advancement in radiologic imaging techniques, the identification of MCD has increased significantly [46,50–53]. Studies carried out among MCD population revealed several developmental anomalies like focal

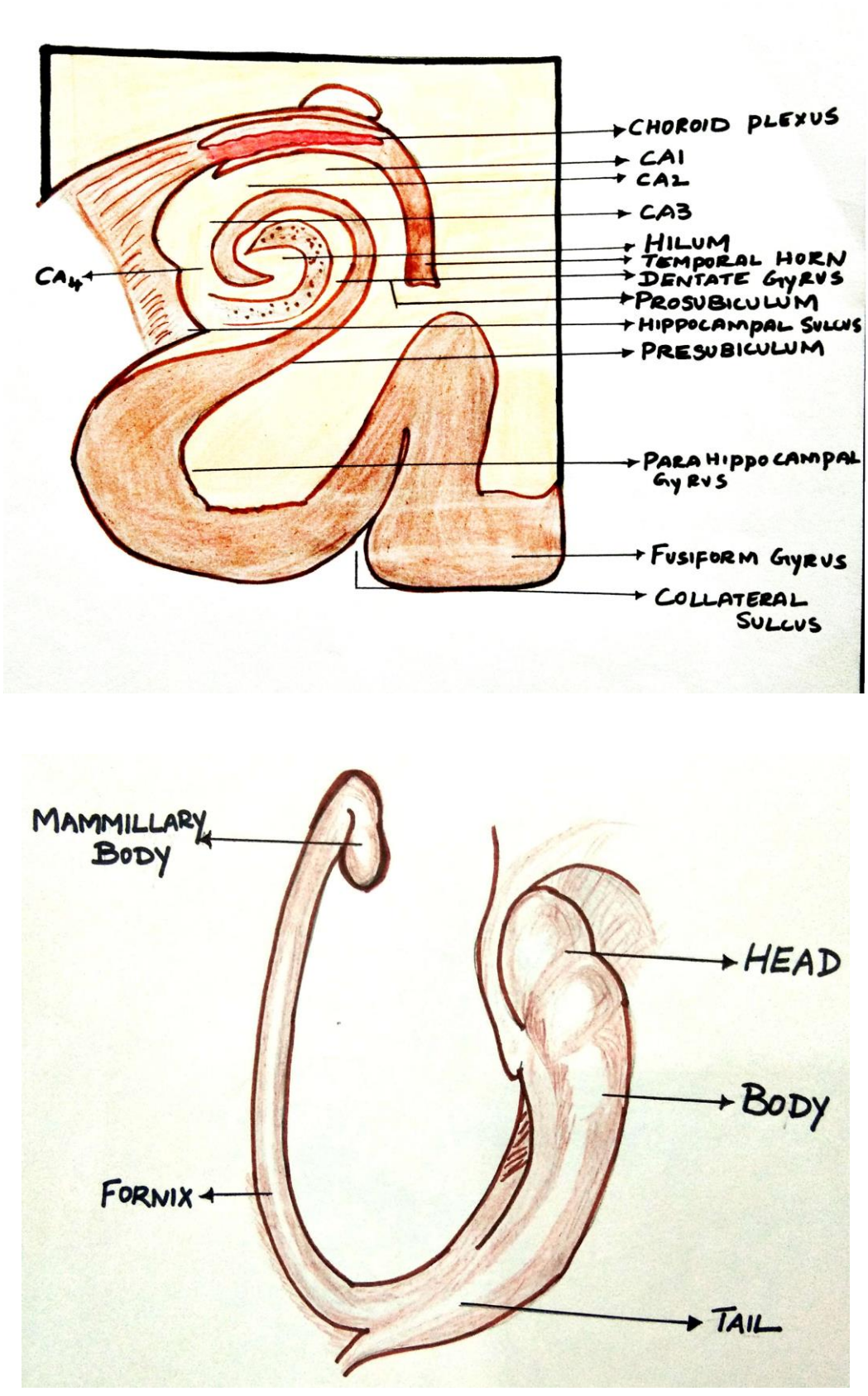


Figure 1: Pictorial representation of normal hippocampus and orientation head, body and tail

cortical dysplasia, Polymicrogyria, Lissencephaly, heterotopias, dysembryonic neuroepithelial tumor, Hemimegalencephaly and others [50,52,54]. Clinical features of MCDs are often heterogeneous. MCD exhibit seizures majorly complex partial seizure to any other form of seizures [49,52], family history [49,52], usually drug resistant and intractable [49,50], change in semiology [51], associated with febrile seizures [52], present with delayed motor or mental milestones [52,54], cognitive deficits and learning disability [49,55]. About a third of patients with MCD had hippocampal abnormalities like the hypoplastic hippocampus, hippocampal sclerosis, malrotation of the hippocampus, and enlarged hippocampus [55]. Febrile seizures with Focal Cortical Dysplasia (FCD) are reported to have dual pathology (FCD with hippocampal sclerosis) [51]. Many patients with FCD report initial seizure semiology as a tonic or generalised tonic-clonic seizure.

1.7.1.2. Incomplete hippocampal inversion

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 [56]. Normal hippocampus and its orientation of head, body and tail arepictorially represented in figure 1. 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 [57]. 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 [58]. The presence of IHI has been reported to be a marker of a more extensive disorder of brain development [57,58]. With the evidence of having IHI as a malformation of brain development, it would be a possible abnormality causing intractable epilepsy.

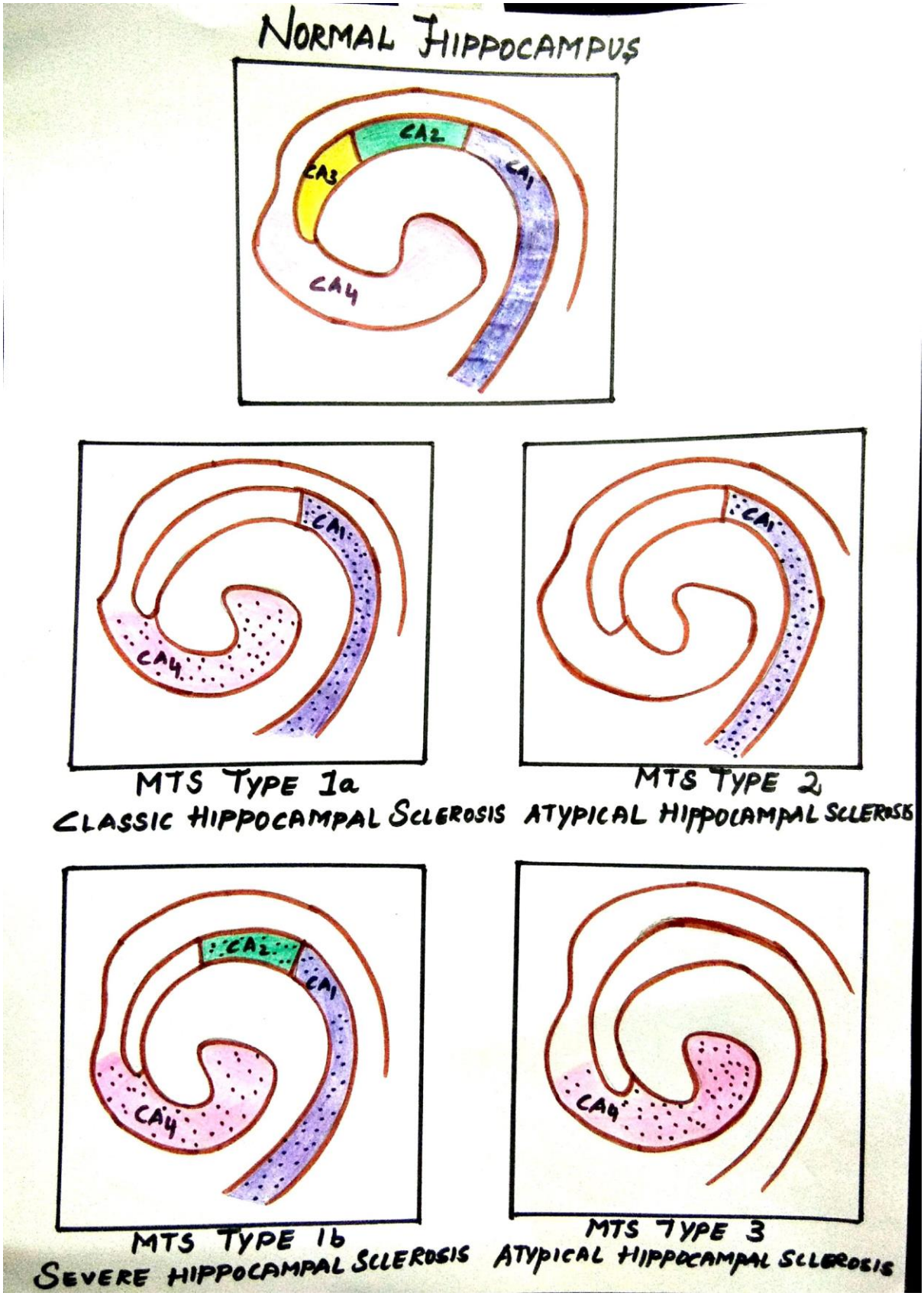


Figure 2: Pictorial representation of histopathological classification of MTS as described by Blümcke et al (2007). Dotted region indicate histopathological changes.

1.7.1.3. 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 [59–61]. Brain abnormalities especially MTS, either alone or in association with another lesion are major predictors of intractable epilepsy [62]. 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)[63]. Classification of MTS is pictorially represented in figure 2. 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 [63]. After the 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 fibers) sprout into a molecular layer which is 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 terminology [64]. The observation supports the concept that extensive bilateral hippocampal circuit rewiring leads to intractability in temporal lobe epilepsy patients [65].

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 hippocampal sclerosis on the affected side. The increased T2 signal in the hippocampus suggestive of gliosis. Gradient echoes help to identify vascular lesions. Fluoro Deoxy glucose positron emission tomography (FDG –PET) a useful test in the presurgical evaluation of patients suffering from temporal lobe epilepsy. Hypometabolism in the temporal lobe ipsilateral to the seizures focus is a positive predictor of 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 neocortical epilepsy lesions like malformation of the cortical development, vascular malformation, encephalomalacia secondary to trauma, inflammation, ischemia, haemorrhage and tumor are seen.

1.7.1.4. Vascular lesions

Most frequently encountered vascular causes of intractable epilepsy isarteriovenous malformations (AVMs) and cavernomas [66]. 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, whereas frontal or Sylvian region AVMs were presenting with generalised seizures. 24.7% of patients with partial epilepsy were reported to be intractable[67]. The severity of the seizure depends on the size of AV malformation, haemorrhage and frontotemporal location[68]. Delay in the intervention leads to structural abnormalities of the brain, namely hemi-atrophy of the brain.

1.7.1.5. Tumors

Intractable epilepsy associated with tumors often present with focal epilepsies. Glioneuronal tumors most commonly arise from the temporal lobe. Studies on a large sample (N= 207) of patients underwent surgical resection of tumor associated with

intractable epilepsy showed 154 patients with classic epilepsy-associated tumors (dysembryoplastic neuroepithelial tumor, ganglioglioma, and pilocytic astrocytomas) and 53 others tumors (astrocytomas and oligodendrogliomas) [69]. Also, cortical dysplasia and other neuronal migration disorders often coexist with these tumors. These are all drug resistant epilepsy and amenable to surgical therapy [70].

1.7.1.6. Post-traumatic epilepsy

Several studies have reported the incidence of post-traumatic epilepsy from 7-31.9% following brain injury [71,72]. Closed traumatic brain injuries often cause haemorrhage, necrosis, edema and white matter lesions [73]. Injury to neurons causes cellular loss with replacement of gliosis, changes in neuronal plasma membrane, sodium and potassium ionic channels leading to excitation causing epilepsy [74,75].

1.7.1.7. 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 is demonstrated by post-surgical studies[76], hippocampal sclerosis (TLE)[77], Rasmussen's encephalitis[78], tuberous sclerosis[79] and antiepileptic effect of anti-inflammatory drugs in West, Landau-Kleffner syndromes, Lennox–Gastaut syndromes [80].

1.7.1.8. Post-stroke epilepsy

Stroke is the one of the common neurological disorder that can often be associated with epilepsy which 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 [81,82]. 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 [82,83]. Acute Metabolic derangements associated with stroke cause early seizures that can be reversed. In contrast, late seizures cause structural changes like gliosis or meningo cerebral scar tissue [84]. Changes in the cell membrane, neuronal loss and collateral sprouting are reported to cause excitation in epilepsy [85]. Cortical infarction is most often reported to be resulting in seizure rather than subcortical involvement [86]. Large cortical infarction [87] especially the involvement of temporal lobe is often reported to a high-risk factor for developing post-stroke seizures.

1.7.1.9. 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 (partial seizures)[88]. Basal ganglia calcifications are often reported to be associated with hypoparathyroidism and pseudohypoparathyroidism. Intracranial calcifications are also considered as incidental in 0.3 to 1.5% of the patients [89]. Calcification due to infections may be associated with perilesional edema. These patients have the tendency to develop seizures intermittently. The pathophysiology of the perilesional edema is not clearly understood, but it may be due to postictal or release of

ionic calcium [90]. Also, 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 perilesional gliosis is reported to have increased seizure frequency, and they were drug resistant [91].

1.7.1.10. Metabolic disorder

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 acids,organic acids, fatty acids, neurotransmitters, urea cycle, vitamins, 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 which in particular include myoclonic seizures [92]. These disorders are reported to be rare in the adult population.

1.7.2. Diffusion Tensor weighted imaging

Diffusion Tensor Weighted Imaging (DTI) is a recently developed MRI technique which has gained importance over time to assess abnormalities with focal epilepsy (Partial seizures) [93–95]. DTI measures the molecular motion of water in tissue in various directions in every voxel, providing information regarding the microstructure of the white matter and grey matter, cellular packing, cellular loss or regional edema in focal status epilepticus [96]. In DTI, Apparent Diffusion Coefficient (ADC) and Fractional Anisotropy (FA) are the commonly recorded tensor measured in structural MRI [97,98].

Diffusion tensor weighted images have been studied well on a small group of individuals with temporal lobe epilepsy (TLE) and extratemporal lobe epilepsy (ETLE).

Interictal DTI imaging studies are reported to be more sensitive in identifying hippocampal involvement rather than conventional MRI in TLE [99]. Interictal imaging studies in patients with medial temporal lobe epilepsy associated with hippocampal sclerosis showed diffusion abnormalities involving pathologic hippocampus and larger network involvement [100]. Diffusion tensor imaging in patients with epilepsy and MCD have shown changes in tissues beyond the areas of MCDs which appeared normal on conventional MRI [101].

Patients with partial seizures and normal MRI findings showed various areas with abnormal anisotropy or diffusion, which were normal in conventional MRI [102]. Interictal studies in patient's normal structural MRI and TLE shows bilateral and extratemporal lobe involvement [95]. In TLE, lateralization of the epileptogenic region using DTI studies highly correlates with the presence of unilateral hippocampal sclerosis on conventional MRI [103]. And patients with non-lateralizing conventional MRI findings, the interictal DTI studies will not provide lateralizing information [99].From the review of the literature, there is ample evidence of DTI image abnormalities unilaterally or bilaterally,when MRI studies of the brain are normal or abnormal.

1.7.3. 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 [56]. 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 [57]. 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 [58]. The presence of IHI has been reported to be a marker of a more extensive disorder of brain development [57,58]. With the evidence of having IHI as a malformation of brain development, it would be a possible abnormality causing intractable epilepsy.

1.8. 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 [104–107]. The psychiatric manifestations may worsen the existing epileptic condition. Gross impairment of cognition may be due to continuous seizure and drugs [106–109]. Mood disorders, personality change, Attention deficit hyperactive disorders, language disorders are also associated with epilepsy [106,107,110,111].

Anxiety and depression often coexist in individuals suffering from epilepsy [104,111–115]. The prevalence of anxiety range 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 [105,110,116–119]. Depression and anxiety have also been reported to be often associated with suicide, suicidal ideation, suicidal attempts [120–122]. Altogether anxiety and depression in patients with epilepsy affect the quality of life [123–125].

Most significant cognitive deficit in Temporal lobe epilepsy (TLE) patients, especially in patients with mesial temporal sclerosis, is memory impairment [126,127]. Wechsler memory scale -III and Wechsler adult intelligence scale –Revised can

differentiate patients with refractory temporal lobe epilepsy from normal subjects, but they cannot differentiate between the right and the left TLE [127]. Also, other factors including long-term antiepileptic drugs, the age of onset, duration of epilepsy, type of seizure also contribute to cognitive defects over the years [128,129].

1.9. Electroencephalography

Interictal Electroencephalography (EEG) in patients with intractable seizure shows generalised abnormality in 75% of the cases rest of the EEG showed focal epileptiform activities which correlate with their clinical conditions [130]. In Focal cortical dysplasia, interictal routine video EEG was reported to show regional epileptic activity in 89% of patients [131]. When compared to routine EEG, intensive EEG monitoring was reported to be useful in detecting epileptic activity in patients with intractable epilepsy[132].

Interictal electroencephalography (EEG) findings in MTLS – spike and sharp waves are seen over the anterior temporal region. Sleep deprivation sometimes activates focal epileptiform discharges. Therefore EEG with sleep recordings is recommended during diagnostic workup. The presence of mid and posterior temporal lobe spikes in EEG may suggest the 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 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, T5 and 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 interhemispheric, 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 hypersynchrony has also described in patients with frontal lobe epilepsy. The epileptiform discharges appear as generalised spikes, polyspikes or spike and wave. It is always differentiated from frontal lobe epilepsy by locating unilateral epileptiform discharges before the generalised discharges.

1.10. Optogenetics in epilepsy

Optogenetics is a technique in which light-sensitive protein called opsin is introduced into the cell thereby cells will shine. Opsin can stimulate light-sensitive channel, pumps, G- protein-coupled receptors and transcriptional receptors. The light-sensitive channel and pumps can inhibit or excite the neurons. There are different kinds of opsins playing at the cellular membrane. The important opsins are channelrhodopsin-2(chR2) which are excitatory and Halorhodopsin (NpHR) which is inhibitory rhodopsin. Channelrhodopsin-2 and its variants are activated by blue light causing passive movements of Na +,k+,Ca2+ and H+ ions following the electrochemical gradient and thus depolarising the cell membrane and generation of action potential. Halorhodopsin on exposure to orange light causes active pumping of chloride ions into the cell results in hyperpolarization of cell membrane and inhibition of action potential generation takes place.

Light can be divided into lasers and light emitting diodes (LED) by different

wavelength and power. LED lights have increased wavelength and more power, easy to generate. This light is thrown into the cell via the optical fibres called optrodes.Thus the orange light, blue light and red light can be generated. Orange light has affinity over Halorhodopsin and glows, and blue light prefers channelrhodopsin. Opsins can be introduced into the cell via the vectors containing the particular inhibitory or excitatory opsins. Using LED sources throwing blue and orange light helps to identify the type of dominant opsins that is present over the cell membrane. Focal cortical seizures, temporal lobe seizures, and thalamo cortical epilepsy are diagnosed by finding out the cellular cause for increased excitability (either reduced Halorhodopsin or increased channelrhodopsin) and suitably treated with vector-mediated implantation of the appropriate opsins over the cell membrane.

1.11. Surgical outcomes in epilepsy

Studies carried out on patients with MCDs especially focal cortical dysplasia was reported to have a good surgical outcome if evaluated and managed with electrical and imaging modalities [133]. Also, favourable surgical outcomes were reported in children with temporal lobe epilepsy with MTS in developing countries when evaluated with a non-invasive protocol [134]. Diffusion tensor weighted imaging studies are also reported to be useful in surgical decision making in epilepsy [135].

2. NEED FOR THE STUDY AND HYPOTHESIS

2.1. Need for the study

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 [27,130] and its risk factors [11]. 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 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 which accounts for 60-70% of the population. 30-40% of them do not show any lesions may manifest with intractable epilepsy. With the advancement of neuroimaging technology especially DTI and 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 in tracing the neural network responsible for epilepsy.

In developing countries like India, where accessibility to neuroimaging facilities are not easily available, the prevalence of intractable epilepsy and various structural lesions associated with them are largely unknown. There are few preliminary studies carried out in India to document the frequency and clinical characteristics of MCD among children [52,136] and adults [52]. These are retrospective studies with data retrieved from case records of epileptic patients [52], and little is known about the prevalence of Mesial temporal sclerosis and incomplete hippocampal inversion in the Indian scenario. Studies in India using Diffusion tensor weighted images [137] are reported to be useful in identifying white matter structural abnormality among extratemporal epileptic patients.

DTWI is also reported to be helpful in predicting the postoperative neurological outcome, surgical decision making and preoperative counselling for the patients.

Moreover, it has been reported that structural abnormalities would give rise to focal seizures which 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 manifestations. 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, identifying neural networks and its clinical manifestations are 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 imaging techniques including CT scan, MRI, DTI and volumetric studies and to correlate with the demographic data, medical history, seizure examination, neurocognitive profiles and EEG.

2.2. Hypothesis

1. There is no association betweenthe type of seizures (generalized and partial seizures) with demographic data (age, gender, employment, 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, neurological examination, comorbid conditions and drugs), psychological assessment findings (Intelligent Quotient (IQ), Mental quotient (MQ), Bender-Gestalt Test (BGT), depression and anxiety scores), structural imaging findings (Computerized tomography (CT) scan, Magnetic Resonance Imaging (MRI), Diffusion Tensor Weighted Imaging (DTI)), electroencephalography findings and Quality of life in adults with intractable epilepsy.

2. There is no association between the type of structural lesions in MRI with the demographics, clinical characteristics, psychological assessment and EEG findings.

3. There is no correlation of the side of abnormality across various neuroimaging investigation (CT, MRI, and DTI) and EEG with the type of seizure.

4. There are no differences between the sensitivity of imaging techniques (CT, MRI, and DTI) to identify structural lesions associated with epilepsy.

3. AIMS AND OBJECTIVES

3.1. Aims

To investigate the prevalence, demographics, clinical characteristics, psychological status, structural abnormalities, EEG and quality of life in patients with intractable epilepsy

3.2. Objectives

1. To estimate the prevalence of intractable epilepsy in adults 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, employment, 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 findings (Intelligent Quotient (IQ), Mental quotient (MQ), Bender-Gestalt Test (BGT), depression and anxiety scores), structural imaging findings (Computerized tomography (CT) scan, Magnetic Resonance Imaging (MRI), Diffusion Tensor Weighted Imaging (DTI)), Electroencephalography and Quality of life.
4. To associate the type of structural lesions in MRI with the demographics, clinical characteristics, psychological assessment and EEG findings.
5. To correlate side of abnormality across various neuroimaging investigation (CT, MRI, DTI) and EEG with the type of seizure.
6. To assess the sensitivity of each imaging techniques (CT, MRI, and DTI) or in combination (CT & MRI and DTI) in identifying the structural lesions.

4. METHODS

4.1. Study design

A prospective study was carried out to investigate prevalence, demographics, clinical characteristics, psychological status, radio-imaging 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. Before the study Ethics Committee clearance was obtained from the local ethics committee in Madras Medical College (Letter No. 40062011 dated 24-06-2011). Data collection 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 patients after investigations (Imaging and interictal EEG recordings) and 4) follow-up and review of patients after neuropsychological assessment.

Phase 1: During 3 years (from 21-09-11 to 20-09-14) at the epilepsy clinic, Institute of Neurology, Rajiv Gandhi Government Hospital, Chennai, a total of 2850 patients were screened to identify patients with intractable epilepsy who were fulfilling the ILAE criteria. Among the patients who fulfilled the inclusion and exclusion criteria, 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 over the period ranging from 5 to 20 years were obtained from the patients. Case histories were obtained from the patient or caregivers with the procedure as mentioned in the methodology. Also,

all patients underwent a neurological examination under the direct supervision of the researcher himself. All the collected data were entered into a personal computer using software designed for entering the data as seen in Appendix 1.

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

Phase 4: Neuropsychological evaluations (Intelligent Quotient (IQ), the mental quotient (MQ), Bender-Gestalt Test (BGT), anxiety and depression scales) were carried out by experienced clinical neuropsychologist within 2-3 months afterthe radiological investigation. 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.

4.2. Participants

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

4.2.1. 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 10 years to 70 years were considered for the study.

4.2.2. 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 with psychogenic nonepileptic seizures were excluded.
4) Patients with any other neurological illness were excluded.

4.3. Material and Procedure

4.3.1. Case history

Detailed Case history evaluation was done using direct one to one clinical interview and questionnaire. The software contained questionnaire containing a 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's record number, name, age, gender, address, contact number, educational status and occupational status. Under medical history, information regarding 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 manifestations were collected.

4.3.2. Neurological examination

Neurological examination included collecting information about seizure from previous medical records, semiology of seizures given by the patients or caregivers and direct observation of seizures by the examiner. The information collected includes data about Seizure type, onset of seizure, duration of seizure, Seizure semiology and its

changes, the presence of neurocutaneous markers, the frequency of seizures, clustering, precipitating factors, status epilepsies, hemiparesis, migraine and trauma.

4.3.3. Neuroimaging investigations

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

4.3.3.1. CT scan protocol

All the subjects underwent conventional CT scan assessment using 16 slices CT scanner system (Siemens, 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[209].

4.3.3.2. MRI protocol

All the subjects underwent conventional MRI and DTI imaging on a 1.5T, 48 Channel System (Siemens Aera, 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[208]. These images were analysed by experienced neuroradiologists who detected the MCDs and hippocampal malformations.

4.3.3.3. DTWI and hippocampal volumetric study Protocol

DTWI was performed in the axial plane by using single-shot echo planar 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 DTWI 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 anisometry Cp, 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 from 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 isotropic voxel dimension of 2mm x 2mm x 2 mm were 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, temporo occipital fasciculus, parieto occipital fasciculus, uncinate fasciculus, hippocampal and parahippocampal region, fornix and fimbriae, cingulate gyrus to identify various tracts or regions which are involved in the maintenance of normal brain function.

