# INDIAN MEDICAL ASSOCIATION
# ACADEMY OF MEDICAL SPECIALITIES
## Head Quarters, Hyderabad, Telangana

# MONOGRAPH ON
# EPILEPSY

2022

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# ACADEMY OF MEDICAL SPECILAITIES

# MONOGRAPH ON EPILEPSY
# (2022)


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# From the Editor's Desk

IMA AMS under the guidance and vision of our Chairman Dr. GN Prabhakara has taken an initiative to bring out monographs on pertinent topics for the benefit of doctors in general and IMA members in particular. We are indebted to him for his innovative ideas and motivation. This monograph on a very important medical condition- Epilepsy -will go a long way in providing in depth knowledge in managing patients with this clinical disorder.

Epilepsy has long been recognized as an important medical problem and its treatment has varied through the ages. Rapid advancements in this field, development of better diagnostic modalities and newer treatment approaches have transformed the management of patients with Epilepsy. It has actually developed into a sub-specialty of Neurology and we now have Epileptologists at the forefront of Epilepsy management. Nonetheless, it being such a common medical condition all of us should be aware of the basics, and the recent advances in this field to treat our patients on evidence based guidelines.

Eminent Clinicians, Neurologists and Neurosurgeons have contributed chapters in this monograph on Epilepsy and their vast experience is truly reflected in the clarity with which the chapters are written. We salute their tremendous efforts in contributing concise yet comprehensive chapters for enriching the understanding on this important subject. I am sure this will be a treasure trove for the reader to enrich their knowledge on this complex yet common subject.

The energy and passion of our visionary leader Dr. Ketan Desai Sir drives us to do our bit and we are indeed blessed to have such a statesman to nurture and guide us.

I am grateful to our National President Dr. Sahajanand PD Singh for his inspirational leadership and encouragement in all our endeavors. My sincere accolades to our Honorary Secretary General Dr. Jayesh M Lele, for being an object lesson in commitment and stimulating us to achieve greater heights.

Our livewire dynamic Secretary of IMA AMS Dr. Sanjeev Singh Yadav deserves a special mention for his hard work and dedication and giving us a free hand in bringing out this monograph.

My special thanks to all the Past Chairmen and Secretaries of IMA AMS for their invaluable contribution in building such a glorious edifice for us to further work on and continue their legacy.

Team IMA AMS including all the office bearers truly deserves appreciation for their support and best wishes in bringing out this monograph.

I am thankful to Mr. Kantilal Shah and Mr. Murali of Atlas printers for their efforts in shaping this monograph into a reality.

Our office staff, Ms. Sarita as usual, leaves no stone unturned to ensure success in all our activities and we appreciate her dedication to IMA AMS.

**Dr. Srirang Abkari**

**Dr. Sahajanand Prasad Singh**
National President, IMA

# Message

I am delighted to note that IMA AMS is releasing a monograph on Epilepsy. Eminent specialists have contributed excellent chapters in this monograph.

IMA AMS has been doing regular avademic activities all across the country under the leaderdhip of its Chairman Dr. GN Prabhakara ably supported by the dynamic Secretary Dr. Sanjeev Singh Yadav.

I am also happy to learn four monographs are planned for the year. Such publications will go a long way in enriching the knowledge of our members ultimately reflecting in better patient care.

I also congratulate the Hony. Editor Dr. Srirang Abkari for his efforts in bringing out this monograph.

My best wishes to IMA AMS for a very fruitful year full of academic activiies

Long live IMA.

Dr. Sahajanand PD Singh
National President, IMA

**Dr. Jayesh M. Lele**
Hony. Secretary General
Indian Medical Association

# Message

Greetings from Indian Medical Association HQs!

It gives me immense pleasure to know that you are releasing a 'Monograph on Epilepsy'. Epilepsy is an always a challenge, it affects any age group and also is due to many underlying causes with varied etiology.

Indian Medical Association AMS wing is releasing a Monograph on the Epilepsy, and I am sure your team has done lot of work in collecting various articles on this complex subject.

This book shall be very informative, useful and a document of study as well as reference.

I congratulate you and your team for the wonderful efforts to release this Monograph, wishing you all the best.

**Dr. Jayesh M. Lele**
Hony. Secretary General, IMA

To,
Dr. Srirang Abkari
Hony. Editor Annals
IMA AMS

**Dr. Prabhakara G.N.**
Chairman
IMAAMS

# Message

Greetings to all Members

Happy Ugadi and a Prosperous new year. The first Annals of IMAAMS is going to release on 16th April. The topic is on epilepsy . A topic to be discussed in the present day scenario.

Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations and sometimes loss of awareness.

Anyone can develop epilepsy. Epilepsy affects both males and females of all races, ethnic backgrounds and ages.

Seizure symptoms can vary widely. Some people with epilepsy simply stare blankly for a few seconds during a seizure, while others repeatedly twitch their arms or legs. Having a single seizure doesn't mean you have epilepsy. At least two seizures without a known trigger (unprovoked seizures) that happen at least 24 hours apart are generally required for an epilepsy diagnosis.

Treatment with medications or sometimes surgery can control seizures for the majority of people with epilepsy. Some people require lifelong treatment to control seizures, but for others, the seizures eventually go away. Some children with epilepsy may outgrow the condition with age.

I thank all the members who have contributed to this Annals. My special thanks to our Secretary for bringing this issue and also this time we are bringing four issues.

**Dr Prabhakara GN**
IMAAMS Chairman

**Dr. E. Ravindra Reddy**
National Vice President
Indian Medical Association

# Message

I am happy to note that IMA AMS the prestigious academic wing of IMA is bringing out a monograph on Epilepsy. Such publications are essential for creating an academic mileu that enriches knowledge and transforms patient care.

IMA AMS under the Chairmanship of Dr. GN Prabhakara is doing a wonderful job and is very vibrant. Dr. Sanjeev Singh Yadav the dynamic secretary ensures that all the branches are active and work in unision.

I must compliment Dr. Srirang Abkari Hony. Editor for his untiring efforts in publication of this monograph on Epilepsy. This compilation on a very complex subject will clarify doubts, clear misconceptions and update us on the various aspects of Epilepsy..

My best wishes to IMA AMS for all their activites and am sure all the members will benefit immensely from this monograph.

**Dr. E. Ravindra Reddy**

**Dr. Sanjeev Singh Yadav**
Hony. Secretary,
IMA AMS HQRS

# Message

IMA AMS has always been in the forefront of academic activities and aims to excel in it. When we were engulfed by the Covid-19 pandemic, IMA AMS released a special issue on Covid-19 which was quite comprehensive and of a very high standard.
Now moving to the non-covid area of medicine, it gives me great pleasure to note that the first of the four quarterly monographs planned has seen the light of the day. Epilepsy is a very important and serious medical problem and I am sure this monograph written by experts in that field will immensely benefit the members.

My special compliments to Dr. Srirang Abkari, Hony. Editor , IMA AMS for his perseverance and dedication in bringing out this wonderful monograph. He has taken a lot of effort in coordinating with all the authors and ensuring that it is of a very high quality.

I request the members to actively participate in all our activities, contribute articles to our forthcoming monographs and send in your ideas and suggestions.

I am extremely thankful to our National President, Dr. Sahajanand PD Singh and Hony. Secretary General Dr. Jayesh Lele for their unstinted support, inspiring advice and motivation.

I am grateful to Dr. GN Prabhakar, Chairman IMA AMS for his guidance and encouragement.

Let us all update and upgrade academically .

Long Live IMA.

**Dr. Sanjeev Singh Yadav**
Hony. Secretary,
IMA AMS HQRS

# INDEX

# Seizure Semiology - An Overview

**Dr. CT Suresh**
**Dr. V Devi**

**Abstract**

International league against epilepsy in 2017 formulated a new classification for seizure semiology which was meant to give more clarity for patients as well as their caregivers. Significant changes included were substitution of old terminologies and some deletions as well as additions. This chapter will discuss the current classification system and highlight the differences when compared to the prior classifications.

## Introduction

Clinical signs or manifestations before, during, or after the ictus are defined as seizure semiology. International league against epilepsy formed a seizure type classification task force in 2015, which, in 2017, formulated an operational classification.1 This classification has more clarity in nomenclature, better communication and interpretation of the mechanisms of epilepsy among clinicians resulting in better research and treatment. A three-level classification for epilepsies was the backbone of the new classification. These three levels were describing the seizure type, diagnosis of epilepsy type, and, finally, the epilepsy syndrome. Etiology is incorporated in every stage of the diagnosis.1,2 In this article we concentrate on the first level, deciphering the seizure types and dwell upon the changes included in the 2017 classification when compared to the 1981 classification.3

## The Old and the New Classifications: International League against Epilepsy, Classification of Seizure—1981

### Partial Seizures

Simple partial:

- With motor symptoms
- With somatosensory and sensory symptoms
- With autonomic symptoms
- With psychic symptoms

**Complex partial:**

- Simple partial with impairment of consciousness
- Seizures with impairment of consciousness at the onset
- Partial seizures with secondary generalization, could be simple partial to secondary generalization or simple partial becoming complex partial and then secondary generalization and complex partial converting to secondary generalization

### Generalized Seizures

It could be convulsive or non-convulsive:

- Absence seizures—typical and atypical
- Myoclonic
- Clonic
- Tonic
- Tonic, clonic
- Atonic seizures

## Clinical Approach to Seizure Semiology—for Focal and Generalized Seizures

The new classification system has two levels of classification: a basic and an expanded version. The basic classification was meant for general practitioners, while the expanded classification was for clinicians interested in epilepsy.

The clinicians can use the following steps for deciphering seizure semiology.

***Step 1:***

Onset of seizure—focal or generalized.

Focal means onset is from one hemisphere while generalized means the onset could be multifocal or focal and then expanding to involve bilaterally distributed network, witnessed clinically or based on EEG.

If the clinician is not sure about the onset and the confidence is less than 80% then the seizure is classified as unknown onset.

***Step 2:***

Awareness—retained during the seizure or impaired during any part of the seizure.

Focal aware and focal impaired seizure has now replaced the terms simple partial and complex partial seizure of the 1981 classification.

Recording awareness is not a must and if the clinician is unsure of the awareness during the seizure he or she can omit. In focal myoclonic seizures, it is unnecessary to record awareness.

***Step 3:***

Once focal is it motor or non-motor.

The motor and non-motor components will be discussed under expanded seizure classification.

Step 4:

The ictus stays focal or becomes bilateral tonic—clonic seizures. This was earlier called as secondary generalized tonic, clonic seizures. It is now called focal to bilateral tonic, clonic seizures. The word generalized is used only if seizure is generalized and the impairment of consciousness is also from the onset.

For generalized onset of seizures, awareness is not used as most of the seizures have impairment of consciousness at the onset.

Seizures whether tonic, clonic, tonic-clonic, or myoclonic should be bilateral from onset, to be called as generalized seizure.

Generalized seizures are further grouped into motor and non-motor seizures.

The unknown onsets of seizures also are grouped as motor and non-motor.

Unknown onsets of seizures are those seizures where the clinician is not sure about the onset whether focal or generalized. Seizures occurring in the night and if the eye witness is unable to give a clear picture of the seizure then these seizures also are grouped under, unknown onset.

A seizure may be unclassified due to inadequate information or inability to place the type in other categories. This has been summarized in **Table 1**.

**Expanded Seizure Classification (Table 2)**

Important points to note in the expanded classification of seizures are

- Intact awareness or its impairment is necessary to differentiate between focal and generalized seizures and it is not mandatory for epileptic spasms and atonic seizures.
- Initial principal manifestation of seizure is motor or non-motor and this guides the name given to the seizure subtype.
- Motor or non-motor defines changes in motor activity.
- Automatisms, hyperkinetic movements, atonic, tonic, clonic, myoclonic, and epileptic spasms are grouped under both focal and generalized motor onset seizures.

**TABLE 1 : ILAE 2017 classification of seizure—basic version**

| Focal onset | Generalized onset | Unknown onset | Unclassified |
|---|---|---|---|
| Aware or impaired awareness | | | |
| Motor or non-motor onset | Motor—Tonic, clonic, & other | Motor—Tonic, clonic, & other | |
| Focal to bilateral tonic, clonic | Non-motor—Absence | Non-motor | |

**TABLE 2 : Expanded seizure classification**

| Focal onset | Generalized onset | Unknown onset | Unclassified |
|---|---|---|---|
| Focal onset | Generalized onset | Unknown onset | Unclassified |
| Aware or impaired awareness | | | |
| ***Motor onset:*** | ***Motor onset:*** | ***Motor:*** | |
| Automatisms | Tonic clonic | Tonic | |
| Atonic | Tonic | Clonic | |
| Tonic | Clonic | Epileptic spasms | |
| Clonic | Myoclonic | | |
| Myoclonic | Myoclonic tonic clonic | | |
| Epileptic spasms | Myoclonic atonic | | |
| Hyperkinetic | Atonic | | |
| | Epileptic spasms | | |
| ***Non-motor onset:*** | ***Non-motor onset:*** | ***Non-motor:*** | |
| Autonomic | Typical | Behavior arrest | |
| Behavioral arrest | Atypical | | |
| Cognitive | Myoclonic | | |
| Emotional | Eyelid myoclonia | | |
| Sensory | | | |
| ***Focal to bilateral tonic clonic*** | | | |

- It's important to note that the above mentioned seizure subtypes now appear both in focal and generalized seizure classification though pathophysiology may be different.

**Focal Motor Seizures**

***Automatisms:***

- Unconscious, involuntary, repetitive motor activity, involving hands and/or mouth.

***Hyperkinetic movements:***

- Previously called hyper motor, characteristic of nocturnal frontal lobe epilepsy. These seizures typically have pedaling, pelvic thrusting, or thrashing movements.

***Focal atonic seizures:***

- Loss of limb tone and limb flops.

***Focal tonic seizures:***

- Sudden contraction and stiffness of limb or neck muscles.

***Focal clonic seizures:***

- Constant rhythmic jerks involving a limb or part of a face, in the form of twitching.

***Focal myoclonic seizures:***

- A transitory, sudden irregular jerk of a limb or neck.

***Epileptic spasms:***

- Previously called as infantile spasms are now renamed as epileptic spasms which involve sudden involuntary flexion at the hip and associated with splaying of arm with flexion or extension.

***Focal non-motor seizures:***

- Alterations in emotion, cognition, and sensation comprise focal non-motor seizures.

***Focal emotional seizures:***

- Formerly called as gelastic seizures—involves excessive laughter without subjective feeling of the same.
- Formerly called as dacrystic seizures—involves excessive crying without subjective feeling of the same.
- This may be associated with sudden outburst of emotion, fear, agitation, and mood swings.

***Focal cognitive seizures:***

***Positive cognitive seizures:***

- Focal cognitive seizure—feelings of familiarity-déjà vu and unfamiliarity—jamais vu.
- Focal cognitive seizure with hallucinations—perception of a stimuli which could be visual in the form of formed images, auditory in the form of hearing voices, or may involve other sensory modalities too.
- Focal cognitive seizures with illusion—is alteration of actual perception involving visual, auditory, sensory, olfactory, or taste sensations.
- Focal cognitive seizure with disassociation—a feeling of disconnection from the surroundings with intact awareness.
- A focal cognitive seizure with forced thinking—includes presence of intrusive thoughts and crowding of ideas at the onset of seizure.
- The negative focal cognitive seizures may involve memory impairment, brief loss of calculation skills, neglect, naming and reading difficulties and right, left confusion.
- All this should be associated with intact awareness to be called as focal.

**Generalized Onset Seizures**

- Subgrouped into motor and non-motor onset.
- The motor onset usually lasts for 2–3 minutes with loss of awareness at the onset.
- Along with loss of awareness stiffening of limbs is the tonic phase followed by rhythmic jerking of limbs and face is the clonic phase.
- Falls, frothing, and urinary incontinence are associated features.
- A purely tonic seizure or a clonic seizure can occur independent of each other.
- A *generalized myoclonic seizure* involves irregular bilateral jerks involving face, limbs, eyes, or eyelids.
- Some generalized tonic clonic seizures are preceded by few myoclonic jerks and is now called as *Myoclonic tonic clonic seizures*, a new addition in 2017 classification.
- Similarly some atonic seizures characterized by limb drop and fall on the buttocks or forwards are preceded by few myoclonic jerks. These seizures are called as *Myoclonic atonic seizures* and when they occur without myoclonic jerks they are called as *Atonic seizures*.

Non-motor generalized seizures are of four types and they are typical and atypical absence seizures, myclonic absence, and eyelid myoclonia with absences.

A *typical absence seizure* involves sudden and abrupt cessation of activity which may be associated with eyelid fluttering and head nodding. Absence seizure lasts for few seconds and immediately patient regains awareness without post ictal confusion. These seizures are provoked by hyper ventillation.

*Atypical absence seizures* will have a slightly longer duration and may have a slower recovery. The EEG in a typical absence is 3 hz per second while in atypical it could be at 2–3 hz per second. Loss of tone and falls may occur in atypical absence seizures.

If the absence seizures are preceded by few myoclonic jerks then the seizure is called as *Myoclonic absence seizures*.

Eyelid jerks with forceful deviation of the eyes upwards is called as *eyelid myoclonia*. It's important to note that eyelid myoclonia is frequently provoked by photic stimulation and also by closure of eyes.

**The Changes in 2017 Classification When Compared to 1981 Classification**

***Deletions:***

- The terminology of simple and complex partial seizure was removed and substituted by the word focal as the word focal localizes the seizure onset location. The word complex partial was not well understood by the public, and hence removed. Also the simple partial seizure may have a complicated pathology and the word simple may be misguiding, and hence removed.
- The word convulsion which was used to describe the motor activity of seizure was discontinued as the word convulsion included all the motor components like tonic, clonic, tonic clonic, and myoclonic.

***Additions:***

- Awareness and impaired awareness is now a classifier of focal seizure.
- The word hypermotor was substituted with hyperkinetic in 2017, classification as the word hyperkinetic was etymologically and historically correct.
- Positive and negative cognitive seizures replaced psychic seizures. Positive cognitive seizures are déjà vu, jamai vu, illusions, and hallucinations. Aphasia, apraxia, and neglect comprised the negative cognitive seizures.
- Affective manifestations without subjective emotionality could be inappropriate laughter or crying are now grouped as emotional seizures under focal non-motor seizures.
- Automatisms, behavioral arrest, cognitive, emotional, and hyperkinetic seizures are now included in focal seizure types.
- Some seizures like epileptic spasms and tonic clonic seizures could be focal, generalized, or of unknown onset, and hence they are grouped under all three categories.

**TABLE 3**Terminology change

| ***Old terms*** | ***New terms*** |
|---|---|
| Unconscious | Impaired awareness |
| Partial | Focal |
| Simple partial | Focal aware |
| Complex partial | Focal impaired awareness |
| Dyscognitive | Focal impaired awareness |
| Psychic | Cognitive |
| Secondary generalized tonic-clonic | Focal to bilateral tonic-clonic |
| Arrest, freeze, pause, interruption | Behavior arrest |

**TABLE 4 : New seizure types**

| *New focal seizures* | *New generalized seizures* | *New combined seizures* |
|---|---|---|
| ***Motor:*** | Absence with eyelid myoclonia | Focal to bilateral tonic—clonic |
| • Atonic | | |
| • Automatisms | | |
| • Clonic | | |
| • Epileptic spasms | | |
| • Hyperkinetic | | |
| • Myoclonic | | |
| • Tonic | | |
| Hyperkinetic | Epileptic spasms | |
| Myoclonic | Myoclonic-atonic | |
| Tonic | Myoclonic-tonic-clonic | |
| ***Non-motor:*** | | |
| • Behavior arrest (autonomic, cognitive) | | |
| • Emotional | | |

- Similarly, epileptic spasms, tonic, clonic, tonic clonic, and myoclonic could be focal in onset or generalized in onset, and hence placed under both the categories.
- Simple or complex partial seizure with secondary generalization has been changed to focal to bilateral tonic, clonic seizure. The basis behind this change in terminology is secondary generalization may suggest involvement of the entire brain, which may not be always true.
- Absence with eyelid myoclonia, myoclonic absence, myoclonic tonic clonic, myoclonic clonic, and epileptic spasms are now seizure types added under generalized category. The terminology changes and new seizure types have been tabulated in **Tables 3 and 4**.

***Conclusion***

The 1981 classification of seizures is still widely acceptable as well as applicable.4 Subsequent classifications in 2001 and 2006 made significant changes and incorporations based on electroencephalography, etiology, therapeutic, and prognostic implications.5,6 Epileptologists accept that a classification based on the science of epilepsy is ideal but impossible as of now.7,8 The 2017, classification is called operational classification as it is practical and simple. The new classification is easy to communicate among clinicians, patients, and their families. It avoids confusing terminologies. At the same time the new classification is flexible, applicable, easy to comprehend, and yet comprehensive.9

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# Approach to a Patient with Epilepsy

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Epilepsy is defined as the occurrence of two or more unprovoked seizures in an individual. Seizure is defined as a transient occurrence of signs and/or symptoms due to an abnormal; excessive, or synchronous neuronal activity in the brain. It is the second most common neurological disease after stroke. It has immense social, economic, and psychological implications for the individual. Its prevalence is about 1% of our population (rural more than urban).[1] With appropriate treatment, 70% of those with epilepsy can become seizure-free. However, it is important to diagnose epilepsy and institute appropriate therapy based on the semiology of the seizure.[2] Diagnosis of epilepsy needs a good history of the event and examination to rule out mimics like syncope. An eyewitness account of a seizure event is the most valuable information for diagnosis.

**HISTORY**:

There are no shortcuts in diagnosing a seizure, and the importance of a detailed history cannot be overemphasized. The role of imaging and EEG is secondary to history taking. When in doubt, re-taking the history again is more useful than repeating the tests. To make a diagnosis of seizure, one needs to know seizure mimics that can present as paroxysmal loss of consciousness or awareness (like syncope, psychogenic episodes, etc.), working knowledge of current seizure classification, and ordering appropriate tests to find the etiology of seizure.

SEIZURE OR MIMIC: In those presenting with a suspected seizure, an attempt should be made to find out the situation when the event occurred, prodromal symptoms, exact description of the attack, and the events following the attack. Seizures may have triggers like sleep deprivation, fever, exposure to flashing lights, etc. A subset of these patients may have an aura (stereotypical usually from event to event). In most individuals, seizures tend to occur suddenly with tonic-clonic limb movements and recover after a variable period (usually a few minutes) of postictal confusion (this phase is one of the most important components of a seizure which should be asked for in the history). Syncope on the other hand usually has a prodromal phase (characterized by light-headedness, a generalized sensation of warmth, a sense of impending doom, etc.). Syncopal events occur gradually, are associated with loss of postural tone (some individuals may have jerky limb movements), recover quickly without any post-event confusion, and may have profuse sweat. Bladder and bowel incontinence can be seen, both in those with seizures and syncope. When present, the location of a tongue bite is useful to differentiate seizure from syncope; it is usually lateral in a seizure and at the tip in those with syncope.[3] Psychogenic events are characterized by the presence of an inciting trigger (usually a stressful event or situation), prolonged periods of the apparent loss of consciousness, erratic limb movements (non-stereotypical movements like rocking, pelvic thrusting, etc.), and usually no post-event confusion.