Shape and position of the hippocampus were also carried out. These images were analyzed by experienced neuroradiologists who detected the MCDs and hippocampal malformations. The criteria for the incomplete hippocampal inversion (malrotation of the hippocampus) included incomplete rotation, the abnormal rounded appearance of the head of the hippocampus, blurry internal structure, changes in shape, size and vertical orientation of collateral sulcus. Patients fulfilling at least three criteria were identified as IHI.

4.3.4. 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 was 70 microvolt/ 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.

4.3.5. 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 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 was 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 was not administered. The following neuropsychological tools were used to assess each patient 1) Bender Gestalt test to assess visuoperceptual functions, 2) Weschler's children or adult intelligence scale to assess intelligence quotient, 3) Wechsler memory scale to assess the memory quotient 4) Multiphasic personality questionnaire to assess anxiety and depression and 5) WHO quality of life Brief (WHOQOL – BRIEF) questionnaire to assess quality of life. World health organisation quality of life scale was used 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 scored 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.

4.3.6. 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, neuroimaging 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, 2014). Some of the statistical analyses carried out for the present study include the 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, $\alpha = 0.05$.

5. RESULTS

5.1. 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 the 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 our epilepsy clinic, the prevalence of intractable epilepsy is reported to be 21.05 % that approximates 1 in 5 patients with epilepsy are intractable to medical management.

5.2. 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 as seen in Table-1. 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%, n= 187) was observed in patients with intractable epilepsy. Only a few proportion of the population were in skilled (13.24%), clerical (3.36%) and professional jobs (1.58%). A significant proportion of patients (13.64%) were underemployed and are working as a daily labourer. 14.62 % (n= 74) of females in the intractable epilepsy group were housewives.

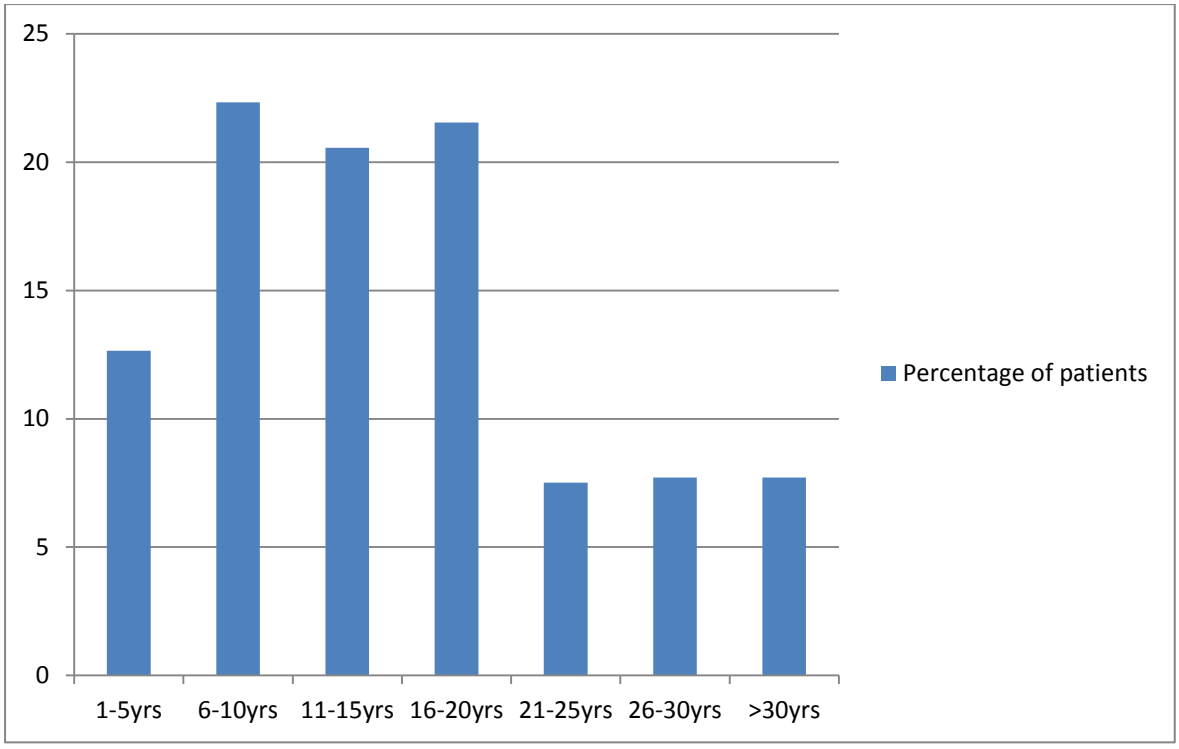


Figure 3: Percentage of patients across duration of seizure

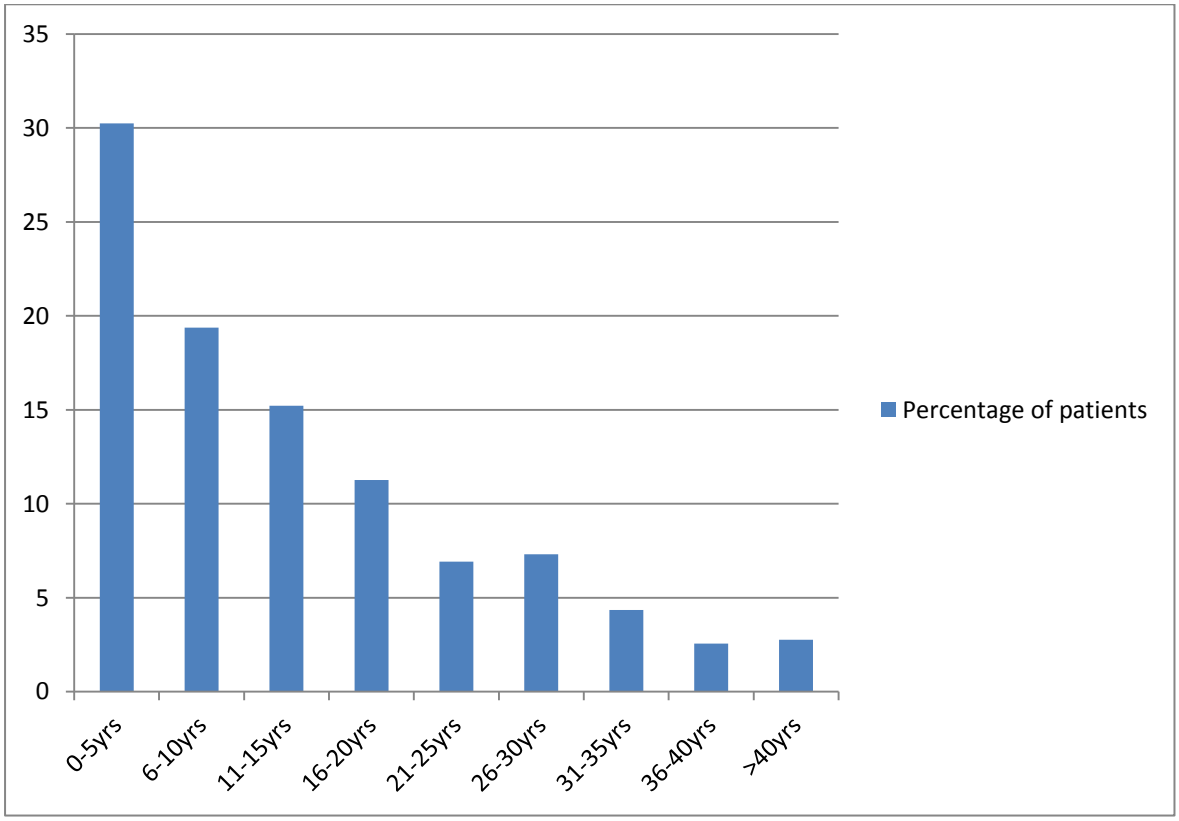


Figure 4: Percentage of patients across age of seizure onset

Table 1: Demographics of 506 patients with intractable epilepsy

Demographics		n	%
Age (in years)	10-15	18	3.56
	16-20	122	24.11
	21-25	67	13.24
	26-30	84	16.60
	31-35	64	12.65
	36-40	54	10.67
	41-45	33	6.52
	46-50	21	4.15
	51-55	25	4.94
	56-60	11	2.17
	>60	7	1.38
Gender	Male	294	58.10
	Female	212	41.90
Education level	No school education	85	16.80
	Elementary (1-8)	163	32.21
	High school (9-12)	195	38.54
	Graduate	63	12.45
Occupational status	Unemployed	187	36.96
	Housewife	74	14.62
	Daily laborer	69	13.64
	Skilled	67	13.24
	Clerical	17	3.36
	Professional	8	1.58
	Student	70	13.83
	Dependent	14	2.77

5.3. Clinical characteristics of patients with intractable epilepsy

5.3.1. Type of seizure

The major type of seizure that caused intractability is partial seizures (72.92%, n=369) followed by generalized seizures (27.08%, n=137). In partial seizures, 319 patients had complex partial seizures, 50 patients had a simple partial seizure, and 7 had mixed type of seizures which 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 which constitutes 23.91% and 3.16% of the total patients with intractable epilepsy. In the present series of 506 patients, we could not observe any patients with absence seizures as seen in Table 2.

5.3.2. Duration of seizures

Most of the patients (77.07%) in the present study had seizure duration ranging from 1-20 years as seen in table 2. Seizure duration (greater than 21 years) was observed in less proportion of patients (22.92%) with intractable epilepsy as seen in figure 3.

5.3.3. Onset of seizures

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 seizures decreased with increase in age range as seen in Table 2. The number of patients decreased as the age of seizure onset increased as seen in figure 4.

5.3.4. Seizure frequency

Most of the patients with intractable epilepsy had seizure frequency of 1-4 episodes per month (54.35%, n=275), followed by 1-6 episodes per week (29.84%, n=151) and daily occurrence (15.81%, n=80) as seen in Table 2.

5.3.5. Seizure semiology

The change in seizure semiology was observed from the clinical records. The most frequently observed change was from generalised to complex partial seizures and also from simple partial to complex partial seizures observed in 329 patients (65.02%) as seen in Table 2. The changes in seizure semiology happened 1-5years after the onset of

an initial episode of seizure. Out 319 patients with CPS 20% of them had initial seizure semiology of partial seizure (64/319) and 47% of them had initial seizure semiology of generalised seizure (150/319).

Table 2: Clinical characteristics of 506 patients with intractable epilepsy

Clinical characteristics		**n**	**%**
Seizure type	Generalized seizure Partial Seizure	137 369	27.08 72.92
Duration of seizure (in years)	0-5 6-10 11-15 16-20 21-25 26-30 30+	64 113 104 109 38 39 39	12.65 22.33 20.55 21.54 7.51 7.71 7.71
Onset of seizure (in years)	0-5 6-10 11-15 16-20 21-25 26-30 31-35 36-40 >40	153 98 77 57 35 37 22 13 14	30.24 19.37 15.22 11.26 6.92 7.31 4.35 2.57 2.77
Seizure frequency	Daily 1-6 / week 1-4 / Month	80 151 275	15.81 29.84 54.35
Clustering	0 1-2 2-3 >3	296 145 44 21	58.50 28.66 8.70 4.15
Semiology change	No change Change	177 329	34.98 65.02
Neurocutaneous markers	Present Absent	10 496	1.98 98.02
Drugs	Monotherapy polytherapy	77 429	15.22 84.78
Status epilepsy	Present Absent	42 464	8.30 91.70

5.3.6. Clustering

Clustering of seizures 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%) as seen in Table 2.

Table 3: Medical history in 506 patients with intractable epilepsy

Medical history		**n**	**%**
Developmental milestones	Normal	433	85.57
	Delayed	73	14.43
Natal history	Not significant	474	93.68
	LSCS	11	2.17
	Asphyxia	21	4.15
Postnatal history	Not significant	478	94.47
	Infections	6	1.19
	Head injury	5	.99
	Stroke	3	.59
	Febrile seizures	10	1.98
	Hypothyroidism	4	.79
Family history	Absent	472	93.28
	Present	34	6.72
Precipitating factor	Not significant	381	75.30
	Sleep deprivation	78	15.42
	Febrile illness	10	1.98
	Nocturnal	16	3.16
	Others	21	4.15
Neuroexamination	Not significant	378	74.70
	Headache	101	19.96
	Stroke	17	3.36
	Neurocutaneousmarkers	10	1.98
Comorbid conditions	Not significant	420	83.00
	Migraine	71	14.03
	Head trauma	12	2.37
	Smoking	3	.59

5.3.7. Precipitating factors

Many patients in the present study population had sleep deprivation as precipitating factor (15.42%, n=78), followed by other factors like menstruation (4.15%, n=21) including sleep (3.16%, n=16) and febrile illness (1.98%, n=10). Precipitating factors for epilepsy were not reported by patients or caregivers in 75.30% of the population (n=381) as seen in Table 3. Other precipitating factors include loud sounds and light (cinema, watching TV and working as a welder).

5.3.8. Status epilepsy

Status epilepsy was reported in 42 patients (8.30%) of the population as seen in Table 2.

5.3.9. Drugs

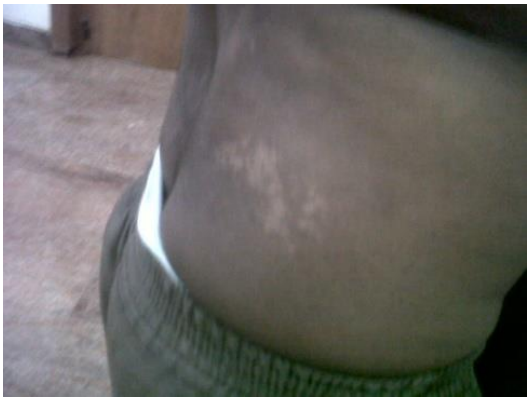
Most of the patients with intractable epilepsy were under polytherapy (84.78%, n=429). 15.22% (n=77) of them were under monotherapy as seen in Table 2. All the patients were treated with one or more of the following drugs (carbamazepine, sodium valproate, phenobarbitone, and phenytoin sodium).

5.3.10. Co-morbid conditions

The major comorbidity of epilepsy in the present study was a migraine which accounted for 14.03% (n=71), followed by stroke (3.36%, n=17), head injury (2.37%, n=12) and smoking (<1%) as seen in Table 3.

5.3.11. Medical history

Medical history findings in 506 patients with intractable epilepsy were summarised in Table 3. 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),



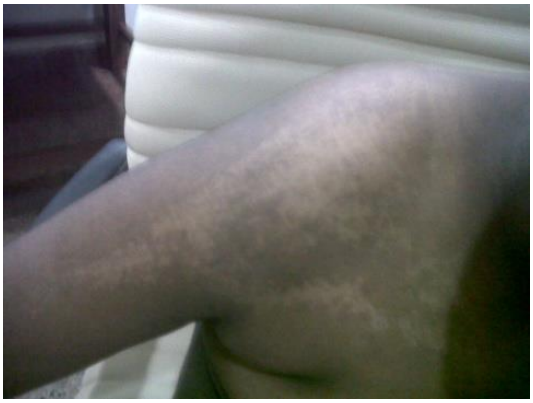


Figure 5: A 16-year-old male with hemimegaloencephaly and hypomelanosis of ito

Figure 6: A 32-year-old male with adenoma sebaceum

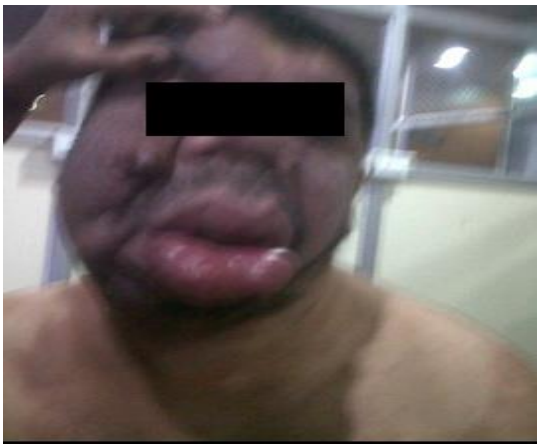


Figure 7: A 30-year-old male with intractable epilepsy and neurofibromatosis

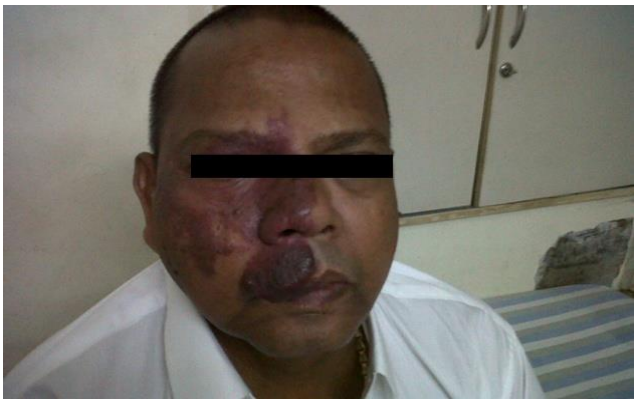


Figure 8: A 36years old male with sturge weber syndrome

followed by 6 patients (1.19%) with infections, 5 patients (0.99%) with a head injury, and 4 patients (0.79%) 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 as seen in Table 3.

5.3.12. Family history

Positive family history for seizures was reported in 34 patients (6.72%) of the population studied as seen in table 3.

5.3.13. Neurocutaneous markers

Neurocutaneous markers like adenoma sebaceum, hypomelanosis of ito, neurofibromatosis and sturge weber syndrome were observed in the present case series as seen in Table 3. A total 10 patients with intractable epilepsy (1.98%) had neurocutaneous markers and associated structural abnormalities in the brain. 6 patients with adenoma sebaceum, 2 patients with neurofibromatosis, one patient with hypomelanosis of ito, and one with Sturge-Weber syndrome. The images of the neurocutaneous markers observed are shown in figure (5-8).

5.3.14. Neurological investigation

During the neurological investigation, the headache was often reported by the patients with epilepsy (19.96%, n=101) followed by hemiparesis (.98%, n=5) as seen in Table 3.

5.3.15. Electroencephalography findings

Interictal EEG showed generalised epileptiform 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 findings as seen in Table 4.

Table 4: Interictal EEG findings in 506 patients with intractable epilepsy

Interictal EEG findings		**n**	**%**
EEG	Normal	220	43.48
	Focal	80	15.81
	Generalised	206	40.71
Side of lesion - EEG	Right	25	4.94
	Left	55	10.87
	Bilateral	206	40.71
	Non-significant	220	43.48

5.4. Neuroimaging results in patients with intractable epilepsy

5.4.1. CT scan findings

In the present study, several neuroimaging 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, neoplasms and lissencephaly were rarely observed in patients with intractable epilepsy in CT imaging. The majority of lesions were bilateral (12.06%, n=61) especially calcifications. Following bilateral lesions, left sided lesion were more common than right-sided lesions as seen in Table 5.

Table 5: Structural abnormalities in patients with intractable epilepsy

Structural Imaging findings		n	%
CT Scan	Not significant	388	76.68
	Calcification	53	10.47
	Infarction	10	1.98
	Gliosis	21	4.15
	Atrophy	27	5.34
	Lissencephaly	1	.20
	Neoplastic	2	.40
	Non-neoplastic cyst	4	.79
Side of lesion CT	Right	20	3.95
	Left	37	7.31
	Bilateral	61	12.06
	Normal	388	76.68
MRI	Normal	119	23.52
	MCD	50	9.88
	MTS	162	32.02
	IHI	35	6.92
	Neoplastic and Non-neoplastic lesions	61	12.06
	Gliosis	29	5.70
	Cyst	5	.98
	Infarction	12	2.37
	Arteriovenous malformations	6	1.18
	Inflammation and Infections	5	.98
	Hemorrhage	2	.39
	Neoplastic	2	.39
	Nonspecific lesions	79	15.61
	Cortical atrophy	11	2.20
	Calcifications	68	13.43
Side of lesion - MRI	Normal	119	23.52
	Right	88	17.39
	Left	180	35.57
	Bilateral	119	23.52
Side of lesion - DTWI	Normal	100	19.76
	Right	95	18.77
	Left	158	31.23
	Bilateral	153	30.24

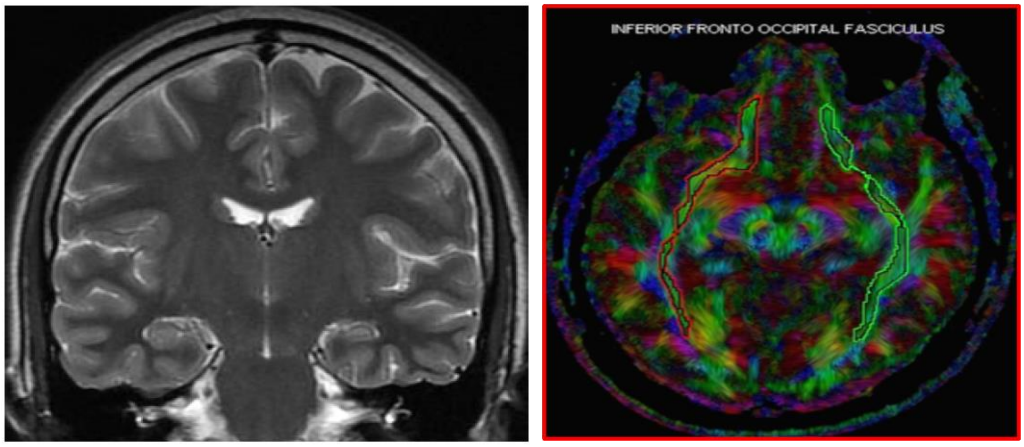


Figure 9: MRI brain (T2 image) of 50-year-old female showing features of left mesial temporal sclerosis. DTI images showing altered fractional anisotropy (FA), Mean Diffusivity (MD) in the left side

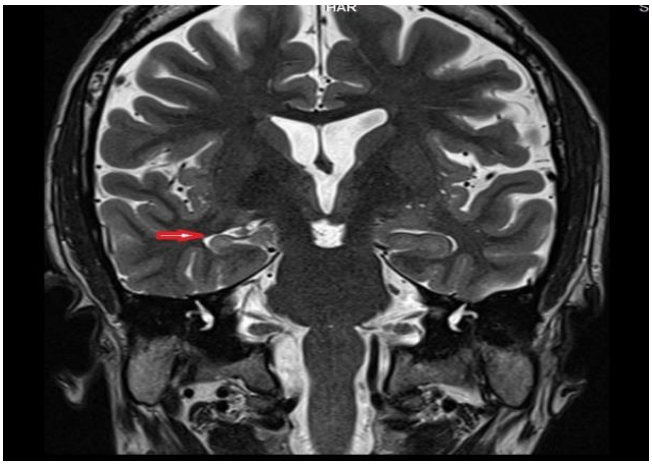


Figure 10: MRI brain of 32-year-old male with moderate atrophy of right hippocampus head, body, and tail with internal T2 hyperintense signal - showing features of right mesial temporal sclerosis

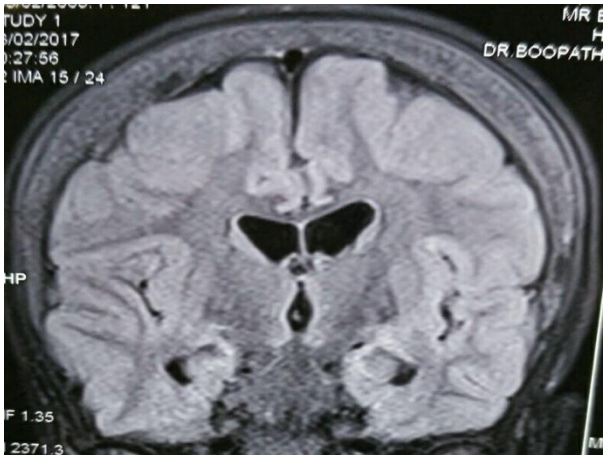


Figure 11: MRI brain of 12-year-old female with bilateral hippocampal atrophy showing features of bilateral hippocampal sclerosis

5.4.2. MRI findings

Most common abnormality (32.02%, n=162) that was observed in patients with intractable epilepsy was Mesial 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, haemorrhage 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. Frequently, lesions were observed on the left side (35.57%, n=180) when 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. Various abnormalities in MRI were summarised in Table 5.

5.4.2.1. 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 was associated with malformation of cortical development, gliosis, nonspecific cystic lesions, infarction, and incomplete hippocampal inversion in 28 patients (5. 53%).These lesions were categorised under multiple lesions as seen in Table 6. Patients with left MTS, right MTS, and bilateral MTS were shown in figure 9, 10 and 11 respectively.

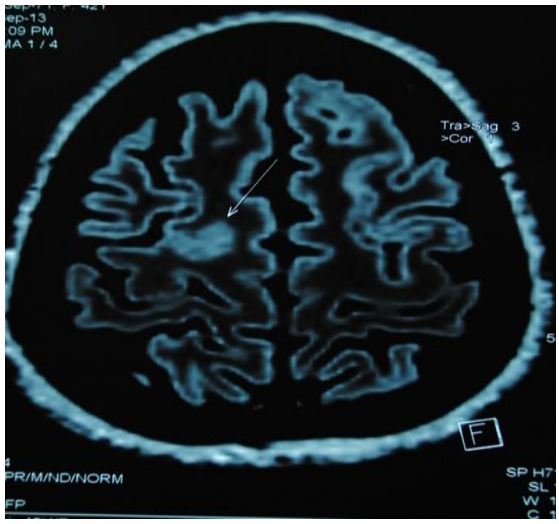


Figure 12: MRI brain (Flair) of 42 years old female showing focal cortical dysplasia in the right paracentral sulcus and left frontal and parietal regions.

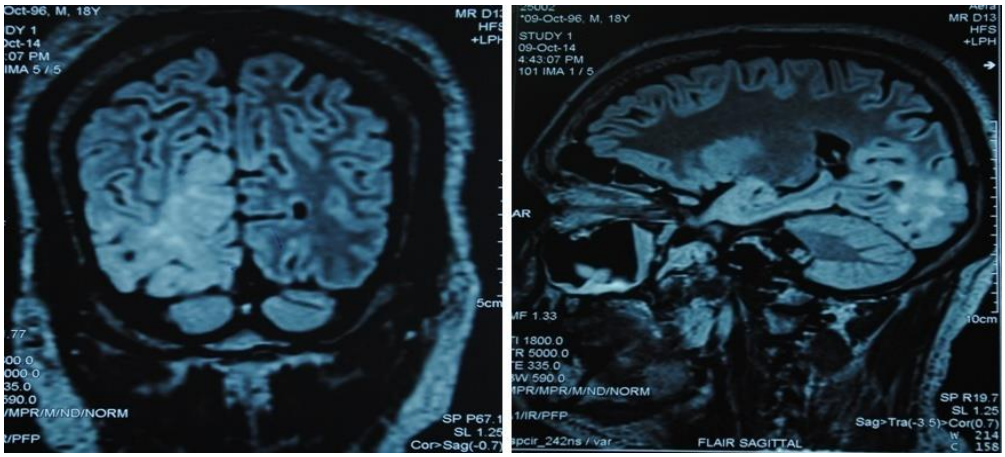


Figure 13: MRI brain (Flair) of an 18-year-old male showing focal cortical dysplasia (thickening) in the temporal, parietal and occipital regions.

Table 6: Multiple lesions associated with MTS

Multiple lesions	n	%
MTS and Gliosis	11	2.17
MTS and Non-specific cystic lesion	9	1.78
MTS and Incomplete hippocampal inversion	2	.40
MTS and Malformation cortical development	5	.98
MTS and Infarction	1	.20

5.4.2.2. 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 7.

5.4.2.2.1. Focal cortical dysplasia

Most commonly observed malformation of cortical development is focal cortical dysplasia (5.13%) in the series of 506 patients with intractable epilepsy. Focal cortical dysplasias (FCD) were observed commonly in temporal and frontal lobes especially on the left hemisphere as seen in Table 7. Also, there were few patients with FCD in parietal and occipital lobes. 5 patients in the FCD group had multiple focal thickening of various lobes in the brain. MRI brain images of 2 patients with FCD are shown in figure 12 & 13.

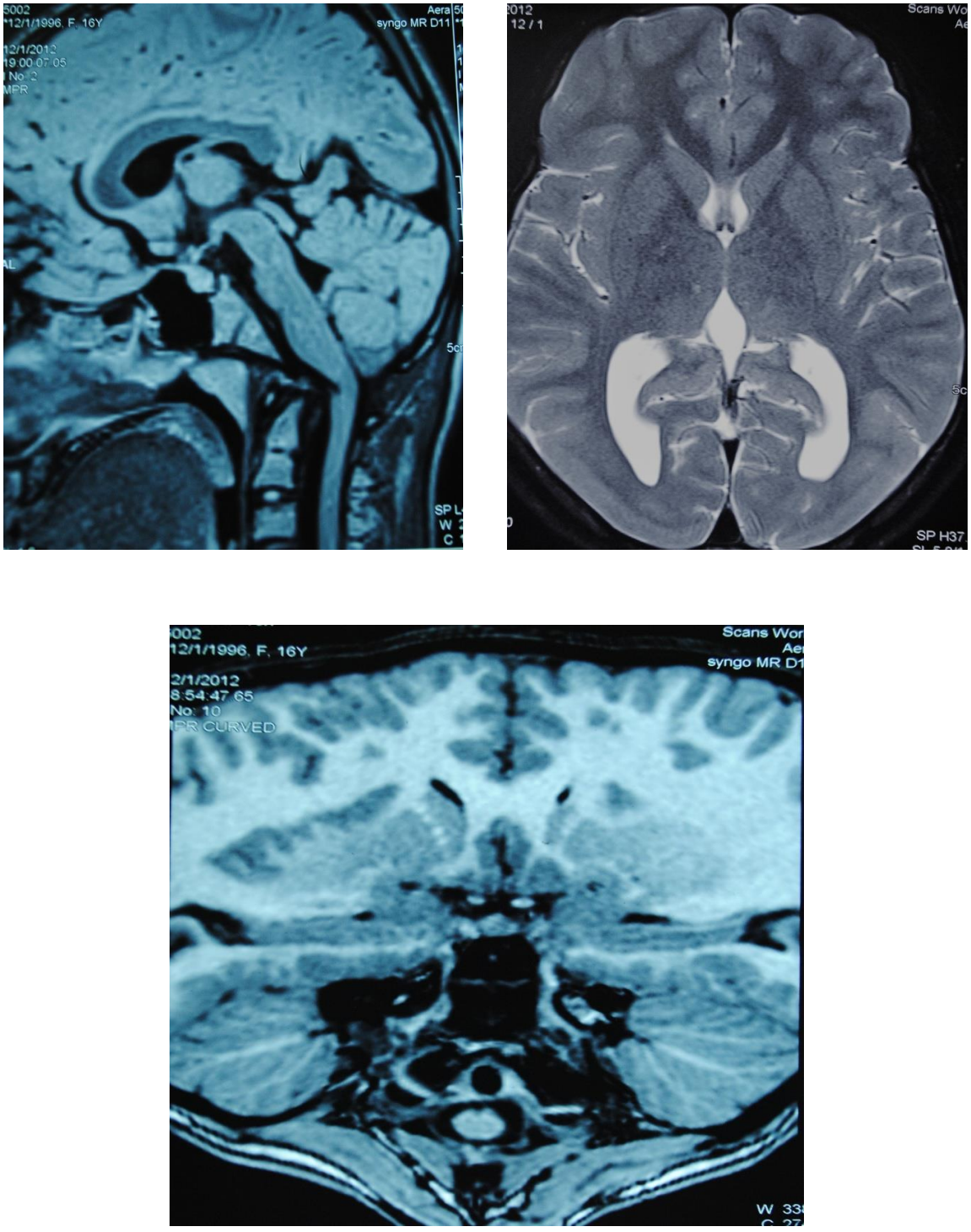


Figure 14: 16 year old twins with polymicrogyria -diffuse cortical thickening of bilateral temporooccipetal region, Vertical orientation of body and tail of left hippocampus, pontine hypoplasia, posteriorly pointing dense with left cerebellar tonsillar herniation and crowding of foramen magnum.

Table 7: Various malformation of cortical development observed in 506 patients with intractable epilepsy

Various Malformation of cortical development		Frequency (n=50)	Percentage
Focal cortical dysplasia		26	5.13
Frontal lobe	Right	3	
	Left	5	
	Bilateral	1	
Temporal lobe	Right	1	
	Left	4	
	Bilateral	2	
Parietal lobe	Right	-	
	Left	1	
	Bilateral	1	
Occipital lobe	Right	1	
	Left	1	
	Bilateral	-	
Multiple FCD		5	
Pachygyria		1	.19
Polymicrogyria		2	.39
Dysembryonic neuroepithelial tumor		2	.39
Heterotopia		4	.79
Lissencephaly		2	.39
Schizencephaly		2	.39
Hemi- megalenchephaly		1	.19
Multiple pathologies		10	1.97
Agenesis of body and tail of caudate nucleus		1	.19

5.4.2.2.2. Polymicrogyria

Polymicrogyria (PMG) was observed in 2 patients. Both the patients were 16-year-old female twins. Both of them had polymicrogyria as evidenced by diffuse cortical thickening of bilateral temporo occipital region with a paucity of sulcation and poor grey and white matter differentiation. The vertical orientation of body and tail of left

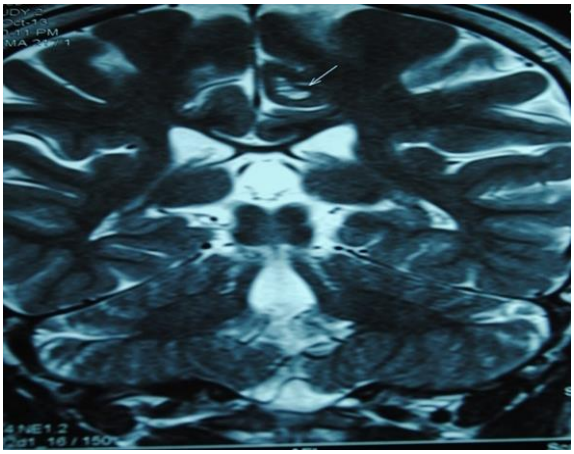


Figure 15: MRI brain of 23-year-old female showing DNET tumor in the left parasagittal frontal region

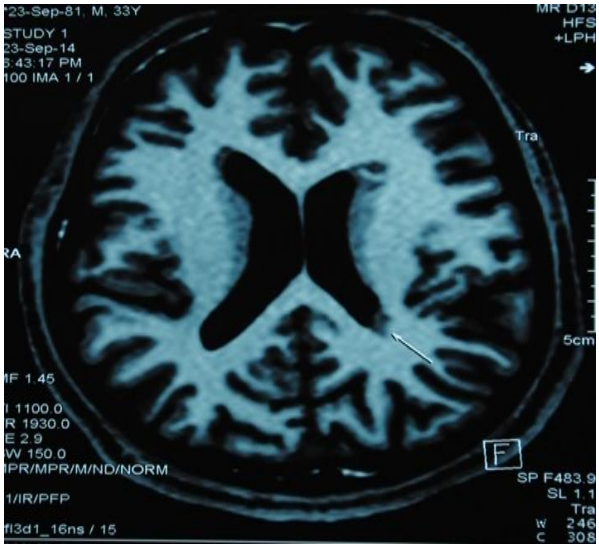


Figure 16: MRI brain of 33year old male with bilateral subependymal nodular heterotopia along the lateral ventricles and transmantle heterotopia along the left superior frontal sulcus

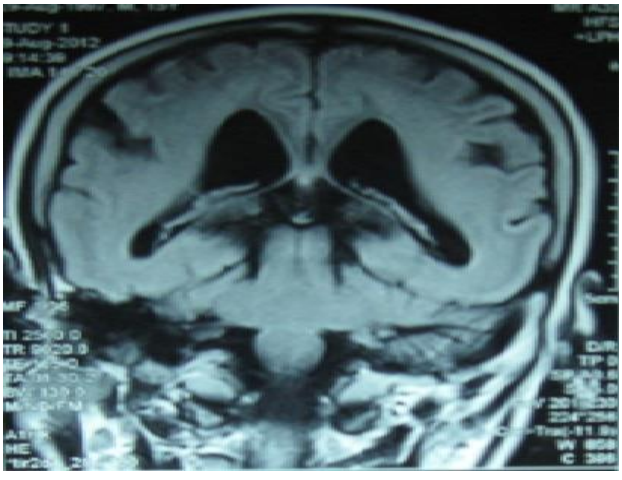


Figure 17: MRI brain of 15-year-old male showing Subcortical band heterotopia or double cortex syndrome

hippocampus, pontine hypoplasia, posteriorly pointing dense with left cerebellar tonsillar herniation causing crowding at foramen magnum were also observed in both the twin patients. MRI brain images of a twin with polymicrogyria are shown in figure- 14.

5.4.2.2.3. Pachygyria

One patient had bilateral pachygyria over the parietal lobe.

5.4.2.2.4. Dysembryonic neuroepithelial tumor

DNET tumors were observed in two patients. MRI brain of a 23-year-old female with DNET tumor in the left parasagittal frontal region is shown in figure 15.

5.4.2.2.5. Heterotopias

Heterotopias were observed in 4 patients with MCDs. MRI brain of 33year old male with bilateral subependymal nodular heterotopia along the lateral ventricles and transmantle hetero topiae at left superior frontal sulcus is shown in figure 16. Also, MRI brain of a 15-year-old male showing Subcortical band heterotopia or double cortex syndrome is shown in figure 17. A 26-year-old male with bilateral subcortical heterotopia in MRI is shown in figure 18

5.4.2.2.6. Lissencephaly

Lissencephaly was present in 2 patients.These patients are suffering from intractable epilepsy characterised by complex partial seizure of extra temporal origin often precipitated by loud sounds with initial generalised myoclonus and mental retardation. MRI brain of 16-year-old male with lissencephaly is shown in figure 19.

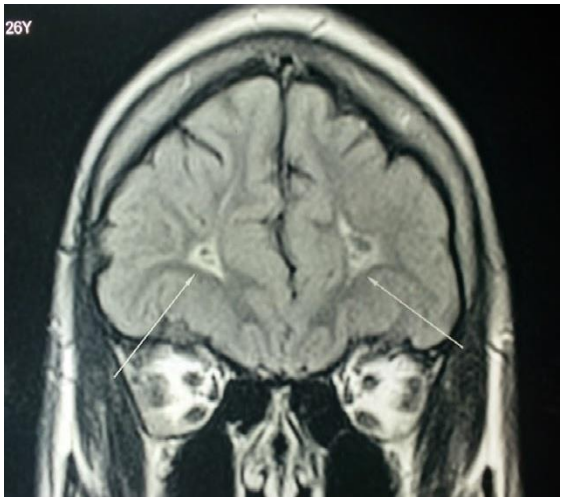


Figure 18: MRI brain of 26year old male with bilateral subcortical lesion (heterotopia)

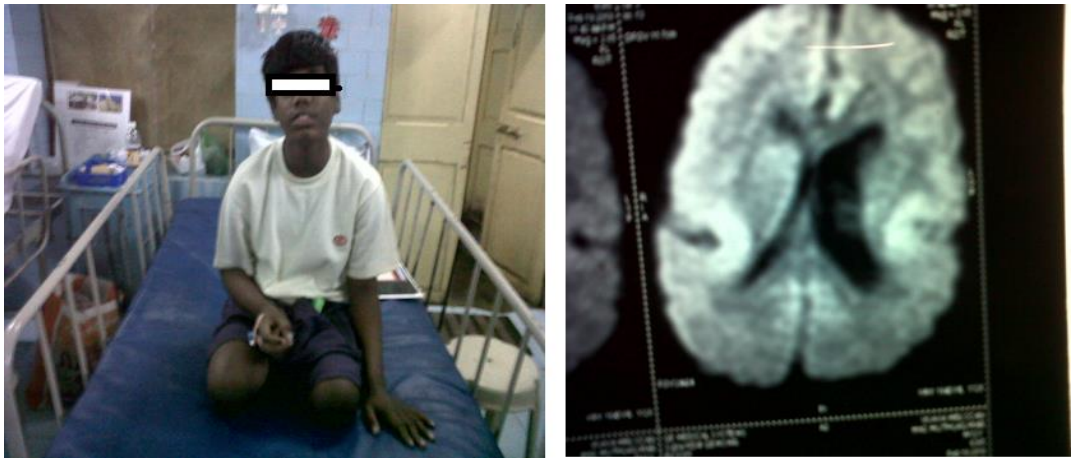


Figure19: MRI brain of 16-year-old male showing lissencephaly

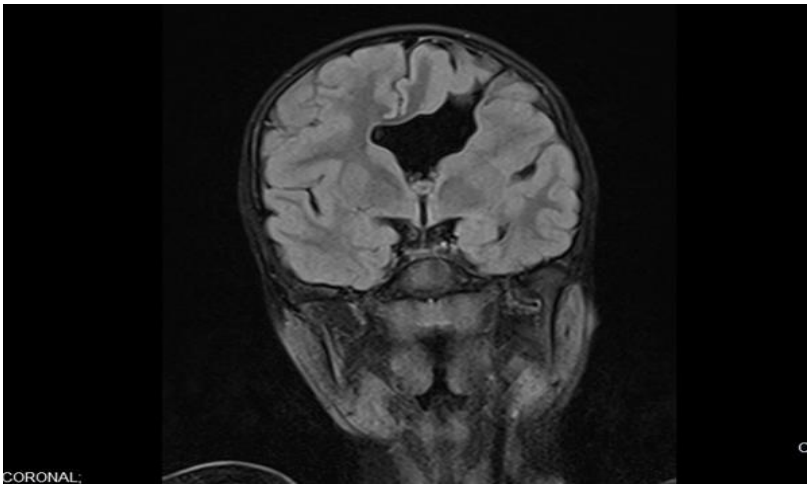


Figure 20: MRI brain (Flair) of 12-year-old male with open type of schizencephaly

5.4.2.2.7. Schizencephaly

Schizencephaly were observed in 2 patients. One patient had open lip schizencephaly, and other had closed type. The cleft in schizencephaly was observed in the parietal region. MRI brain images of 12-year-old male and a 44-year-old male with the open and closed type of schizencephaly were seen in figure 20 and 21 respectively.

5.4.2.2.8. Hemimegalencephaly

Hemimegalencephaly was observed in one patient in the right hemisphere. Neurocutaneous markers (hypomelanosis of ito) was observed in this patient over the shoulder, trunk, and back of the right arm. MRI brain of 16-year-old male with Right sided hemimegalencephaly, and hypomelanosis of ito is shown in figure 22.

5.4.2.2.9. Agenesis of body and tail of caudate nucleus

Agenesis of body and tail of caudate nucleus were observed in 1 patient

5.4.2.2.10. Multiple pathologies

Following FCD, most common abnormalities observed were multiple pathologies. Commonly FCDs were observed with hippocampal sclerosis (dual pathology) in five patients, hippocampal malrotation was observed with FCD and ependymal nodules in three patients indicating features of tuberous sclerosis complex. Monozygotic twins showing multiple lesions were observed in the present study. Both the females patients had bilateral temporo occipital PMG, pontine hypoplasia, and posteriorly pointing dense with left cerebellar tonsillar herniation 8mm below the foramen magnum.

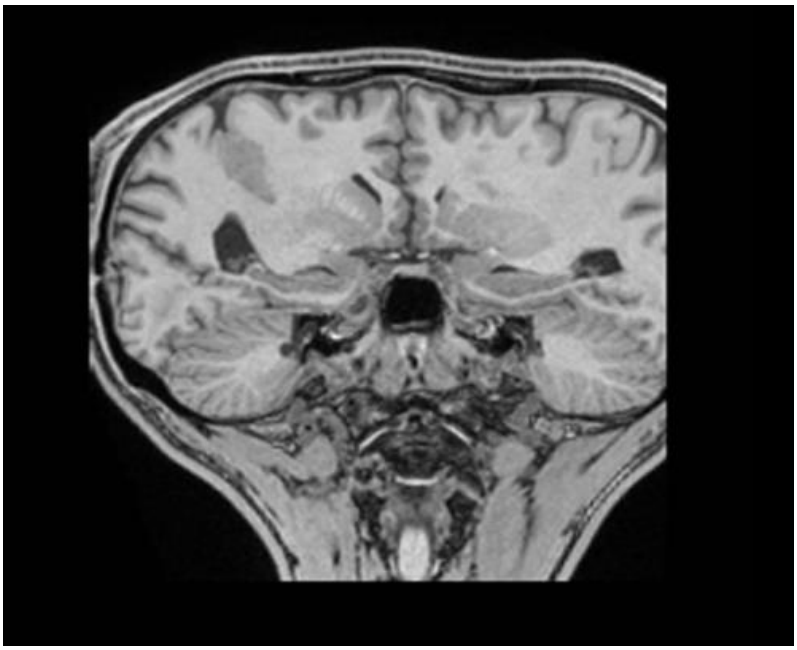


Figure 21: MRI brain (Flair) of a 44-year-old male showing closed type of schizencephaly

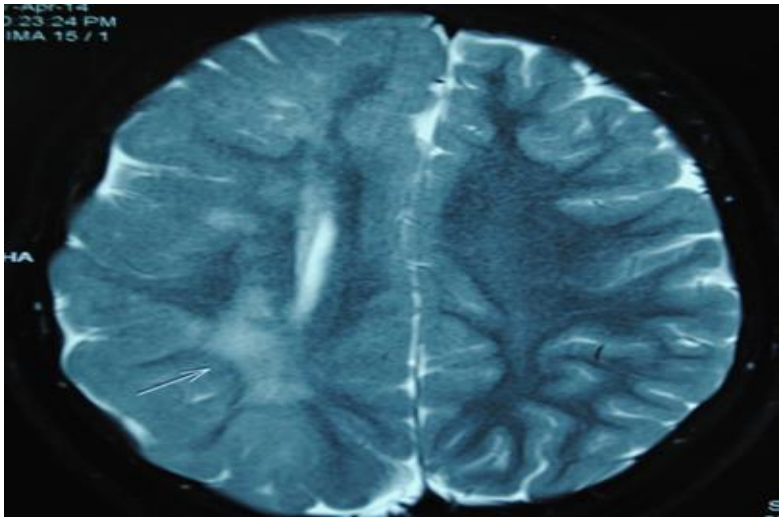


Figure 22: MRI brain of 16-year-old male with Right side hemimegaloencephaly and hypomelanosis of ito

5.4.2.3. 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 which 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. MRI brain showing left IHI and FCD with right IHI are shown in figure 23 and 24.

5.4.2.4. Neoplastic and nonneoplastic lesions

5.4.2.4.1. Neoplasms

Neoplastic lesions were observed in two patients. One patient with glioma and another patient with Gliomatosis cerebri. MRI Brain of a 30-year-old male showing glioma in the left temporal region is shown in figure 25.

5.4.2.4.2. Inflammation

Inflammation and Infections like herpes simplex encephalitis with granuloma (1 patient), tuberculous meningoencephalitis (1 patient), neurocysticercosis (1 patient), Hashimoto’s autoimmune encephalitis (1 patient) and Rasmussen's encephalitis (1 patient) were observed in 5 patients with intractable epilepsy. MRI brain images of patients with herpes simplex infection, neurocysticercosis, autoimmune encephalitis and Rasmussen's encephalitis are shown in figure 2,27, 28 and 29 respectively.

5.4.2.4.3. Gliosis

Gliosis at various regions of the brain especially parieto occipital and orbitofrontal regions was observed in 29 patients (5.70%) with intractable epilepsy signifying nonspecific lesion secondary to trauma, ischemia and inflammation.

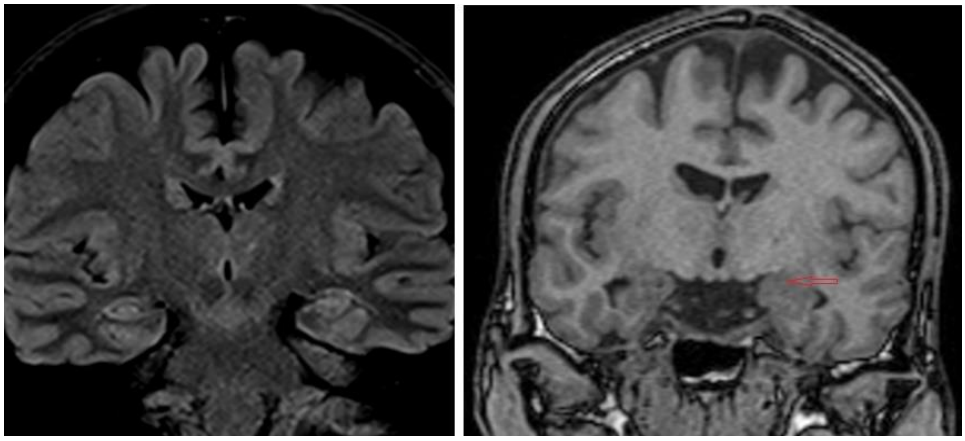


Figure 23: MRI brain showing normal hippocampus (Left side) and Left incomplete hippocampal inversion (Right side)

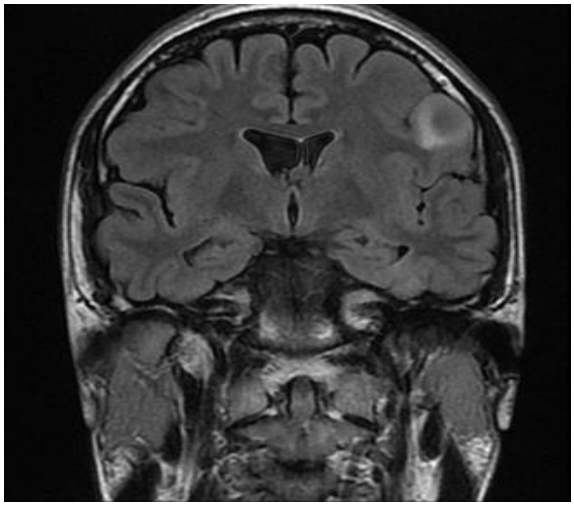


Figure 24: MRI brain (T1 Flair) of 24-year-old male showing Left parietal FCD and Right sided incomplete hippocampal inversion

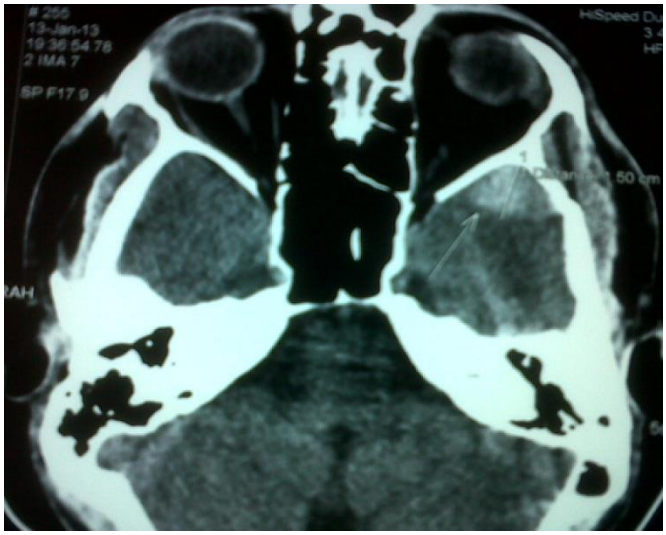


Figure 25: MRI Brain of 30-year-old male showing glioma in left temporal region

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. MRI brain of a 40-year-old male with left parieto occipital lobe infarction and gliosis is shown in figure 30.