Once the clinician is reasonably confident about the diagnosis of a seizure, extra information about the seizure should be sought.

TYPE OF SEIZURE: A revised classification for seizures has been published by the International League Against Epilepsy in 2017.[4] Seizures are now classified as focal onset, generalized onset, or unknown onset. In most of the patients, this is

evident in the history and physical examination. When the description is vague, the relative can be asked to capture the next event on a mobile phone. In some, investigations (MRI, EEG) may help. Those with focal onset are further sub-classified as focal aware or focal with impaired awareness (previously called complex partial seizures). This is an important aspect of history as it helps in choosing an anti-epileptic drug (AED); also, the causes and outcomes vary depending on the nature of seizure onset.

**PROVOKED OR UNPROVOKED:**

Those with a single provoked seizure tend to have transient cerebral insults (fever, head injury, intoxication, intracerebral bleed, cerebral venous sinus thrombosis, alcohol withdrawal, hypoglycemia, etc.) and may not need prolonged AEDs. In those with unprovoked seizures, the chances of recurrence are high.

**DESCRIPTION OF THE SEIZURE:**

It is important to ascertain from the history whether the seizure was a generalized tonic-clonic, myoclonic, absence, or associated with drop attacks. In some patients, especially those with focal onset seizures, auras may be present before the seizure. Auras can help localize the site of seizure origin: the presence of colored lights before a seizure localizes the site of origin to the occipital lobe and also helps to differentiate a seizure from a migraine mimic (migraine auras tend to be black and white zig-zag lines). Most eyewitnesses tend to recollect the dramatic motor movements of a seizure but are largely unaware of the presence or absence of a postictal confusion state. The presence of a postictal confusion state confirms the diagnosis of a seizure (it is absent in syncope and psychogenic events).

**FIRST EVENT OR MINOR EVENTS IN THE PAST:**

Patients need to be asked repeatedly about a prior history of seizures, minor events like myoclonus, or absences which can point to underlying epilepsy and need for prolonged treatment.

**MEDICAL HISTORY:**

A detailed history of any birth insults (hypoxia), serious CNS infections, head injury, or febrile seizures should be sought. A note should be made of any recent stressor that may have triggered a psychogenic seizure. A detailed drug history should be sought. If on AEDs, the dose and compliance should be ascertained. The recent use of epileptogenic drugs should be asked for: quinolones, tramadol, etc. The patient should also be quizzed for any illicit substance abuse, alcoholism, or abrupt withdrawal of benzodiazepines.

**FAMILY HISTORY:**

Though this is one of the most important aspects of history taking; the information may be inaccurate and often, purposely concealed due to the associated social stigma.

**EXAMINATION:** For those presenting for the first time with a seizure, a careful inspection of the tongue should be done to look for a lateral tongue bite. A structural abnormality (tumor, abscess, subdural, etc.) may be a few of the sinister underlying causes of a focal seizure. These patients should be carefully examined for the presence of raised intracranial pressure and long tract signs (pyramidal tract distribution of weakness, brisk reflexes, and extensor plantar). A careful examination for neurocutaneous markers (port-wine stain of Sturge Weber syndrome, adenoma sebaceum of tuberous sclerosis, etc.) should be done in those with chronic epilepsy and especially, in children. In those with chronic epilepsy, one should keep a careful watch for AED side effects which may need a dose adjustment or change of the AED: tremors, hair fall with valproic acid; gingival hyperplasia with phenytoin, and ataxia.

When evaluating a suspected psychogenic seizure, suggestions in the clinic can help trigger the event. Hyperventilation done in an OPD can elicit the typical absence seizure.

**INVESTIGATIONS:**

All patients with seizures need evaluation. These

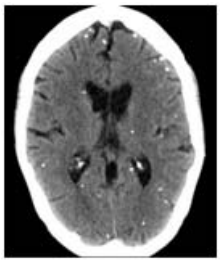
need to be done expeditiously, especially in those with focal seizures.

**ELECTROENCEPHALOGRAM (EEG):**

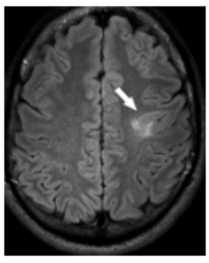
The presence of an abnormal EEG (which detects abnormal discharges from the cortical surface) with a compatible history is confirmation of a seizure. It is important to do a sleep-deprived EEG as soon as possible after a suspected seizure as the probability of detecting abnormal EEG discharges is 70% in the first 24- 48 hours after an event.[5] An EEG helps confirm that the reason for a 'daydreaming' child is the presence of absence seizure and the clumsiness in getting up in the morning is due to myoclonus. EEG can help differentiate focal from generalized epilepsies and these have therapeutic implications. EEG also helps in identifying epileptic encephalopathies and syndromes like West syndrome, Rolandic epilepsy, etc. Demonstrating a normal EEG during abnormal limb movements would confirm the diagnosis of a psychogenic seizure. Sometimes a prolonged video EEG may be needed to identify a seizure focus or to confirm a pseudo seizure. However, an EEG can be normal even in about 30% of patients with epilepsy.

**BRAIN IMAGING:**

An MRI or a CT scan is done in most patients with seizures; urgently in those with focal seizures. MRI can detect mesial temporal sclerosis, cortical dysplasia, or certain tumors which can be missed by a CT. CT is useful in those with calcific lesions or intracranial bleed.



Calcific Cysticercosis



Focal Cortical Dysplasia

**LABORATORY INVESTIGATIONS:**

Though it is normal in most patients with seizures; the presence of severe hypoglycemia, hypocalcemia, or hypo/hypernatremia can explain the occurrence of seizures. Serum prolactin levels can be elevated even in those with a hypotensive syncope and have no role in the diagnosis of seizure.

**TREATMENT:** Treatment decisions for seizures should be individualized based on whether it is a provoked or unprovoked seizure and the presence of risk factors that increase the risk of seizure recurrence.

Risk factors for seizure recurrence are: Pre-existing brain pathologies (gliosis etc.) that are causative for the seizure, focal seizures, focal neurological findings, focal or generalized abnormality on the EEG, parenchymal tumors, presentation as status epilepticus, family history of epilepsy and history of febrile seizures in childhood.[6]

The risk of recurrence after a first unprovoked seizure is 42% over the next 2 years; with a maximum risk (60-70%) in the first six months.[7]

The decision to start AED after a first seizure should be taken after considering the risk of seizure recurrence and discussing the drug's side effects with the individual and his family. Once it is decided to start an AED, it should be continued for a minimum of 2 years of a seizure-free period before attempting a slow taper over 6 months.

**WHICH DRUG TO USE:**

Though there are no head-to-head comparisons between the various AEDS about which is the best drug to use, broad guidelines are available. The choice of the first AED depends on the nature of the seizure, presence of an epilepsy syndrome (e.g.: valproate for juvenile myoclonic epilepsy), age, sex, side effect profile of the AED, efficacy, cost of therapy, and the presence of special situations (females of childbearing age, pregnancy, and the elderly).

Start AED in the lowest possible dose, avoid polypharmacy and drugs like phenobarbitone which can impair cognition at all ages.

**For focal seizures:**

Carbamazepine, oxcarbazepine, clobazam,

lamotrigine, levetiracetam, brivaracetam, lacosamide and perampanel.

**For generalized seizures:** Valproate, lamotrigine, topiramate, levetiracetam, and phenytoin (avoid in those with juvenile myoclonic epilepsy).

Pregnancy: Levetiracetam and lamotrigine.

**MONITORING PATIENTS WITH EPILEPSY:**

Epilepsy is a chronic disease and patients need to be monitored regularly. Individuals should be encouraged to be compliant in taking the AEDs, avoid sleep deprivation, and avoid driving or indulging in hazardous activities (like swimming, sky diving, etc.). Monitoring is also needed to detect AED side effects and avoid teratogenicity in those who are pregnant on AEDs.

**CONCLUSION**:

The diagnosis of a seizure is dependent on detailed history taking and is supplemented by investigations (EEG or brain imaging). It must be differentiated from mimics like psychogenic seizures or syncope. Treatment decisions should be individualized after discussing the risk of seizure recurrence and the possibility of side effects with AEDs. The goal is to optimize quality of life and achieve a balance between minimal drug side effects with reduced risk for seizure recurrence.

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# Epilepsy Management

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Epilepsy is a common neurological disorder affecting approximately 0.5 to 1 % of population in our country. It is a chronic disorder characterised by recurrent unprovoked seizures. Up to two third of the patients can lead normal life with proper treatment of epilepsy. Unfortunately in our country more than 50% of people with epilepsy receive either no treatment or inappropriate treatment because of social stigma and inadequacies in health care.

**DIAGNOSIS**

All people with epilepsy have seizures but all those who have seizures do not have epilepsy.

Accurate diagnosis is important for starting proper treatment.

Detailed history from patient, family member and eye witness along with careful physical and neurological examination is important for correct diagnosis.

Epileptic seizures may present with various features and not all features need to be present in an individual patient.

Epileptic seizure should be classified according to current internationally accepted classification. Failure to classify the epileptic seizure may lead to inappropriate treatment

It is recommended that wherever possible all patients with epilepsy should be seen by a medical practitioner with knowledge and experience in epilepsy to ensure a correct diagnosis and early initiation of appropriate treatment

***The following conditions may be mistaken for seizures:***

Syncope

Hypoglycemic attacks

Transient ischeamic attacks

Movement disorders (eg. Tics)

Panic attacks

Breath holding spells in children

Physiologic jerks during sleep

Psychogenic attacks (pseudoseizures)

Migraine aura

**INVESTIGATIONS:**

History and clinical examination are most important in diagnosis of epilepsy.

EEG abnormality helps identify seizure type or epilepsy syndrome and thereby choice of antiepileptic medication and prediction of prognosis.

CT scan or MRI helps in identification of possible etiology of seizures

**EEG:**

Normal EEG does not rule out epileptic disorder

Abnormal EEG is seen in approximately 0.5% to 4% of the normal population

Epileptiform activity is specific, but not sensitive, for diagnosis of epilepsy as the cause of a transient loss of consciousness or other

paroxysmal event that is clinically likely to be epilepsy.

EEG has relatively low sensitivity in epilepsy, ranging between 25–56%. Specificity is better, but again variable at 78–98%.

In practice, diagnosis should be mainly based on the clinical features. However, when history is unclear (un-witnessed "blackouts" or brief impairment of awareness), EEG can sometimes help distinguish between different seizure types

**Does abnormal EEG predict seizure recurrence?**

Subjects presenting with their first unprovoked seizure have a higher risk of seizure recurrence when the initial EEG is abnormal; if so, treatment should be offered after the first tonic-clonic seizure.

**EEG AND MANAGEMENT OF EPILEPSY**

There is no value in repeating the routine EEG if seizures become more frequent, or to assess treatment effect, with few exceptions

**Long term video or ambulatory EEG:** has an important role in the assessment of patients who present diagnostic or management difficulties following clinical evaluation and routine EEG.

Continuous EEG monitoring is helpful in treating patients with status epilepticus

**NEUROIMAGING:**

Neuroimaging is not mandatory in the diagnosis of all people with epilepsy.

CT is less expensive and useful in evaluation of acute situations like head injury, brain haemorrhage

MRI is the investigation of choice and may be performed taking into consideration patient's socioeconomic status and type of epilepsy specially if CT is negative or inconclusive..

**TREATMENT**

The treatment options for epilepsy have come a long way from the bromides to the current era in which we now have multiple treatment modalities, including medications, implantable devices, and surgery.

The goal for treatment should be to enable patients with epilepsy to lead a lifestyle consistent with their capabilities.

**PATIENT EDUCATION**

Management of epilepsy should start with educating patient and family about epilepsy's risks, including injury and mortality.

Parents of children with epilepsy need information about the disorder and available support resources.

Children and youth with epilepsy need information about the disorder and its implications for their future.

Women need information about hormonal influences on the disorder and the potential effects of seizure medications on pregnancy.

Adults need information related to employment, driving, and management of stress

Older adults also may have specific information needs, given the likelihood they are taking medications for other chronic health conditions and have an increased risk of falls.

**FIRST AID DURING SEIZURE (PATIENT EDUCATION):**

Educating all care givers about first aid during a seizure attack is important

Common practices in our society *which should be avoided are* –

To keep iron objects in hands when someone has a tonic clonic seizure (object may injure the patient while he is having tonic clonic movements)

To keep a spoon or piece of cloth in the mouth to prevent tongue bite (may damage the teeth, cause choking, temporomandibular joint dislocation)

Holding limbs forcibly to stop tonic clonic movements (may cause joint dislocation, fractures or muscle/tendon injuries).

They are harmful and will not do any good to the patient.

First aid steps can be tailored to what happens during the seizure and the setting where it occurs. For example, changes in a person's awareness or alertness and or physical movements during a seizure pose different safety risks.

Also how to keep a person safe and respond to a seizure may vary in different settings, for example in water or on the street.

**All approaches focus on 3 STEPS:**

STAY - SAFE - SIDE

**Seizures Without Any Change in Awareness**

- Stay calm and reassure the person they are safe.
- If the person is frightened or anxious, encourage them to take slow deep breaths or do something that is calming or relaxing.
- Stay with the person until the seizure is over. Make sure that they are fully aware of what is going on before they are left alone.

**Seizures with Altered Awareness**

Most often these seizures are not considered as epileptic disorders, even by paramedical staff; Educating people about these symptoms will help in early recognition of epileptic disorders

Sometimes people may look awake during a seizure, but they really are not aware of part or all of what is going on around them. They may not remember what happens during the seizure or have difficulty talking about it during or after it. The person may walk around during the seizure, but not be in control of where they are going, and they may not be able to protect themselves. These seizure behaviors may be seen with complex partial seizures or clusters of absence seizures. During these episodes, in addition to basic first aid, pay particular attention to the following:

- If the person has a warning before they lose awareness, help them to a safe place.
- Stay with the person and don't let them wander away. Let them walk in an enclosed area if possible.
- Keep the person away from sharp objects or dangerous places.
- If the person tries to run or is in a dangerous situation, call for help and hold them back if needed to keep them out of danger.
- Do not assume that they can talk or that they can hear you and follow instructions. Assure them they are safe and repeat instructions on what they should do next.
- Make sure that they are alert, oriented and safe after the event before they are left alone.
- Time the seizure – these types of seizures are usually longer than convulsions or tonic clonic seizures. It may be hard to tell when the seizure ended and when the recovery period begins and ends.
- Seizure may turn into a convulsive seizure sometimes

**Seizures with Loss of Consciousness**

Most of the general population will not have any difficulty in recognising these seizures but because of misconceptions and lack of proper awareness, people do more harm to the patient in the process of helping them.

Following information should be given to increase the awareness

**Things to DO:**

Do call for emergency assistance when needed.

Do safely cushion the person's head.

Do protect the person from any nearby objects.

Do turn the patient to keep the airway open

Do time the length of the seizure.

Do stay with the person until they recover.

**Things you should NOT DO:**

Don't put anything in the person's mouth.

Don't try to move the person.

Don't try to restrain the person.

Don't try to feed them or give water till they are completely awake

**PHARMACOLOGICAL TRATMENT**

**GENERAL PRINCIPLES**

The AED treatment strategy should be individualised according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, person's lifestyle, and the preferences of the person and their family

Treatment is generally recommended after a second unprovoked seizure

Treatment should be started after confirming the diagnosis of epilepsy

Treatment should start with lowest possible dose of a single AED (monotherapy) wherever possible.

Gradually increase the dose until seizures are controlled or side effects occur.

If the initial treatment is unsuccessful, then monotherapy using another drug can be tried.

If an AED has failed because of adverse effects or continued seizures, a second drug should be started and built up to an adequate or maximum tolerated dose and then the first drug should be tapered off slowly.

If the second drug is unhelpful drug with lesser efficacy should be tapered off. It is better to refer the patient to a specialist.

Combination therapy should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom.

The formulation or brand should preferably not be changed

Modified release formulations have the advantage of ease of administration, but they are costlier.

Once daily preparations should be used with caution during pregnancy.

Do not offer sodium valproate to women or girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless other options are ineffective or not tolerated.

**CHOICE OF AEDS**

**FIRSTLINE TREATMENT FOR NEWLY DIAGNOSED FOCAL SEIZURES:**

Lamotrigine - women and girls of childbearing potential

Lamotrigine or Carbamazepine - boys, men and women who are not of childbearing potential

**IF ABOVE DRUGS ARE UNSUITABLE OR NOT TOLERATED**

Levetiracetam, Oxcarbazepine or Sodium valproate

Other options available are - carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, phenytoin, phenobarbitone or topiramate.

Oxcarbazepine, Topiramate can impair effectiveness of hormonal contraceptives; SODIUM VALPRAOTE SHOULD BE AVOIDED IN WOMEN WITH CHILD BEARING POTENTIAL.

**FIRSTLINE TREATMENT FOR NEWLY DIAGNOSED GENERALISED TONIC CLONIC SEIZURES:**

Lamotrigine - women and girls of childbearing potential (may exacerbate myoclonic jerks in people with myoclonic epilepsy)

Sodium valproate - boys, men and women who are not of childbearing potential

**OTHER OPTIONS AVAILABLE ARE:**

Carbamazepine, phenytoin, phenobarbitone, oxcarbazepine, clobazam, lamotrigine, levetiracetam, sodium valproate or topiramate

If there are absence or myoclonic seizures, or if JME is suspected, do not offer carbamazepine,

gabapentin, oxcarbazepine, phenytoin.

**FOLLOW UP**

First follow up should be planned within 2 weeks

Subsequent follow-ups at 3 to 6 months interval depending on the seizure control and side effects.

Patient or care giver should be encouraged to maintain seizure dairy to assess tolerability, efficacy and compliance of drugs

Life style issues such as sleep, regular food intake, driving, pregnancy should also be discussed

**BREAKTHROUGH SEIZURES IN WELL CONTROLLED PATIENTS:**

Factors responsible for breakthrough seizure should be assessed

No more than 80% of patients will be compliant – common reason for breakthrough seizure is noncompliance (because of economic reasons, adverse effects, misconceptions etc.)

Any new drug started for other reasons which can change antiepileptic drug levels or drugs which are epileptogenic may be the reason

Changing brand of the drug may sometimes alter drug levels, which should be avoided as far as possible

Switching of anticonvulsants done for any reason( eg: because of adverse effects)

Sleep deprivation, emotional stress, febrile illness, exposure to flickering lights, alcohol use are other common precipitating factors.

**BLOOD TESTS**

Regular blood test monitoring is not recommended unless clinically indicated

Full blood count, electrolytes, liver enzymes, vitamin D levels, serum calcium and alkaline phosphatase every 2–5 years for adults taking enzyme-inducing drugs.

Indications for monitoring of AED blood levels are:

- detection of non-adherence to the prescribed medication
- suspected toxicity
- adjustment of phenytoin dose
- specific clinical conditions, for example, status epilepticus, organ failure and certain situations in pregnancy

**WITHDRAWAL OF AEDS**

In most cases after seizure free period of 2 to 3 years, mainly based on cause of seizure and epilepsy syndrome

Should be taken after discussion of risks and benefits

Should be avoided in certain epilepsy syndromes, Eg: juvenile myoclonic epilepsy, because of higher risk of relapse after AED withdrawal.

**HOW TO WITHDRAW AEDS**

Usually withdrawn gradually over a period of 2 to 3 months or longer

Benzodiazepines are tapered at slower rate (6 months or longer)

If a person is on multiple drugs, one drug is withdrawn at a time

If seizure recurs during withdrawal, person is advised to revert to their AED dose before withdrawal and seek medical attention.

**WOMEN WITH EPILEPSY (WWE)**

Women with epilepsy who are in reproductive age group should be ideally evaluated by a specialist.

Addressing issues related to pregnancy should begin well before conception in order to maximize pregnancy outcomes.

**PRECONCEPTION:**

We should keep in mind about possibility of marriage and pregnancy in all WWE in reproductive age group

They should be reassured that more than 90%

have normal pregnancy and children under proper supervision.

They should be advised to plan their pregnancy.

**CONTRACPTION:**

Because of possibility of contraceptive failure if oral pills are used, barrier method may be advised.

If contraceptive pills are used specialist consultation may be taken for starting antiepileptics. Depot injections of progesterone or oral pills containing higher doses of estrogen(more than 50 microgram) may be preferred in consultation with obstetrician.

**FETAL RISK:**

The risk of major fetal malformations is 2-3% in normal deliveries which is 5% less compared to children born to WWE who are exposed to antiepileptic drugs.

This risk can be further reduced by single drug therapy in lowest possible dose along with folic acid supplementation.

All WWE in reproductive age group should be started on Folic acid (5mg/day) at the time of starting of antiepileptics.

During preconception consultation diagnosis, need for AED, selection of the drug and dosage should be carefully evaluated.

In well controlled patients it may be possible to stop the treatment, decrease the dose or shift to monotherapy; however seizure relapse risk should be weighed against possible benefits of treatment modification.

**PREGNANCY:**

In all WWE in reproductive group it should be advised to plan the pregnancy, as unplanned pregnancies are the norm in most societies

Having a seizure (especially if it is generalised) during pregnancy is risk to both mother and foetus. Seizure free interval of at least 9 months prior to conception is associated with lesser risk of seizures during pregnancy.

AEDs should never be stopped for the fear of foetal side effects, once pregnancy occurs.

Once pregnancy occurs, counselling to the patient should reinforce the need for AEDs, and that any potential AED risk to the foetus will be balanced against the risk of increased seizures to both the mother and the developing foetus

All WWE should be stated on Folic acid if not previously started and continued till delivery.

Serum drug levels are of help during pregnancy

If antiepileptic blood levels are not available, it is reasonable to consider an increase in dose after the first trimester, at least in women whose epilepsy includes focal to bilateral or generalized tonic-clonic seizures, who have been sensitive to changes in drug levels before pregnancy, and who have entered pregnancy on the lowest effective dose of their medication, and provided that they are treated with AEDs known to be subject to marked changes in clearance (lamotrigine, levetiracetam, and oxcarbazepine)

A detailed ultrasonogram by experienced ultrasonologist should be advised at 18 weeks gestational age.

If preterm labor is threatened in those who are on enzyme inducing AEDs 48 mg betamethasone (double the normal dose) should be given over 48 hours

All WWE should be given 2 doses of vitamin K - 10mg IM at 34 and 36 weeks of pregnancy unless there is a contraindication

All infants born to mother taking AEDs should be given vitamin K - 1 mg intramuscularly at birth.

**LABOUR :**

The diagnosis of epilepsy in itself is not an indication for a caesarean section. Vaginal deliveries are the norm.

WWE should have delivery done at the hospital with access to specialist if required. Neonatal care and facility for caesarean section should be available.