5.4.2.4.4. Non-neoplastic cysts

Non-neoplastic cysts were observed in 5 patients with intractable epilepsy (0.98%). T1 weighted images (MRI brain) of a 36year old male with a cystic lesion in right medial temporal region is shown in figure 31.

5.4.2.4.5. Arteriovenous malformation

Arteriovenous malformation (AVM) was associated with focal intractable epilepsy with secondary generalisation in 6 patients (1.18%). All of them had AVM at Parieto temporal region.2 patients with intractable epilepsy presented with haemorrhage in the brain (0.39%). Figure 32 shows MRI (brain) of a 27-year-old female with left Parietal Arteriovenous malformation, left parietal gliosis and atrophic changes.

5.4.2.5. 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 perilesional edema were observed in 68 patients (13.43%). MRI (brain) of a 36-year-old male with cavernous hemangioma in right medial temporal region is shown in figure 33. Figure 34 shows X-ray (skull), CT scan (brain), and MRI (brain) of a 21-year-old male with large calcification and gliosis at the left Parietal region. A 55year old female with bilateral Subcorticalcalcifications with thyroidectomy scar is shown in figure 35. MRI images of patients with focal calcifications and multiple calcifications are shown in figure 36 and 37 respectively

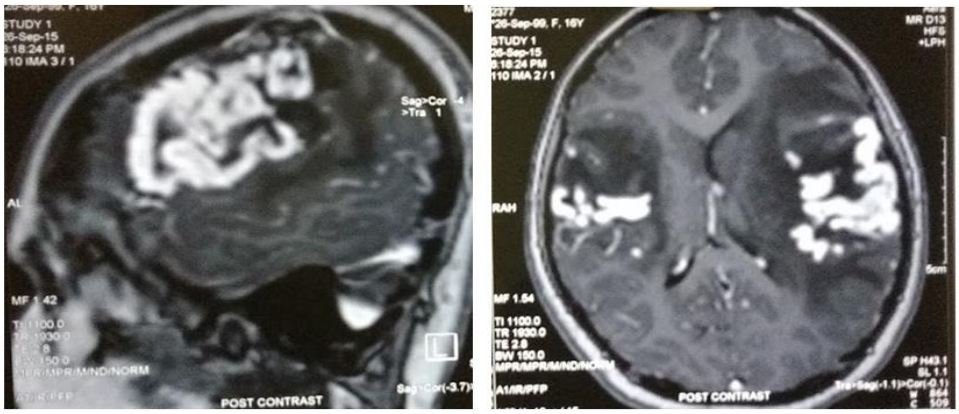


Figure 26: MRI brain (contrast) of a 16year old female with herpes simplex infection & Hyper-IgM syndrome showing granulomatous lesion in the bilateral peri-rolandic and parietal regions.

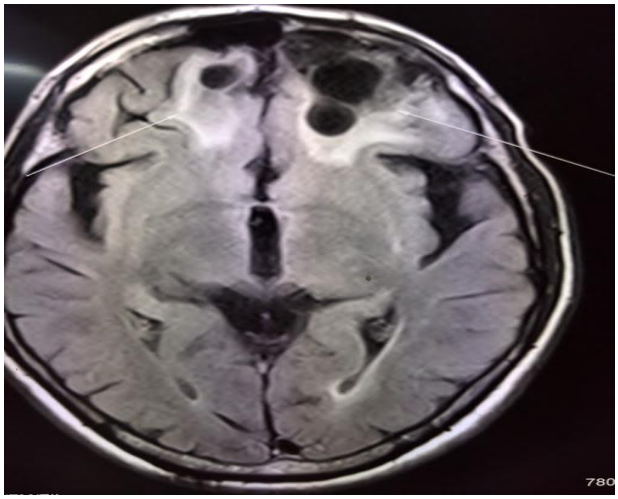


Figure 27: MRI brain (contrast) of a 16-year-old male with multiple lesion-neurocysticercosis.

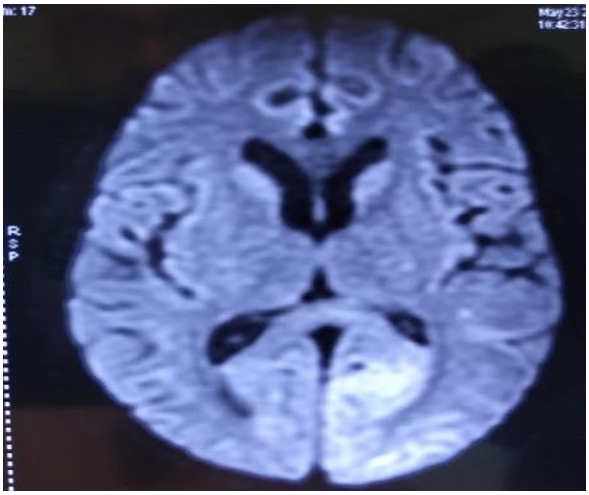


Figure 28: MRI brain of a 15-year-old male with autoimmune encephalitis showing inflammation over the left parietooccipital region.

Table 8: Number of patients with abnormal ADC and FA values in DTWI across various regions of interest

Regions of interest	No. of patients (N=506)
Hippocampal and parahippocampal region	217
Middle cerebellar peduncle	134
Uncinate fasciculus	110
Frontotemporal fasciculus	10
Frontoparietal fasciculus	4
Temporoparietal fasciculus	30
Temporooccipital fasciculus	46
Parietooccipital fasciculus	13
Fornix	48
Fimbriae	59
Cingulate gyrus	9
Thalamus	27
Corpus callosum	28

5.4.3. DTWI findings

Diffusion tensor weighted images (DTI) 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 of interest considered for the present study. DTI were significantly abnormal in 406 (80.23%) intractable epilepsy patients. Of these 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, temporo occipital fasciculus, parieto occipital fasciculus, uncinate fasciculus, hippocampal and parahippocampal region, thalamus, corpus callosum, fornix and fimbriae and cingulate gyrus. 217 patients especially

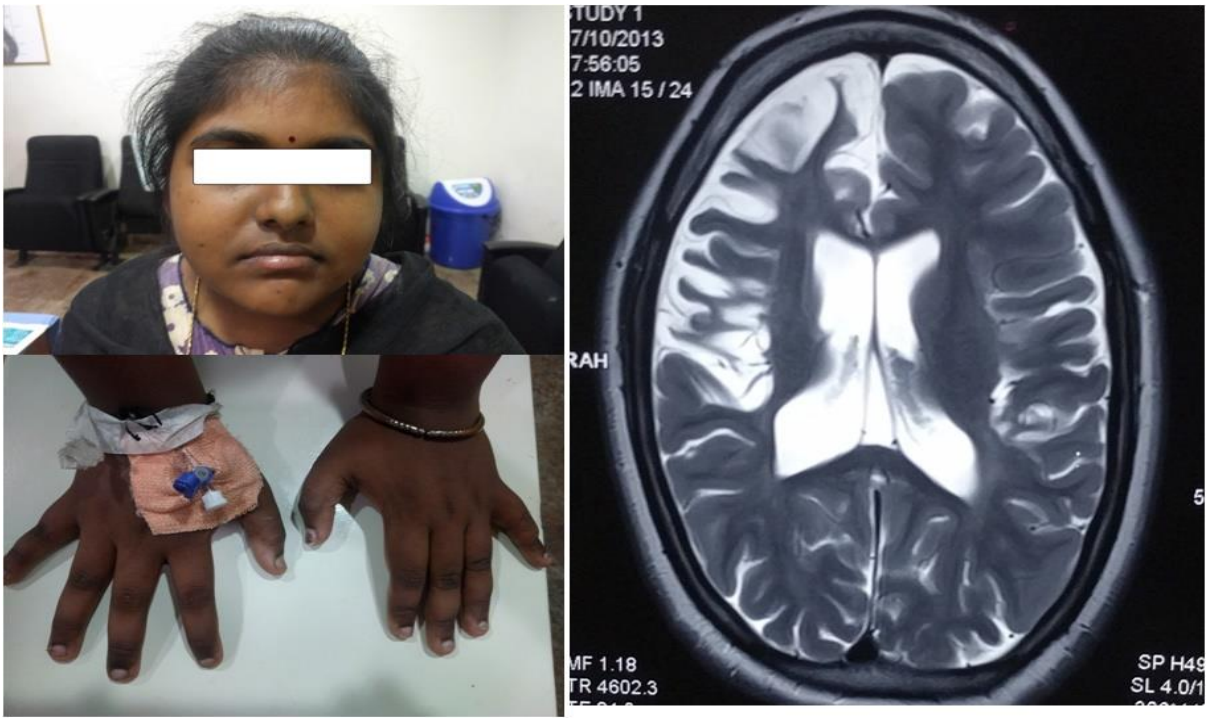


Figure 29: MRI brain of a 14 year old female with frontoperital atropy (Rasmussen's encephalitis)

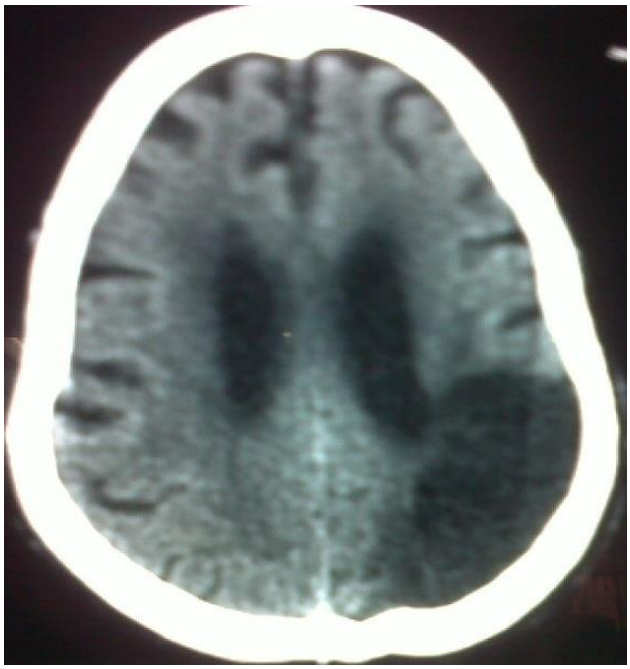


Figure 30 : MRI (brain) of a 40-year-old male with left parietooccipital lobe infarction and gliosis.

patients with MTS showed abnormal DTI values in hippocampal and parahippocampal regions. Abnormal ADC and FA values were observed in higher frequencies at middle cerebellar peduncle, uncinate fasciculus, temporo occipital fasciculus, temporoparietal fasciculus, fimbriae, fornix, thalamus and corpus callosum. The involvement of cingulate gyrus, parieto occipital fasciculus, frontoparietal fasciculus was less commonly observed in patients with intractable epilepsy as seen in Table 8.

5.5. Neuropsychological assessment findings in patients with intractable epilepsy

Wechsler's intelligence scale classified I.Q. scores into 1) mental retardation, 2) dull normal slow learners and 3) average intelligence. Wechsler's Memory scale classified M.Q. scores into 1) normal and 2) deficits of memory dysfunction. Out of 506 patients with intractable epilepsy, 147 patients (29.05%) had mental retardation ($\leq$69) score in Wechsler intelligence scale. 20% (n=104) of them had dull normal intelligence. 255 patients (50%) of them had average intelligence. Wechsler memory quotient scores were low ($\leq$70) in 194 patients (38.34%) and showed memory dysfunction. 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%) as seen in Table 9.

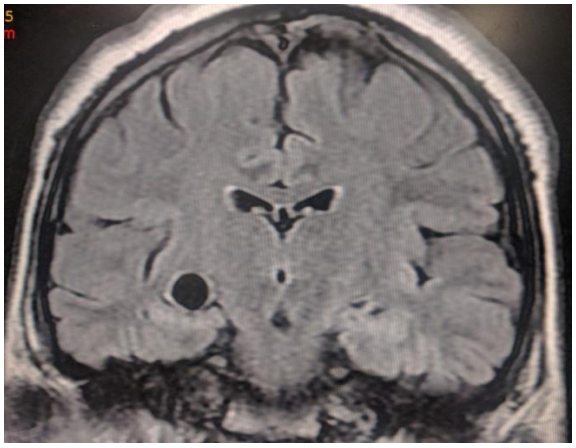


Figure 31: MRI Brain – T1 weighted images of a 36year old male with a cystic lesion in right medial temporal region.

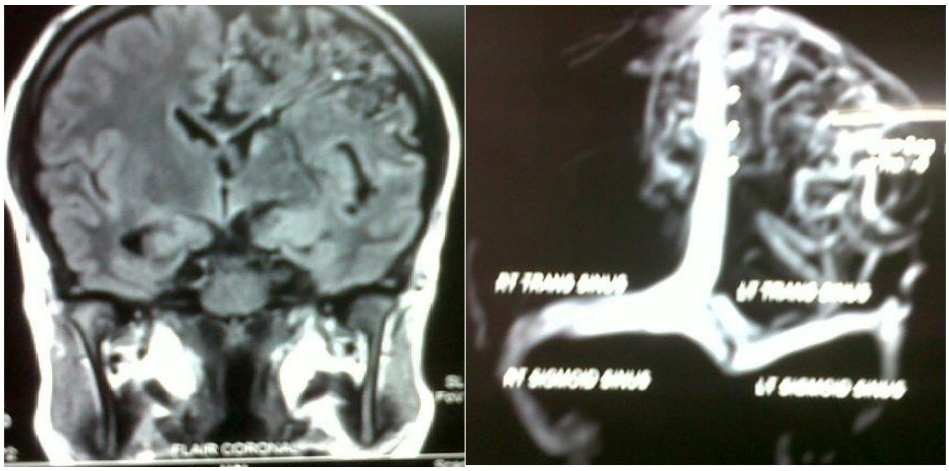


Figure 32: MRI (brain) of a 27-year-old female with left Parietal Arteriovenous malformation showing left parietal gliosis and atrophic changes.

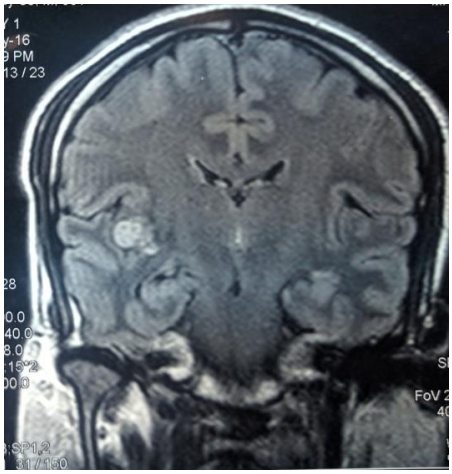


Figure 33: MRI (brain) of 36-year-old male with cavernous hemangioma in right medial temporal region

Table 9: Neuropsychological findings in patients with intractable epilepsy

Neuropsychological assessment		n	%
IQ	≤ 69: Mental retardation	147	29.05
	70 - 90: Dull normal slow learners	104	20.55
	> 90: Average intelligence	255	50.40
MQ	≥ 70: Normal	312	61.66
	< 70: Deficits of memory dysfunction	194	38.34
BGT	Normal	288	56.92
	Abnormal	218	43.08
Anxiety	Absent	198	39.13
	Present	161	31.82
	CNT	147	29.05
Depression	Absent	217	42.89
	Present	142	28.06
	CNT	147	29.05
Anxiety and Depression	Absent	233	46.05
	Present	126	24.90
	CNT	147	29.05

CNT: could not test

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 as seen in Table 10. Most of the patients with intractable epilepsy had a poor and very poor quality of life scores in all the four domains as seen in Table 10.

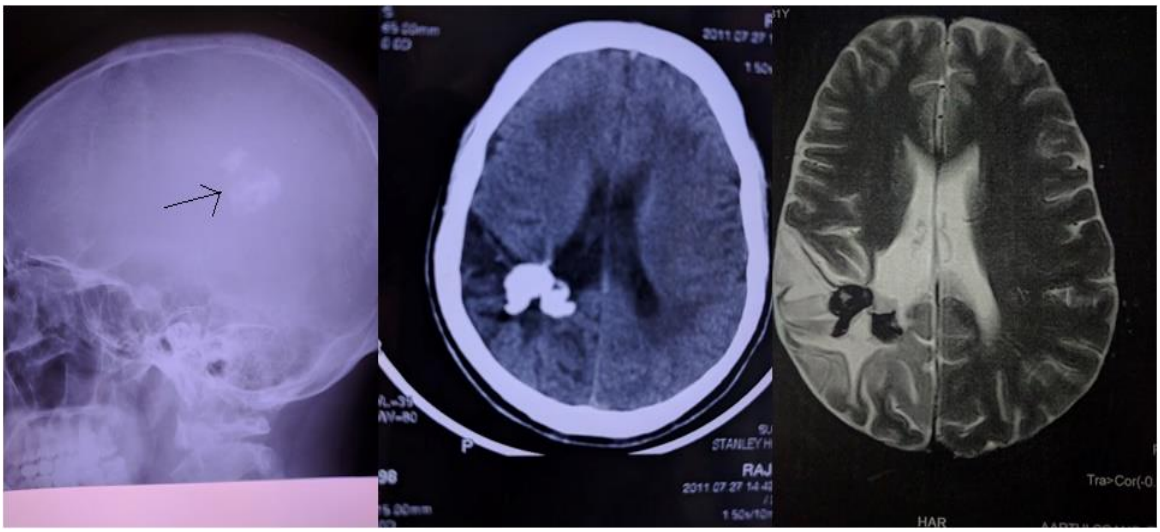


Figure 34: X-ray (skull), CT scan (brain), and MRI (brain) from left to right of a 21year old male with large calcification and gliosis at the left Parietal region.

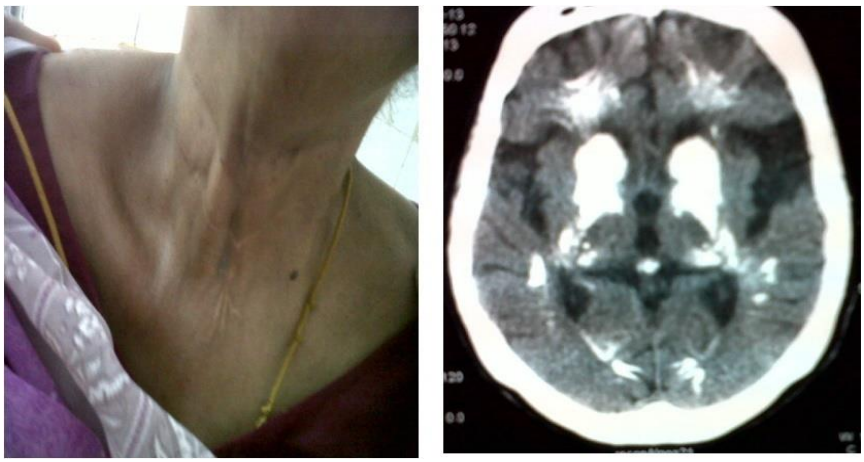


Figure 35: MRI brain of a 55year old female with bilateral subcortical calcification (right) with thyroidectomy scar (left).

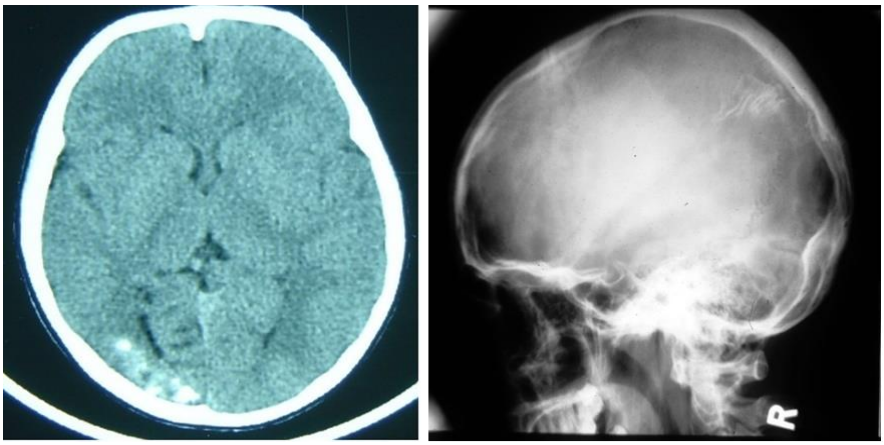


Figure 36: CT Brain (right) and MRI brain(left) images of 13-year-old male with calcification in the right posterior parietooccipital region

Table 10: WHO Quality of life scores in 506 patients with intractable epilepsy

Domains		n	%
Physical Health	Very Poor	147	29.05
	Poor	97	19.17
	Good	262	51.78
Psychological Health	Very Poor	147	29.05
	Poor	143	28.26
	Good	216	42.69
Social Relationship	Very Poor	147	29.05
	Poor	183	36.17
	Good	176	34.78
Environment	Very Poor	147	29.05
	Poor	101	19.96
	Good	258	50.99
Total Quality of Life	Very Poor	147	29.05
	Poor	50	9.88
	Average	215	42.49
	Good	94	18.58

5.6. Comparison of the 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 an 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 a strong association ($p<0.05$) with age ranges between 16 years to 40 years as seen in Table 11.

No significant association ($p>0.05$) was observed between the type of seizure and other demographic variables like gender, occupational status, and educational level.

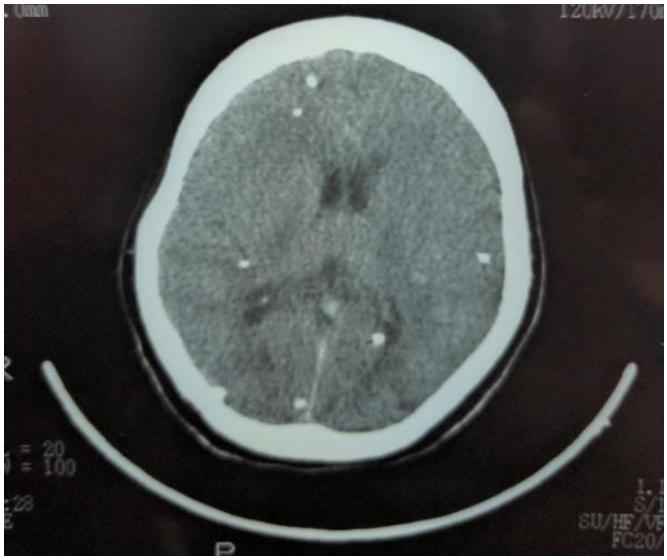


Figure 37: CT (Brain) of 41-year-old female with multiple calcification and perilesional edema

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 the present population. In 58% of patients with intractable epilepsy irrespective of the types of seizure did not show any clustering of seizure ($p<0.05$). But a few proportion of patients (25%, n=127) in partial seizure group had a significant association with the clustering of 1-2 times as seen in Table 12 . In the neurological examination, none of the comorbid conditions except a headache had an association with the type of seizures. Partial 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%). No change in seizure semiology was observed among 43.07% of patients in generalised seizure and 31.98% patients with partial seizures which were also statistically significant ($p<0.05$) as seen in Table 12.

Table 11: Association of age and seizure type

Demographics		**Seizure type**				**Pearson's Chi-Square Test**	
		Generalised		**Partial seizure**			
		n	**%**	**n**	**%**	**Value**	**Sig.**
Age	10-15	9	6.57	9	2.44	22.618	0.012
	16-20	40	**29.20***	82	**22.22***		
	21-25	10	7.30	57	**15.45***		
	26-30	17	**12.41***	67	**18.16***		
	31-35	19	**13.87***	45	**12.20***		
	36-40	9	6.57	45	**12.20***		
	41-45	11	8.03	22	5.96		
	46-50	6	4.38	15	4.07		
	51-55	11	8.03	14	3.79		
	56-60	2	1.46	9	2.44		
	>60	3	2.19	4	1.08		

*level of significance <.05

Table 12: Comparison of clinical characteristics between generalise and partial seizures

Clinical characteristics		**Generalised seizure**		**Partial seizure**		**value**	**sig**
		n	**%**	**n**	**%**		
Clustering of present seizure	0	102	**74.45***	194	**52.57***	24.782	0.000
	1-2	18	13.14	127	**34.42***		
	2-3	13	9.49	31	8.40		
	>3	4	2.92	17	4.61		
Neuro examination	Not significant	113	**82.48***	265	**71.82***	11.935	0.008
	Headache	15	10.95	86	**23.31***		
	Hemiparesis	4	2.92	13	3.52		
	Neurocutaneousmarkers	5	3.65	5	1.36		
Semiology change	No change	59	**43.07***	118	**31.98***	5.400	0.020
	Change	78	**56.93***	251	**68.02***		

*level of significance <.05

CT scan findings did not reveal significant results with both type of seizures ($p<0.05$). Both types of seizures showed strong association with MTS, neoplastic and nonneoplastic lesions (gliosis, cyst, vascular malformation and infectious) and non-specific lesions ($p<0.05$). 39.02% of patients with partial seizures were significantly associated with MTS when compared to generalised seizures (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 nonneoplastic lesions were observed almost in equal proportion among patients with generalised (13.87%) and partial seizures (11.38%) as seen in Table 6. 38.69% patients with generalised seizures had statistically significant normal MRI findings. **DTI findings showed the significantly higher proportion of abnormalities in 85.09% of patients with complex partial seizures followed by 67.15% of patients with generalised seizures.** DTI findings were significantly normal in 32.85% of patients with generalised seizures. DTI were normal

in only 14.91% of patients with partial seizures which was not statistically significant as seen in Table 6. 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 were seen in 20.05% of patients with partial seizures. Focal epileptiform discharges were rarely observed (4.38%) in patients with generalized seizures. 45.99% of patients with generalized epilepsy had bilateral epileptiform generalized discharges followed by 38.75% of patients with partial seizures as seen in Table 13.