AED default should be avoided when the patient is in maternity ward. There is no contraindication for epidural or spinal anaesthesia.

Regular dose of oral medication should be continued during labour. In those who can not be given oral dose, parenteral AEDs can be given.

Elective caesarean section should be considered in women having frequent seizures towards the end of pregnancy.

If seizure occurs during labour it should be immediately terminated with lorazepam or diazepam

If seizure occurs during peripartum period after prolonged remission, other causes of seizures like eclampsia, CSVT should be considered.

**POSTPARTUM**

All WWE with epilepsy should be encouraged to breast feed.

The dosages of levetiracetam, lamotrigine and oxcarbazepine may have to be decreased to prepregnancy levels if they were increased during pregnancy usually done at 2 weeks postpartum.

Care should be taken to avoid dropping the baby during a seizure or myoclonic jerk.

They should be informed about importance of having sufficient sleep .

All WWE should be informed about the need to have sufficient spacing between the pregnancies.

**EPILEPSY IN ADOLESCENTS AND YOUNG ADULTS**

Counselling should be given about job options – to avoid jobs requiring shift work, jobs requiring driving, working with heavy machinery etc.

To avoid sleep deprivation, alcohol and substance abuse

Prolonged TV viewing, playing video games, dancing in dark room with flickering lights may precipitate seizures.

**EPILEPSY IN ELDERLY**

Toxic and metabolic causes should be considered in elderly presenting with generalised seizures. vascular and space occupying lesions are commonly seen in elderly presenting with focal seizures.

Elderly person presenting with seizure should undergo atleast CT scan, MRI is preferable in most of the situations.

Convulsive status eilepticus is more frequent compared to younger age group.

Any elderly person presenting with acute onset altered mental status, non convulsive status should be suspected even when there is no clinical seizure

Drug interactions will be an issue in elderly with associated co morbidities; most of the newer antiepileptics can be safely used in elderly

In majority of elderly with epilepsy seizures can be controlled with single conventional AED and 70% can expect a 5 year remission.

**STROKE AND EPILEPSY**

Routine treatment with antiepileptics in all stroke patients is not recommended though often practised.

Risk of seizure recurrence after one acute symptomatic seizure (which occured within one week of onset of stroke) is relatively low; In these patients antiepileptics if administered may be withdrawan after acute phase.

Risk of seizure recurrence is high in patients who have atleast one unprovoked seizure (which occurred approximately one week after stroke onset). These patients require antiepileptics for longer periods. Choice of antiepileptics should be individualised.

Central venous sinus thrombosis (CSVT) has high incidence of seizures, status epilepticus; In CSVT antiepileptics are recommended for one year after the acute episode.

Risk of seizure recurrence is higher in cortical lesions, haemorrhagic strokes

## HEAD INJURY AND EPILEPSY

In mild head injury no prophylactic antiepileptics are required.

Headache, vomiting after mild head injury do not influence the occurrence of seizures. EEG is not helpful in predicting the seizure.

Severe traumatic brain injury (GCS less than 8/15), depressed skull fracture, penetrating injuries, post traumatic amnesia, present of brain contusions seen on imaging are the factors associated with increased risk of seizure.

Short term use of phenytoin, fosphenytoin or levetiracetam in these patients is associated with reduced occurrence of early seizures; continuation of these drugs after the acute phase will not have any additional benefit and not recommended.

Seizures occurring within one week of brain injury should not influence long term antiepileptic therapy.

Seizures occurring after one week of trauma(first late post traumatic seizure) are associated with high risk of recurrence and require long term antiepileptic therapy.

In patients who have not had a late post traumatic seizure long term anti-epileptic medication is not recommended. There is lack of efficacy in this setting and many potential adverse events with these medications.

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# Neonatal & Childhood Epilepsy

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## Introduction

Epilepsy is a common heterogenous group of neurological problems in children. It exerts a significant physical, psychological, economic and social toll on children and their caregivers. The problem is compounded in developing countries as they add about 75-80% of new cases of epilepsy. The seizures and epilepsies in children are extremely diverse, differing markedly in age of onset, seizure characteristics, associated comorbidities, treatment options and varied prognosis. Given that there is a shortage of pediatric epileptologists practicing around the world, it is impossible for all children with recurrent seizures to receive their care from sub specialists all the time. So, it is very important for the general pediatrician to be aware of the basic evaluation and the management of these patients. Also, pediatricians and practitioners should play a vital a role in preventing epilepsy by minimizing neurological insults in early infancy and childhood. There is a need to focus on role of primary health care providers by educating them with guidelines for optimal practices, rational therapy, and counseling.

## Definition

A seizure is defined as an excessive burst of abnormal synchronized neuronal activity affecting small or large neuronal networks that results in clinical manifestations that are sudden, transient and usually brief.

Epilepsy is defined as a disorder of the brain characterized by any of the following conditions:

1. At least two unprovoked (or reflex) seizures occurring more than 24 hours apart.
2. One unprovoked seizure and a probability of further seizures, similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years.
3. Diagnosis of epilepsy syndrome

An epileptic syndrome is a disorder that manifests as one or more specific seizure types and has a specific age of onset and has a specific prognosis. Epilepsy is resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

A seizure that is provoked by a transient event, in an otherwise normal brain leading to a temporary reduction of the seizure threshold does not count toward a diagnosis of epilepsy (e.g., febrile seizure).

## Incidence

Epileptic Seizures affect 1-2% of the population and 4% of children. Developing countries have higher prevalence due to the poorer perinatal care and standards of nutrition, public hygiene and the greater risk of brain injury, cerebral infection or other symptomatic cerebral conditions. Incidence of seizures is age dependent. The highest incidence rate (100 per 1,00,000) is observed in the first year of life, declining to approximately 20 cases per 1,00,000 per year in adolescence. Childhood epilepsy has a prevalence of approximately 0.5-0.8% and comprises a heterogenous group of disorders, including a variety of epilepsy syndromes that range in severity from benign to progressive and catastrophic.

## Classification of Epilepsy

In 2017 the International League against epilepsy proposed a uniform operational classification for epilepsies (Figure 1).

This allows for uniformity across the borders of countries and continents and helps in grouping of patients based on their clinical presentation and pathophysiology. This describes the seizure in a better manner, allows for a unified treatment approach and makes research easier.

## Neonatal Seizures

Neonatal seizures are usually associated with underlying neurological insult or a metabolic abnormality. Figure 2 shows the various types of neonatal seizures. Focal clonic, multifocal clonic and focal tonic seizures usually show ictal EEG activity whereas subtle, generalized tonic and myoclonic episodes may not. It is important to differentiate neonatal seizures from non-epileptic phenomena like jitteriness and benign sleep myoclonus. Both events are extremely common in the neonatal period. Serum glucose, electrolytes, calcium, magnesium and neurosonogram must be done in all cases. CSF studies and culture must also be done, except when the diagnosis is definite e.g., hypoxic ischemic encephalopathy or hypocalcemia. The world health organization recommends EEG in all neonates with symptomatic seizures. MRI with diffusion tensor imaging is the modality of choice, done immediately for etiology and at 3-6 months for prognosis. The management algorithm is as shown in Figure 3.

## Febrile Seizures

Febrile seizures are the most common seizure disorder of childhood. About 2–5% of children suffer a febrile seizure at some point in their childhood. Simple febrile seizure is defined as a short (<15 min) generalized seizure, not recurring within 24 hours, that occurs during a febrile illness not resulting from an acute disease of the nervous system in a child aged between 6 months and 5 years, with no neurologic deficits and no previous afebrile seizures. On the other hand, focal, or generalized and prolonged seizure (>15 min), recurring more than once in 24 hours, and/or associated with postictal neurologic abnormalities, or a febrile seizure in a child with prior neurologic deficits – all are called as complex febrile seizure. A child presenting with a prolonged febrile seizure controlled with an AED before the 15-minute cut off also qualifies for a complex febrile seizure. If a complex febrile seizure is prolonged for > 30 minutes or there are shorter but multiple seizures, without regaining consciousness, then it is termed as febrile status epilepticus.

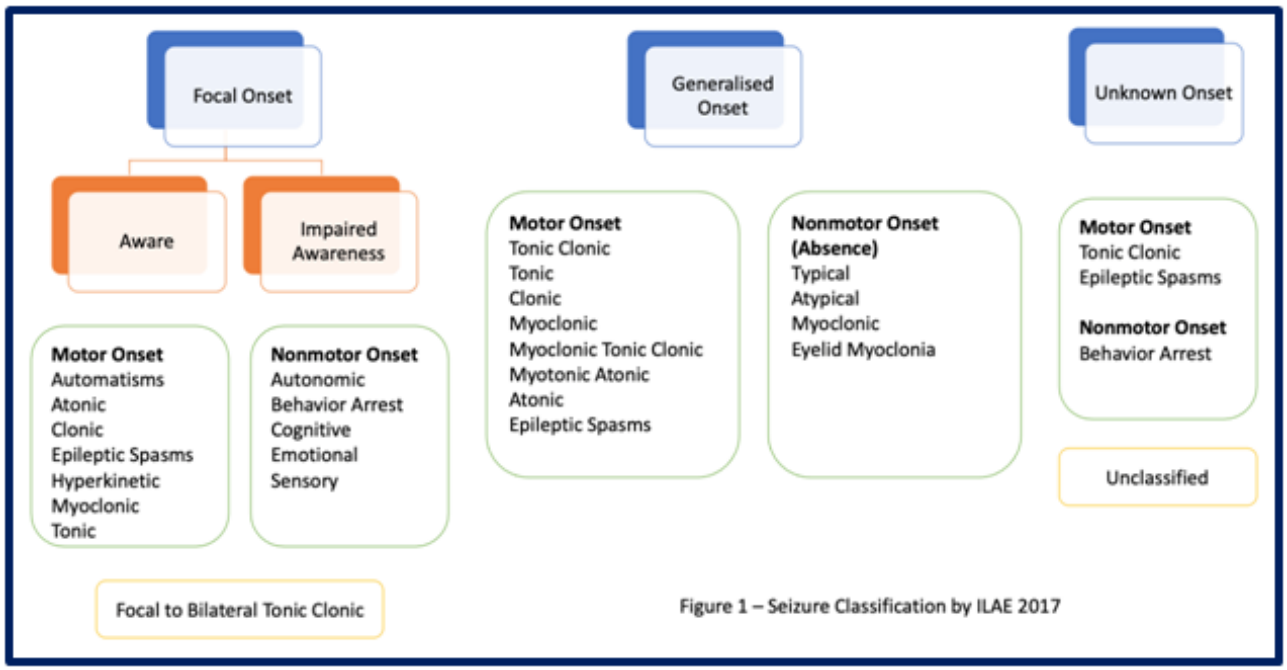
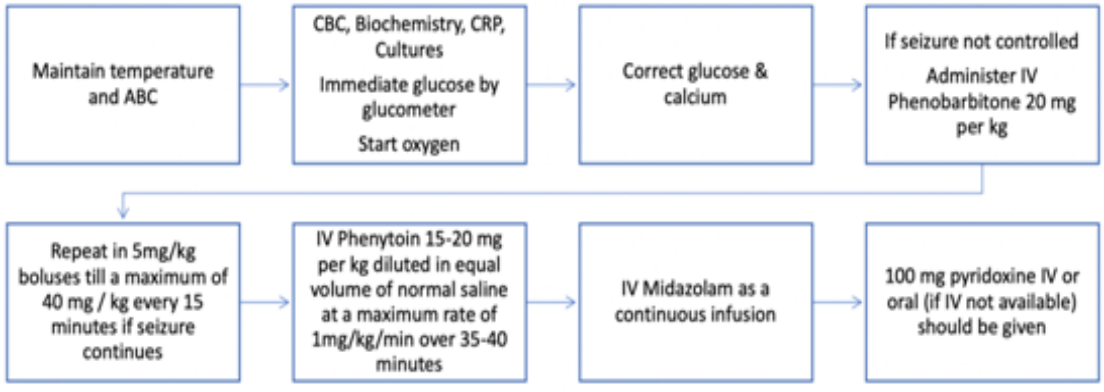



Figure 1 – Seizure Classification by ILAE 2017

| Seizure Type | Clinical Features |
|---|---|
| Focal Clonic | Repetitive rhythmic contractions of muscle groups, Unifocal or multifocal / synchronous or asynchronous, Cannot be suppressed by restraint |
| Focal Tonic | tonic asymmetric posturing of limbs / trunk / eye deviation, Cannot be provoked or suppressed |
| Generalized Tonic | Symmetric posturing of whole body, Flexor / extensor / mixed |
| Myoclonic | Random jerky contractions of muscle groups, Generalized or focal or fragmentary, May be provoked by stimulation |
| Spasms | Like above but occur in clusters, Flexor / extensor / mixed, Cannot be provoked |
| **Motor Automatisms (Subtle Seizures)** | |
| Ocular | Random or roving eye movements, Nystagmus, My be provoked by stimulation |
| Oral Buccal Lingual | Sucking / chewing / tongue movements, May be provoked by stimulation |
| Abnormal Extremity Movements | Rowing or swimming or pedaling or cycling movements, May be provoked and can be suppressed |
| Complex Purposeless Movements | Sudden arousal with random but intense limb activity |

Figure 2 – Types of Neonatal Seizures

Figure 3 – Neonatal Seizure Management Algorithm




Note:

1. IV glucose dose is 2ml per kg of 10% dextrose bolus. If there is delay in doing a blood sugar or bedside facility is not available, empirical bolus dose should be given.
2. If hypoglycemia has been treated or excluded as a cause of convulsions, the neonate should receive 2 mL/kg of 10% calcium gluconate IV over 10 minutes under strict cardiac monitoring. If serum calcium levels are suggestive of hypocalcemia, the newborn should receive calcium gluconate at 8 mL/kg/d for 3 days.
3. A lot of neonatal units and neurologists have shifted to the use of levetiracetam as a first line drug for neonatal seizures. The available evidence and the WHO guidelines however recommend phenobarbitone as first line AED.
4. Based on the available evidence, the WHO guidelines on neonatal seizures recommend either midazolam or lidocaine as the second-line AED in neonatal seizures. However, given the lack of robust evidence and the need for respiratory support with the above drugs, it seems a logical choice to use phenytoin or Fosphenytoin as a second line drug. According to the Nelson textbook of pediatrics half of neurologists prefer to use it as second line drug.
5. IV Midazolam - an initial IV bolus of 0.15 mg/kg, followed by continuous infusion (1 µg/kg/min) increasing by 0.5 to 1 µg /kg/min every 2 minutes until a favourable response or a maximum of 18 µg/kg/min

There is no role for routine EEG and neuroimaging in a simple febrile seizure. Lumbar puncture should be considered in those with clinical signs of meningitis, children already on antibiotics (signs may be masked) and age <18 months (clinical signs may not be clear. But this has been a controversial recommendation and debatable). A child with complex febrile seizure will require all the above work up.

The treatment of an acute episode would be to correct the ongoing seizure episode and treat the underlying cause of fever. The most important crux of managing a febrile seizure is prevention of future episodes. The general risk of febrile seizure recurrence is estimated at around 30–40%. Age of first episode <15 months, seizure, or febrile seizure in a first degree relative, lower temperature at the febrile seizure and frequent febrile illness increase the likelihood of recurrence. Prophylaxis of febrile seizures reduces the recurrence of seizures but does not reduce the risk of future epilepsy. The western guidelines do not recommend the routine use of intermittent or continuous prophylaxis. However, the Indian Academy of Pediatrics recommends the use of intermittent prophylaxis with oral clobazam in a dose of 0.75 mg/kg for 2-3 days in 2 divided doses during fever. Febrile status, complex and recurrent febrile seizures (>6 per year despite intermittent prophylaxis) may need EEG, neuroimaging, and continuous prophylaxis with AED (phenobarbitone or valproate). Parental education is an important aspect of treatment in febrile seizure, as it is a recurring event in many cases.

**Granulomas in Children**

New-onset partial or generalized convulsive seizures occurring in clusters in an otherwise normal child is the commonest presentation of single small contrast enhancing CT lesion (SSECTL). It mandates neuroimaging to establish the cause. The commonest etiology is neurocysticercosis (NCC) followed by tuberculoma. Along with treatment for the underlying cause these children require AEDs till the lesions disappear or are completely inactive (no edema, no enhancement, calcified). This is usually for a period of 6 months or more. Children who present with de novo or a relapse seizure due to an already calcified lesion will require treatment for 2 year seizure free interval.

**Epileptic Syndromes in Children**

**Neonatal Epileptic Syndromes**

- **Benign familial neonatal epilepsy syndrome**

  Rare, dominantly inherited disorder due to the mutations affecting voltage gated potassium channel genes (KCNQ2, KCNQ3). In 80% of the cases seizures start on the second or third day of life. Typically, clonic but preceded by a tonic component often unilateral but can also be bilateral. The Interictal EEG is usually normal. Spontaneous resolution within two to six months.

- **Early myoclonic encephalopathy**

  Most closely associated with Aicardi syndrome. Characterized by focal myoclonus involving limbs or face, shifting from one area to another. Generalized massive clonus may appear. Epileptic spasms typically develop later during the disorder. Neurological status is abnormal either at birth or with the development of seizures. Suppression burst pattern is seen in EEG. Increased mortality in first few years of life and survivors may have significant developmental delay.

- **DEND Syndrome**

  DEND syndrome (developmental delay, epilepsy, neonatal diabetes) is a very rare, generally severe form of neonatal diabetes mellitus characterized by a triad of developmental delay, epilepsy, and neonatal diabetes. It is caused by an activating mutation in the KCNJ11 gene, which encodes the Kir6.2 subunit of the potassium ion channel. Oral sulfonylurea therapy appears to be more effective than insulin in

controlling hyperglycemia and can also lead to improved seizure control and psychomotor development.

Epileptic Syndromes with Onset During Infancy and Childhood

- **Childhood Epilepsy with Centrotemporal Spikes**

  Benign childhood epilepsy with centrotemporal spikes (Benign Rolandic Epilepsy) which typically starts during childhood and is resolved in adolescence. The child typically wakes up at night owing to a focal seizure causing buccal and throat tingling and tonic or clonic contractions of one side of the face, with drooling and inability to speak but with preserved consciousness. EEG shows a typical broad-based centrotemporal spikes that are markedly increased in frequency during drowsiness and sleep. MRI when done, is normal. Patients respond very well to AEDs – carbamazepine is the drug of choice. In some patients who have rare and very mild seizures, treatment may not be indicated. This syndrome has an excellent prognosis.

- **Benign Epilepsy with Occipital Spikes**

  Benign epilepsy with occipital spikes can occur in early childhood and manifests with a unique seizure type that has prominent autonomic features including vomiting and pallor. The seizures are usually nocturnal and last more than five minutes, or they appear in later childhood with frequent seizures with prominent visual symptoms (hallucinations, blindness) and migraine headaches. The mean age of onset is between eight and nine years. EEG reveals occipital spikes, activated by eye closure. This also responds very well to carbamazepine and levetiracetam. The prognosis is usually very good.

- **Epilepsy of Infancy with Migrating Focal Seizures**

  Epilepsy of infancy with migrating focal seizures is a rare, infantile epileptic encephalopathy characterized by normal early development, refractory focal seizures arising independently from both hemispheres and severe psychomotor retardation.

- **Temporal Lobe Epilepsy**

  Any lesion in the temporal lobe can cause temporal lobe epilepsy. Mesial temporal sclerosis is the commonest cause of this. It is a condition which is often preceded by febrile seizures and later develops into focal seizures. It is the commonest surgically remediable epilepsy.

- **Rasmussen's Encephalitis**

  Rasmussen's encephalitis is a form of chronic encephalitis that manifests with unilateral intractable focal seizures, epilepsia partialis continua and progressive hemiparesis of the affected side, with progressive atrophy of the contralateral hemisphere. The etiology is usually unknown. Cases have been attributed to cytomegalovirus infection and anti-NMDA receptor autoantibodies.

- **Childhood Absence Epilepsy**

  Childhood Absence Epilepsy (CAE) is a form of idiopathic, genetically determined, generalized epilepsy that is characterized by absence seizures and in 10% of cases, generalized tonic-clonic seizures. The majority (65-70%) of children with childhood absence epilepsy have remission of seizures in adolescence; good prognostic signs are earlier age at onset and absent other types of seizures.

- **Juvenile Absence Epilepsy**

  Juvenile Absence Epilepsy (JAE) is classified as an idiopathic generalized epilepsy. The age of onset is typically at or after puberty between the ages of 10-17. The seizures are like childhood absence epilepsy (CAE) except for the later age of onset (childhood

absences occur between ages of 5 – 8 years). The ictal EEG pattern may resemble that of CAE (3 Hz spike and wave) but more often the discharges tend to vary slightly in frequency (usually 4 – 6 Hz), are more irregular and include more polyspike discharges.

- **Myoclonic Epilepsy in Infancy (MEI)**

  Myoclonic seizures may begin in the first year of life. Myoclonic jerks may be focal, multifocal, or generalized and are more likely to be flexor than extensor. Myoclonus is termed epileptic when it occurs with a cortical epileptic form discharge, usually a generalized spike and wave discharge or spikes/sharp waves over the motor cortex.

- **Juvenile Myoclonic Epilepsy**

  Juvenile Myoclonic Epilepsy (JME) is also known as juvenile myoclonic epilepsy of Janz. The age of onset is in the mid-teens between the ages of 12-18. Patients may present with myoclonic jerks upon awakening in the morning. Patients may first ignore the myoclonic jerks, often attributing them to clumsiness. Sometimes the diagnosis is not made until the patient has a generalized tonic-clonic seizure. The myoclonus usually involves the neck, shoulders, arms, or legs with the upper extremities being most frequently affected. Consciousness is usually not impaired during the myoclonic seizures. Generalized tonic clonic and absence seizures are also seen. Generalized tonic clonic and absence seizures are also seen. Generalized tonic-clonic seizures may also occur in the morning upon awakening and can be triggered by sleep deprivation, alcohol, and stress. Often, several myoclonic jerks may precede a generalized tonic-clonic seizure, which is known as a clonic-tonic-clonic seizure. Approximately 50% of patients can be photosensitive. The diagnosis of the condition is based on the clinical history and EEG, which shows generalized irregular 4 to 6 Hz spike and wave activity occurring in bursts. The EEG is more likely to record discharges after awakening.

- **Benign Familial Infantile Epilepsy**

  Autosomal dominant epilepsy syndrome characterized by febrile seizures in an otherwise normal infant beginning at about six months of age.

- **Ohtahara Syndrome**

  Early Infantile Epileptic Encephalopathy (EIEE) has also been referred to as Ohtahara syndrome. The onset is within the first two to three months of life. At the onset the neurologic examination is abnormal with developmental delay, spasticity, and motor asymmetries. Ohtahara syndrome is characterized by tonic spasms as the predominant seizure type, but a third of affected infants also have other seizure types, including focal motor seizures, hemi convulsions and generalized motor seizures. The background EEG pattern in Ohtahara syndrome is suppression-burst with relatively prolonged bursts (2-6 sec) and shorter periods of suppression (3-5 sec). The EEG may evolve from the initial suppression-burst pattern to a hypsarrhythmia pattern, typical of West syndrome. The prognosis is poor, half of the patients die in infancy; survivors have severe neurologic impairment.