Table 13: structural imaging findings across type of seizures

Clinical characteristics		**Seizure type**				**Pearson's Chi-Square Test**	
		Generalized		**Partial seizure**			
		n	**%**	**n**	**%**	**Value**	**Sig.**
CT Scan findings	Not significant	97	70.80	291	78.86	8.835	0.265
	Calcification	16	11.68	37	10.03		
	Infarction	3	2.19	7	1.90		
	Gliosis	9	6.57	12	3.25		
	Atrophy	9	6.57	18	4.88		
	Lissenchephaly	1	.73	0	.00		
	Neoplastic	0	.00	2	.54		
	Non-neoplastic	2	1.46	2	.54		
MRI findings	Normal	53	38.69*	66	17.89	43.127	0.000
	MCD	10	7.30	40	10.84		
	MTS	18	**13.14***	144	**39.02***		
	IHI	10	7.30	25	6.78		
	Neoplastic and Non neoplastic lesions (gliosis, cyst, vasclar malform,infectious)	19	**13.87***	42	**11.38***		
	Nonspecific lesion (cortical atropy, periventcular white matter, calcification)	27	**19.71***	52	**14.09***		
DTWI findings	Normal	45	**32.85***	55	14.91	20.281	0.000
	Abnormal	92	**67.15***	314	**85.09***		
EEG findings	Normal	68	**49.64***	152	**41.19***	18.447	0.000
	Focal	6	4.38	74	**20.05***		
	Generalised	63	**45.99***	143	**38.75***		

*level of significance <.05

Neuropsychiatry findings and type of seizures were compared using Pearson's Chi- Square test. Comparatively, a similar proportion of patients with the generalized seizure and partial seizure had low IQ and mentally retarded, reduced MQ, abnormalities in BGT, anxiety and depression and quality of life. Pearson's 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 seizures as seen in Table 14.

Table 14: IQ, MQ, BGT, anxiety, depression and quality of life scores in different type of seizures among intractable epilepsy

Neuropsychological aspects		**Seizure type**				**Pearson's Chi-Square Test**	
		Generalized		**Partial seizure**			
		n	**%**	**n**	**%**	**Value**	**Sig.**
IQ	≤ 69 : Mental retardation	40	29.20	107	29.00	2.553	0.279
	70 - 90: Dull normal slow learners	22	16.06	82	22.22		
	> 90: Average intelligence	75	54.74	180	48.78		
MQ	≥ 70: Normal	88	64.23	224	60.70	0.526	0.468
	< 70: Deficits of memory dysfunction	49	35.77	145	39.30		
BGT	Normal	77	56.20	211	57.18	0.039	0.844
	Abnormal	60	43.80	158	42.82		
Anxiety	Absent	63	45.99	135	36.59	5.151	0.076
	Present	34	24.82	127	34.42		
	CNT	40	29.20	107	29.00		
Depression	Absent	67	48.91	150	40.65	4.133	0.127
	Present	30	21.90	112	30.35		
	CNT	40	29.20	107	29.00		
Anxiety and Depression	Absent	71	51.82	162	43.90	4.010	0.135
	Present	26	18.98	100	27.10		
	CNT	40	29.20	107	29.00		
Total Quality of Life	Very poor	40	9.49	37	10.03	2.330	0.507
	Poor	13	38.69	162	43.90		
	Average	53	22.63	63	17.07		
	Good	31	9.49	37	10.03		

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

5.7.1. 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 patients being more in the present study population showed a significant increase in the frequency of structural lesions as seen in Table 15.

5.7.2. Clinical characteristics of 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, postnatal, developmental and 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 markers, family history, the age of onset of a seizures, clustering, neurological examination and comorbid conditions using chi-square test, many of the cells had frequencies less than 5, thus they were not considered as significant measures (Table 16).

Table 15: Association of demographics with structural abnormalities in brain

Demographic variables		Structural lesions (MRI)												Pearson's Chi-Square Test	
		Without structural lesions		MCD		MTS		IHI		Neoplastic and Non-neoplastic lesions		Nonspecific lesion			
		n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	Value	Sig.
Age	10-15	5	27.78	3	16.67	2	11.11	2	11.11	4	22.22	2	11.11	83.255[a]	.002
	16-20	28	22.95	18	14.75	38	31.15	16	13.11	10	8.20	12	9.84		
	21-25	16	23.88	5	7.46	20	29.85	1	1.49	6	8.96	19	28.36		
	26-30	16	19.05	11	13.10	29	34.52	5	5.95	12	14.29	11	13.10		
	31-35	14	21.88	3	4.69	24	37.50	6	9.38	7	10.94	10	15.63		
	36-40	13	24.07	7	12.96	21	38.89	2	3.70	4	7.41	7	12.96		
	41-45	6	18.18	1	3.03	14	42.42	1	3.03	3	9.09	8	24.24		
	46-50	4	19.05	0	.00	9	42.86	1	4.76	5	23.81	2	9.52		
	51-55	12	48.00	1	4.00	3	12.00	0	.00	3	12.00	6	24.00		
	56-60	4	36.36	1	9.09	1	9.09	1	9.09	3	27.27	1	9.09		
	>60	1	14.29	0	.00	1	14.29	0	.00	4	57.14	1	14.29		
Gender	Male	66	22.45	31	10.54	88	29.93	16	5.44	50	17.01	43	14.63	18.520	.002
	Female	53	25.00	19	8.96	74	34.91	19	8.96	11	5.19	36	16.98		
Education level	No school education	17	20.00	9	10.59	27	31.76	11	12.94	11	12.94	10	11.76	17.171	.309
	Elementary (1-8)	34	20.86	14	8.59	54	33.13	10	6.13	22	13.50	29	17.79		
	High school (9-12)	44	22.56	23	11.79	64	32.82	10	5.13	22	11.28	32	16.41		
	Graduate	24	38.10	4	6.35	17	26.98	4	6.35	6	9.52	8	12.70		
Occupational status	Unemployed	34	18.18	20	10.70	71	37.97	21	11.23	18	9.63	23	12.30	62.486[a]	.003
	Housewife	20	27.03	4	5.41	27	36.49	1	1.35	4	5.41	18	24.32		
	Daily labour	15	21.74	7	10.14	24	34.78	2	2.90	8	11.59	13	18.84		
	Skilled	15	22.39	7	10.45	18	26.87	3	4.48	15	22.39	9	13.43		
	Clerical	8	47.06	0	.00	3	17.65	0	.00	3	17.65	3	17.65		
	Professional	5	62.50	0	.00	0	.00	0	.00	2	25.00	1	12.50		
	Student	20	28.57	10	14.29	15	21.43	7	10.00	7	10.00	11	15.71		
	Dependent	2	14.29	2	14.29	4	28.57	1	7.14	4	28.57	1	7.14		

Note: [a] indicates that more than 10% of cells have expected frequencies less than 5

Table 16: Association of clinical characteristic with structural lesions

Clinical characteristics	Pearsons chi-square test	Value
Developmental milestones	9.658	.086
Natal history	14.533[a]	.150
Post natal history	25.334[a]	.444
Neurocutaneous markers	13.667[a]	.018
Family history	16.611[a]	.005
Duration of seizure	39.098[a]	.124
Age of onset	70.373[a]	.002
Seizure frequency	17.578	.063
Clustering of present seizure	45.779[a]	.000
Precipitating factor	25.130[a]	.196
Status epilepsy	5.048[a]	.410
Neuro examination	191.922[a]	.000
Comorbid conditions	100.161[a]	.000
Drug	7.447	.189

Note: [a] indicates that more than 10% of cells have expected frequencies less than 5

5.7.3. Association of structural abnormalities, EEG with neuroimaging findings

The side of the lesion in CT, MRI, DTI 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 DTI was significantly associated with MTS (right, left and bilateral lesions). CT scan findings were associated with neoplastic- nonneoplastic 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 as seen in Table 17.

Table 17: Association of structural lesion with side of lesion in CT, MRI, DTWI and EEG investigations

Neuro radiological investigations		Structural lesions (MRI)												Pearson's Chi-Square Test	
		Without structural lesions		MCD		MTS		IHI		Neoplastic and Nonneoplastic lesions		Nonspecific lesion			
		n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	Value	Sig.
Side of lesion CT	Right	0	.00	0	.00	0	.00	3	15.00	9	45.00*	8	40.00*	174.106[a]	.000
	Left	3	8.11	0	.00	4	10.81	1	2.70	16	43.24*	13	35.14*		
	Bilateral	1	1.64	4	6.56	16	26.23	3	4.92	10	16.39	27	44.26*		
	Normal	115	29.64*	46	11.86	142	36.60*	28	7.22	26	6.70	31	7.99		
Side of lesion - MRI	Normal	119	100.00	0	.00	0	.00	0	.00	0	.00	0	.00	617.945	.000
	Right	0	.00	11	12.50	42	**47.73***	5	5.68	17	19.32	13	14.77		
	Left	0	.00	13	7.22	93	**51.67***	30	16.67	26	14.44	18	10.00		
	Bilateral	0	.00	26	21.85	27	22.69	0	.00	18	15.13	48	40.34*		
Side of lesion - DTWI	Normal	46	46.00	4	4.00	13	13.00	1	1.00	14	14.00	22	22.00	63.508	.000
	Right	16	16.84	12	12.63	35	**36.84***	8	8.42	14	14.74	10	10.53		
	Left	29	18.35	13	8.23	66	**41.77***	11	6.96	16	10.13	23	14.56		
	Bilateral	28	18.30	21	13.73	48	**31.37***	15	9.80	17	11.11	24	15.69		
Side of lesion - EEG	Right	2	8.00	1	4.00	14	56.00*	0	.00	6	24.00	2	8.00	45.090[a]	.000
	Left	3	5.45	6	10.91	23	41.82*	3	5.45	12	21.82	8	14.55		
	Bilateral	41	19.90	27	13.11	63	30.58*	18	8.74	23	11.17	34	16.50		
	Normal	73	33.18	16	7.27	62	28.18	14	6.36	20	9.09	35	15.91		

Note: [a] indicates that more than 10% of cells have expected frequencies less than 5

*indicate level of significance $p<0.05$.

Table 18: Association of Neuropsychological test results with structural lesions in brain

Neuropsychological test results		Structural lesions (MRI)												Pearson Chi-Square Test	
		Without structural lesions		MCD		MTS		IHI		Neoplastic and Non-neoplastic lesions		Nonspecific lesion			
		n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	Value	Sig.
IQ Category	Abnormal	31	12.35	37	14.74	89	**35.46***	17	6.77	38	15.14	39	15.54	44.104	.000
	Normal	88	**34.51***	13	5.10	73	28.63	18	7.06	23	9.02	40	15.69		
MQ Category	Abnormal	25	12.89	27	13.92	71	**36.60***	13	6.70	28	14.43	30	15.46	23.872	.000
	Normal	94	**30.13***	23	7.37	91	29.17	22	7.05	33	10.58	49	15.71		
BGT	Normal	91	**31.60***	21	7.29	83	28.82	21	7.29	26	9.03	46	15.97	30.499	.000
	Abnormal	28	12.84	29	13.30	79	**36.24***	14	6.42	35	16.06	33	15.14		
Anxiety	Absent	63	**31.82***	15	7.58	56	28.28	14	7.07	20	10.10	30	15.15	28.740	.001
	Present	40	24.84	11	6.83	52	**32.30***	10	6.21	24	14.91	24	14.91		
	CNT	16	10.88	24	16.33	54	36.73	11	7.48	17	11.56	25	17.01		
Depression	Absent	65	**29.95***	18	8.29	65	**29.95***	15	6.91	22	10.14	32	14.75	27.711	.002
	Present	38	26.76	8	5.63	43	**30.28***	9	6.34	22	15.49	22	15.49		
	CNT	16	10.88	24	16.33	54	36.73	11	7.48	17	11.56	25	17.01		
Anxiety and Depression	Absent	68	29.18	19	8.15	72	**30.90***	16	6.87	22	9.44	36	15.45	29.838	.001
	Present	35	27.78	7	5.56	36	28.57	8	6.35	22	17.46	18	14.29		
	CNT	16	10.88	24	16.33	54	36.73	11	7.48	17	11.56	25	17.01		

*indicate level of significance $p<0.05$

Table 18: Association of Neuropsychological test results with structural lesions in brain

Neuropsychological test results		Structural lesions (MRI)												Pearson Chi-Square Test	
		Without structural lesions		MCD		MTS		IHI		Neoplastic and Non-neoplastic lesions		Nonspecific lesion			
		n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	n	Row %	Value	Sig.
IQ Category	Abnormal	31	12.35	37	14.74	89	**35.46***	17	6.77	38	15.14	39	15.54	44.104	.000
	Normal	88	**34.51***	13	5.10	73	28.63	18	7.06	23	9.02	40	15.69		
MQ Category	Abnormal	25	12.89	27	13.92	71	**36.60***	13	6.70	28	14.43	30	15.46	23.872	.000
	Normal	94	**30.13***	23	7.37	91	29.17	22	7.05	33	10.58	49	15.71		
BGT	Normal	91	**31.60***	21	7.29	83	28.82	21	7.29	26	9.03	46	15.97	30.499	.000
	Abnormal	28	12.84	29	13.30	79	**36.24***	14	6.42	35	16.06	33	15.14		
Anxiety	Absent	63	**31.82***	15	7.58	56	28.28	14	7.07	20	10.10	30	15.15	28.740	.001
	Present	40	24.84	11	6.83	52	**32.30***	10	6.21	24	14.91	24	14.91		
	CNT	16	10.88	24	16.33	54	36.73	11	7.48	17	11.56	25	17.01		
Depression	Absent	65	**29.95***	18	8.29	65	**29.95***	15	6.91	22	10.14	32	14.75	27.711	.002
	Present	38	26.76	8	5.63	43	**30.28***	9	6.34	22	15.49	22	15.49		
	CNT	16	10.88	24	16.33	54	36.73	11	7.48	17	11.56	25	17.01		
Anxiety and Depression	Absent	68	29.18	19	8.15	72	**30.90***	16	6.87	22	9.44	36	15.45	29.838	.001
	Present	35	27.78	7	5.56	36	28.57	8	6.35	22	17.46	18	14.29		
	CNT	16	10.88	24	16.33	54	36.73	11	7.48	17	11.56	25	17.01		

*indicate level of significance $p<0.05$

5.7.4. 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. A significant proportion of patients with intractable epilepsy who had no structural abnormalities had normal IQ scores, MQ scores, and BGT results. A significant proportion of patients with MTS had anxiety and depression as seen in Table 18. 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 ($P<0.05$) as seen in Table 18.

Table 19: Association of Quality of life scores in various structural imaging findings

Total Quality of Life		**MRI**						**Total**
		Normal	**MCD**	**MTS**	**IHI**	**Neoplastic and Non neoplastic lesions**	**Nonspecific lesion**	
Very Poor	Count	16	24	54	11	17	25	147
	Row %	10.88*	16.33*	36.73*	7.48	11.56*	17.01*	100.00
Poor	Count	12	2	18	3	7	8	50
	Row %	24.00*	4.00	36.00*	6.00	14.00*	16.00*	100.00
Average	Count	59	19	66	13	25	33	215
	Row %	27.44*	8.84	30.70*	6.05	11.63*	15.35*	100.00
Good	Count	32	5	24	8	12	13	94
	Row %	34.04*	5.32	25.53*	8.51	12.77*	13.83*	100.00
Total	Count	119	50	162	35	61	79	506
	Row %	23.52	9.88	32.02	6.92	12.06	15.61	100.00
Pearsons's Chi-Square Value: 29.941; Sig.: 0.012								

*indicate level of significance $p<0.05$

Total quality of life was very poor in MCD, MTS, neoplastic and nonneoplastic, nonspecific lesions and patients without any structural abnormalities as seen in Table 19. 36.73% of MTS patients followed by MCD (16.33%), non specific lesions (17.01%), neoplastic and nonneoplastic lesions (11.56%) had very poor quality of life. IHI patients did not show any association with the quality of life.

5.8. Association of side of lesion across neuroimaging investigation (CT, MRI, DTI) and EEG

5.8.1. 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 the present the study is (115+18+29+48)/506 (*100) = 41.5%. If CT and MRI of patients with no structural abnormalities were ignored, 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 the lesion in more than 80% of patients as seen in Table 20.

Table 20: Association of Side of lesion in CT and MRI

Side of lesion CT		Side of lesion - MRI				Total
		Normal	Right	Left	Bilateral	
Right	Count	0	18	1	1	20
	Row %	.0	**90.0***	5.0	5.0	100.0
Left	Count	3	3	29	2	37
	Row %	8.1	8.1	**78.4***	5.4	100.0
Bilateral	Count	1	1	11	48	61
	Row %	1.6	1.6	18.0	**78.7***	100.0
Normal	Count	115	66	139	68	388
	Row %	**29.6***	17.0	**35.8***	17.5	100.0
Total	Count	119	88	180	119	506
	Row %	23.5	17.4	35.6	23.5	100.0
Pearson Chi-square Test: Value: 220.781; Sig.: 0.000						

*Note: *level of significance P<0.05*

5.8.2. Association of side of lesion on MRI and DTWI

From the present study, we observed a significant proportion of patients who have normal MRI showed significant DTI 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 DTI results in the present study is [(54 + 103 +68)/ (79 +129+125)] * 100 = 67.57%

Table 21: Association of side of lesion in MRI with DTWI

Side of lesion - MRI		Side of lesion – DTWI				Total
		Normal	Right	Left	Bilateral	
Normal	Count	46	16	29	28	119
	Row %	**38.7***	13.4	**24.4***	**23.5***	100.0
Right	Count	11	54	5	18	88
	Row %	12.5	**61.4***	5.7	**20.5***	100.0
Left	Count	24	14	103	39	180
	Row %	13.3	7.8	**57.2***	**21.7***	100.0
Bilateral	Count	19	11	21	68	119
	Row %	16.0	9.2	17.6	**57.1***	100.0
Total	Count	100	95	158	153	506
	Row %	19.8	18.8	31.2	30.2	100.0
Pearson's Chi-Square Test: Value: 236.226; Sig.: 0.000						

*Note: *level of significance P<0.05*

5.8.3. Association of side of lesion in MRI and side of abnormality in 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 as seen in Table 22. The consistency of MRI and EEG results in the present study is [(22+45+74)/ (23+52+165)] * 100 = 58.75%.

Table 22: Association of side of lesion in MRI and EEG

Side of lesion - MRI		**Side of lesion – EEG**				**Total**
		Right	**Left**	**Bilateral**	**Non-significant**	
Normal	Count	2	3	41	73	119
	Row %	1.7	2.5	**34.5***	**61.3***	100.0
Right	Count	22	3	25	38	88
	Row %	**25.0***	3.4	**28.4***	**43.2***	100.0
Left	Count	1	45	66	68	180
	Row %	.6	**25.0***	**36.7***	**37.8***	100.0
Bilateral	Count	0	4	74	41	119
	Row %	.0	3.4	**62.2***	**34.5***	100.0
Total	Count	25	55	206	220	506
	Row %	4.9	10.9	40.7	43.5	100.0
Pearson's Chi-Square Test: Value: 169.417; Sig.: 0.00						

*Note: *level of significance P<0.05*

5.8.4. Association of side of lesion between DTI and EEG

Patients who had normal DTWI finding, 24% showed significant bilateral EEG abnormalities and 64% of them did not show any EEG abnormalities. A 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 the present study is [(19+34+95)/ (22+46+182)] * 100 = 59.2%.

Table 23:Association of side of lesion in DTWI and EEG

Side of lesion - DTWI		Side of lesion – EEG				Total
		Right	Left	Bilateral	Non-significant	
Normal	Count	3	9	24	64	100
	Row %	3.0	9.0	**24.0***	**64.0***	100.0
Right	Count	19	5	25	46	95
	Row %	20.0	5.3	**26.3***	**48.4***	100.0
Left	Count	0	34	62	62	158
	Row %	.0	21.5	**39.2***	**39.2***	100.0
Bilateral	Count	3	7	95	48	153
	Row %	2.0	4.6	**62.1***	**31.4***	100.0
Total	Count	25	55	206	220	506
	Row %	4.9	10.9	40.7	43.5	100.0
Pearson's Chi-Square Test: Value: 125.043; Sig.: 0.000						

*Note: *level of significance P<0.05*

5.9. Role of Neuroimaging results (CT, MRI, and DTI) 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, DTI also has a greater chance of detecting an abnormality in MTS (36.7%). EEG revealed abnormal results in MTS which 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, DTI could identify an abnormality in 7.91% (n=40) of patients with intractable epilepsy apart from all other investigations. If MRI and DTI were combined for investigating intractable epilepsy

patients, the frequency of identifying structural abnormalities increased to 18.58% (n= 94). If MRI, DTI 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). Comparison of results among various techniques is shown in Table 24 and 25.

Table 24: Comparison of structural lesions identified through various neuroimaging investigation with each imaging techniques

Structural lesions	**CT Result**				**MRI result**				**DTWI Result**				**EEG Result**			
	Normal		**Abnormal**		**Normal**		**Abnormal**		**Normal**		**Abnormal**		**Normal**		**Abnormal**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Normal	115	29.6	4	3.4	119	100.0	0	.0	46	46.0	73	**18.0***	73	33.2	46	**16.1***
MCD	46	11.9	4	3.4	0	.0	50	**12.9***	4	4.0	46	**11.3***	16	7.3	34	**11.9***
MTS	142	36.6	20	**16.9***	0	.0	162	**41.9***	13	13.0	149	**36.7***	62	28.2	100	**35.0***
IHI	28	7.2	7	5.9	0	.0	35	9.0	1	1.0	34	8.4	14	6.4	21	7.3
Neoplastic and Non neoplastic lesions	26	6.7	35	**29.7***	0	.0	61	**15.8***	14	14.0	47	**11.6***	20	9.1	41	**14.3***
Nonspecific lesion	31	8.0	48	**40.7***	0	.0	79	**20.4***	22	22.0	57	**14.0***	35	15.9	44	**15.4***

*Note: *level of significance P<0.05*

Table 25: Comparison of various imaging abnormalities in identifying structural abnormalities of brain

Imaging techniques	n	%
All normal	31	6.13
CT alone abnormal	1	.20
MRI alone abnormal	14	2.77
DTWI alone abnormal	**40**	**7.91**
EEG alone abnormal	13	2.57
CT & MRI abnormal	18	3.56
CT & DTWI abnormal	1	.20
CT & EEG abnormal	1	.20
MRI & DTWI abnormal	**94**	**18.58**
MRI & EEG abnormal	12	2.37
DTWI & EEG abnormal	31	6.13
CT, MRI & EEG abnormal	10	1.98
CT, MRI & DTWI abnormal	21	4.15
CT, DTWI & EEG abnormal	1	.20
MRI, DTWI & EEG abnormal	**153**	**30.24**
All abnormal	**65**	**12.85**

5.10. Association between education and occupation in intractable epilepsy

Chi-square test was applied to associate education and occupational levels in intractable epilepsy. Occupational status was grouped into 1) unemployed (unemployed + housewife), 2) Employed (daily labourer, skilled, clerical, professional) and 3) Students for analysis. Intractable epilepsy being a heterogeneous group (cognitive functions, structural abnormalities) showed the 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 as seen in Table 26. Also, 31.28% of the population with high school education and 42.86% of the population with a graduate level of education were significantly associated with employment.

Table 26: Association of education status and occupation in patients with intractable epilepsy.

Education level		Occupation			Total
		Unemployed	**Employed**	**Student**	
No school education	Count	54	30	1	85
	Row %	**63.53***	35.29	1.18	100.00
	Col %	19.64	18.63	1.43	16.80
Elementary (1-8)	Count	107	43	13	163
	Row %	**65.64***	26.38	7.98	100.00
	Col %	38.91	26.71	18.57	32.21
High school (9-12)	Count	91	61	43	195
	Row %	**46.67***	**31.28***	22.05	100.00
	Col %	33.09	37.89	61.43	38.54
Graduate	Count	23	27	13	63
	Row %	36.51	**42.86***	20.63	100.00
	Col %	8.36	16.77	18.57	12.45
Total	Count	275	161	70	506
	Row %	54.35	31.82	13.83	100.00
	Col %	100.00	100.00	100.00	100.00
Pearson Chi-Square Value: 40.732; Sig.: **0.000**					

5.10.1. 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 have 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%). An 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 the elementary level as seen in Table 28. No significant association of employment was observed with a medical history as seen in Table 27.

Table 27: Association of medical history findings with educational and occupational status

Clinical Characteristics		**Education level**								**Pearson Chi-Square Test**	
		No school education (n = 85)		**Elementary (1-8) (n = 163)**		**High school (9-12) (n = 195)**		**Graduate (n =63)**			
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**Value**	**Sig.**
Developmental milestones	Normal	69	81.18	144	88.34	171	87.69	49	77.78	6.155	.104
	Delayed	16	18.82	19	11.66	24	12.31	14	22.22		
Natal history	Not significant	75	88.24	151	92.64	187	95.90	61	96.83	9.387	.153
	LSCS	2	2.35	5	3.07	3	1.54	1	1.59		
	Asphyxia	8	9.41	7	4.29	5	2.56	1	1.59		
Post natal history	Not significant	80	94.12	152	93.25	188	96.41	58	92.06	16.984	.320
	Infections	0	.00	5	3.07	0	.00	1	1.59		
	Head injury	1	1.18	1	.61	2	1.03	1	1.59		
	Stroke	2	2.35	1	.61	0	.00	0	.00		
	Febrile seizures	2	2.35	3	1.84	3	1.54	2	3.17		
	Hypothyroidism	0	.00	1	.61	2	1.03	1	1.59		
Family history	Absent	76	89.41	151	92.64	185	94.87	60	95.24	3.310	.346
	Present	9	10.59	12	7.36	10	5.13	3	4.76		

Table 28: Association of clinical characteristics of intractable epilepsy with education

Clinical Characteristics		Education level								Pearson Chi-Square Test	
		No school education (n = 85)		Elementary (1-8) (n = 163)		High school (9-12) (n = 195)		Graduate (n =63)			
		n	%	n	%	n	%	n	%	Value	Sig.
Duration of seizure	0-5	8	9.41	17	10.43	25	12.82	14	**22.22***	35.593	**.008**
	6-10	9	**10.59***	31	**19.02***	52	**26.67***	21	**33.33***		
	11-15	22	**25.88***	41	**25.15***	33	**16.92***	8	**12.70***		
	16-20	26	**30.59***	33	**20.25***	40	**20.51***	10	**15.87***		
	21-25	4	4.71	13	7.98	15	7.69	6	9.52		
	26-30	6	7.06	13	7.98	18	9.23	2	3.17		
	30+	10	11.76	15	9.20	12	6.15	2	3.17		
Age of onset	0-5	35	**41.18***	48	**29.45***	59	**30.26***	11	**17.46***	40.164	**.021**
	6-10	9	**10.59***	38	**23.31***	39	**20.00***	12	**19.05***		
	11-15	13	**15.29***	29	**17.79***	27	**13.85***	8	**12.70***		
	16-20	5	5.88	16	9.82	28	**14.36***	8	**12.70***		
	21-25	8	9.41	10	6.13	13	6.67	4	6.35		
	26-30	6	7.06	7	4.29	15	7.69	9	**14.29***		
	31-35	3	3.53	6	3.68	6	3.08	7	**11.11***		
	36-40	1	1.18	3	1.84	6	3.08	3	4.76		
	> 40 Years	5	5.88	6	3.68	2	1.03	1	1.59		
Seizure frequency	Daily	15	17.65	24	14.72	34	17.44	7	11.11	3.245	.778
	1-6 Weekly	24	28.24	54	33.13	56	28.72	17	26.98		
	1-4 Month	46	54.12	85	52.15	105	53.85	39	61.90		
Clustering of present seizure	0	45	52.94	99	60.74	111	56.92	41	65.08	8.465	.488
	1-2	27	31.76	38	23.31	63	32.31	17	26.98		
	2-3	10	11.76	18	11.04	13	6.67	3	4.76		
	>3	3	3.53	8	4.91	8	4.10	2	3.17		
Precipitating factor	Not significant	62	72.94	122	74.85	152	77.95	45	71.43	10.054[a]	.611
	Sleeep deprivation	14	16.47	21	12.88	31	15.90	12	19.05		
	Febrile illness	3	3.53	5	3.07	2	1.03	0	.00		
	Nocturnal	4	4.71	6	3.68	4	2.05	2	3.17		
	Others	2	2.35	9	5.52	6	3.08	4	6.35		
Status epilepsy	Absent	77	90.59	150	92.02	180	92.31	57	90.48	.379	.945
	Present	8	9.41	13	7.98	15	7.69	6	9.52		
Neuro examination	Not significant	63	74.12	118	72.39	150	76.92	47	74.60	10.497	.312
	Headache	14	16.47	33	20.25	40	20.51	14	22.22		
	Hemiparesis	6	7.06	7	4.29	2	1.03	2	3.17		
	Neurocutaneous markers	2	2.35	5	3.07	3	1.54	0	.00		
Comorbid conditions	Not significant	77	90.59	131	80.37	158	81.03	54	85.71	14.517	.487
	Migraine	7	8.24	26	15.95	32	16.41	6	9.52		
	Headtrauma	1	1.18	6	3.68	2	1.03	3	4.76		
	Alcohol	0	.00	0	.00	1	.51	0	.00		
	Smoking	0	.00	0	.00	1	.51	0	.00		
	Substanceabuse	0	.00	0	.00	1	.51	0	.00		
Drug	Monotherapy	7	8.24	18	11.04	37	18.97	15	**23.81***	11.152	**.011**
	Polytherapy	78	**91.76***	145	**88.96***	158	**81.03***	48	**76.19***		

Note: * indicate level of significance <0.05

The various structural lesions, side of lesion across various neuroimaging techniques and EEG did not associate significantly with any category of education being considered for the study as seen in Table 29. 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 an 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 as seen in Table 30.

Table 29: Association of radio-imaging techniques and EEG with education

Structural and EEG findings		Education level								Pearson Chi-Square Test	
		No school education (n = 85)		Elementary (1-8) (n = 163)		High school (9-12) (n = 195)		Graduate (n =63)			
		n	%	n	%	n	%	n	%	Value	Sig.
CT Scan	Not significant	59	69.41	118	72.39	161	82.56	50	79.37	30.857[a]	.076
	Calcification	9	10.59	20	12.27	19	9.74	5	7.94		
	Infarction	4	4.71	5	3.07	0	.00	1	1.59		
	Gliosis	3	3.53	11	6.75	5	2.56	2	3.17		
	Atrophy	9	10.59	7	4.29	6	3.08	5	7.94		
	Lissenchephaly	1	1.18	0	.00	0	.00	0	.00		
	Neoplastic	0	.00	1	.61	1	.51	0	.00		
	Non-neoplastic	0	.00	1	.61	3	1.54	0	.00		
Side of lesion CT	Right	2	2.35	10	6.13	5	2.56	3	4.76	14.010[a]	.122
	Left	10	11.76	10	6.13	12	6.15	5	7.94		
	Bilateral	14	16.47	25	15.34	17	8.72	5	7.94		
	Normal	59	69.41	118	72.39	161	82.56	50	79.37		
CT Result	Abnormal	26	30.59	45	27.61	34	17.44	13	20.63	8.216	.042
	Normal	59	69.41	118	72.39	161	82.56	50	79.37		
Structural lesions (MRI)	Normal	17	20.00	34	20.86	44	22.56	24	38.10	17.171	.309
	MCD	9	10.59	14	8.59	23	11.79	4	6.35		
	MTS	27	31.76	54	33.13	64	32.82	17	26.98		
	IHI	11	12.94	10	6.13	10	5.13	4	6.35		
	Neoplastic lesions	11	12.94	22	13.50	22	11.28	6	9.52		
	Nonspecific lesion	10	11.76	29	17.79	32	16.41	8	12.70		
MRI - Classification	Abnormal	68	80.00	129	79.14	151	77.44	39	61.90	8.767	.033
	Normal	17	20.00	34	20.86	44	22.56	24	38.10		
Side of lesion - MRI	Normal	17	20.00	34	20.86	44	22.56	24	38.10	19.473	.021
	Right	9	10.59	32	19.63	37	18.97	10	15.87		
	Left	42	49.41	51	31.29	71	36.41	16	25.40		
	Bilateral	17	20.00	46	28.22	43	22.05	13	20.63		
MRI result	Abnormal	68	80.00	129	79.14	151	77.44	39	61.90	8.767	.033
	Normal	17	20.00	34	20.86	44	22.56	24	38.10		
Side of lesion - DTWI	Normal	18	21.18	32	19.63	34	17.44	16	25.40	12.308	.197
	Right	9	10.59	40	24.54	38	19.49	8	12.70		
	Left	29	34.12	49	30.06	64	32.82	16	25.40		
	Bilateral	29	34.12	42	25.77	59	30.26	23	36.51		
DTWI Result	Abnormal	67	78.82	131	80.37	161	82.56	47	74.60	2.036	.565
	Normal	18	21.18	32	19.63	34	17.44	16	25.40		
EEG	Normal	28	32.94	65	39.88	97	49.74	30	47.62	12.272	.056
	Focal	13	15.29	34	20.86	26	13.33	7	11.11		
	Generalised	44	51.76	64	39.26	72	36.92	26	41.27		
Side of lesion - EEG	Right	1	1.18	11	6.75	11	5.64	2	3.17	16.810[a]	.052
	Left	12	14.12	23	14.11	15	7.69	5	7.94		
	Bilateral	44	51.76	64	39.26	72	36.92	26	41.27		
	Non-significant	28	32.94	65	39.88	97	49.74	30	47.62		
EEG Result	Abnormal	57	67.06	98	60.12	98	50.26	33	52.38	8.255	.041
	Normal	28	32.94	65	39.88	97	49.74	30	47.62		
Semiology change	No change	30	35.29	58	35.58	64	32.82	25	39.68	1.042	.791
	Change	55	64.71	105	64.42	131	67.18	38	60.32		

Table 30: Association of neuropsychological findings with education

Neuropsychological findings		Education level								Pearson Chi- Square Test	
		No school education (n = 85)		Elementary (1-8) (n = 163)		High school (9-12) (n = 195)		Graduate (n =63)			
		n	%	n	%	n	%	n	%	Value	Sig/
IQ	≤ 69 : Mental retardation	41	**48.24***	47	**28.83***	50	**25.64***	9	14.29	32.539	**.000**
	70 - 90: Dull normal	11	12.94	42	25.77	43	22.05	8	12.70		
	> 90: Average intelligence	33	**38.82***	74	**45.40***	102	52.31	46	**73.02***		
MQ	≥ 70: Normal	38	**44.71***	92	**56.44***	128	65.64	54	**85.71***	28.939	**.000**
	< 70: Deficits of memory dysfunction	47	**55.29***	71	**43.56***	67	34.36	9	14.29		
BGT	Normal	35	41.18	84	**51.53***	124	**63.59***	45	**71.43***	19.466	**.000**
	Abnormal	50	**58.82***	79	**48.47***	71	**36.41***	18	28.57		
Anxiety	Absent	30	35.29	65	**39.88***	73	**37.44***	30	**47.62***	26.609	**.000**
	Present	14	16.47	51	**31.29***	72	**36.92***	24	**38.10***		
	CNT	41	**48.24***	47	28.83	50	25.64	9	14.29		
Depression	Absent	29	**34.12***	74	**45.40***	84	**43.08***	30	**47.62***	24.945	**.000**
	Present	15	17.65	42	25.77	61	**31.28***	24	**38.10***		
	CNT	41	**48.24***	47	**28.83***	50	25.64	9	14.29		
Anxiety And Depression	Absent	31	**36.47***	81	**49.69***	88	**45.13***	33	**52.38***	26.214	**.000**
	Present	13	15.29	35	21.47	57	**29.23***	21	**33.33***		
	CNT	41	**48.24***	47	**28.83***	50	25.64	9	14.29		

Note: * indicate level of significance <0.05

Table 31: Association of medical history with occupational status

Medical History		Occupation						Pearson Chi-Square Test	
		Unemployed (n = 275)		Employed (n=161)		Student (n = 70)			
		n	%	n	%	n	%	Value	Sig.
Developmental milestones	Normal	231	84.00	147	91.30	55	78.57	7.615	.062
	Delayed	44	16.00	14	8.70	15	21.43		
Natal history	Not significant	251	91.27	157	97.52	66	94.29	7.077[a]	.132
	LSCS	9	3.27	1	.62	1	1.43		
	Asphyxia	15	5.45	3	1.86	3	4.29		
Post natal history	Not significant	259	94.18	153	95.03	66	94.29	10.154[a]	.427
	Infections	2	.73	4	2.48	0	.00		
	Head injury	3	1.09	1	.62	1	1.43		
	Stroke	3	1.09	0	.00	0	.00		
	Febrile seizures	7	2.55	1	.62	2	2.86		
	Hypothyroidism	1	.36	2	1.24	1	1.43		
Family history	Absent	257	93.45	153	95.03	62	88.57	3.277[a]	.194

5.10.2. Factors contributing to occupation in patients with intractable epilepsy

Among clinical characteristics duration of seizure (longer than 16-20 years) was significantly associated with unemployment. Patients who had a younger age of onset (6-10 years) had a significant association with employment. Almost equal proportion of patients with intractable epilepsy for whom 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 associated with employment status ($p>0.05$) as seen

in Table 32. Medical history was not associated with occupation in the present population as seen in Table 31.

Among structural imaging techniques, none of them had an association with employment as seen in Table 33. 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 low 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 as seen in Table 34.

Table 32: Association of clinical characteristics with employment

Clinical Characteristics		Occupation				Pearson Chi-Square Test			
		Unemployed (n = 275)		Employed (n=161)		Student (n = 70)			
		n	%	n	%	n	%	Value	Sig.
Neurocutaneous markers	Absent	272	98.91	156	96.89	68	97.14	2.453[a]	.293
	Present	3	1.09	5	3.11	2	2.86		
Duration of seizure	0-5	29	10.55	22	13.66	13	18.57	43.568	**.000**
	6-10	51	18.55	41	**25.47***	21	**30.00***		
	11-15	53	19.27	25	15.53	26	**37.14***		
	16-20	71	**25.82***	29	18.01	9	12.86		
	21-25	23	8.36	14	8.70	1	1.43		
	26-30	21	7.64	18	11.18	0	.00		
	30+	27	9.82	12	7.45	0	.00		
Age of onset	0-5	90	32.73	26	16.15	37	52.86	90.658[a]	.000
	6-10	64	23.27	13	8.07	21	30.00		
	11-15	39	14.18	30	18.63	8	11.43		
	16-20	29	10.55	25	15.53	3	4.29		
	21-25	19	6.91	16	9.94	0	.00		
	26-30	14	5.09	22	13.66	1	1.43		
	31-35	11	4.00	11	6.83	0	.00		
	36-40	5	1.82	8	4.97	0	.00		
	> 40 Years	4	1.45	10	6.21	0	.00		
Seizure frequency	Daily	48	17.45	16	9.94	16	22.86	13.680[a]	.008
	1-6 Weekly	91	33.09	40	24.84	20	28.57		
	1-4 Month	136	49.45	105	65.22	34	48.57		
Clustering of present seizure	0	160	58.18	96	59.63	40	57.14	4.131	.659
	1-2	79	28.73	49	30.43	17	24.29		
	2-3	23	8.36	12	7.45	9	12.86		
	>3	13	4.73	4	2.48	4	5.71		
Precipitating factor	Not significant	209	76.00	119	73.91	53	75.71	6.183	.627
	Sleeep deprivation	41	14.91	28	17.39	9	12.86		
	Febrile illness	7	2.55	2	1.24	1	1.43		
	Nocturnal	5	1.82	7	4.35	4	5.71		
	Others	13	4.73	5	3.11	3	4.29		
Status epilepsy	Absent	251	**91.27***	154	**95.65***	59	**84.29***	8.425	**.015**
	Present	24	8.73	7	4.35	11	15.71		
Neuro examination	Not significant	200	72.73	122	75.78	56	80.00	6.277	.393
	Headache	62	22.55	30	18.63	9	12.86		
	Hemiparesis	10	3.64	4	2.48	3	4.29		
	Neurocutaneous markers	3	1.09	5	3.11	2	2.86		
Comorbid conditions	Not significant	224	81.45	136	84.47	60	85.71	12.845	.232
	Migraine	44	16.00	20	12.42	7	10.00		
	Headtrauma	7	2.55	3	1.86	2	2.86		
	Alcohol	0	.00	1	.62	0	.00		
	Smoking	0	.00	1	.62	0	.00		
	Substanceabuse	0	.00	0	.00	1	1.43		
Drug	Monotherapy	31	11.27	32	19.88	14	20.00	7.266	**.026**
	Polytherapy	244	**88.73***	129	**80.12***	56	**80.00***		

Note: * indicate level of significance <0.05

Table 33: Association of radio-imaging techniques and EEG with employment

Structural and EEG findings		Occupation				Pearson Chi-Square Test			
		Unemployed (n = 275)		Employed (n=161)		Student (n = 70)			
		n	%	n	%	n	%	Value	Sig.
CT Scan	Not significant	213	77.45	117	72.67	58	82.86	17.861[a]	.213
	Calcification	28	10.18	19	11.80	6	8.57		
	Infarction	4	1.45	6	3.73	0	.00		
	Gliosis	10	3.64	7	4.35	4	5.71		
	Atrophy	18	6.55	7	4.35	2	2.86		
	Lissenchephaly	1	.36	0	.00	0	.00		
	Neoplastic	1	.36	1	.62	0	.00		
	Non-neoplastic	0	.00	4	2.48	0	.00		
Side of lesion CT	Right	9	3.27	7	4.35	4	5.71	6.910	.329
	Left	18	6.55	17	10.56	2	2.86		
	Bilateral	35	12.73	20	12.42	6	8.57		
	Normal	213	77.45	117	72.67	58	82.86		
CT Result	Abnormal	62	22.55	44	27.33	12	17.14	3.033	.219
	Normal	213	77.45	117	72.67	58	82.86		
Structural lesions (MRI)	Normal	56	**20.36***	43	**26.71***	20	**28.57***	20.585	**.024**
	MCD	26	9.45	14	8.70	10	14.29		
	MTS	102	**37.09***	45	**27.95***	15	**21.43***		
	IHI	23	8.36	5	3.11	7	10.00		
	Neoplastic and Non neoplastic lesions	26	9.45	28	17.39	7	10.00		
	Nonspecific lesion	42	15.27	26	16.15	11	**15.71***		
MRI - Classification	Abnormal	219	79.64	118	73.29	50	71.43	3.426	.180
	Normal	56	20.36	43	26.71	20	28.57		
Side of lesion - MRI	Normal	56	20.36	43	26.71	20	28.57	7.122	.310
	Right	48	17.45	26	16.15	14	20.00		
	Left	101	36.73	61	37.89	18	25.71		
	Bilateral	70	25.45	31	19.25	18	25.71		
MRI result	Abnormal	219	79.64	118	73.29	50	71.43	3.426	.180
	Normal	56	20.36	43	26.71	20	28.57		
Side of lesion - DTWI	Normal	46	16.73	42	26.09	12	17.14	8.381	.211
	Right	56	20.36	23	14.29	16	22.86		
	Left	86	31.27	52	32.30	20	28.57		
	Bilateral	87	31.64	44	27.33	22	31.43		
DTWI Result	Abnormal	229	83.27	119	73.91	58	82.86	5.962	.051
	Normal	46	16.73	42	26.09	12	17.14		
EEG	Normal	112	40.73	79	49.07	29	41.43	3.355	.500
	Focal	44	16.00	25	15.53	11	15.71		
	Generalised	119	43.27	57	35.40	30	42.86		
Side of lesion - EEG	Right	14	5.09	8	4.97	3	4.29	3.448	.751
	Left	30	10.91	17	10.56	8	11.43		
	Bilateral	119	43.27	57	35.40	30	42.86		
	Non-significant	112	40.73	79	49.07	29	41.43		
EEG Result	Abnormal	163	59.27	82	50.93	41	58.57	3.014	.222
	Normal	112	40.73	79	49.07	29	41.43		
Semiology change	No change	88	32.00	63	39.13	26	37.14	2.437	.296
	Change	187	68.00	98	60.87	44	62.86		

Note: * indicate level of significance <0.05

Table 34: Association of neuropsychological findings with employment

Neuropsychological findings		Occupation						Pearson Chi-Square Test	
		Unemployed (n = 275)		Employed (n=161)		Student (n = 70)			
		n	%	n	%	n	%	Value	Sig.
IQ	≤ 69 : Mentalretardation	110	**40.00***	21	13.04	16	22.86	46.653	**.000**
	70 - 90: Dull normal slow learners	60	21.82	35	21.74	9	12.86		
	> 90: Average intelligene	105	**38.18***	105	**65.22***	45	**64.29***		
MQ	≥ 70: Normal	142	**51.64***	121	**75.16***	49	**70.00***		
	< 70: Deficits of memory dysfunction	133	**48.36***	40	24.84	21	30.00		
BGT	Normal	132	**48.00***	101	**62.73***	55	**78.57***	24.524	**.000**
	Abnormal	143	**52.00***	60	37.27	15	21.43		
Anxiety	Absent	89	32.36	75	**46.58***	34	**48.57***	39.017	**.000**
	Present	76	27.64	65	**40.37***	20	**28.57***		
	CNT	110	40.00	21	13.04	16	22.86		
Depression	Absent	92	**33.45***	89	**55.28***	36	**51.43***	40.247	**.000**
	Present	73	26.55	51	31.68	18	25.71		
	CNT	110	**40.00***	21	13.04	16	22.86		
Anxiety and Depression	Absent	102	37.09	93	**57.76***	38	**54.29***	38.842	**.000**
	Present	63	22.91	47	29.19	16	22.86		
	CNT	110	**40.00***	21	13.04	16	22.86		

Note: * indicate level of significance <0.05

6. DISCUSSION

6.1. Demographics of intractable epilepsy

6.1.1. Prevalence of intractable epilepsy

The prevalence of intractable epilepsy (21.05%) of the present study was comparable to the western studies [8,138], that considered Drug-resistant Epilepsy (ILAE, 2010) criteria. The prevalence rates of adults with intractable epilepsy were similar to those studies done with drug-resistant epilepsy criteria. Despite differences in the definition, the prevalence of intractable epilepsy in this study was congruent to that of the western studies [5,7,138] 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 yrs [108], a hospital-based study in Singapore. The present results were not in congruence with results of a population-based study in North Italy [138] which showed increased prevalence in the age range of 35 - 54 years. Decreased prevalence was observed in the age range >60 years (1.38%) were similar to both the studies [108,138] 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-resistant epilepsy (ILAE, 2010) criteria.**

6.1.2. Gender differences

In the present study, the prevalence of intractable epilepsy was majorly observed in males compared to females [3, 4, 78, 106] which is comparable to several studies done in India except for a study which indicates a high prevalence in females rather than males. This could be possible due to the patient attending the epilepsy clinics were majorly males compared to females. There may be influences of low socioeconomic status, educational and cultural factors over the patients who avail treatment in developing countries that cause treatment gap among females [10,139–141]. Also, the low prevalence in

women receiving treatment for epilepsy in the present study is supported by a study done in a tertiary care centre in Kerala state [142].

6.1.3. Educational status

The present study revealed 16.8% of illiteracy in adults with intractable epilepsy. Currently, there is no literature regarding the educational status of adults with intractable epilepsy. The preliminary studies carried out in children with epilepsy show a high prevalence of educational problems (36%) [143]. They attributed the low academic performance to psychiatric illness like attention deficit hyperkinetic disorder, conduct disorder and depression (47%) followed by decreased learning opportunities (22.2%) and borderline intelligence (19.4%). Another hospital-based report showed poor academic performance in 26.1% of urban patients and 38.3% of rural patients with epilepsy [144]. In the study population, a majority of intractable epilepsy patients have discontinued education at the elementary level (32.21%, n=163) and at high school level (38.54%, n=195) which could be due to the chronicity of the disease, low cognition, memory deficits, low socioeconomic status, anxiety and depression.

6.1.4. Occupational status

Though a significant group of the population has completed high school (38.54%) and graduation (12.45%) a high proportion of patients with intractable epilepsy (36.96%) were unemployed. A Study of 872 patients with epilepsy at an outpatient clinic at Spain showed employment rates of 58%, 10.9% unemployed and 12.5% occupationally incapacitated [145]. They concluded that the employment rates were similar to those of the general population and slightly higher levels of unemployment. They unemployment in their population were significantly associated with refractory epilepsy, the low level of education and polytherapy. We compared unemployment rates in the

present study with the unemployment rates in India. In India from1983 to 2011, unemployment rates were reported to be range from 3.8 to 9.4% [146]. **The unemployment in patients with intractable epilepsy (36.96%) is significantly higher than the unemployment in general population and patients with epilepsy.**

6.2. Clinical characteristics of adults with intractable epilepsy

6.2.1. Type of seizure

The type of seizure mostly observed in the present study population is of partial type, especially complex partial seizures. The order of seizure type in the present study are comparable to the reports by Tripathi et al.[11] in North India where they reported majorly partial seizures (83%) followed by generalised seizures (7%), myoclonic (6.5%) and mixed epilepsy (3.5%). There are differences between the frequencies of seizure type among the studies can due to the differences in subjects selection criteria considered for intractable epilepsy [147]. We have followed the ILAE (2010) criteria for the subject selection. The type of seizure and clinical characteristics of intractable epilepsy in India is comparable to the studies done in Singapore [8] and Italy [7]. From the present study, we observed commonly partial seizures (72.92%) followed by generalised seizures (27.08%) that are comparable to both studies that have similar findings.

6.2.2. Duration and onset of seizure

Most of the patients in the present study showed a longer duration of seizure intractability that ranges from 6 years to 20 years. Almost 30% of them had a younger age of onset of seizures (less than 5 years of the age) which reported being a predictor for intractable epilepsy among a large sample of epilepsy patients [133]. Most of the patients in the intractable epilepsy group were mesial temporal sclerosis (32.02%, n=162) and incomplete hippocampal inversion. MTS being a hippocampal lesion that occurs after an

initial precipitating injury during birth or 0-5 years of age, may cause damage to the cells (CA1, CA4) in the hippocampus and may remain silent. After sprouting of dentate gyrus granule cell layer and its axons (mossy fibers) into molecular layer, there is an excitation and inhibition mismatch leading to increased excitation resulting in recurrence of seizure with a change in semiology [64]. From the present study, it was observed that high proportion of patients with intractable epilepsy from the age range of 6-20 years who had an early onset of seizure which were due to various conditions like febrile illness, infection and birth trauma, also these patients had a silent period before developing intractability.

6.2.3. Seizure frequency

From the present study, it was observed that seizure frequency were 1-4 episodes per month (54.35%, n=275), followed by 1-6 episodes per week (29.84%,n=151) and daily occurrence (15.81%, n=80) which signifies severity of damage to the brain parenchyma. Patients having a seizure more than one per day was associated with structural lesions like MCD [52]. 54.35% of intractable epilepsy patients had seizure frequency of 1-4 episode of seizure per month in this large cohort. These findings were supported by a study done using DRE criteria in Singapore who report pretreatment seizure frequency of more than once monthly to be a predictor of drug-resistant epilepsy [108]. Also in India higher frequency of initial seizure of more than one per month is reported to be a predictor of intractable epilepsy [11].

6.2.4. Seizure semiology changes

Also from the records and neurological investigations, it was observed that 65.02% had changed in seizure semiology. The majority of the patients have one or several identifiable structural abnormalities in 93.9% of the population using several

radiological investigations. These changes in seizure semiology may be due to aberrant neural connections caused by axonal sprouting from the excitatory cells as the disease progresses [35,64]. This results in excitatory and inhibitory mismatch causing increased excitation leading recurrent firing.