- **Dravet Syndrome**

  Dravet syndrome, also called severe myoclonic epilepsy of infancy, is usually due to a de novo mutation affecting the SCN1A gene encoding the á1 sodium channel subunit. De novo mutations account for about 70-95% of cases. The typical clinical presentation is that a previously normally developing infant has febrile status epilepticus at around 6 months of age and then recurrent generalized or shifting hemi-clonic seizures are seen, often triggered by fever. After 1 year of age, other seizure types

appear, including myoclonic seizures, absence seizures and complex partial seizures as well as atonic seizures at times. The seizures are drug resistant and may be exacerbated by some sodium channel blockers such as carbamazepine and lamotrigine. The EEG becomes increasingly abnormal with age. Abnormalities include focal, multifocal and/or generalized epileptiform activity and changes in background activity. The prognosis is poor; most individuals develop intellectual disability and at times ataxia and spasticity.

- **West Syndrome**

  Infantile Spasms (IS) is an age-specific convulsive disorder of infancy and early childhood. The triad of epileptic spasms, arrest or deterioration of psychomotor development and a characteristic EEG pattern called hypsarrhythmia; is known as West syndrome. West syndrome has a later age at onset; the peak incidence of onset (50-77%) is between 3 and 7 months of age. The disorder is heterogeneous in its etiology. Approximately two-thirds of infants have brain lesions or preceding developmental delay (symptomatic west syndrome). The remaining have a normal development (Idiopathic or cryptogenic west syndrome). Psychomotor development may be abnormal prior to onset, but there is a clear deterioration after onset.

  Epileptic spasms are usually the initial manifestation. They tend to occur in clusters, sometimes multiple times a day. Three clinical types of spasms have been recognized as flexor, extensor, and mixed flexor-extensor. Most infants have more than one type of spasm. Hypsarrhythmia is characterized by high-voltage disorganized EEG activity with slow waves and multifocal spikes and sharp waves punctuated by periods of generalized attenuation.

- **Lennox-Gastaut Syndrome**

  Lennox-Gastaut Syndrome (LGS) is classified as an epileptic encephalopathy. The age of onset is usually before age 8 years, with a peak age of onset between 3-5 years of age. Rarely, the disorder can present in early adulthood. The syndrome is characterized by a triad of multiple seizure types (tonic and atypical absence are the most common), slow spike and wave on EEG (1-2.5 Hz) and cognitive dysfunction. It may evolve from West syndrome. Tonic seizures are considered a prerequisite for the diagnosis. Atypical absence and atonic seizures are also common.

  Myoclonic, generalized tonic-clonic, unilateral clonic and partial seizures can occur less frequently. Nonconvulsive status epilepticus can occur in >50% of patients and involves near continuous atypical absence seizures interrupted by brief tonic seizures. The diagnosis may be difficult to do at first because not all features of the syndrome may be present. The seizures are typically refractory to medical treatment.

- **Myoclonic Atonic Epilepsy**

  Myoclonic atonic epilepsy is a syndrome like, but, milder than Lennox-Gastaut syndrome that usually does not have tonic seizures or polyspike bursts in sleep. The prognosis is more favorable than that for Lennox Gastaut syndrome.

- **Generalized Epilepsy with Febrile Seizures Plus**

  A group of genetic epilepsy syndromes that often begin during the first year of life, referred to as "generalized epilepsy with febrile seizures plus" (GEFS+), are characterized by multiple febrile seizures, generalized tonic-clonic seizures and other seizure types including absences, myoclonic seizures, and focal seizures.

- **Landau Kleffner Syndrome (LKS)**

  This is a rare syndrome characterized by loss of language skills due to auditory agnosia in a previously normal child. 70% have associated clinical seizures which can be focal, generalized, absence or myoclonic. EEG is more abnormal during non-REM sleep recording and MRI is normal. Valproate is often the first anticonvulsant used in this disorder and nocturnal benzodiazepine may help aphasia.

- **Metabolic Epilepsies**

  The discussion on these is beyond the scope of this article but it is important to understand that treatable metabolic seizures are increasingly recognized. A few notable ones are pyridoxine dependent epilepsy, pyridoxal phosphate responsive neonatal encephalopathy, cerebral folate deficiency, biotinidase deficiency and GLUT 1 deficiency.

**Investigations**

**EEG**

EEG is a part of work up for all children with new onset episode. It supports the clinical diagnosis (if abnormal), may help in diagnosis specific syndromes, and help in prognosis. Normal EEG, however, does not rule out a seizure. In children with uncontrolled seizures, an EEG may help in reclassifying the seizure type or identify an epilepsy syndrome. A sleep deprived EEG is ideal in all children above 3 years of age and should be done at least 3 – 4 days after an ictal episode to avoid interference from post ictal slowing.

**Indications of EEG**

- All children with clinically diagnosed epilepsy
- After an episode of status epilepticus
- Unexplained coma and encephalopathy
- Suspicion of non-convulsive status in children with learning difficulties and epilepsy
- Acquired regression of speech or language function or scholastic function (e.g., SSPE)
- Developmental regression
- To monitor progress in West syndrome and non-convulsive status
- Before discontinuation of an AED

**Neuroimaging**

MRI is the modality of choice and is superior to CT except detecting calcifications. In an emergency like trauma and status CT becomes a modality of choice due the ease of doing it.

**Indications for MRI Brain**

- Focal epilepsy
- Epilepsy in children aged less than two years
- Myoclonic epilepsy
- Intractable seizures
- Loss of previous good control
- Seizures continuing in spite of first line medication
- Associated neurological deficits or appearance of new neurological signs
- Developmental regression in children
- Infantile spasms

**Other Investigations**

- Sleep or sleep deprived EEG, if awake EEG is normal
- Video telemetry
- Drug levels
- Metabolic work up – ammonia, lactate, pyruvate, blood gas, blood tandem mass spectrometry, urine organic acid analysis, plasma aminoacidogram, biotidinase levels, CSF metabolic investigations
- Muscle biopsy in mitochondrial disorders
- Genetic testing

### The First Unprovoked Seizure

A thorough history is the most important step in understanding the semiology of the event. Deviation of eyes, face and head, tongue bite and incontinence are all specific to an epileptic event. Confusion state, loss of consciousness and even abnormal movements may be seen in other non-epileptic paroxysmal disorders also (e.g., breath holding spell). Once life threatening conditions are ruled out the next logical step is identifying the onset and nature of the seizure. Focal seizure in a adolescent usually indicates a localized lesion, the same may not be true always for an infant and child. Tonic seizures are characterized by rigidity or increased tone. Clonic movements are fast rhythmic movements with relaxations. Myoclonic jerks are repeated shock like contractions of muscles. Aura or abnormal behavior prior to the onset of seizure leads towards a possibility of a complex partial seizure. Routine examination apart from general physical and neurological, should also focus on eyes – to look for markers of a bigger neurological problem (e.g., cherry red spot, chorioretinitis, macular changes etc.), skin – for neurocutaneous markers (neurofibroma, ash leaf macule, sha green patch, port wine stain etc.).

In an ideal scenario and in contrast to adults, AED is not recommended after first episode of a seizure in children, except in status epilepticus. The choice of AED depends on the predominant seizure type, keeping in mind the side effects. Certain drugs may exacerbate certain types of seizures (e.g., carbamazepine can exacerbate absence seizures and myoclonic seizures). The drug should be started in lowest effective dose and escalated as per the need. Monotherapy is always preferred. Only when 2 different monotherapies have failed, one should consideration of addition of a second drug. Most of the time drugs can be withdrawn after a 2-year seizure free interval. In the event of an abnormal EEG at the end of 2 years, drug withdrawal after 4 years is attempted. The drug should be decreased slowly over a period of 3 – 6 months.

### Pharmacotherapy (AEDs)

A detailed description of individual drugs and epilepsy syndromes is beyond the scope of description here. Figures 4 & 5 below give a brief overview of the various therapeutic options in pediatric epilepsies. In general, the first drugs of choice for focal seizures are carbamazepine and oxcarbazepine; for absence seizures ethosuximide & valproate; for JME valproate & lamotrigine. Potential for exacerbation of certain seizures must be kept in mind at initiation of therapy (Precipitation of myoclonic seizures by lamotrigine in Dravet syndrome and exacerbation of absence seizure by carbamazepine).

Valproate is to be used in caution in children less than 2 years, especially when there is suspicion of a metabolic disorder. In these group of children can be toxic to the liver and at times potentially fatal. In situations where a rapid rise in drug level is needed, use of drugs which can be administered intravenously and titrated quickly are preferred over something like lamotrigine or topiramate that requires slow titration. Coexisting seizures may warrant careful drug selection (e.g., valproate is better than ethosuximide when generalized tonic clonic seizures coexist with absence seizures). Less frequent dosing in a day and the availability pediatric syrup formulations is a big help when treating a child. Monitoring for drug related side effects is an important aspect, especially when polytherapy is being given.

### Additional Therapy

Patients who have failed at least 2 fair trials appropriate medications are labelled to have drug resistant epilepsy. They need to be re-evaluated to rule out metabolic conditions, degenerative disorders, one of the resistant epilepsy syndromes or inflammatory conditions like Rasmussen encephalitis.

Steroids in the form of ACTH or prednisolone are used in the treatment of West syndrome, LGS and

| Seizure Type | Drug(s) of Choice |
|---|---|
| Generalized Tonic Clonic Seizure | Valproate, Levetiracetam, Lamotrigine, Topiramate |
| Focal Seizure | Carbamazepine, Oxcarbazepine, Topiramate, Levetiracetam, Valproate |
| Absence Seizure | Ethosuximide, Valproate, Lamotrigine |
| Myoclonic Epilepsy in Infancy | Valproate, Levetiracetam, Lamotrigine, Clonazepam |
| Infantile Spasms | ACTH, Prednisolone, Vigabatrin |
| LGS | Lamotrigine, Topiramate, Valproate, Clobazam |
| Dravet Syndrome | Valproate, Clobazam, Topiramate, Stiripentol |
| JME | Levetiracetam, Valproate, Topiramate |
| Benign Rolandic Epilepsy | Carbamazepine, Oxcarbazepine, Valproate, Levetiracetam |
| Landau Kleffner Syndrome | Levetiracetam, Valproate, Steroids, Benzodiazepines |

Figure 4 – Type of Epilepsy & Choice of AED

Figure 5 – AEDs & Role in Seizure Types

| Drugs | Focal seizure | Generalized seizure | | | | Epileptic spasms | Induced aggravation of seizure type / epilepsy syndrome |
|---|---|---|---|---|---|---|---|
| | | Primary GTC | Absence | Myoclonic | Lennox-Gastaut | | |
| Gabapentin | + | | | | | | ABS, MCS, LGS |
| Topiramate | + | + | + | + | + | + | |
| Lamotrigine | + | + | + | (+) | + | + | MCS, JME, LGS, BECTS, Dravet syndrome |
| Levetiracetam | + | + | (+) | + | (+) | (+) | ABS |
| Rufinamide | + | | | | + | + | Little information |
| Vigabatrin | + | | | | (+) | + | ABS, MCS, LGS, Dravet syndrome |
| Oxcarbazepine | + | | | | | | ABS, MCS, JME, LGS |
| Perampanel | + | + | | | | | Little information |
| Lacosamide | + | | | | | | Little information |

ABS: absence seizure, BECTS: benign epilepsy with centro-temporal spikes, GTC: generalized tonic-clonic, JME: juvenile myoclonic epilepsy, LGS: Lennox-Gastaut syndrome, MCS: myoclonic seizure, +: effective, (+): most likely effective.

LKS. The course is for 2 – 3 months with a slow taper. LGS and LKS usually tend to relapse. IVIG has also been used in these group of epilepsies. Ketogenic diet is believed be effective in several drug resistant epilepsies. A metabolic disorder of fatty acids (absolute contraindication) needs to be ruled out before any such dietary initiation. The lack of palatability, vomiting, diarrhea, dehydration, and hypoglycemia make it difficult for children to tolerate such diets.

Patients who have failed 3 drugs are candidates for epilepsy as the chance of achieving seizure control with drugs is < 10%. Children with metabolic and degenerative conditions are not candidates for such a surgery. Identification of a

proper epileptic zone is of paramount importance for the surgery to succeed. Focal resection, hemispherectomy, multiple subpial transection and corpus callosotomy are few of the described procedures.

### Discontinuation of Therapy

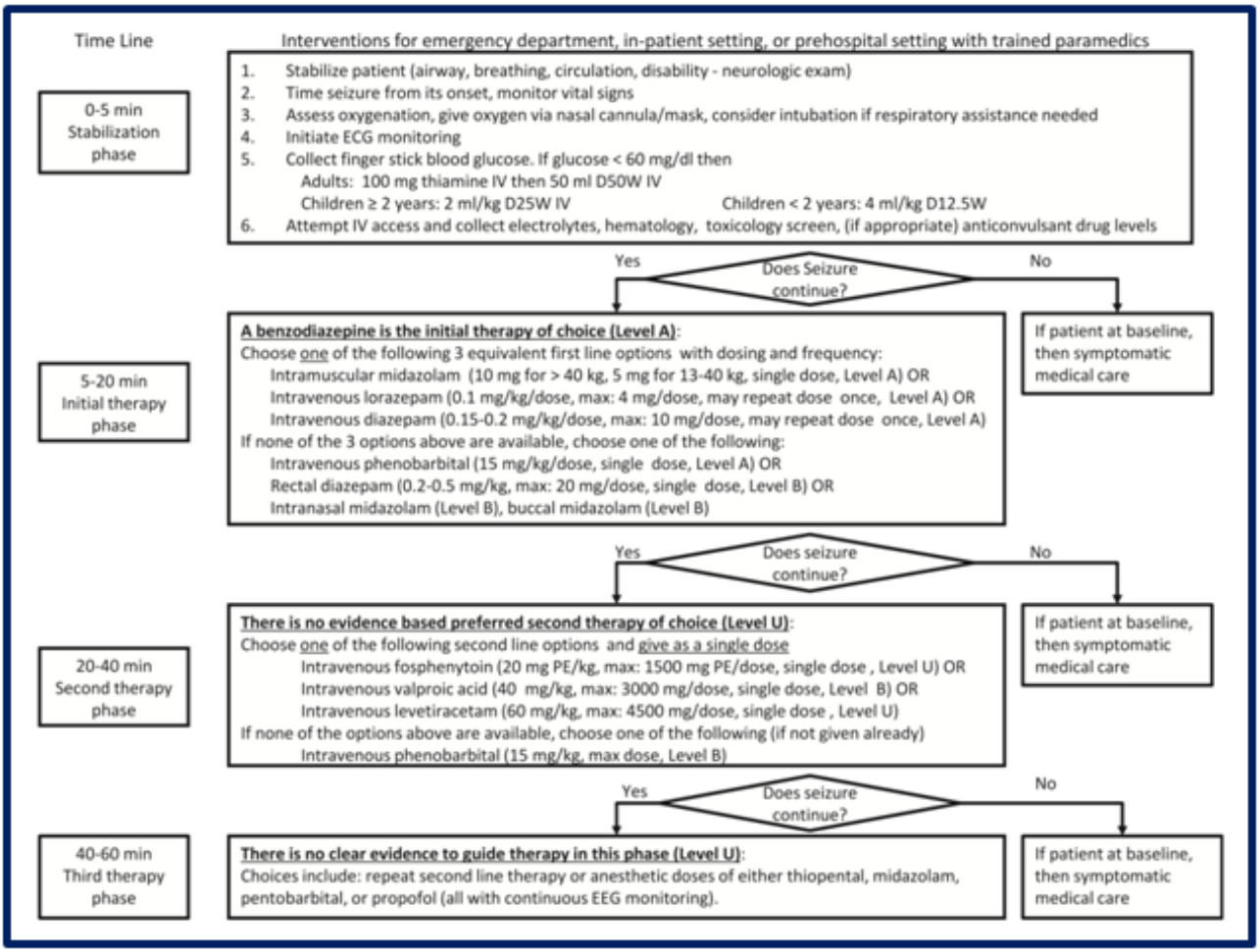
If a child is seizure free for 2 years medications can be withdrawn. In certain conditions like mesial temporal sclerosis, LGS or severe myoclonic epilepsy it may be difficult to withdraw therapy even after longer treatment duration. In some benign seizures drugs may be withdrawn even after a shorter period of 6 months.

Most children who are seizure free for 2 years and have a normal EEG at the time of discontinuation remain event free. Most relapses if they occur, will happen in the first 6 months of discontinuation. The most important risk factor for a relapse is an abnormal EEG at the time of discontinuation of drug. Children with a structural problem are more likely to relapse than those with idiopathic seizures. Patients on valproate for absence or generalized seizures may also have a higher tendency to relapse despite a normal EEG. Valproate normalizes EEGs with spike sharp wave abnormalities, and a EEG during drug withdrawal may be helpful in these patients. Apart from an abnormal EEG, older age of onset, longer duration, multiple drugs, certain genetic or idiopathic epilepsy syndromes are all associated with a higher risk of relapse.

Discontinuation should happen slowly over 3 – 6 months, one drug at a time. The clinician should discuss al these matters with the family and a prescription for intra nasal midazolam should be given when attempting to withdraw drugs.

### Status Epilepticus

As per ILAE, status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally



prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

Generalized tonic clonic seizure – time t1 is 5 minutes and time t2 is 30 minutes

Focal seizures with impaired consciousness – time t1 is 10 minutes and time t2 is 60 minutes

Absence seizures – time t1 is 10 – 15 minutes and optimal time t2 is unknown.

Status can be convulsive or non-convulsive depending on whether there are clinical manifestations or only EEG changes in a comatose patient. For this reason, all children with status should undergo ideally a continuous EEG monitoring. Undiagnosed non convulsive status has an extremely mortality. Patients who continue to experience either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug are having refractory status epilepticus (RSE). Super refractory status epilepticus (SRSE) is defined as continuous or recurrent seizures without normalization of consciousness lasting for 24 h or more despite administration of an intravenous (IV) anesthetic (midazolam, propofol, ketamine, or barbiturate), or recurrence of status epilepticus (SE) on weaning of IV anesthetics. The treatment algorithm is described below in Figure 6

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# Epilepsy and Infections

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## Introduction:

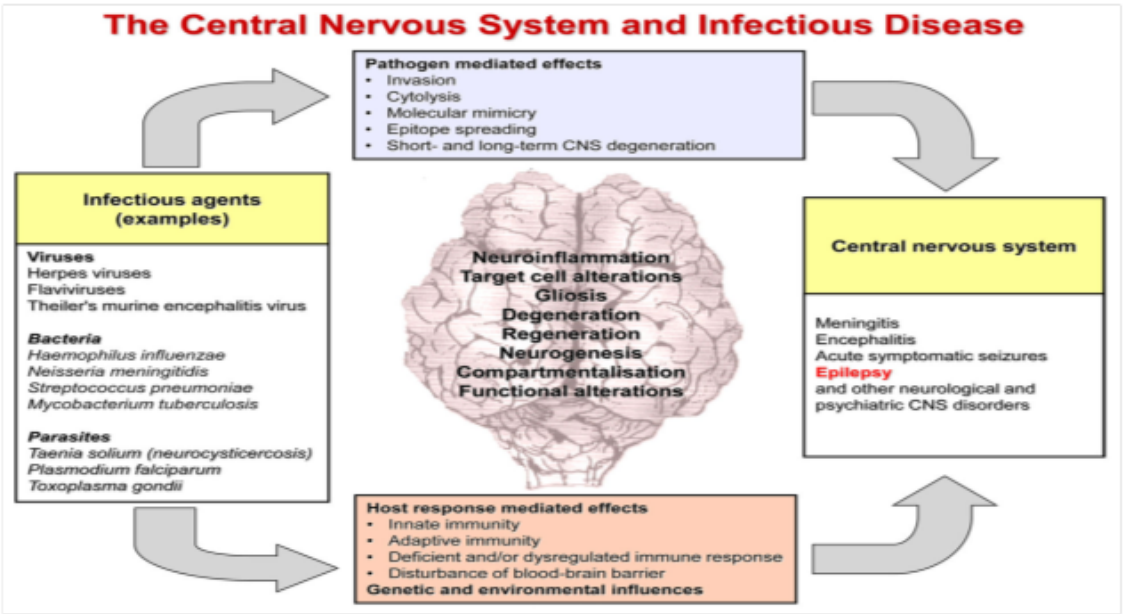
Epilepsy is often secondary to infectious diseases of the Central Nervous System (CNS). The etiology of the infectious diseases varies based on the geographical location – developed countries versus developing countries. A 20-year risk of developing unprovoked seizures after a CNS infection was 6.8% in a large study published in 2002; with the highest incidence in the 1st 5 years. The risk was around 10% for Viral encephalitis without seizures at onset and up to 22% when the viral encephalitis has seizures at onset. Under the same conditions, for bacterial meningitis, it was 13% versus 2.4%. For few of the "triggering infections" seizures may be the only presenting symptom – like for Neurocysticercosis (NCC). In a much later study of more than 12,000 patients, published in 2020, the 10-year risk of epilepsy after HSV encephalitis was 26.6% and after brain abscess was 30.2%.

## Pathogenesis and Etiology:

The pathogenesis of infection induced epilepsy is considered to be alterations in the brain response to neurotropic agents or immune responses to systemic conditions – all resulting in alterations in blood-brain-barrier and neuronal hyperexcitability. The infectious etiologies for epilepsy can be classified typically under bacterial, viral, fungal and parasitic infections.

## Bacterial Infections:

Bacterial infections can be generalized brain involvement from pyogenic meningitis or development of focal cerebral abscesses. While pyogenic meningitis is caused by Meningococci, Pneumococci and Haemophilus influenzae; the cerebral abscess are mostly due to anaerobic bacteria like Bacteroides, Fusobacterium etc. Both the healed abscess cavity/capsule and the gliosis following surgical drainage of the abscess function



as nidus for epilepsy. Mycobacterium tuberculosis is of significant importance in both these diagnostic possibilities – meningitis and abscess – in the setting of developing country. Again, seizures can be the only presentation in a patient with tuberculoma of the brain.

**Parasitic Infections:**

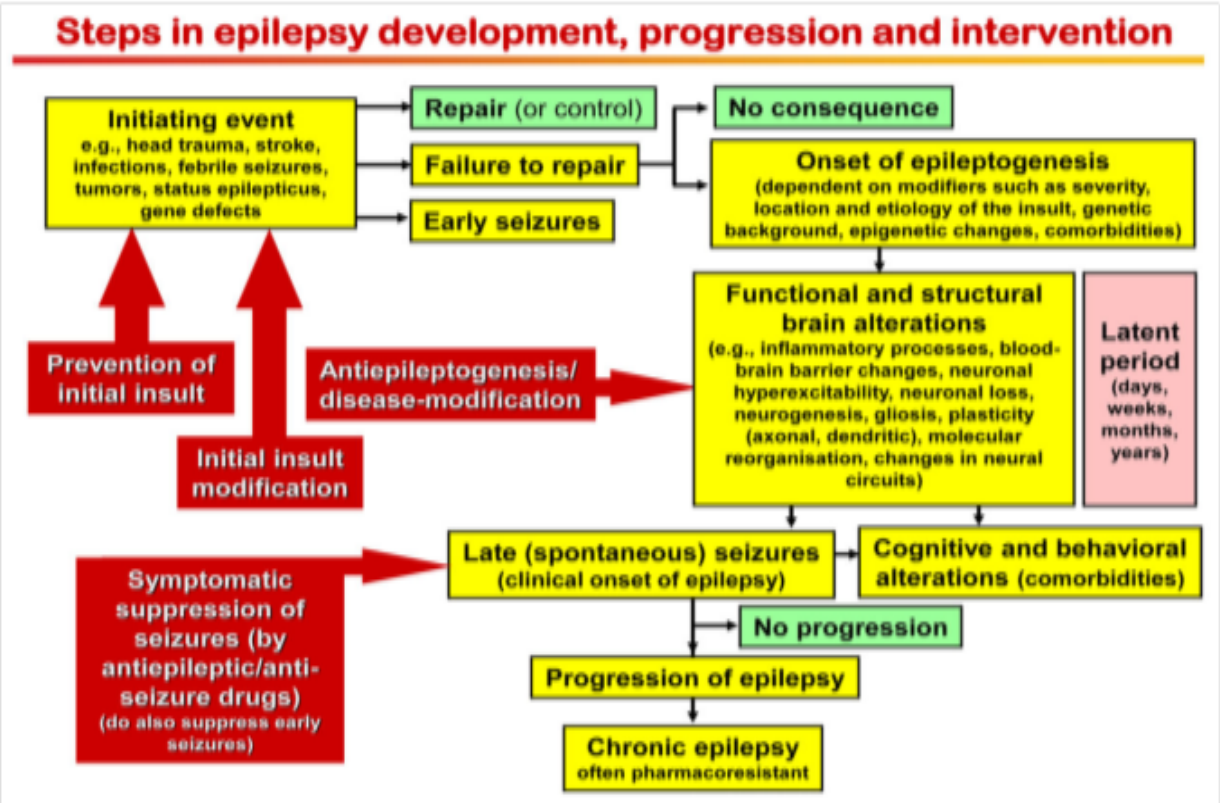
While there are a multitude of parasites associated with epilepsy, the causation is difficult to establish in many because of difficulty in establishing the etiology in the brain and because of the poor specificity of serological tests in these conditions. Hence, especially in the developing world, the possible diagnosis of parasitic infection of the brain/CNS is concluded with clinical, radiological and epidemiological data rather than conclusive diagnostic tests. Of the many parasitic infections, the most common are presumed to be Neurocysticercosis (NCC) and Toxoplasmosis. In fact, it is believed that 30-50% of epilepsy cases in an endemic region is due to NCC. The association of Toxoplasmosis and epilepsy (both cryptogenic and active convulsive) was demonstrated in a meta-analysis published in 2019 (which included > 7000 patients). Cerebral Malaria is mostly associated with acute encephalopathy but has been shown to have positive association with epilepsy in the endemic areas of Africa. Onchocerciasis is another parasitic infection that has demonstrated positive association with epilepsy in published meta-analysis – particularly in the endemic regions of Africa and South America.

**Fungal Infections:**

Multiple fungal infections are known to infect the brain – from Cryptococcus to Aspergillus and endemic mycoses like Histoplasma. The risk of progression to epilepsy is always based on the severity of presentation and seizures during the clinical disease.

**Viral Infections:**

Viral infections of the CNS have the highest risk to progression to epilepsy. Viral infections can result in seizures through direct invasion of the neurons as well as through inducing the release of pro-inflammatory cytokines. In more than half



the cases of Temporal Lobe Epilepsy studied in one case series, HHV-6 DNA and proteins were isolated from the hippocampus of these adult patients. Other Herpes group of viruses like HSV, arboviruses like Japanese Encephalitis Virus and West Nile Virus are among others that have been associated with high risk of seizures. Following viral encephalitis complicated with acute seizures, there is a 22-fold increase in developing unprovoked seizures – especially in the first 5 years.

**Prevention of Epilepsy after Brain Infections**: We could attempt to reduce the risk of epilepsy associated with CNS infections by either modifying the severity or duration of the infectious insult or/ and by introducing medications that will alter the epileptogenic pathogenesis. Early initiation of treatment for the etiological agent and aggressive management of fluid and electrolyte balance in the patient is recommended. Unfortunately, we do not have a "pathogenesis modifying" agent identified yet.

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# Status Epilepticus

**Dr. Aparna Pai**

**Introduction:**

Status epilepticus(SE) is a neurological emergency encountered frequently in medical and neurocritical care. Refractory and super refractory status epilepticus are extremely challenging situations requiring emergency rational polytherapy. Any delays in recognition and management of status epilepticus results in significant morbidity and mortality. As the duration of continue seizure activity increases, outcomes become progressively bleak.

**Definition:**

The defining criteria of status epilepticus has evolved over time to incorporate current understanding of concepts. Early definitions described status epilepticus as seizures persisting for a prolonged length of time or seizures are repeated frequently enough to produce a fixed or enduring epileptic condition. To facilitate practical clinical care a time frame was introduced in 1993 definiton as "seizures lasting more than 30 minutes or occurrence of two or more seizures without regaining of consciousness in between. The "International League Against Epilepsy Task Force on Classification of Status epilepticus , defines status epilepticus as " condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures".Operationally, the International League Against Epilepsy established two time-points of utmost clinical importance: time-point 1, at which point the seizure is considered abnormally prolonged and treatment should be started; and time-point 2, at which point ongoing seizure activity is likely to result in long-term consequences and may warrant implementation of aggressive therapy. Four classification axes are recognised: semiology; aetiology; electroencephalogram (EEG) correlates; and age.

**Refractory status epilepticus(RSE):**

Although there is no uniform definition of RSE, it typically describes SE refractory to benzodiazepines and one additional parenteral first-line anti-seizure medication.

**Superrefractory status epilepticus(SRSE):**

If seizures cannot be terminated with the use of an intravenous (IV) anaesthetic in addition to benzodiazepines and standard anticonvulsants, the condition is termed SRSE. About 15% of status epilepticus evolve into super-refractoriness with no response to benzodiazepine, first line anti-seizure medications and IV anaesthetic drugs. As status epilepticus persists motor convulsive seizures become less prominent or are accompanied by subtle motor signs or electrographic seizures resulting in non-convulsive status epilepticus(NCSE).Status epilepticus can occur in a previously known patient with epilepsy or can occur denovo in previously healthy individuals. New-onset RSE (NORSE) describes RSE in premorbidly healthy individuals where no cause of SE is immediately apparent.The Salzburg consensus criteria for non -convulsive status epilepticus have high sensitivity and specificitybased on electrographic/electroclinical features that constitute EEG evidence of rhythmic epileptiform discharges occurring at a frequency > 2.5 Hz, or rhythmic EEG discharges occurring at a frequency d" 2.5 Hz and with either: spatio-temporal evolution; subtle clinical changes

correlating with EEG changes; or EEG and clinical improvement after intravenous (i.v.) anti-epileptic drug therapy

**Aetiology:**

Previously diagnosed patients with epilepsy.

1) Low anticonvulsant drug levels.
2) Medication non-compliance.
3) Recent medication change
4) Febrile illness or metabolic derangements.

**New onset status epilepticus:**

1) Stroke
2) Toxic –metabolic encephalopathy.
3) Hypoxic ischemic encephalopathy.
4) Intracranial space occupying lesion.
5) Meningoencephalitis.
6) Trauma and head injury.
7) Autoimmune encephalitis.
8) Paraneoplastic encephalitis.

**Children:**

1) CNS infections-meningoencephalitis.
2) Inherited metabolic disorders.
3) Epileptic encephalopathy syndromes.
4) Hypoxic ischemic encephalopathy.
5) Autoimmune encephalitis.

**Pathophysiology:**

Seizures are caused by dysregulation in the normal balance of excitatory and inhibitory processes. Hypersynchronous neuronal firing is the physiologic hallmark of seizure. It is mediated mainly by glutamate a excitatory neurotransmitter and voltage-gated ionic sodium and calcium channels. Seizure termination is achieved by the inhibitory effects of gamma-aminobutyric acid (GABA)-receptor activation and voltage-gated potassium channel.The continued phase of SE is due to synaptic internalization of GABA receptors with expression of excitatory N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors..

*Phases of convulsive status epilepticus:Patients with convulsive SE progress through physiologic stages. In the early compensated phase, seizures are accompanied by sympathetic hyperactivity. Hypertension, increased cardiac output, increased cerebral blood circulationis seenin this stage, and serum markers of hyper metabolism such as lactic acid and glucose will be elevated. After prolonged and recurrent seizure activity , decompensation occurs. This is characterized by loss of cerebral autoregulation, cardiovascular dysfunction, and signs of systemic metabolic crisis: hypoxia, hypoglycaemia, and metabolic acidosis. Failure to prevent profound metabolic disturbances may exacerbate secondary brain injury associated with RSE.*

**Diagnosis:**

The diagnosis of convulsive status epilepticus is easy but confounders like paroxysmal non-epileptic events should be kept in mind.In hospitalized patients with encephalopathy disproportionate to known laboratory and imaging findings, non-convulsive seizures can be detected by continuous EEG (cEEG). Nonspecific motor movements, like posturing, rigidity, shivering, tremor, myoclonus, and spontaneous gaze deviation, can be misdiagnosed as convulsive status epilepticus. Facial twitching is associated with a more likelihood of electrographic seizures compared to other subtle signs. Suspicion for SE should be high in the patient in ICU .

**Management:**

Management of SE and RSE is carried out in three phases: seizure termination, prevention of SE recurrence and minimization of complications. This is a realtime process, where metabolic complications occur during all clinical phases and treatment plans should be streamlined to control for seizure recurrence and new metabolic findings. An emergency treatment strategy simultaneously

addresses airway, breathing and circulation while trying quickly to abort seizure activity within 5 minutes of onset.

**Stage 1 Management**:

Parenteral benzodiazepines are the initial therapy of choice. Lorazepam is easily available, fast to administer, and terminates overt SE in 65% of cases. Compared to diazepam, IV lorazepam is preferred because it is less lipid soluble and undergoes slower peripheral distribution. Intramuscular midazolam is effective when IV access cannot be established .In patients who are already intubated, full-dose lorazepam (0.1 mg/kg) or equivalent benzodiazepine can be given.

***Stage2 Management***:

*Benzodiazepines lose effectiveness in prolonged SE and are not recomended for long-term seizure control; therefore, next-line anti seizure medications should be ordered and administered early, within 10 minutes of seizure onset. First-line conventional AEDs are selected for their broad spectrum of activity and their ability to be given safely as an IV loading dose in attempts to abort SE and reach therapeutic levels rapidly.*

**Stage III treatment: Termination of RSE seizure**s

Optimal therapy after non response to benzodiazepines and first line aniseizure medications is unknown. Although a second conventional antiseizure medication is typically added in this setting, the likelihood of success is marginal and may delay seizure termination. Development of RSE should warrant ICU admission, intubation nd ventilation, initiation of a general anesthetic agent. Seizure activity is definitively suppressed with use of a single anesthetic agent, or with combination of agents in SRSE, with no agent proven more efficacious than another.

Continuous EEG is required for RSE management, and , is recommended initially for all patients requiring anesthetics.In status epilepticus seizure is associated with electromechanical dissociation, no longer manifests overt clinical signs, successful seizure control is determined by EEG suppression. In SRSE, 'burst suppression' is typically achieved and maintained with close monitoring and tapering of anaesthetic agents.

Immunotherapy:Immunotherapy in SRSE, till autoantibody testing is available in suspected autoimmune encephalopathies , may be started empirically in select cases. . Treatment typically begins with high-dose steroids (1 g IV methylprednisolone for 3 to 7 days). If there is no response to corticosteroids, plasma exchange or IV immunoglobulins over 3 to 5 sessions may be employed.Longstanding-immunomodulation can be continued with maintenance prednisone or other immune-modulators such as rituximab and cyclophosphamide.

Ketogenic diet: A ketogenic diet has both anti-seizure and anti-inflammatory effects, and can be used as an adjunct to AEDs.

**Surgical management:**When multiple antiseizure medications fail to control SRSE, surgical intervention should be considered. In patients with a known etiologic structural lesion, early neurosurgical consultation is recommended; however, in the absence of such lesions, work-up and surgical management is challenging. The optimal timing for surgery is unknown, but evaluation is appropriate after 2 weeks of failed medical therapy.

**Miscellaneous:**

Complications:Following termination of prolonged convulsive status epilepticus , patients should be monitored for rhabdomyolysis and acute renal injury, affecting the choice of antiseizure medications. Direct adverse effects of antiseizure medications include arrhythmia, hypotension, liver function abnormalities, renal injury, and cutaneous reactions. The risk of complications increases substantially with use of polytherapy and anesthetic agents. Because patients are often in coma, clinical manifestations of adverse events may be blunted. Patients on high-dose anesthetics, especially propofol, should have serial chemistries and trigylcerides followed.

**Parenteral first-and second-line antiepileptic medications**

| Drug | Initial dose | Initial maintenance dose | Clinical consideration |
|---|---|---|---|
| **First-line scheduled antiepileptic drug** | | | |
| Phenytoin/fosphenytoin | 15–20 mg/kg IV | 100 mg every 8 h | Linear pharmacokinetics; Cardiac arrythmias |
| Levetiracetam | 30 mg/kg IV | 500–1,000 mg every 12 h | Few drug interactions |
| Valproic acid | 20–30 mg/kg IV | 500 mg every 12 h | teratogenicity, hyerammonemia abnormal liver function |
| Phenobarbital | 10–20 mg/kg IV bolus | 1 mg/kg every 12 h | Patients can develop drug tolerance. |
| **Second-line antiepileptic drug** | | | |
| Lacosamide | 200–400 mg IV | 200 mg every 12 h | PR-prolongation on electrocardiogram; Minimal drug interactions |
| Topiramate | 200–400 mg PO | 300 mg every 6 h | Cannot be rapidly built up |
| Gabapentin | 300–900 mg PO | 300–900 mg every 8 h | Minimal drug interactions; |

Third line oral antiseizure drugs include carbamazepine, oxcarbamazepine, zonisamide, vigabatrin, rufinamide, ezogabine, and perampanel.

**Anesthetic infusions used for definite treatment of refractory status epilepticus**

| Drug | Loading dose (mg/kg) | Maintenance dose (mg/kg/h) | Clinical consideration |
|---|---|---|---|
| Propofol | 2–5 | 0.2–2.0 | Rapid onset and offset facilitates neurologic examination; monitoring for propofol infusion syndrome with extended use |
| Midazolam | 0.1–0.3 | 5–30 | Alternate to propofol that may cause less cardiovascular depression; associated with tachyphylaxis and drug accumulation |
| Ketamine | 1–3 | 0.5–10 | Associated with hypertension; least amount of evidence to support its use |
| Pentobarbital | 5–10 | 0.5–5 | Reserved for cases of failure of propofol and midazolam; associated with hypotension, hypothermia, and immunosuppression. |

Conclusions: Status epilepticus is a complex neurological emergency which requires urgent rational polytherapy with parenteral antiseizure medications and anaesthetics if required to achieve rapid seizure freedom. Serial or continuous EEG monitoring aids in monitoring non convulsive seizures. Close monitoring for medical complications is required in prolonged status epilepticus to ensure favourable outcomes.

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# New-onset Refractory Status Epilepticus (Norse) And Febrile Infection-related Epilepsy Syndrome (Fires)

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## INTRODUCTION:

New-onset refractory status epilepticus (NORSE) is a rare but devastating condition. Overall, approximately 200 cases of NORSE in adults and 200 cases of FIRES in children have been reported in the literature. The term is used to describe the cases of super refractory status epilepticus with no identifiable underlying cause and without a previous history of epilepsy. Febrile infection-related epilepsy syndrome( FIRES) is a catastrophic epileptic encephalopathy with a yet undefined etiology, affecting healthy children, which is characterized by acute and recurrent seizures or refractory status epilepticus preceeded by febrile illness, but without evidence of infectious encephalitis. [1] Ten years ago, NORSE and FIRES were poorly recognized terms with no consistent definition or treatment guidelines. Now they have become well recognized and recently consensus definitions have been put forth.

## CONSENSUS DEFINITION OF NEW-ONSET REFRACTORY STATUS EPILEPTICUS (NORSE)

New-onset refractory status epilepticus is a clinical presentation, not a specific diagnosis, in a patientwithout active epilepsy or other pre-existing relevant neurological disorder, with new-onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause. This includes patients with viral or autoimmune causes. [1] If no cause is found after extensive evaluation, this is considered "cryptogenic NORSE" or "NORSE of unknown cause".

## CONSENSUS DEFINITION OF FEBRILE INFECTION- RELATED EPILEPSY SYNDROME (FIRES)

FIRES is a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hours prior to onset of refractory status epilepticus, with or without fever at onset of status epilepticus [1]

## EPIDEMIOLOGY OF NORSE AND FIRES

NORSE and FIRES most commonly occurs in previously healthy young adults and school children, although adults more than 60 years can also be affected. There is a female preponderance in most adult case series, while boys are more frequently affected than girls in pediatric case series. The incidence is not known but it can be estimated that they represent up to 20 % of cases of RSE.[2]

NORSE IN ADULTS & FIRES IN CHILDREN: ARE THEY SIMILAR OR DIFFERENT CONDITIONS?

By using the terms NORSE and FIRES in different age groups (adults and children, respectively), the existing literature suggests that they represent different conditions. First, a preceding fever is the rule with FIRES, whereas it is not seen in one-third of NORSE cases. Second, though there is a male predominance in FIRES in children, NORSE in adults more often affects women.With respect to similarities,both conditions occur in patients with no previous history of epilepsy and commonly present as a progressive build-up of seizures that evolve to prolonged refractory SE. Nonspecific CSF and imaging findings are found in both

conditions with a similar frequency, and cerebral biopsy, when available, does not provide any specific findings that can distinguish one condition from the other. [3] The outcome in both is similarly poor as well, with severe neurological sequelae, refractory epilepsy, and mortality in up to one-fifth of patients**.** While earlier literature frequently used NORSE for adult patients and FIRES for children, current working definitions do not make this distinction, and both terms now apply in all ages. FIRES is now considered as a subcategory of NORSE, irrespective of age.

## CLINICAL FEATURES OF NORSE AND FIRES

- Non-specific mild illness with gastro-intestinal, upper respiratory or flu-like symptoms precedes the onset of seizures in two-third of cases and in up to 90% of cases of unknown cause.
- Fever is documented in at least a third of adult cases of NORSE and is by definition the rule in FIRES.
- The prodromal phase precedes the onset of seizure and SE by 1 to 14 days and the patient may be asymptomatic for a few days during the interval.
- Seizures are initially brief and infrequent, increasing within a few hours to days in frequency (up to hundreds per day) and evolving into SE. The most frequent seizure type is focal seizure with secondary bilateralization [2]

**FIRES in previously healthy children generally has three phases:**

- The first phase is the unremarkable febrile illness.
- The second phase follows between 24 hours and 2 weeks later, with acute, highly recurrent seizures, rapidly evolving into refractory SE. There may or may not be fever at the time of seizure

Seizures may be focal or multifocal at onset, ranging from dozens to hundreds per day .

Seizure onset typically presents as a focal seizure, focal seizures with secondary generalization, or secondarily generalized seizures only

SE typically lasts for 1 to 12 weeks, with an average of 3 weeks in duration

- The third and chronic phase of FIRES is a drug-resistant epilepsy with neuropsychological and cognitive impairment, occurring without latency as SE decreases. Cluster seizures may occur every 2 to 4 weeks. [2]

## ETIOLOGY

NORSE etiology is either unknown (cryptogenic) or an uncommon cause is identified after an extensive work-up. Near to 200 rare causes of SE have been reported in the literature and they can be divided in 4 categories:

1. Inflammatory and autoimmune encephalitis,
2. Uncommon infectious encephalitis,
3. Genetic disorders and
4. Toxic disorders.