6.2.5. Clustering

In the present study, we observed a high proportion (41.5%) of patients with clustering more than 1-2 times. Clustering has been reported to be one of the risk factors for intractability [148]. A study by Haut et al. have reported clustering in 29% of their subjects out of 141 patients with epilepsy. They reported extratemporal epilepsy and head trauma as risk factors for clustering. Increased clustering in the study population could be due to extensive involvement of various extratemporal areas in temporal lobe epilepsy and longer duration of seizures resulting in an extensive epileptogenic network.

6.2.6. Precipitating factors

Precipitating factors like sleep deprivation, febrile illness and sleep were observed in the study population. Studies with intractable epilepsy do not report precipitating factors as risk factors for intractability [11,12,149,150]. Seizure precipitant among 400 patients with epilepsy report stress (30%), sleep deprivation (18%), sleep (14%), fever or illness (14%), and fatigue (13%) in patients with epilepsy [151]. In data collection, we did not consider stress as one of the precipitating factors. Moreover, one-third of the patient with intractable epilepsy was mentally retarded where the data regarding stress could not be collected. Similar to the above study we observed sleep deprivation (15.42%) as a major precipitating factor followed by sleep (3.16%) and febrile illness (1.98%).

6.2.7. Status epilepsy

The present study investigated the percentage of intractable epilepsy patients who had a history of status epilepsy. Status epilepsy being an emergency medical condition often associated with clustering and intractability. Status epilepsy is most often reported in children with early onset of epilepsy. one study which included 613 children with epilepsy, 56 (9.1%) were reported to have one or more episodes of status epilepsy [152]. Another study which recruited 128 patients with status epilepsy, episodes (22.6%) were reported to be refractory to first- and second-line antiepileptic treatments [153]. Similar to the above studies, we observed 8.3% of adult intractable epilepsy in the study population reported to have had status epilepsy which is lower than expected. This may be due to poor maintenance of medical records and poor cognitive status of the patients included in the study and also the information regarding status epilepsy collected from the caregivers may be inadequate.

6.2.8. Drugs

As reported by several authors intractable epilepsy patient were often under polytherapy [7,108,133,149,150]. Studies carried out using drug-resistant epilepsy criteria (ILAE criteria) report 94% (113/120) of their patients under polytherapy. Similar to the above study, in the present study population, 85% of them were under polytherapy.

6.2.9. Co-morbid conditions

Comorbid conditions like a migraine were observed in 14% of the population with intractable epilepsy in the present study. A migraine was reported to be prevalent around 26.3% among 388 patients with epilepsy [154]. The reduction in the percentage of patients with migraine in intractable epilepsy patients could be due to methodological differences between the studies where the above study have used International

Classification Headache Disorders (ICHD –II) for classifying headaches. The present study used reports from the clinical examination on migraine headaches.

6.2.10. Developmental History

15% (73/506) of patients with intractable epilepsy in the study had delayed developmental milestones. Delay in developmental milestones has been reported in the literature as a predictor for intractable epilepsy [11]. 50 patients with intractable epilepsy had MCDs and one-third of patients with intractable epilepsy had a younger age of onset. Thus one would expect a high proportion of them have delayed developmental milestones. Also, one-third of the patients with MTS became intractable after an initial precipitating injury and latency period. In such a case, less number of patients were having congenital malformations affecting developmental milestones in this study. Moreover, information provided by the caregivers may be inaccurate and developmental records were not available with the patients might have had reduced the percentage of patients with delayed developmental milestones.

6.2.11. Family history

Family history of seizures was observed only in 6.72% of patients with intractable epilepsy. Family history has been reported as a common risk factor for intractability in childhood refractory epilepsy [136,149]. Since only 10% of the study population had MCDs, a low frequency of family history of seizures can be expected in the present study population. In adult population, family history may not be a significant predictor for intractable epilepsy as supported by the study conducted by Tripathi et al (2011). The prevalence of family history of seizures in the present study is similar to that of the study carried out in Karnataka where they reported a family history of seizure in 8.4% in a cohort of 196 patients with epilepsy [155].

6.2.12. Neurocutaneous markers

Neurocutaneous markers as reported in several malformations of cortical development and syndromes associated with epilepsy were observed in a cohort of 506 patients with intractable epilepsy. Neurocutaneous markers like adenoma sebaceum, neurofibromas, hypomelanosis of ito, and sturge weber syndrome reported [48,49,136] to be associated with intractable epilepsy had been observed during the study.

6.2.13. Neurological findings

19.96% of patients in the study population had headache. The prevalence of a postictal headache is similar to the study by Mainieri et al (2015) who report a postictal headache in 19.1% of 388 patients with epilepsy [156]. Also, 3.36% of them had hemiparesis following stroke causing intractable epilepsy.

6.3. Structural imaging findings in patients with intractable epilepsy

6.3.1. CT scan findings

23.32% of the population in the study showed focal or multiple brain abnormalities in CT scan. The present study results revealed an increased percentage of CT abnormalities in patients with intractable epilepsy when compared to a study done among 905 patients with epilepsy showing CT abnormalities in 13.81% of them [157]. This study considered CT scan to identify structural lesion like calcifications which were reported to be a cause of seizure especially in the Indian subcontinent [88]. Interestingly in the present series of patients, we observed a significant proportion of patients with intractable epilepsy having calcifications which are in contrary to the finding in epileptic population showing cerebrovascular disorders as major finding in CT scan [157]. Focal cortical –subcortical calcifications [88], focal cortical calcifications [91,158], basal ganglia calcifications [89], multiple calcifications, calcifications with gliosis and cortical atrophy as

reported by several authors were observed in13.43% of the present study population.

6.3.2. MRI findings

6.3.2.1. Malformations of cortical development

9.88% of patients with intractable epilepsy had MCDs. These observations from the present study represent that MCDs were observed in higher proportion among intractable epilepsy when compared to people with epilepsy. In a cohort of 303 patients with epilepsy, Brodtkorb et al [159] have reported 4.3% with neuronal migration disorders. Li et al [160] in 1995 have reported 12% of cortical dysgenesis among a cohort of 341 patients with chronic refractory epilepsy. A higher proportion (9.88%, n=50) of patients with MCD were observed in the present study which is comparable to study carried out by Li et al. Difference in the percentage of frequency for MCD could be due to the criteria considered (ILAE, 2010) in the present study.

Most common type of MCD in the present study was focal cortical dysplasia which constitutes 5.13% of the total population. These results were contrary to the studies of Mathew et al [52] who report heterotopia as most common cortical malformation observed in patients with epilepsy among the Indian population. Though we have observed few patients with heterotopia, we observed predominantly focal cortical dysplasia as the common malformation in the cohort of 506 intractable epilepsy patients. These findings of the present study were supported by a study done by Papayannis et al [49] on 3000 adult epilepsy patients who report FCDs as a most common abnormality. Many of the patients with focal cortical dysplasia often presented with multiple FCDs and hippocampal abnormalities like incomplete hippocampal inversion [51,54]. Other cortical malformations like pachygyria, polymicrogyria, dysembryonic neuroepithelial tumor, heterotopia, schizencephaly and hemimegalencephaly were observed in the study

as reported by studies done in adults and children in Indian population [52,136]. Most of the patients under focal cortical dysplasia group had seizures during the early developmental period. 80% of the patients with malformations of cortical development had partial seizures which are considered to be a common finding as reported by studies [52] done on patients with epilepsy presenting with MCDs (35.3%). These dissimilarities may be due to the difference in the patient selection criteria in a specific population.

6.3.2.2. Incomplete hippocampal Inversion

The present study considered isolated IHI for analysis because it is one of the possible structural abnormalities often reported to be associated with temporal lobe epilepsy and MCDs [57]. We analyzed the MRI images of patients with intractable epilepsy using 3 selection criteria for IHI. IHI is an atypical anatomical pattern of hippocampus often reported to be present in healthy controls [56,58] and epileptic population [57]. There are controversies in considering IHI as abnormal in epileptic patients. Studies conducted by Bernasconi et al [57,161] on MCD and temporal lobe epilepsy have reported that IHI occurs in 50% of their population. In the present study, we observed isolated IHI in 6.92% (n=35) among a cohort of 506 patients, which was very low when compared to the prevalence of IHI (23%) in 2000 normal population [162]. This discrepancy could be due to the difference in the criteria between the studies for analyzing and identifying IHI. The above studies have used several criteria for defining complete and partial IHI whereas we have used only 3 criteria for defining IHI. Also, we observed IHI in MCD (40%, n=20) population which were excluded from analysis and we considered only isolated IHI which might have caused the reduction of its prevalence in intractable epilepsy.

Similar to the studies that show IHI as a most common finding in left hippocampus [58], we observed a high proportion of left hippocampal IHI abnormality

(30/35) in the present population. Along with MCD and MTS, IHI has been reported to occur as an abnormal migration developmental disorder [57]. Currently, there are no studies in the literature about isolated IHI in patients with intractable epilepsy. But in the present study, it was observed that a significant amount of population without any abnormality in the brain but still showing isolated IHI. This may be interesting to analyze and consider IHI as one of the causes for intractability in epilepsy.Histopathological studies and in-depth imaging with higher resolution MRI in the study population may improve our understanding of IHI and its importance in intractability.

6.3.2.3. Mesial temporal lobe sclerosis

Mesial temporal lobe sclerosis has been reported by several authors as one of the common causes of intractability [4,18,51,63]. Similarly, in the present study, we observed a large population of patients with MTS had intractability that constitute 32.02% (n=162) of the total population. A similar study carried out in Singapore [8] that has used Drug resistant epilepsy (2010) criteria has reported MTS in 32/120 (27%). The present study is carried out using the same drug resistant epilepsy criteria on a large population with intractable epilepsy showed the slightly high prevalence of MTS in patients with intractable epilepsy (i.e in one-third of patients with intractable epilepsy). There are no studies in Indian population regarding the prevalence of MTS in intractable epilepsy population. The results of the present study emphasize the importance of identifying MTS in intractable epilepsy patients who may benefit from surgery [135,137]. Also along with MTS other lesions like nonspecific gliosis, cystic lesions, MCD, IHI, and infarction were observed in 28 patients with MTS.

6.3.2.4. Neoplastic and nonneoplastic lesions (tumors, gliosis, cyst, vascular malformations, inflammation, and infection)

Similar to various studies which reported several neoplastic and nonneoplastic lesions as a cause for intractable seizures, we observed some of the pathologies in the present population. One patient with glioma and another patient with Gliomatosis cerebri having focal epilepsy (partial seizure) were observed to be present with intractable epilepsy. Similar tumors were reported to be seen in intractable epilepsy in literature [69]. Also, cortical dysplasia and other neuronal migration disorders often coexist with DNET tumors. Similarly, we observed one patient with DNET tumor and FCD [70]. Inflammation and Infections like herpes simplex encephalitis with granuloma (1 patient), tuberculous meningoencephalitis (2 patients), neurocysticercosis (1 patient) and Hashimoto's autoimmune encephalitis were also seen in the study population similar to other studies [77], Rasmussen's encephalitis[78] and tuberous sclerosis [79] were also seen. Gliosis at various regions of the brain especially parieto occipital and orbitofrontal regions was observed in 29 patients (5.70%) with intractable epilepsy signifying nonspecific lesion secondary to trauma, ischemia, and inflammation. Changes like gliosis [84] were observed in 5.70% of the population who might have had trauma, stroke leading to changes in the cell membrane, neuronal loss and collateral sprouting causing excitation [85]. Intractable epilepsy associated with infarctions was observed in 12 patients (2.37%).

Arteriovenous malformations (AVM) were associated with focal intractable epilepsy with secondary generalization in 6 patients (1.18%). All of them had AVM at the parietotemporal region.2 patients with intractable epilepsy found to have intracerebral hemorrhage (.39%). Most frequently encountered vascular causes of intractable epilepsy isarteriovenous malformations (AVMs) and cavernomas [66]. The severity of the seizures depend on the size of AV malformation, hemorrhage and frontotemporal location [68].

6.3.2.5. 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 perilesional edema were observed in 68 patients (13.43%).

Focal cortical – subcortical calcifications are reported to be associated with focal or generalized epilepsy especially in India. 77.5% of patients with calcifications are reported to have focal epilepsy [88]. Basal ganglia calcifications are often reported to be associated with hypoparathyroidism and pseudohypoparathyroidism. Intracranial calcifications are also considered as an incidental finding in 0.3 to 1.5% of the patients [89]. Calcification due to infections may be associated with perilesional edema. These patients have the tendency to develop seizures intermittently. The pathophysiology of the perilesional edema is not clearly understood but it may be due to postictal or release of ionic calcium [90]. Also, focal cerebral calcifications seen in CT scan were found to be associated with gliosis around the calcified lesion on T1 weighted MRI images. 33.3% of patients with perilesional gliosis is reported to be have increased seizure frequency and they were drug resistant [91].

6.3.3. DTWI findings

It has been well documented that DTI shows microstructural abnormalities in epileptic population (both near the area of abnormality which may be congenital or acquired and also away from the seizure loci). Several studies have reported microstructural abnormalities in one or several regions among patients with epilepsy associated with MCD or MTS[93–103,135]. Similar to these above studies, we found microstructural abnormalities in several areas of brain's white matter that are involved in

intractable epilepsy as described in Table 8. Because diverse abnormalities were observed in DTWI we could not classify and group the intractable epilepsy patients into subcategories. To simplify the analysis, we classified them into right, left or bilateral abnormalities to correlate with other structural imaging techniques. In MTS patients were who constitute one-third of the total population were observed abnormal DTI in hippocampal and parahippocampal white matter regions along the fimbriae and fornix on the same side or on the contralateral side. This shows the involvement of wide neural network i.e. medial temporal lobe circuit.

6.4. Neuropsychological assessment in patients with intractable epilepsy

Several studies have reported significant cognitive impairment and psychological illness in epilepsy patients (temporal and extratemporal lobe epilepsy), which were accounted due to the disease process (frequency and chronicity) and a side effect of antiepileptic drugs[104,106,107,118,121,127,163]. In the present study, we evaluated the intelligence, memory, visual perceptual skills, anxiety, depression and quality of life among patients with intractable epilepsy.

Out of 506 patients with intractable epilepsy, 147 patients (29.05%) had mental retardation ($\leq$69 scores) in Wechsler intelligence scale. Similar studies carried out using drug-resistant epilepsy criteria have reported that the 18% of 120 drug-resistant epilepsy patients showing mental retardation [8]. Compared to the above study, we observed increased proportion of patients with mental retardation. The results of the present study in congruence with the studies (Sayin et al, 2004; Moore et al, 2002) who report chronicity (longer seizure duration), early onset of a seizures and recurrent attacks, long-term antiepileptic drug medication, duration of epilepsy and type of seizure as cause for mental retardation[128,129]. All these factors might have caused extensive epileptogenic

network leading to significant cognitive impairments.

Memory impairments are also reported in persons with epilepsy by several studies [12,18,20,96,127,164–166]. In the present study, it was observed that 194 patients (38.34%) with significant low scores in Wechsler's memory scores (≤70). One-third of patients in intractable epilepsy group were mesial temporal lobe epilepsy showed significant memory impairments [18,126,127,167,168]. Other structural abnormalities like MCD, calcification, nonspecific lesion in temporal lobe could also impair the intelligence and memory scores. **From the review of the literature, we could not find a study assessing intelligence and memory score among a large number of patients with intractable epilepsy using drug-resistant epilepsy criteria. Hence the present study would highlight the significant cognitive impairment in intractable epilepsy.**

Bender Gestalt test revealed abnormal visuoperceptual gestalt functions in 218 patients (43.08%) which indicate a significant proportion of patients with intractable epilepsy having abnormal visuoperceptual abnormality as reported in the literature [169,170]. 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%). Similar to the studies on anxiety and depression in a person with epilepsy [114,117,118,171], the study population also showed significant anxiety and depression symptoms. This could be due to temporal lobe epilepsy [172] which was observed in one-third of the population, frequent epileptic attacks and multiple drug interaction [173,174]. In a large cohort study of 568 patients with epilepsy by Kwon and Park, (2013) reported 27.8% with depression and 15.3% with anxiety [175]. When compared to the above study, intractable epilepsy patients had a higher prevalence of patients with anxiety and depression. Univariate and multivariate logistic regression in 318 refractory epilepsy patients have shown significant association of

pharmacoresistance with depression [176]. Also, they reported that the underlying neurobiological process behind anxiety, depression, and psychosis would increase the extent of brain dysfunction and intractability.

Patients who are mentally retarded and dependent had a poor quality of life due to severe cognitive dysfunctions. Apart from the patients who had severe mental retardation, we could administer WHO Quality Of Life questionnaire in rest of the population. The results revealed that a higher proportion (39%) of patients found to have poor quality of life (total quality of life less than 60). Among the domains, social relationship (36.17%) was more affected followed by psychological health, environment, and physical health domains. The factors that might have contributed to poor quality of life could be cognitive deficits [53,124,167,177], anxiety and depression [123–125] and unemployment [104,112,145,178] as reported by several authors in literature.

6.5. Electroencephalography findings

Interictal EEG in the study population showed generalized abnormalities in 40% of the population irrespective of the seizure type. These findings are similar to the reports of EEG in persons with epilepsy often showing generalized abnormalities in a greater proportion of patients followed by focal epileptiform discharges [130]. 15.81% of the study population showed focal epileptiform discharges. These findings were commonly observed in MTS, focal cortical dysplasia, neoplastic and nonneoplastic lesions and nonspecific lesion. Studies with MTS and Focal cortical dysplasia often shows focal epileptiform discharges as reported by several authors [88,130,131,179]. Routine interictal EEG were reported to be normal in 40% of patients with epilepsy by several authors [70,130,131,133,134,138,158,179]. When compared to routine EEG, intensive EEG monitoring was reported to be useful in detecting epileptic activity in patients with

intractable epilepsy [132]. Similar to the above studies the present study showed a significant proportion of patients (43.48%) having normal interictal EEG recordings despite intractable epilepsy.

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

Chi-square test did not show any significant association between the type of seizure and other demographic variables like gender, educational level, and occupational status. Clinical characteristics also did not show any association with the type of seizure in patients with intractable epilepsy. These findings indicate that intractable epilepsy is a heterogeneous group with varying demographics and clinical presentations [11,133].

Among neurological comorbidities, the postictal headache had an association with the type of seizure in the present study. Partial type of seizure had a strong association with a headache in 23.31% of the population which was incongruent with the study done by Mainieri et al (2015) who reported headache was more common in generalized tonic-clonic seizures. The present study showed a prevalence of a postictal headache (19.96%) which is similar to the study by Mainieri et al (2015) who report a postictal headache in 19.1% of 388 patients with epilepsy [156].

Seizure semiology change was observed slightly higher (68.02%) in patients with partial seizures followed by generalized seizure (56.93%). These seizure semiology changes have been reported in both temporal lobe epilepsy patients [180–182] and focal cortical dysplasias [51]. In the present study population, 40% of the patients who had complex partial seizure were MTS patients. The semiology changes observed in the present study could be due to changes due to maturation of brain [180], abnormal sprouting of axons in the granule cell layer in MTS thereby aberrant neural conduction in the epileptogenic network [18] and also due to restricted information available on seizure

semiology with the caregivers of patients who had seizure onset at younger age [51].

CT scan findings did not reveal a significant association with both type of seizures. 39.02% of patients with partial seizure were significantly associated with MTS in MRI. DTWI showed abnormalities in 80.23% of the intractable epilepsy patients. These findings were supported by several authors [93–103,135,137,183], who showed microstructural abnormalities even in the absence of a structural lesion in MRI. DTI findings showed the significantly higher proportion of abnormalities in 85.09% of patients with complex partial seizures followed by 67.15% of patients with generalized seizures. There are no studies in literature that compare types of seizure with DTWI findings.

Interictal EEG findings were significantly normal in both CPS and generalized seizures. These findings were consistent with several studies using interictal EEG who report a low sensitivity of this specific technique in evaluating the seizure types and seizure focus [20,49,138]. Focal epileptiform discharges were noted in 20.05% of patients with partial seizures. Especially these observations were present in patients with MTS and FCD. These findings were similar to the reports that state MTS and FCDs do present with focal epileptiform discharges in EEG [131].

The present study did not reveal any significant difference between the IQ, MQ, BGT, anxiety, depression and quality of life scores between the generalized and partial seizure. This could be due to the fact that all patients considered for the study had intractable seizures were undergoing polytherapy, longer seizure duration, had early seizure onset and increased frequency of seizures which might affect their intelligence, memory, visuoperceptual functions, emotion, and quality of life irrespective the type of seizures [118,124,163,167,177,184].

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

Among structural abnormalities, MTS patients did not differ significantly from other structural lesions in demographic and clinical characteristics. This could be because irrespective of the focus and type of lesion, intractable epilepsy patients were observed with varying age ranges, seizure semiology, clustering, polytherapy, precipitating factors, comorbid factors, medical history, family history and EEG. As reported by several other authors [185–192], the present study showed MTS being more common on the left side, followed by the right side and both sides. A similar pattern was observed in DTI investigation among MTS patients. 40% of patients with nonspecific lesions showed bilateral abnormalities in MRI.

Comparing cognitive impairment among various structural lesions revealed significant low IQ, MQ scores BGT abnormalities among MTS patients in intractable epilepsy. Neurobiological factors in MTS such as a lesion in the early stage of life reduces the brain growth and cognitive development as reported by several authors [167,193–195]. Also, drug interaction and risk factors during the developmental period have been reported to a contributing factor to the cognitive decline in MTS population.

Anxiety and depression were significantly associated with MTS in the present study. These findings were supported by the studies which have evaluated anxiety and depression in temporal lobe epilepsy [110]. Hippocampus is an important anatomical structure associated with anxiety and depression [118], MTS patients often had anxiety and depression which may lead to suicidal ideation and poor quality of life [104,110,114,115,117,118,121,171,176,196,197]. Quality of life being multidimensional, they are severely affected across all patients with intractable epilepsy irrespective of structural lesions [27,68,111,112,118,122–125,145,148,149,175,177,198–204].

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

Early seizure onset, longer duration of seizures, polytherapy, and low IQ & MQ scores [112,114,145,178,205] were significantly associated with lower education levels and unemployment in intractable epilepsy. Patients without any schooling, elementary or high school level of education were associated with unemployment. The unemployment rates in intractable epilepsy population were significantly higher when compared to the unemployment rates in general population in India[146]. 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 [143,145,178]. Patient who have completed high school or graduation were underemployed. Studies that have compared education and employment status in intractable epilepsy were sparse in both western and Indian population. **The present study highlights high percentages of patients with intractable epilepsy having cognitive impairment (low IQ -29%, low MQ -38%) causing educational underachievement and unemployment in India.**

6.9. Localizing side of abnormality across various neuroimaging techniques and EEG

CT and MRI could identify the same side of the lesion in more than 80% of patients which imply the sensitivity of these neuroradiological investigations to localize these lesions. The sensitivity of CT in patients with epilepsy has not been found to be higher than 30% in unselected patient populations [42,90]. The lower sensitivity of CT is due to poor resolution of the temporal fossa due to which it is not useful in detecting

mesial temporal lobe sclerosis, one of the most common pathologies in refractory epilepsy. CT scan may fail to detect abnormalities in up to 50% of patients with epileptogenic structural lesions such as mesial temporal sclerosis, small tumors, malformations, etc.[206]

In intractable epilepsy patients who had normal MRI showed significant DTI abnormalities in left and bilateral hemispheres of the brain. Similarly, patient with right or left hemisphere abnormalities in MRI lesions showed the same side or bilateral hemispheric abnormalities in DTI. Also, a significant proportion of patients who showed bilateral lesions in MRI showed bilateral abnormalities in DTI.

These findings in DTI of the present study are supported by researchers who used DTI in epileptic population [20,93,94,96–103,135,137,183,185–187,189,190,192] and they reported microstructural white matter abnormalities in a significant proportion of patients. In temporal lobe epilepsy, we observed same side abnormalities and bilateral abnormalities involving the hippocampus, parahippocampus, dentate gyrus, extending to fimbriae and fornix. The involvement of the above-mentioned structures reported to be associated with white matter abnormalities in temporal lobe epilepsy [94,95,99,100,103,183,185–192]. In MCD population, DTI were useful in evaluating the white matter lesion beyond the lesion site [101]. In patients with normal MRI results we observed commonly on left-sided or bilateral lesions. These findings were supported by diffusion studies in cryptogenic epilepsy [102].

Less proportion of patients with a focal lesion in right or left hemisphere in MRI showed similar hemispherical lateralization in interictal EEG [131,180]. A significant association was observed in bilateral lesions in MRI with bilateral abnormalities in EEG [131,179,182]. Similarly, a significant proportion of patients with bilateral microstructural changes in DTWI showed bilateral EEG abnormalities. There are limited numbers of

studies with DTI and EEG in patients with intractable epilepsy. This present study highlights the extensive involvement of neural network in intractable epilepsy using DTI.

From the present study, it was observed that CT scan is useful in identifying non-specific lesion like calcifications which is reported in Indian population [88]. MRI results were more associated MTS and MCDs. Interestingly it was observed that a small group of patients (14.42%) who did not have any lesions in CT and MRI but showed microstructural abnormalities in DTI [93,94,95,96,97]. These findings were consistent with studies carried out by Dichl et al. (2005), Arfanakis et al. (2002), Gross et al. (2006), Tuch et al. (2003). 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, DTI and EEG could help us to trace out the structural abnormalities in intractable epilepsy. **The present study showed 6.13% of intractable epilepsy patients did not have any structural abnormalities in the brain using conventional CT, MRI, DTI and EEG.**

7. SUMMARY

7.1. Summary

The present study was carried out prospectively to investigate the prevalence, demographics, clinical characteristics, psychological status, structural abnormalities, EEG and quality of life in patients with intractable epilepsy. From 2850 epilepsy patients who were screened using drug-resistant epilepsy criteria, a cohort of 600 patients with intractable epilepsy was considered for data collection over a period of 3 years. Out of 600 patients who have been prospectively followed up only 506 patients with intractable epilepsy completed all the investigations. All patients with intractable epilepsy underwent detailed case history, neurological examination, CT, MRI and DTI imaging of the brain, EEG, and neurological investigations.