The most frequently identified cause is autoimmune encephalitis, including sporadic and paraneoplastic cases, highlighting the importance of a complete auto-immune workup.The most frequently identified antibodies target the N-methyl-D-aspartate (NMDA) receptor and the voltage-gated potassium channel (VGKC) complex. One study found anti-glutamate receptor (GluR) epsilon 2 antibodies in the CSF of a few FIRES cases but their role and significance remain unknown. A retrospective study which compared the clinical features of 11 cryptogenic NORSE with Anti-NMDA receptor encephalitis, revealed more frequent prodromal fever, symmetric brain MRI abnormalities, had less frequent involuntary movements, absent psychobehavioral symptoms, and absent cerebrospinal fluid (CSF) oligoclonal bands and had more severe SE with ventilatory support requirement. [2]

## A GENETICALLY DETERMINED, POSTINFECTIOUS, CYTOKINE-MEDIATED DISORDER?

NORSE and FIRES might be caused by a fulminant inflammatory response in the Central nervous system. An intrathecal overproduction of proinflammatory cytokines and chemokines has been described in children with FIRES. These molecules have proconvulsant activity. This accumulation could be the product of the activation of T cells, perivascular cells, and glia and could take several days, perhaps explaining the latency between the febrile episode and the onset of SE. It is unclear whether intrathecal inflammation is the cause or the consequence of the prolonged episode of refractory SE (RSE). Changes in cytokines/chemokines levels were more prominent in the CSF than in the serum, suggesting that the inflammation primarily occurs in the central nervous system (CNS). Progressive accumulation of inflammatory cytokines could then give way to a vicious cycle of aberrant hyperexcitability and/or a structural epileptogenic remodeling of brain networks . [2] Additionally, intrinsic factors, such as a genetic predisposition, may be responsible for the lack of an efficient resolution of the epileptogenic process. **In conclusion**, the underlying pathogenic mechanism of FIRES is likely to be a two-hit process, involving 1)the synergistic effect between an immune response to a febrile illness or infection affecting the brain and 2) an intrinsic predisposition toward an auto-sustaining epileptogenic process

## DIAGNOSIS AND INVESTIGATIONS

- Early investigations (blood tests, brain imaging, CSF analysis and EEG), within 24–48 hours, can rapidly exclude important and treatable or reversible structural, infective, toxic and metabolic causes. Second-stage investigations may identify rarer causes. There is currently no available CSF or serological marker. [3]
- 1/2 to 2/3 of the cases of unknown etiology present mild CSF pleocytosis (less than 10 cells/ìl) and slightly increased protein

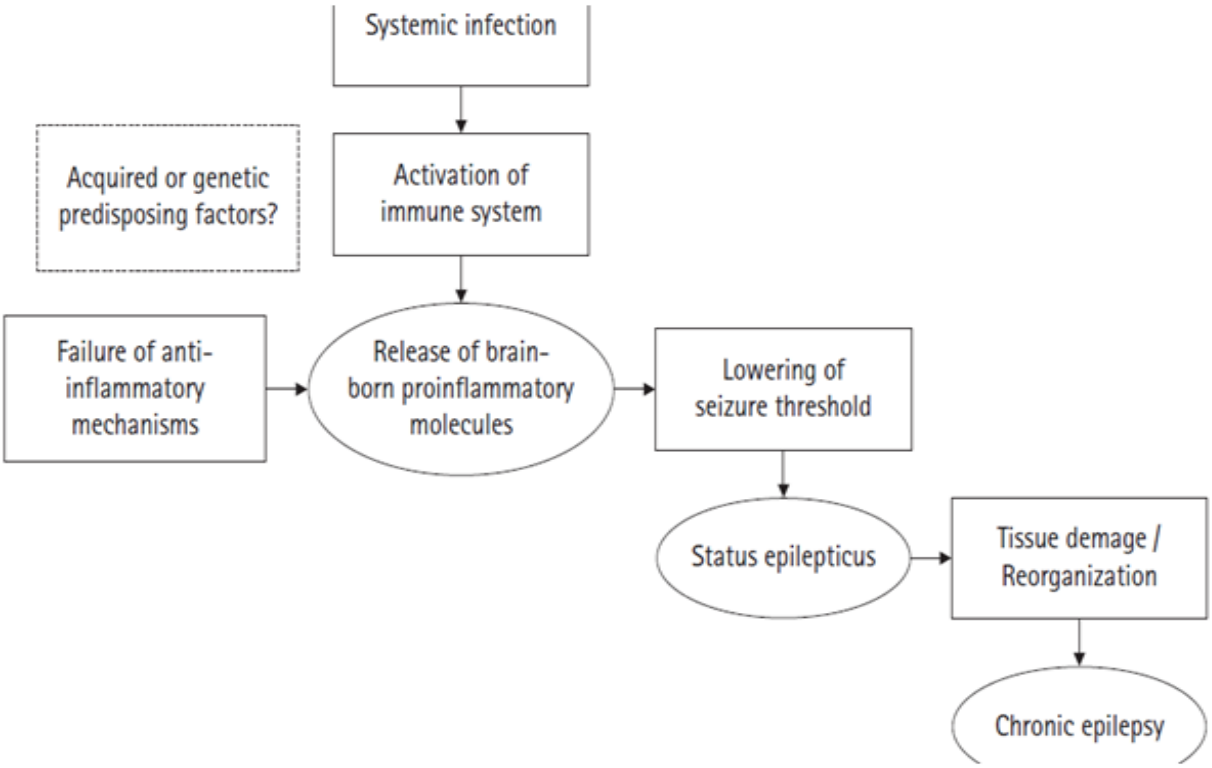


**Fig. 1.** A possible model of mechanism of epileptogenesis in NORSE and FIRES, showing neuroinflammatory cascade.

level,but these findings could result from the intense seizure activity rather than indicate an inflammatory or infectious etiology.

- Brain MRI findings are usually absent in the early phase and repeating imaging is not always practical.
- EEG can be performed early and continuously throughout the course of SE

**MRI Brain imaging**

- Non-specific abnormalities on MRI brain scan include most commonly (on T2/FLAIR sequences) hyperintensity in limbic and medial temporal or neocortical areas, sometimes bilateral, with signal changes in the basal ganglia or the peri-insular region.[3]
- Repeat imaging later may show hippocampal or generalised atrophy.
- Characteristic claustrum high signal ('claustrum sign') on T2/FLAIR and diffusion-weighted imaging, with normal apparent diffusion coefficient without contrast enhancement.

**EEG:**

Three common early patterns: [3]

- Initially infrequent seizures gradually evolving into status epilepticus
- a beta-delta complex resembling delta brushes
- a characteristic seizure onset pattern with focal fast activity with shifting seizures.
- Most series reported periodic discharges (generalised, lateralised, bilateral independent and multifocal) and multiple seizure patterns (generalised, focal and multifocal).
- Stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDS)

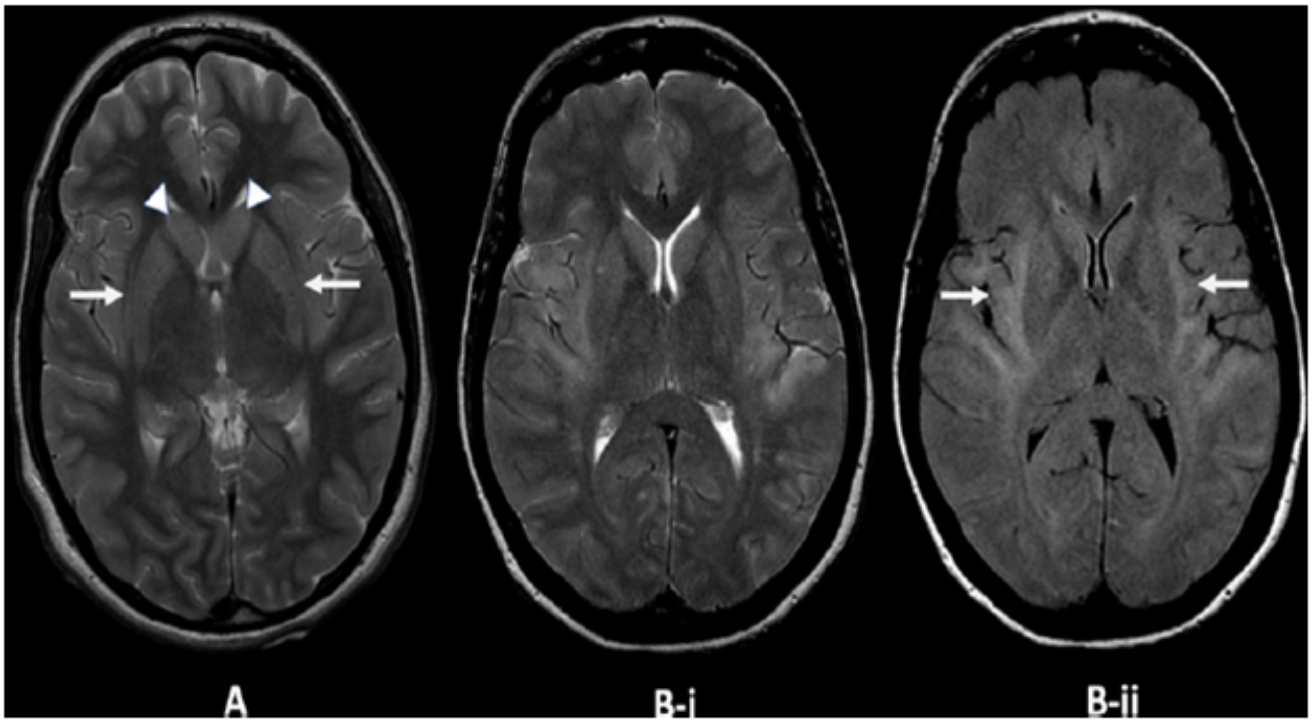


**Fig.2 (A**) Axial T2 weighted image showing faint T2 high signal in the claustrum on both sides(arrows) with faint T2 high signal and slight swelling in both caudate nuclei( arrowheads). (B) Axial T2- weighted (i) and FLAIR (ii) showing T2 high signal involving claustrum , external capsule and insula and temporal opercula on both sides( arrows).

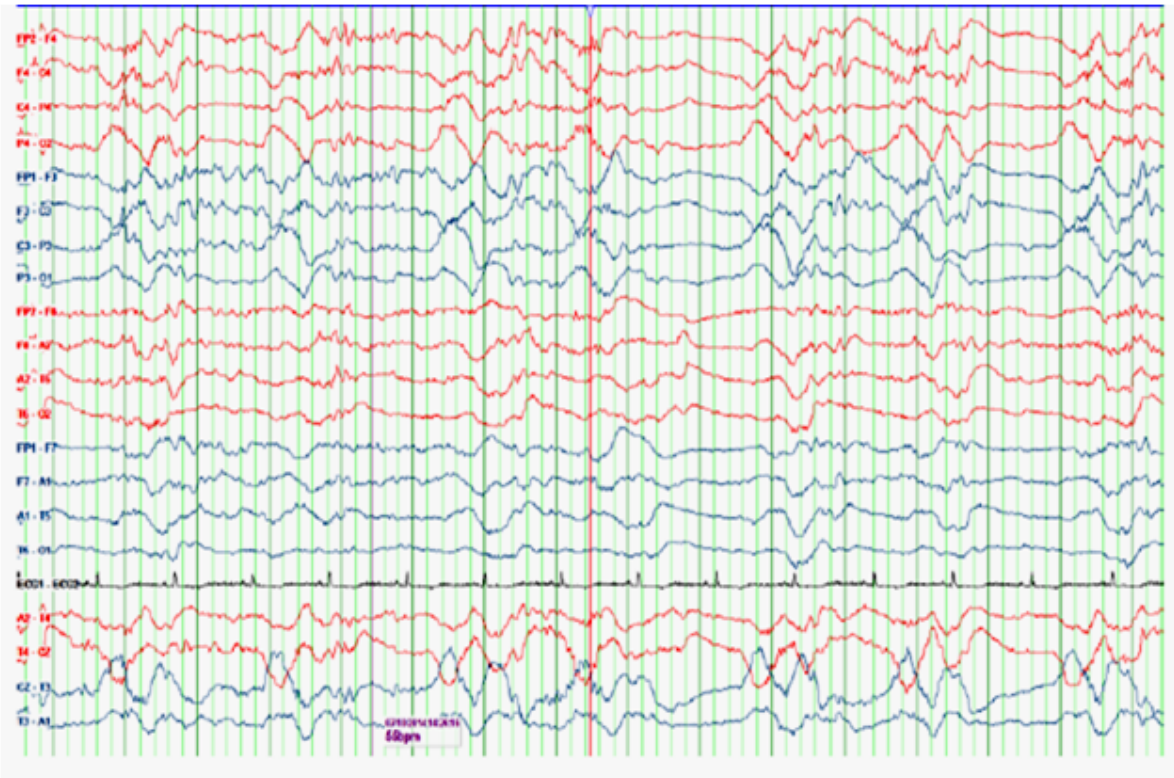

**Fig.3**. A periodic pattern can be seen consisting of delta waves preceded by fast activity and followed by electrodecrement in this routine EEG (bipolar montage). A beta-delta complex resembling extreme delta brushes is highlighted (red line)

**TABLE 1: Investigations to be considered**

| Screen | Disease/agent tested |
|---|---|
| Section 1: initial workup | **Recommended in most or all patients:**<br>*Whole blood/serum*: full blood count, bacterial and fungal cultures, RPR-VDRL, HIV-1/2 immunoassay with confirmatory viral load if appropriate.<br>*Serum*: IgG and IgM testing (acute and convalescent) for *Chlamydia pneumoniae*, *Bartonella henselae*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, shigella species and Chlamydia *psittaci*.<br>*Nares or nasopharyngeal swab (the latter preferred)*: respiratory viral direct fluorescent antibody panel; SARS-CoV-2 PCR.<br>*CSF*:<br>Cell counts, protein and glucose, bacterial and fungal stains and cultures.<br>RT-PCR for HIV, PCR for HSV1, HSV2, varicella zoster virus, Epstein-Barr virus, M.Tb; consider Western Nile virus, VDRL, encephalitis panel.<br>PCR for *Chlamydia pneumoniae* and *Chlamydia psittaci*, *Bartonella henselae*, *Mycoplasma pneumoniae*, *Coxiella burnetii* and shigella species.<br>Autoimmune epilepsy panel (see section 2).<br>Consider metagenomics for any non-human nucleic acid material.<br>Consider cytokine profile (section 7).<br>Consider cytology and flow cytometry.<br>**Recommended in immunocompromised patients:**<br>*Serum*: IgG cryptococcus species, IgM and IgG *Histoplasma capsulatum*, IgG *Toxoplasma gondii*.<br>*Sputum*: M Tb gene Xpert.<br>*CSF*: eosinophils, silver stain for CNS fungi, PCR for JC virus, cytomegalovirus, Epstein-Barr virus, HHV6, eastern equine encephalitis, enterovirus, influenza A/B, HIV, Western Nile virus, parvovirus. listeria, measles (rubeola).<br>*Stool*: adenovirus PCR, enterovirus PCR.<br>**Recommended if geographic/seasonal/occupational risk of exposure:**<br>► Serum buffy coat and peripheral smear.<br>► Lyme enzyme immunoassay with IgM and IgG reflex.<br>► Hepatitis C immunoassay and viral load if appropriate.<br>► Send further serum and CSF samples to CDC DVBID Arbovirus Diagnostic Laboratory, CSF and serum rickettsial disease panel, flavivirus panel, bunyavirus panel.<br>► Serum testing for acanthamoeba spp, *Balamuthia mandrillaris*, *Baylisascaris procyonis*.<br>► Other.<br>Consider *CSF metagenomics* for any infectious genetic material. |

| | |
|---|---|
| Section 2: auto-immune/ paraneoplastic | **Recommended:**<br>*Serum and CSF paraneoplastic and autoimmune epilepsy antibody panel.*<br>To include antibodies to: LGI-1, CASPR2, Ma1, Ma2/TaDPPX, GAD65, NMDA, AMPA, GABA-B, GABA-A, glycine receptor, Tr, amphiphysin, CV-2/CRMP-5, neurexin-3alpha, adenylate kinase, anti-neuronal nuclear antibody types 1/2/3 (Hu, Yo and Ri), Purkinje cell cytoplasmic antibody types 1, 2, GFAP-alpha, anti-SOX1, N-type calcium Ab, PQ-type calcium channel, acetylcholine receptor (muscle) binding Ab, Ach-R ganglionic neuronal Ab, AQP4, MOG Ab, IgLON5 Ab, D2R Ab.<br>*Additional serological studies-serum.*<br>(likely not pathogenic but hint towards an autoimmune cause)<br>ANA (detection and identification), ANCA, anti-thyroid antibodies (anti-thyroglobulin, anti-TPO), anti-endomysial, ESR, C reactive protein, SPEP, IFE, RA, ACE, cold and warm agglutinins, tests for MAS/HLH (serum triglycerides and sIL2-r, ferritin).<br>**Suggestion: store extra frozen CSF and serum for possible further autoimmune testing in a research lab.** |
| Section 3: neoplastic | **Recommended:**<br>CT scan of chest/abdomen/pelvis, pelvic or scrotal ultrasound, mammogram, CSF cytology, flow cytometry, cancer serum markers. Pelvic MR. Whole body PET-CT if above tests are not conclusive.<br>**Optional: bone marrow biopsy.** |
| Section 4: metabolic | **Recommended:**<br>*Whole blood/serum:* BUN/Cr, LDH, liver function tests, electrolytes, Ca/Mg/Phosphate, ammonia.<br>*Urine:* porphyria screen (spot urine), UA with microscopic urinalysis.<br>Consider: vitamin B1 level, B12 level, homocysteine, folate, lactate, pyruvate, CK, troponin; tests for mitochondrial disorder (lactate, pyruvate, MR spectroscopy, muscle biopsy). |
| Section 5: toxicological | **Recommended:**<br>Benzodiazepines, amphetamines, cocaine, fentanyl, alcohol, ecstasy, heavy metals, synthetic cannabinoids, bath salts.<br>Consider: extended opiate and overdose panel, LSD, heroin, PCP, marijuana. |
| Section 6: genetics | Consider: obtain genetics consult, if possible. Genetic screens for mitochondrial disorders (MERRF, MELAS, POLG1, SURF1, MT-ATP6) and VLCFA screen. Consider ceruloplasmin and 24-hour urinary copper.<br>Consider mendeliome or whole exome sequencing (also look for gene polymorphisms in IL-1B, IL-6, IL-10, TNF-alpha, HMBG1, TLR4, IL1RN, SCN1A and SCN2A), mitochondrial genome sequencing and CGH array. |
| Section 7: cytokine assay | *Serum and CSF:* cytokine assay for quantitative measure of IL-1β, IL-1Ra, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-17, granulocyte-macrophage colony stimulating factor, tumour necrosis factor-α, HMGB1, CCL2, CXCL8, CXCL9, CXCL10, CXCL11. |

## TREATMENT OF NORSE AND FIRES:

### Management of NORSE/FIRES includes:

- Investigating for an underlying cause.
- Controlling status epilepticus, while avoiding iatrogenic complications
- Treating the presumed inflammatory/ immune mediated process
- Supporting the patient's family
- Rehabilitation

- Treatment with anti-seizure medications is often disappointing. At least 75% of patients require anesthetics in continuous infusion and prolonged burst-suppression coma is often unavoidable to stop the seizures. Status often resumes once the anesthetics are weaned off. At least a third of patients require multiple anesthetic drugs to achieve seizure control. Some studies have suggested better outcome with immunotherapies. This hypothesis is supported by the fact that half of NORSE cases are caused by auto-immune encephalitis.[3]

- Early immune therapy is recommended, as delaying treatment may contributes to worse outcome, as in auto-immune and viral encephalitis. These include first-line (steroids, intravenous immunoglobulins, and plasma exchange) and second-line therapies (e.g., tacrolimus, rituximab, cyclophosphamide, anakinra).

## IMMUNOMODULATORY TREATMENT

- First-line medications typically include intravenous corticosteroid, intravenous immunoglobulins and plasma exchange.[4]
- Second-line medications include cyclophosphamide, rituximab, tocilizumab (IL-6 inhibitor) and anakinra (IL-1 inhibitor).
- Other antiseizure interventions also exert anti-inflammatory action, including ketogenic diet and cannabidiol.

- First-line immunomodulatory treatment is a course of intravenous methylprednisolone, plasma exchange then intravenous immunoglobulin.
- Where possible, this is followed by the ketogenic diet, and if there is no contraindication, an interleukin inhibitor.
- Also consider rituximab if anything points to an autoimmune cause
- Cannabidiol (CBD) works by decreasing glutamate and gamma-aminobutyric acid synaptic transmission in the brain.
- The resultant decrease in excitatory neurotransmitter release may increase the seizure threshold

## KETOGENIC DIET

It is high-fat, low-carbohydrate diet that mimics fasting and exerts both antiseizure activity (possibly through decanoic acid inhibiting excitatory AMPA receptors) and anti-inflammatory action (reduced proinflammatory cytokine levels) and improves mitochondrial function. If there is no improvement after 2 weeks of ketosis, the diet is considered unsuccessful and stopped. Multiple different therapeutic options have been reported and none seems to be superior, with the possible exception of the ketogenic diet. Showing improvement after 1 to 4 days of ketonuria. Experts recommend to start it as soon as possible once FIRES is suspected

## NEUROMODULATION FOR NORSE/FIRES

It works by desynchronising networks by deep-brain stimulation may improve seizure control. Vagus nerve stimulation and Repetitive transcranial magnetic stimulation (rTMS) are increasingly used for refractory and super-refractory status epilepticus[4]

## THERAPEUTIC HYPOTHERMIA

It is used for neuroprotective and anti-inflammatory effect. The targeted temperature is 31-35 degree celcius for 1 to several days. The mechanisms of action may include the reduction of proinflammatory cytokines and protecting the

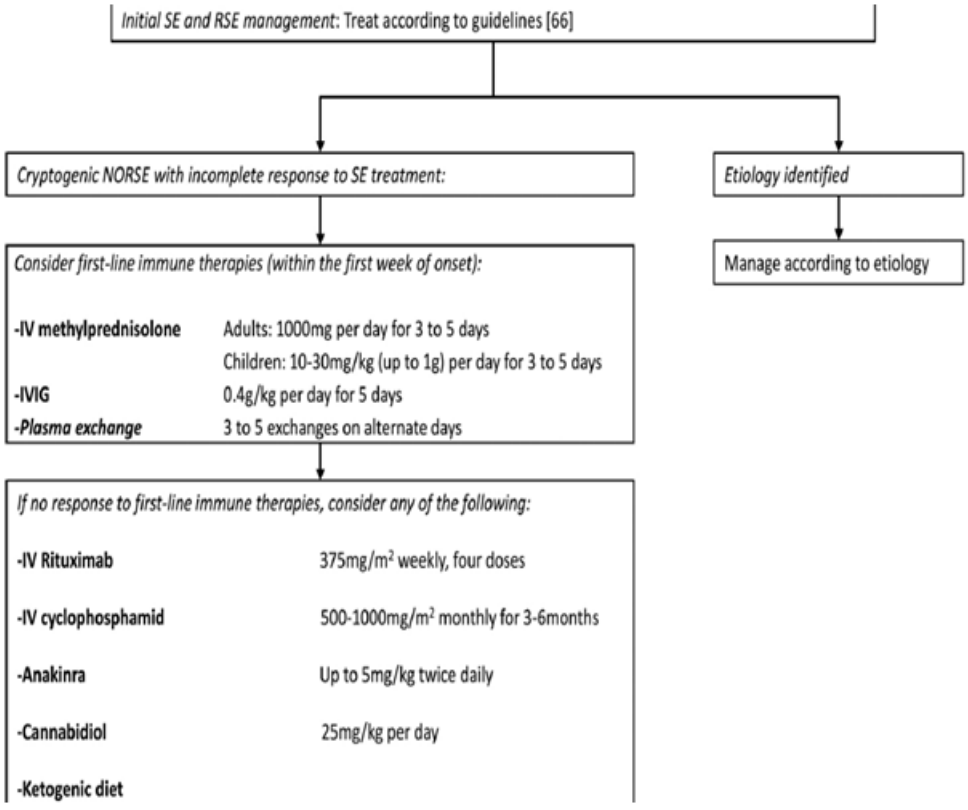


**Fig.4.** Showing treatment algorithm for management of NORSE and FIRES

integrity of the blood brain barrier.[4]

**OUTCOME:**

Most cases of FIRES and NORSE evolve to SRSE, a category of SE associated with prolonged intensive care unit (ICU) stay and poor outcome. The median duration of ICU stay in FIRES and NORSE ranges from 20 to 40 days in children and 15 days in adults. Mortality rate is around 12% in children and reaches 16 to 27% in adults, with neurological sequelae in most survivors. Drug-resistant epilepsy is the rule in most survivors.[5]

**CONCLUSION:**

NORSE and FIRES are rare ,but devastating disorders, which occurs in previously healthy patients. Rare, but treatable etiologies, such as autoimmune encephalitis, can be identified in few patients, especially adults, which opens way for extensive investigations. However, a large number of cases remain without a known etiology and little is currently known regarding the underlying pathogenesis, although an inflammatory cause is suspected. Treatment is generally disappointing and the prognosis is often poor, although very few patients resume their previous normal life. The ketogenic diet looks promising but it require larger prospective studies.[6] The recent publication of consensus definitions will be helping future research and aims to understand the cause and to improve the patient care.

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# Surgery for Medically Refractory Epilepsy

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## Introduction

It is estimated that a quarter of the world's patient with medically refractory epilepsy are in India, meaning that about a million patients with medically refractory epilepsy need treatment in India. That means that every neurosurgeon in India can theoretically do only epilepsy surgery throughout the year!

## Definition of medically refractory epilepsy:

A classical way of defining medically refractory epilepsy is that the patient is given two anticonvulsants for 2 years without relief from epilepsy.

## Brain growth & Cognitive development:

The problem with this definition is that many epilepsy syndromes occur in pediatric age group. The maximum brain growth occurs in first two years of life and the initial years of cognitive development is most essential for every individual. A serious illness like epilepsy interferes with the brain/cognitive/scholastic development of the child. This occurs because brain is an electrical organ and epilepsy is like an electrical storm which interferes with the normal working of the brain.

## Brain Plasticity:

Another reason to operate early is a child brain's plasticity is present till 6 years of age. This means that language area in the brain (Broca's & Wernicke's) for example can shift to opposite hemisphere if any insult occurs to these brain areas before 6 years of age. After 6 years the brain function becomes fixed to particular region and potentially devastating neurological deficits can occur by operating on eloquent areas on a older patient.

Social Issues of medically refractory epilepsy: A child will have difficulty in attending school. Learning becomes a problem due to side effects of anticonvulsant drugs. Many of these children may have memory problems due to effects of epilepsy and anticonvulsants. In order to allow maximum development potential children with medically refractory surgical syndromes need surgery at the earliest.

Adults with medically refractory epilepsy develop psychological issues too. They may difficulty in marrying and face the probability of divorce. They also have issues of employability. In fact, these patients may face the "burden of normalcy" after getting cured of long-standing epilepsy as relatives and society may expect these persons to function normally, which they have not done so far in their lives! Sadly, some of these patients may commit suicide to escape the burden of normalcy.

Considering all these facts, it is important to offer early surgery to patients with medically refractory epilepsy with surgical treatable epilepsy syndromes.

**Surgically remediable epilepsy syndromes (Table 1):**

Given below are the causes of surgically remediable epilepsy syndrome.

**A. Malformations of cortical development**

1. Focal malformations of cortical development
2. Heterotopias
3. Polymicrogyria and pachygyria
4. Microdysgenesis/ MRI negative dysplasias
5. Cortical tubers

**B. Mesial temporal sclerosis**

**C. Low grade neoplasms**

1. Dysembryoplastic neuroepithelial tumor
2. Ganglioglioma
3. Low grade astrocytomas

**D. Nonspecific gliosis secondary to various pre- and postnatal insults**

**E. Large unihemispheric pathologies**

1. Rasmussen's encephalitis
2. Hemiconvulsion -hemiplegia-epilepsy (HHE) syndrome
3. Sturge Weber syndrome
4. Hemimegalencephaly

**F. Vascular malformations**

1. Arterio-venous malformation
2. Cavernoma

**G. Miscellaneous**

1. Hypothalamic Hamartoma

In this article examples are shown of these different pathologies later on.

**How to approach a patient with intractable epilepsy?**

The fundamentals are the same in every branch of medicine. The approach to a medical refractory patient can be as shown in the preoperative evaluation steps (1-10) below: -

1. A very good history of seizure semiology- means defining the aura (like raising epigastric sensation, fear, abnormal sensations in the body, flashes of light, auditory aura etc) progression and ending of seizures has to be obtained. This history gives a very good clue as to where in the brain seizure is starting and finally ending.
2. A video-EEG is an essential step to classify the epilepsy and also elucidate the semiology accurately.
3. MRI brain (1.5T or 3T) with epilepsy protocol. MRI is very likely to show lesions which are elaborated in table 1.
4. Neuropsychological evaluation. Will show with clinical tests which region of the brain is malfunctioning. E.g.: Right temporal lobe dysfunction is associated with visual memory loss and left temporal lobe dysfunction is associated with left temporal lobe dysfunction
5. PET (positron Emission Tomography) will show hypometabolism (cold spot) in the seizure generating lesion area and the surrounding network of the brain generating the epilepsy.
6. ICTAL SPECT (single photon emission tomography) will show hypermetabolism (hot spot)
7. fMRI (functional MRI) will show functional areas of the brain like speech area, vision area, motor area and its relation to the epileptogenic lesion/brain
8. DTI MRI (Diffusion Tensor imaging) will show the fiber tracts like corticospinal tracts and its relation to the lesion

9. MEG Magnetic encephalography scan of the brain will show cluster of magnetic dipoles in the epileptogenic region of the brain

10. Invasive brain monitoring like SEEG in discordant cases

Steps 1-3 are enough in many cases to establish concordance. fMRI, DTI are done routinely during brain MRI. Nowadays PET, SPECT which are noninvasive tests are also done routinely to give additional information for establishing concordance. MEG is another way of getting data noninvasively to look at the epileptogenic zone. MEG though expensive is available in India. In some patients when concordance cannot be established, invasive brain monitoring is done to prove concordance and to establish the epileptogenic zone.

**What is Concordance & Discordance?**

Concordance is the term used to denote a situation where all the presurgical steps 1-5, show that a particular brain region is producing epilepsy -for e.g.: Right temporal Lobe.

Discordance is term used when, for example, the steps 1,2,4 & 5 show left temporal lobe involvement but MRI brain is normal.

The importance of concordance is that the success of epilepsy surgery is likely to be high. In discordant situations, invasive brain monitoring is used to establish concordance.

**What determines success of epilepsy surgery?**

A patient with medically refractory epilepsy undergoes preoperative evaluation as discussed above and is found to be concordant. In such a patient resection of the epileptogenic zone determines the success of epilepsy surgery

**What is the Epileptogenic zone?:**

The epileptogenic zone, is de?ned as "the minimum amount of cortex that must be resected (inactivated or completely disconnected) to produce seizure freedom". Thus, this de?nition of the epileptogenic zone is a theoretical one which must be validated post-surgery (Carreno & Luders,2001).

In contrast, the concept of the epileptogenic zone, as proposed by Talairach and Bancaud, in 1966, derived primarily from a working hypothesis:

since the seizure was the symptom to be cured, it was the region of cortex generating the epileptic seizures that had to be determined electrophysiologically, and then translated into anatomical terms and used for determining extent of surgery.

We have reached a point where the patient with medically refractory epilepsy has been determined to benefit from epilepsy surgery. What are the types of epilepsy surgery available)?

**Types of epilepsy surgeries. ( (table 2)**

**A. Curative surgeries**

**a. Removal of an epileptogenic focus or discrete lesions**

1. Focal corticectomy
2. Gyrectomy
3. Lesionectomy
4. Anterior mesial temporal lobectomy
5. Selective amygdalohippocampectomy

**b. Gross removal/Disconnection of malfunctioning brain tissue**

1. Multilobar resections
2. Hemisherectomy / hemispherotomy

**c. MRI Guided Laser Interstitial Thermal Therapy**

**d. Radiofrequency guided lesioning(e.g.: hypothalamic hamartoma)**

**B. Palliative surgeries**

1. Corpus callosotomy
2. Multiple subpial transections
3. Vagus nerve stimulation
4. Responsive Neurostimulation (not yet introduced in India)

5. Deep Brain stimulation

Curative surgeries are done with the intent of removing the epileptogenic zone in partial epilepsies. When successful , antiepileptic drugs can be tapered and stopped.

Palliative surgeries are done when the epilepsies are diffuse or generalized. For e.g.: corpus callosotomy is done in Lennox-Gastaut syndrome patients to stop dangerous drop attacks.

**Now we present examples of epilepsy surgeries done in our series of patients**

1. A 24 years girl presented with complex partial seizures. VEEG localized the seizures onset to right temporal lobe. MRI (fig1)showed right mesial temporal sclerosis

   PET scan of the brain (fig2) showed right temporal hypometabolism(red arrows)

   Postop CT scan (fig.3.) after temporal Lobectomy and amygdalo-hippocampectomy

Follow-up: This patient has 11 years follow-up after surgery ,is seizure free and is of anticonvulsants.

2. A 29 years old engineer presented with left temporal CPS which was medically refractory. Usual protocol was followed with VEEG followed by MRI(fig4) which showed left hippocampal atrophy (red arrows)with normal temporal lateral neocortex

   PET scan brain(fig.5) showing selective mesial temporal hypometabolism sparing the lateral neocortex.

   Postop CT scan brain (fig6) showing selective amygdalo-hippocampectomy sparing the neocortex

Follow-up: This patient has been on follow-up for 11 years; he is seizure free and continues to work as an engineer.

3. A 2-year-old girl presented with epilepsy partialis continua of right leg and hand. Evaluation proceeded as per protocol. Her MRI brain (Fig.7.) showed a large premotor focal cortical dysplasia:

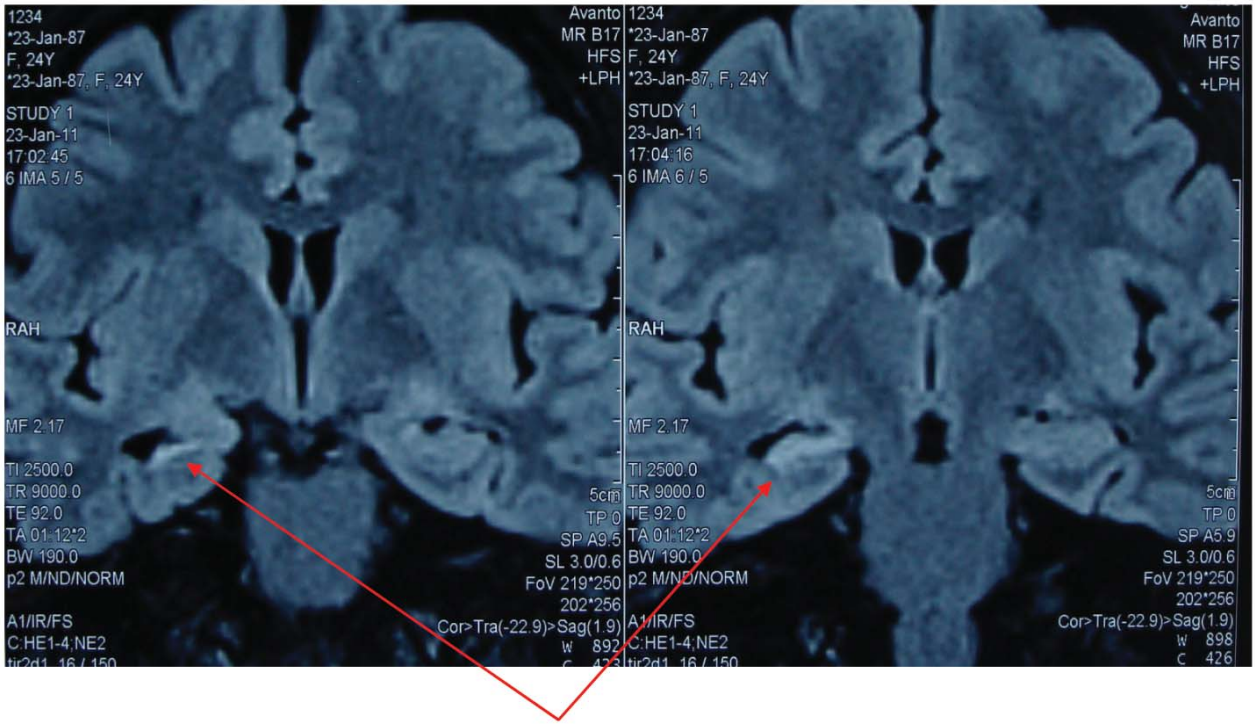


Fig.1.Shrunk Right Hippocampus with hyperintensity on flair images

PET scan of the brain (fig2) showed right temporal hypometabolism(red arrows)

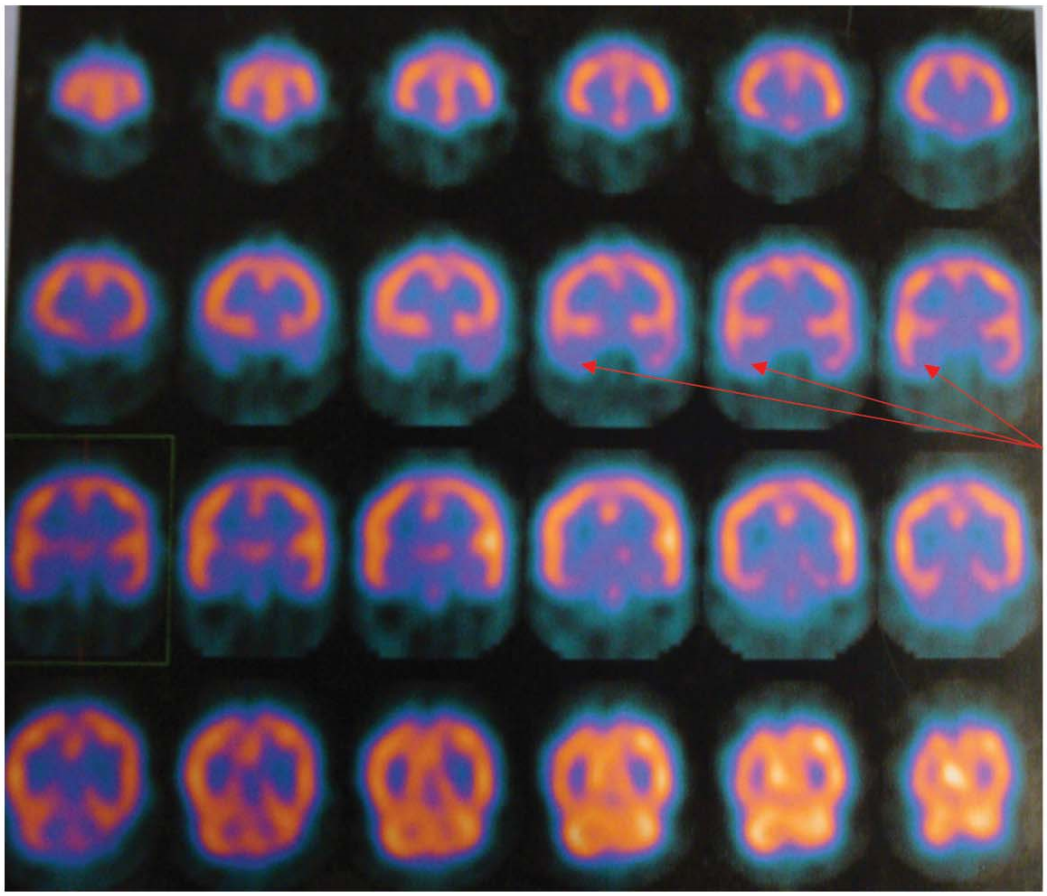

Fig.2

Postop CT scan (fig.3.) after temporal Lobectomy and amygdalo-hippocampectomy

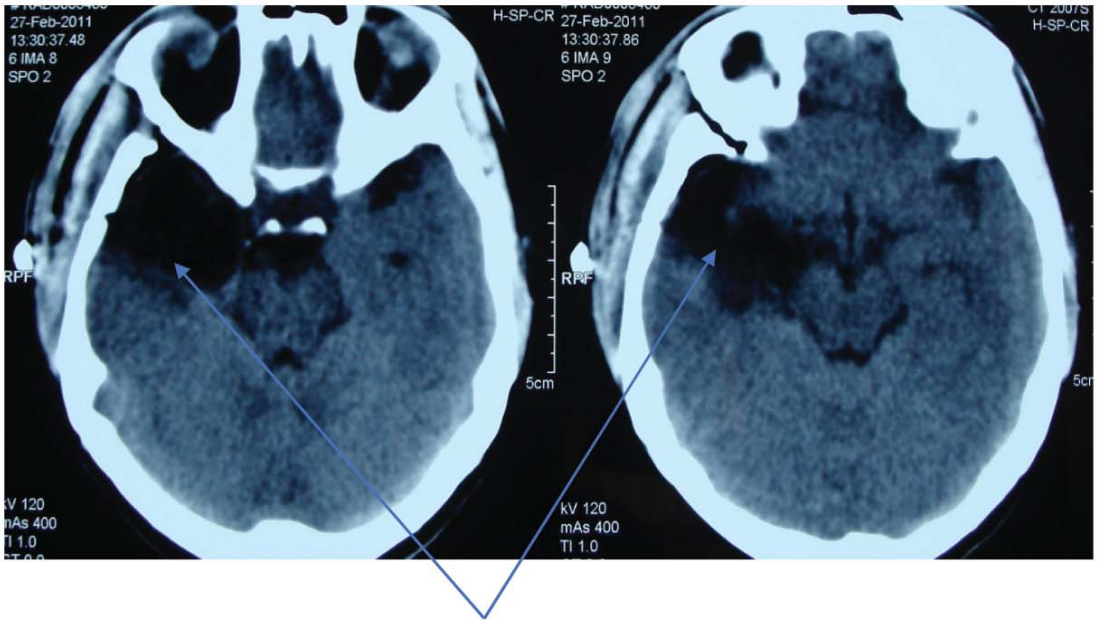


Fig.3.Resection cavity after right temporal lobectomy and amygdalohippocampectomy

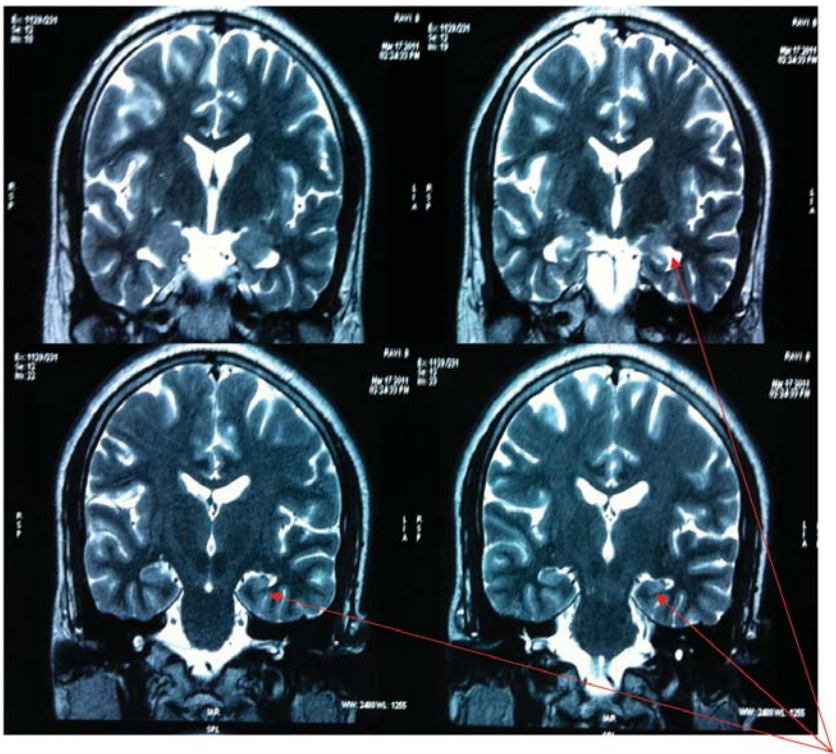

Fig.4 .MRI shows left hippocampal atrophy

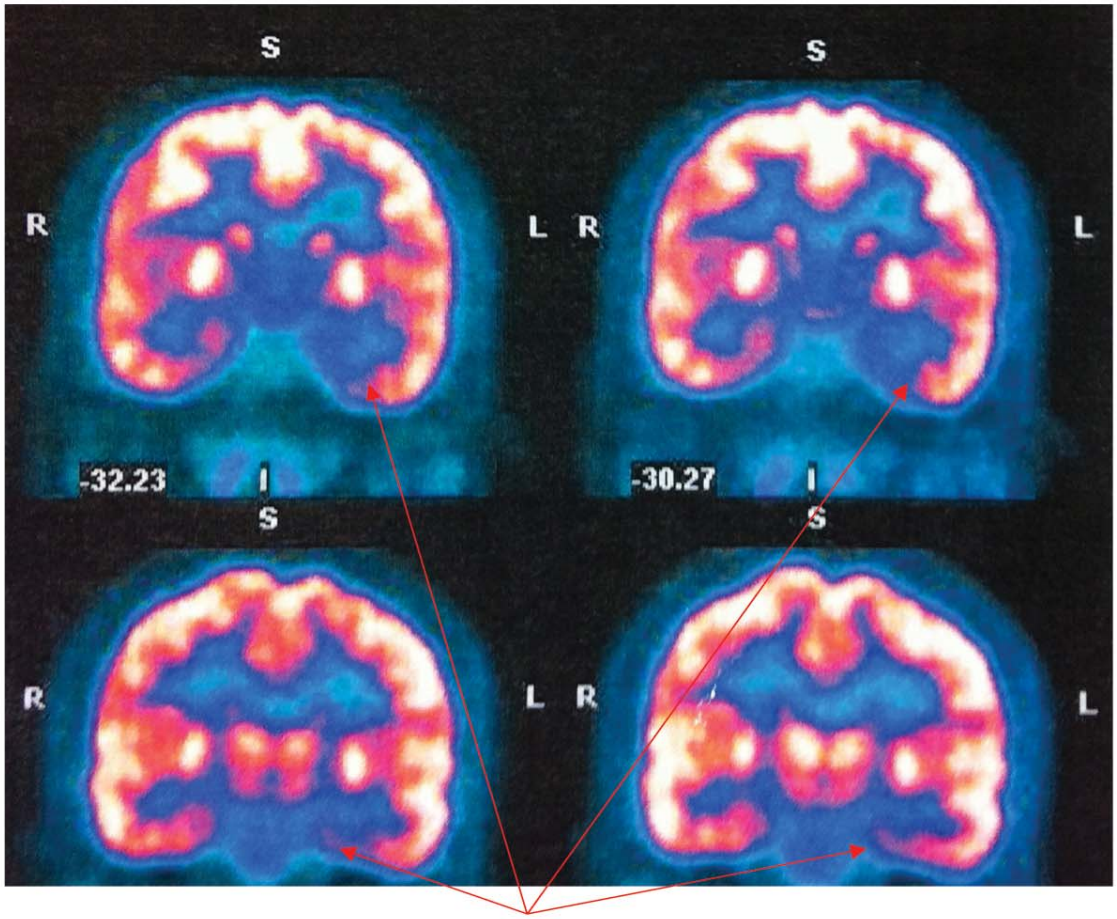


Fig.5. PET scan showing left mesial temporal hypometabolism sparing lateral neocortex

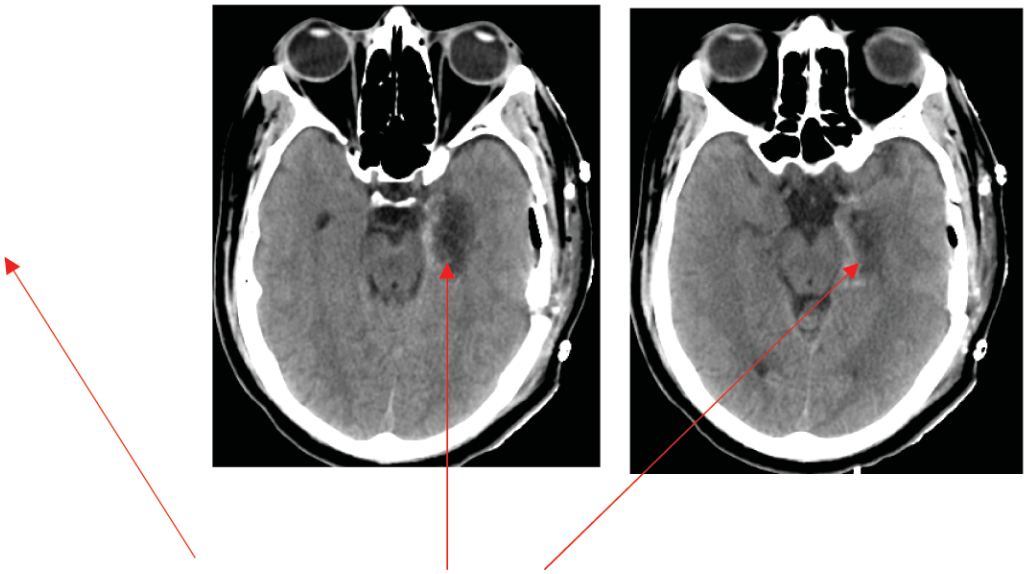

Fig.6. Selective amygdalo-hippocampectomy

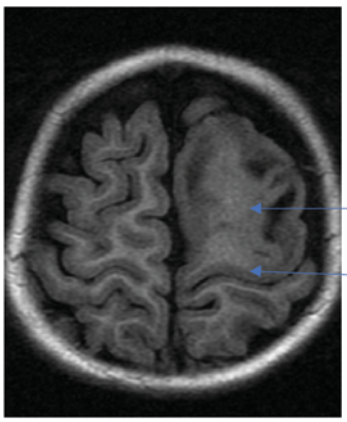


Fig.7. MRI brain

Intraoperative picture (Fig.8) showing the focal cortical dysplasia and the motor cortex after resecting the dysplasia.