Out of 2850 patients (1523 males and 1327 females) seen at our epilepsy clinic, 600 (21.05%) patients had drug-resistant epilepsy. The prevalence of intractable epilepsy is reported in the study population is estimated to be 21.05 % that approximates 1 in 5 patients with epilepsy. In the present study, the prevalence of intractable epilepsy was observed more in males compared to females possibly due to the patient attending the clinics were majorly males compared to females. Analysis on educational and occupational status showed that high proportions of patients with intractable epilepsy were illiterate (16.8%) and large proportion of them discontinued school at elementary level (32.21%) causing high levels of unemployment (37%). Early seizure onset, longer duration of seizure, polytherapy, and low IQ and MQ scores were significantly associated with lower education levels and unemployment in intractable epilepsy.

Clinical characteristics of intractable epilepsy patients were often heterogeneous and do correlated with several studies carried out in literature by several authors in Indian and Western literature. It was observed that partial type of seizures, younger age

of seizure onset, change in seizure semiology, clustering and polytherapy contribute to intractability. Interictal EEG studies in intractable epilepsy are highly variable and insensitive in providing information regarding the foci of seizure onset. But in 15% of the population it is often sensitive to identify seizure foci in focal cortical dysplasia and MTS.

Structural imaging investigations revealed various congenital malformations of cortical development, mesial temporal sclerosis, neoplastic and nonneoplastic lesions, nonspecific lesions and incomplete hippocampal inversion of brain approximately in 94% of population. Interestingly in the series of 506patients, it was observed that significant proportion of patients with intractable epilepsy have calcifications. Diffusion tensor weighted images showed significant white matter structural changes in 80% of patients which signify DTWI as an important tool to trace the epileptogenic network.

One third of patients (29.05%) with intractable epilepsy were mentally retarded, and around 40% of them had significant memory impairments and visuoperceptual abnormalities. Cognitive impairments were significantly associated with early age of seizure onset, MTS, polytherapy and chronicity of the disease in the study population. Also anxiety and depression were associated in one third of intractable epilepsy patients who were not mentally retarded. These populations are high risk for suicidal ideation as reported in literature. Quality of life were similarly poor in 40% of the population who were not mentally retarded. Thus the present study highlights that cognitive impairment and psychological co-morbidities are very common in patients with intractable epilepsy which requires necessary action to address these psychological problem by means of psychological counselling to rehabilitate them in a right way.

Though intractable epilepsy patients were studied by neuroimaging and electrophysiological (EEG) techniques, they are insensitive in identifying structural abnormalities in 6.18% in whom structural abnormalities are still unknown. High resolution imaging facilities may help to identify structural lesions in these populations. Moreover biochemical and other investigations for metabolic disorders would add an additional value in identifying the cause for intractability in patients without any structural abnormalities. Intractable epilepsy being a heterogeneous group which is difficult to manage, use of modern diagnostic tools may aid in identifying the epileptogenic zone and thereby it may help in surgical intervention for the management of intractable epilepsy.

8. LIMITATIONS OF THE STUDY

8.1. Limitations of the study

Though intractable epilepsy patients were prospectively studied, the various clinical manifestations, structural, electrophysiological and psychological findings in patients with intractable epilepsy, it is often difficult to group them into sub-categories. This study had tried to include most of the investigations to understand intractable epilepsy but still, a few percentage of them remained to be a clinical conundrum.

One of the major limitations of the study is not having a control group of the epileptic population to identify the major risk factors in intractability. Though the aim of the present study is not to study the predictors for intractable epilepsy adding a control group might lead us in a better understanding of intractable epilepsy.

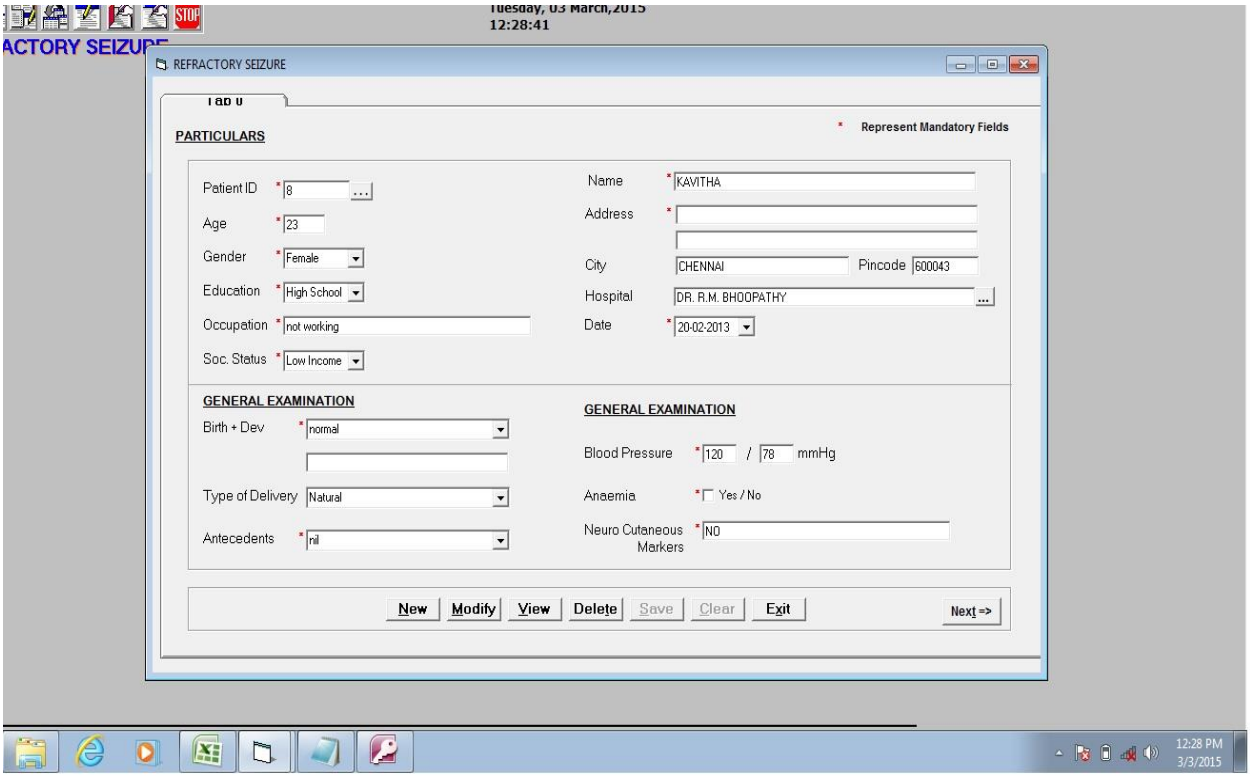
9. FUTURE DIRECTIONS FOR RESEARCH

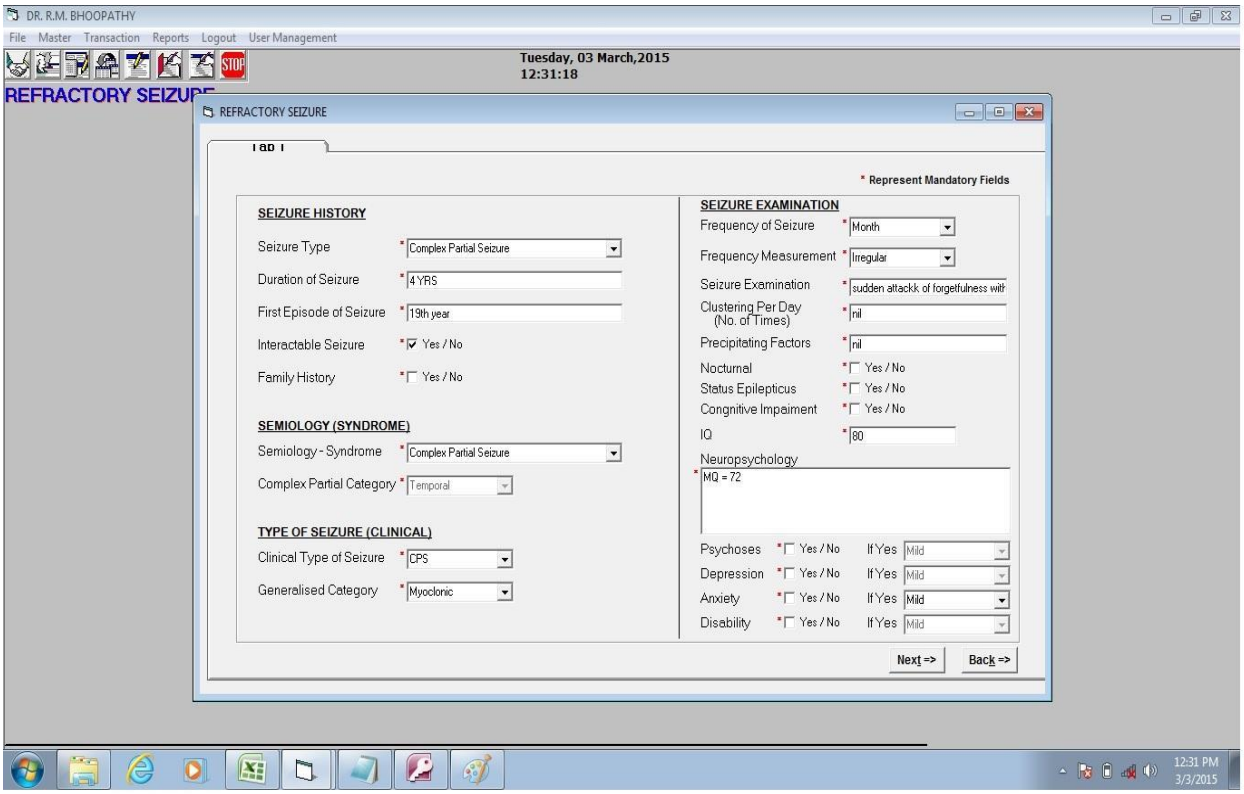
9.1. Future directions for research

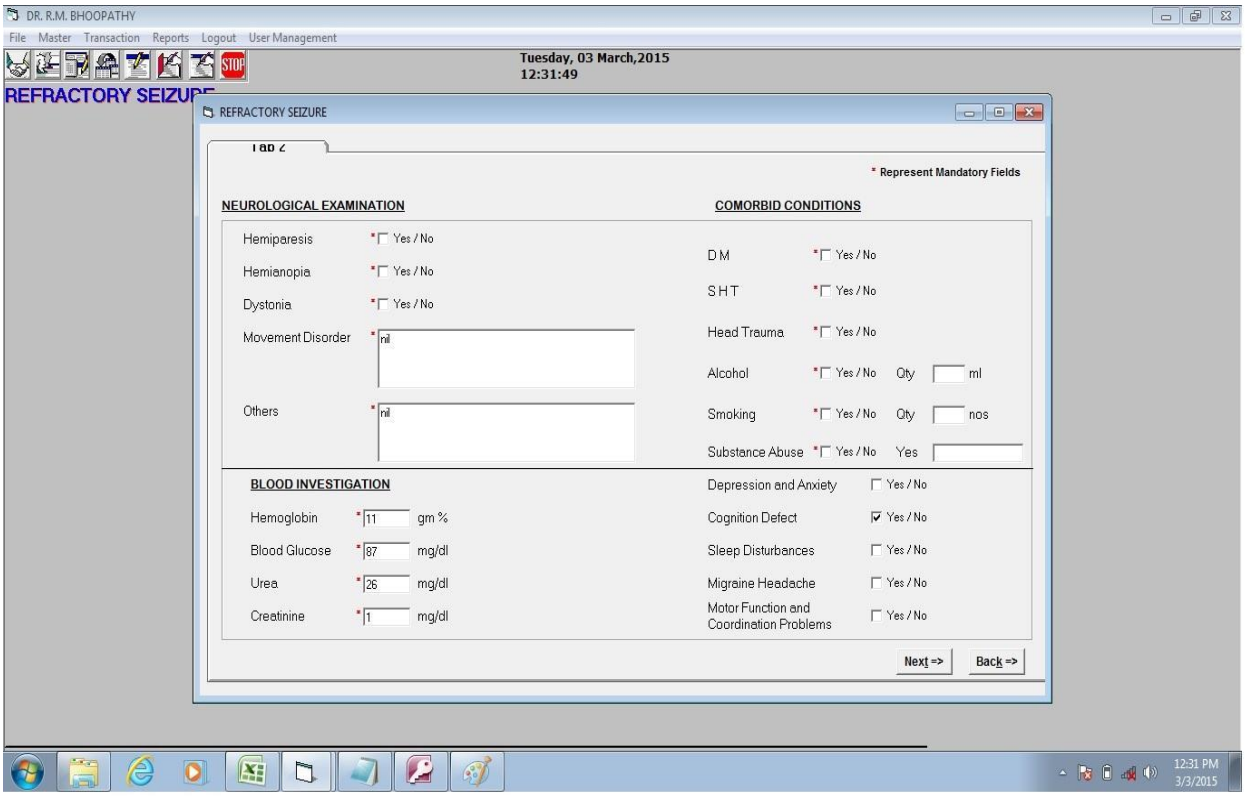
- To investigate for Incomplete Hippocampal Inversion in patients presenting with intractable epilepsy after excluding other common causes for intractability
- To assess role of cerebellum in intractable epilepsy patients using DTI
- To investigate histopathological abnormalities in MTS and IHI
- It would be appropriate to investigate the predictors of intractable epilepsy at an early age.
- Among patients who did not show any structural lesions, few of them had metabolic encephalopathy (Mitochondrial cytopathy, GLUT 1 deficiency disorder and Lafora body disease). Patients whose conventional radio imaging including DTI could not demonstrate any structural abnormalities; higher Tesla MRI between 7 to 9 Tesla may be necessary to detect hidden MCD with abnormal histopathological changes in the cells.

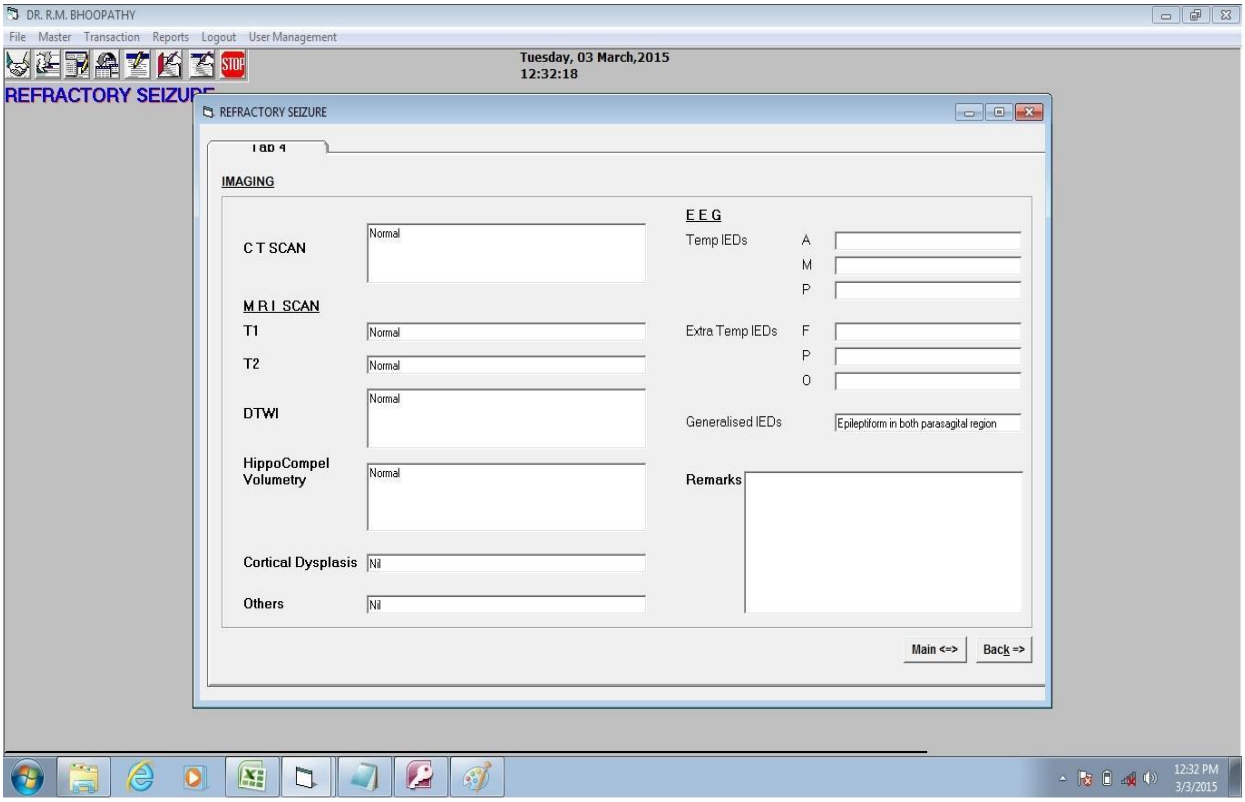
10. APPENDIX

10.1. Appendix 1: Screenshots of the software developed






DR. R.M. BHOOPATHY
File Master Transaction Reports Logout User Management
Tuesday, 03 March,2015
12:31:49
REFRACTORY SEIZURE
REFRACTORY SEIZURE
Tab 2
* Represent Mandatory Fields
NEUROLOGICAL EXAMINATION
Hemiparesis * Yes / No
Hemianopia * Yes / No
Dystonia * Yes / No
Movement Disorder * nil
Others * nil
COMORBID CONDITIONS
DM * Yes / No
SHT * Yes / No
Head Trauma * Yes / No
Alcohol * Yes / No Qty ml
Smoking * Yes / No Qty nos
Substance Abuse * Yes / No Yes
BLOOD INVESTIGATION
Hemoglobin * 11 gm %
Blood Glucose * 87 mg/dl
Urea * 26 mg/dl
Creatinine * 1 mg/dl
Depression and Anxiety Yes / No
Cognition Defect Yes / No
Sleep Disturbances Yes / No
Migraine Headache Yes / No
Motor Function and Coordination Problems Yes / No
Next =>
Back =>
12:31 PM
3/3/2015


DR. R.M. BHOOPATHY
File Master Transaction Reports Logout User Management
Tuesday, 03 March,2015
12:32:18
REFRACTORY SEIZURE
REFRACTORY SEIZURE
Tab 4
IMAGING
C T SCAN Normal
M R I SCAN
T1 Normal
T2 Normal
DTWI Normal
HippoCompel Volumetry Normal
Cortical Dysplasis Nil
Others Nil
E E G
Temp IEDs A
M
P
Extra Temp IEDs F
P
O
Generalised IEDs Epileptiform in both parasagital region
Remarks
Main <=>
Back =>
12:32 PM
3/3/2015

11. CONCLUSION

11.1. Conclusion

- From the present study, it was found that the prevalence of intractable epilepsy in our population is 21.05 % using ILAE criteria (2010).
- The present study revealed 16.8% of illiteracy in adults with intractable epilepsy.
- The unemployment in patients with intractable epilepsy (36.96%) is significantly higher than the unemployment in general population and patients with epilepsy.
- Partial seizure is the major type of seizure (72.92%) often associated with intractable epilepsy.
- The present study highlights that patients with intractable epilepsy are often associated with neuropsychological manifestations such as cognitive impairment (mental retardation -29.05%, memory impairment – 38.34%, abnormal visuoperceptual gestalt functions –43.08%), anxiety (31.82%), depression (28.06%), and mixed anxiety-depression (24.90%).
- It was observed from this study that various structural abnormalities like MTS, MCDs, calcification often present with intractable epilepsy.
- CT investigations could not detect abnormalities in 76% of the population whereas MRI could not detect structural abnormalities in 23.52% of the study population. MRI is superior to CT in identifying structural lesions in brain. DTWI further elucidated 14.42% of structural abnormalities over MRI (who do not show any structural lesions).
- A small percentage of patients (6.13%) did not show any structural abnormalities in CT, MRI, DTWI but these patients presented with intractable epilepsy which is still a clinical conundrum.

12. PUBLICATIONS

12.1. Publications and presentations

As a part of the Ph.D thesis 4 publications in indexed journals and several presentations in national and international conferences were carried out. Acceptance email for 2 articles in neurology india, published article copy are enclosed.

12.1.1. List of publications

- Bhoopathy R M, Amarnath Chellathuri Arthy B, Vignesh S S, Bhanu Keshavamurthy, Srinivasan A V. Prevalence and clinical characteristics of malformations of cortical development and incomplete hippocampal inversion with medically intractable seizures in Chennai - A prospective study - Neurology India (accepted for publication: email enclosed)
- Bhoopathy R M, Arthy B, Vignesh S S, Smita Ruckmani, Srinivasan A V. Involvement of Incomplete Hippocampal Inversion in intractable epilepsy: evidence from neuropsychological studies - Neurology India (accepted for publication : email enclosed)
- Bhoopathy R M, Arthy B, Vignesh S S, Srinivasan A V.Use of Magnetic resonance imaging and Diffusion tensor weighted imaging in intractable epilepsy. International Journal of Scientific Research. 2017. vol: 6 (3)
- Amarnath C, Bhoopathy R M, Suhasini B, Prem Chand, Gopinathan K, Philson J, Kanimozhi D.Role of Diffusion Tensor Imaging In Intractable Unilateral Mesial Temporal Lobe Epilepsy,IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 6 Ver. IV (June. 2017), PP 01-08.

12.1.2. List of paper presented in national and international conferences

- Anxiety and Depression in Patients with Malformations of Cortical Development and Incomplete Hippocampal Inversion - American Society for Neuro Rehabilitation.
- Clinical conundrum of medically intractable seizures - A prospective study - Japanese Society of Neurology (2015), Niigata, Japan.
- Use of Magnetic Resonance Imaging and Diffusion Tensor Weighted images in identifying Epileptogenic Network in 383 intractable epileptic patients – American Academy of Neurology

[NI]:Article provisionally accepted. Inbox x

Neurology India <editor@neurologyindia.com> May 3

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Status of the manuscript titled 'Prevalence and clinical characteristics of malformations of cortical development and incomplete hippocampal inversion with medically intractable seizures in Chennai - A prospective study' submitted by Prof. Bhoopathy Rangappan Munirathinam has been changed and a copy of the mail is as;

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We are pleased to inform that your manuscript "Prevalence and c linical characteristics of malformations of cortical development and incomplete hippocampal inversion with medically intractable seizures in Chennai - A prospective study" is provisionally accepted. You would receive an edited version of article in about 2-3 weeks from now for a final check and correction.
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Status of the manuscript titled 'Involvement of Incomplete Hippocampal Inversion in intractable epilepsy: evidence from neuropsychological studies' submitted by Prof. Bhoopathy Rangappan Munirathinam has been changed and a copy of the mail is as;

Dear Prof. Rangappan munirathinam,

We are pleased to inform that your manuscript "Involvement of Incomplete Hippocampal Inversion in intractable epilepsy: evidence from neuropsychological studies" is provisionally accepted. You would receive an edited version of article in about 2-3 weeks from now for a final check and correction.

Original Research Paper

VOLUME-6 | ISSUE-3 | MARCH - 2017 • ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

Use of Magnetic resonance imaging and Diffusion tensor weighted imaging in intractable epilepsy

Radiology

KEYWORDS: Mesial temporal sclerosis, Intractable epilepsy, diffusion tensor imaging, malformation of cortical development.

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ABSTRACT

506 patients with intractable epilepsy were assessed using magnetic resonance imaging (MRI) and Diffusion Tensor Weighted Imaging (DTWI) to identify structural lesions. A significant proportion of patients in MRI presented with Malformation of cortical development (MCD), Mesial temporal sclerosis (MTS) and non specific lesions. DTWI could identify various white matter abnormalities in same side or in bilateral hemispheres. Though the MRI revealed structural abnormalities at one hemisphere, the DTWI revealed white matter abnormalities in same or both hemispheres. In addition patients suffering from complex partial seizure and MRI (without any abnormalities) revealed white matter abnormalities in various region of interest studied bilaterally or unilaterally. Thus the epileptic network in intractable epilepsy is extensive and stresses the need to study further.

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Role of Diffusion Tensor Imaging In Intractable Unilateral Mesial Temporal Lobe Epilepsy

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Abstract: *We evaluated 21 patients with unilateral MTLS by using DTI, MRI, clinical and EEG parameters to assess changes in DTI metrics in hippocampal formation, white matter tracts and gray matter nuclei. Out of these 10 were Right sided and 11 were left sided MTLS. We compared the mean diffusivity (trace D) and fractional anisotropy (FA) from symmetrical voxels by sampling the following areas namely hippocampus, parahippocampal white matter, fimbriae and fornix middle cerebellar peduncle, corpus callosum ,uncinate fasciculus, inferior fronto occipital fasciculus, superior longitudinal fasciculus, ,anterior and posterior cingulum, thalamus, internal capsule, caudate and lentiform nucleus. There was statistically significant decrease in FA values with increased mean diffusivity was seen in ipsilateral hippocampus, parahippocampal white matter, fimbrae and fornix, inferior fronto- occipital fiber and posterior cingulate. On comparison with controls, we noted increased MD and decreased FA values in contralateral hippocampus, parahippocampal white matter, fimbriae and fornix middle cerebellar peduncle, corpus callosum, uncinate fasciculus, inferior fronto occipital fasciculus , superior longitudinal fasciculus, and cingulum. DTI is highly sensitive to micro structural changes in brain that underlie epilepsy. It shows microstructural abnormalities beyond the involved hippocampus extending to ipsilateral and contralateral major white matter tracts which is not apparent on conventional MRI.*

Keywords: *DTI, Mesial Temporal lobe Epilepsy, Mean diffusivity, Fractional Anisotropy, Hippocampal sclerosis.*

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