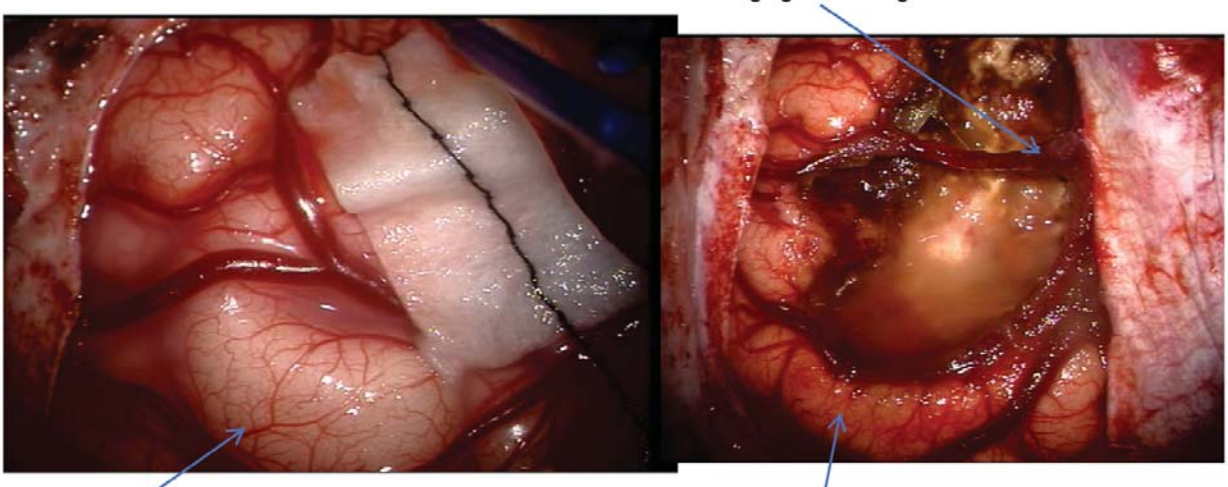


Fig.8A.Expanded rock like gyrus containing the dysplasia

Fig.8B.Motor cortex intact after resecting the dysplasia

Intraoperative picture (Fig.8) showing the focal cortical dysplasia and the motor cortex after resecting the dysplasia.

Figure.9. Postoperative CT scan brain showing excision of the dysplasia

Figure10: Postoperatively hand function is preserved.

Follow-up. This girl has been under follow-up for 12 years and is seizure free & off anticonvulsant drugs.

4. A 23 year old gentleman presented with symptomatic complex partial seizures of left occipitotemporal localization with medically refractory epilepsy. Preoperative evaluation

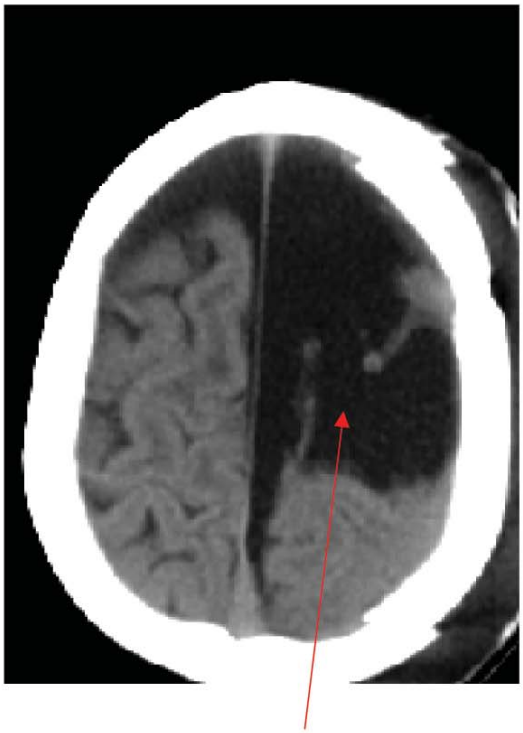

Fig.9.CT scan brain postop showing excision of dysplasia

Figure10: Postoperatively hand function is preserved.

was carried out. MRI scan(fig.11.) showed extensive left parietooccipital gliosis with temporal sclerosis

Visual field charting(fig.12) showed right homonymous hemianopia consistent with left parieto-occipital gliosis with loss of function in the damaged brain which is generating the seizures.

fMRI (fig.13) shows normal visual function in right occipital lobe and loss of visual function in left occipital lobe. DTI shows optic pathway is intact in right occipital lobe (top panel, left image)

fMRI for motor function(fig.14) shows intact left motor cortex in front of the gliotic area, which needs to be preserved

Language fMRI (fig.15) shows shift of language function to right hemisphere(brain plasticity) which occurs when the insult is before 6 years of age

With data available from preoperative evaluation, the conclusion was that seizures was arising from left posterior quadrant (parietal, occipital and temporal lobes) due to the gliosis resulting from ischemic damage to the brain during early infancy. A left posterior quadrantic disconnection was

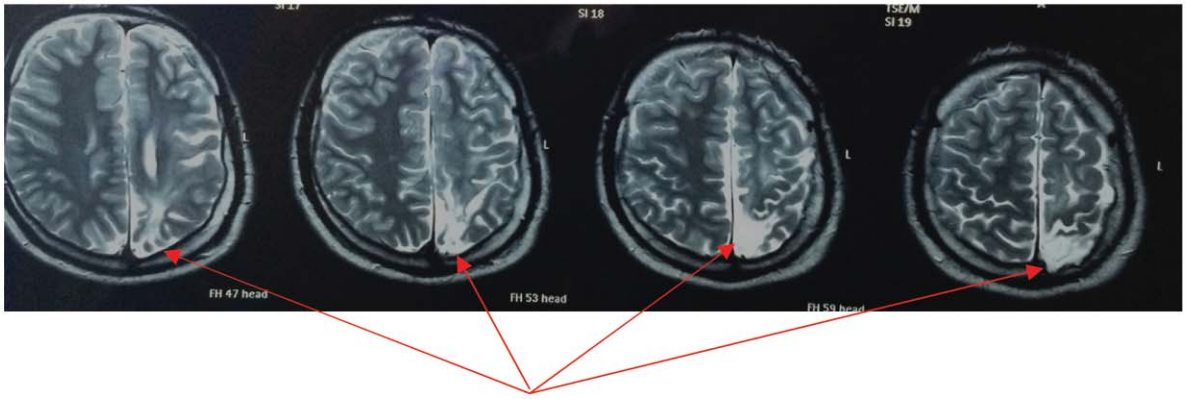


Fig 11.Left parieto-occipital gliosis

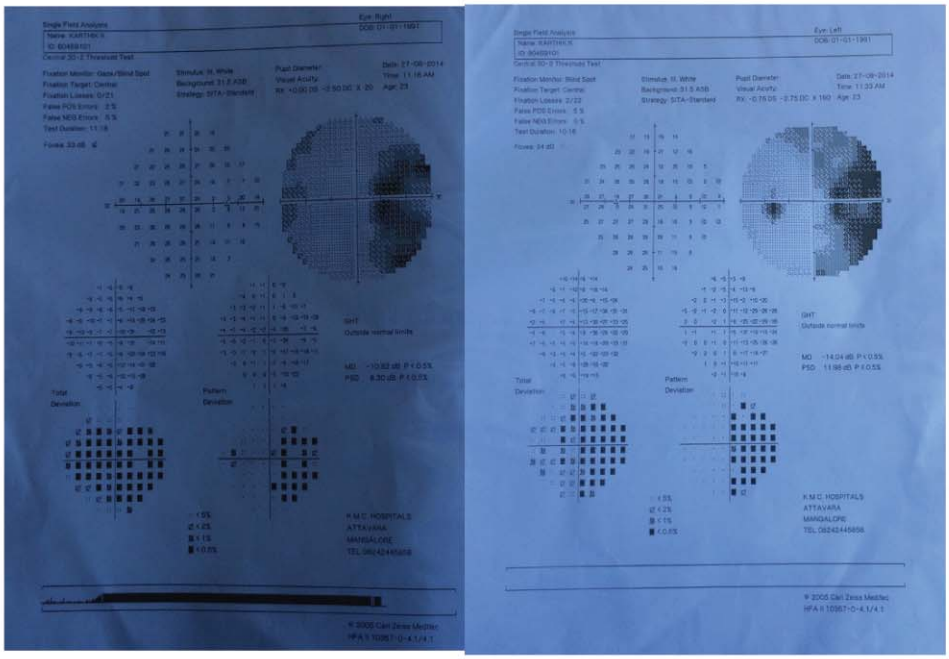

Fig.12.Visual field charting shows homonymous hemianopia consistent with parieto-occipital gliosis

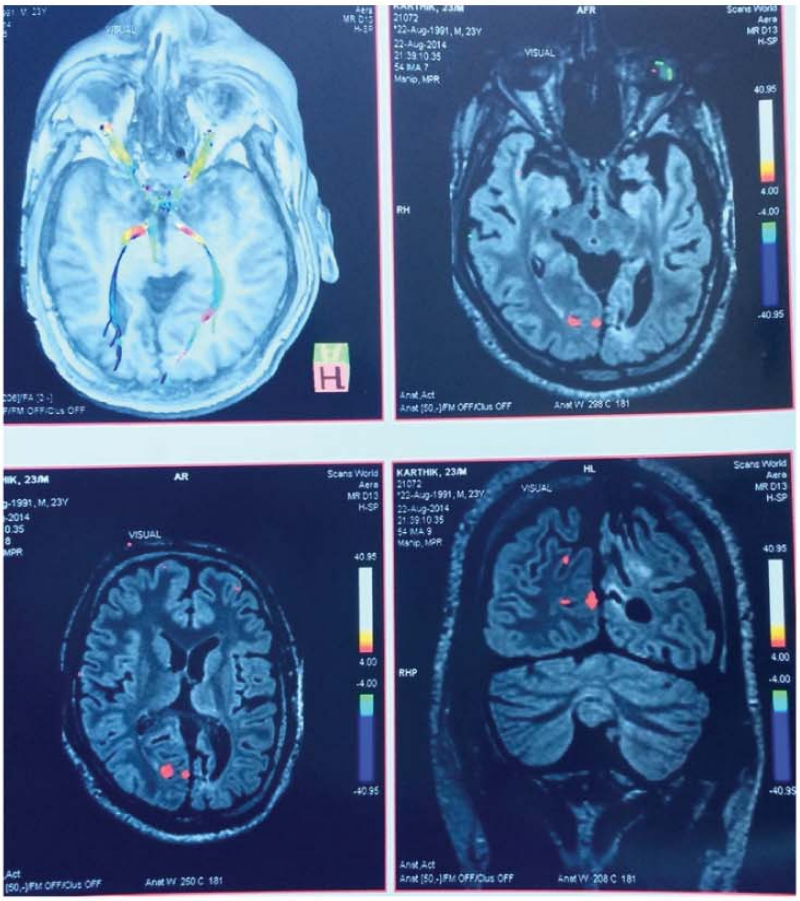


Fig13. fMRI shows normal visual function in right occipital lobe

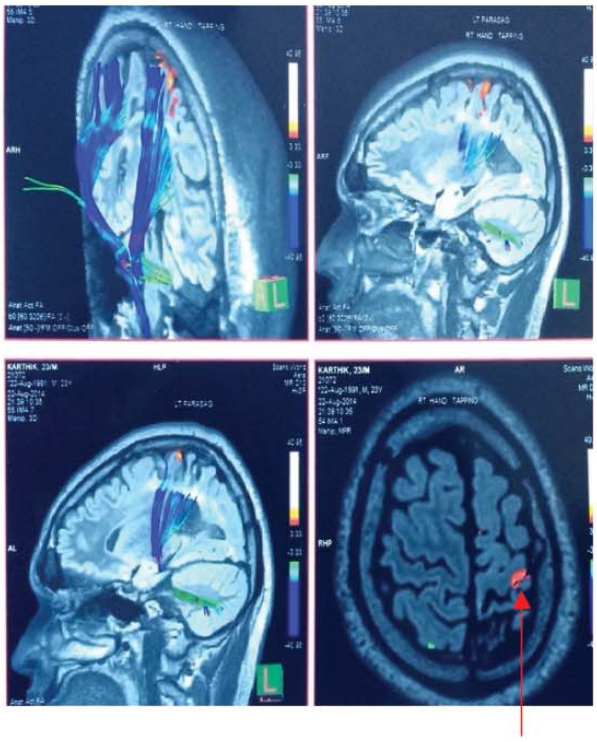


Fig.14.Motor fMRI shows motor cortex is intact in the affected left hemisphere with intact corticospinal descending fibers (left upper and lower panel)

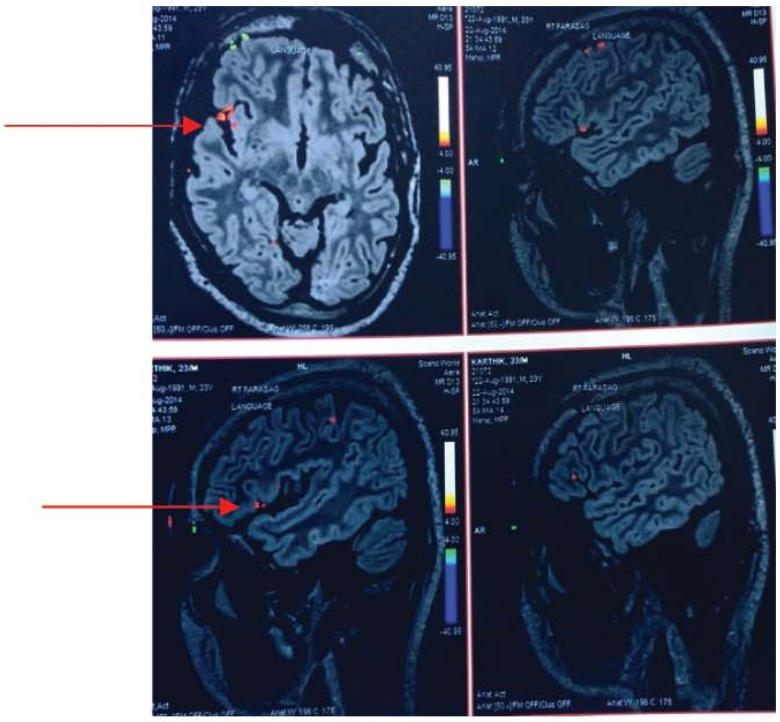

Fig.15.language fMRI shows shift of language function to right side

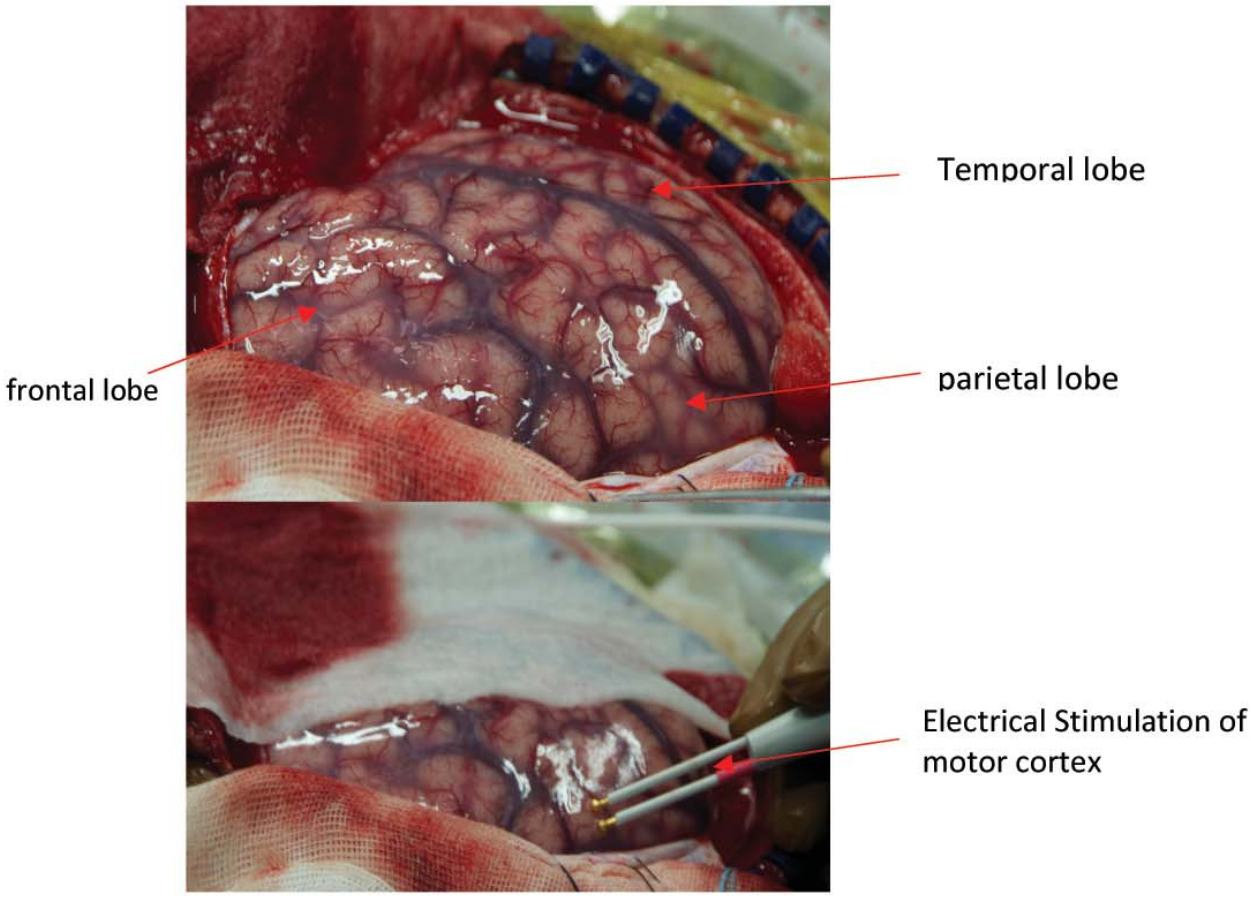


Fig.16.Motor cortex stimulation during surgery

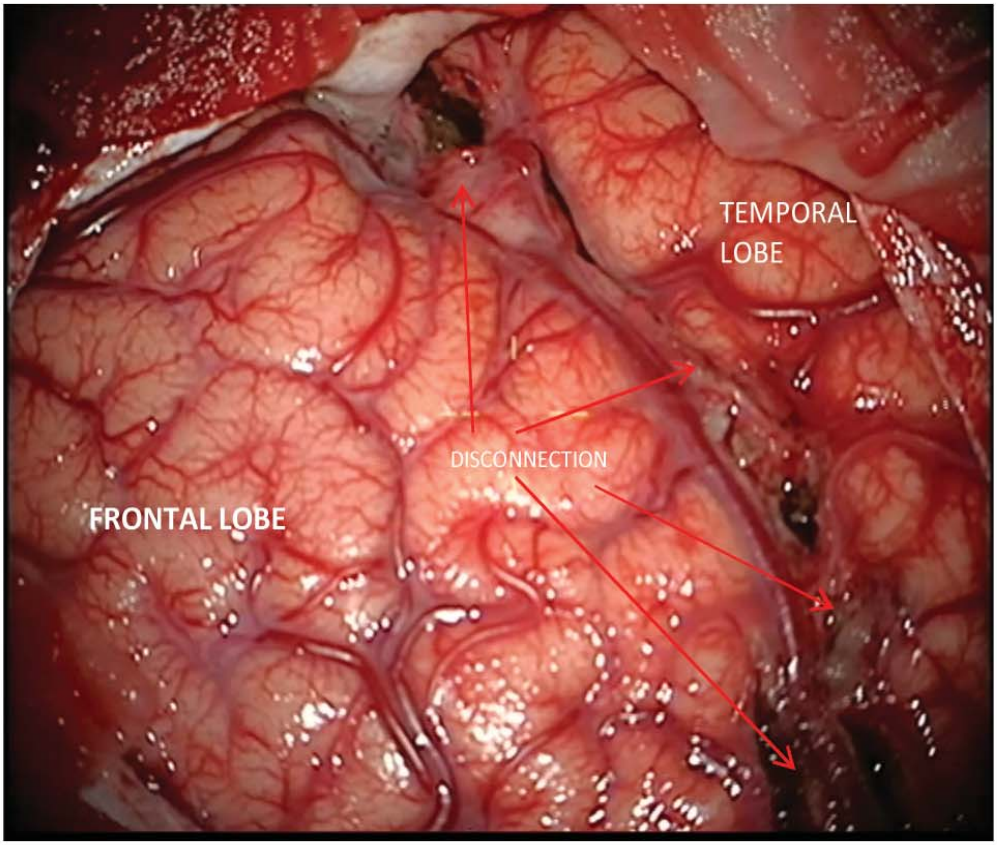


Fig.17.Intraoperative view of left posterior quadrant disconnection from frontal lobe and right hemisphere

CT scan(fig18) showing posterior quadrant disconnection in another patient

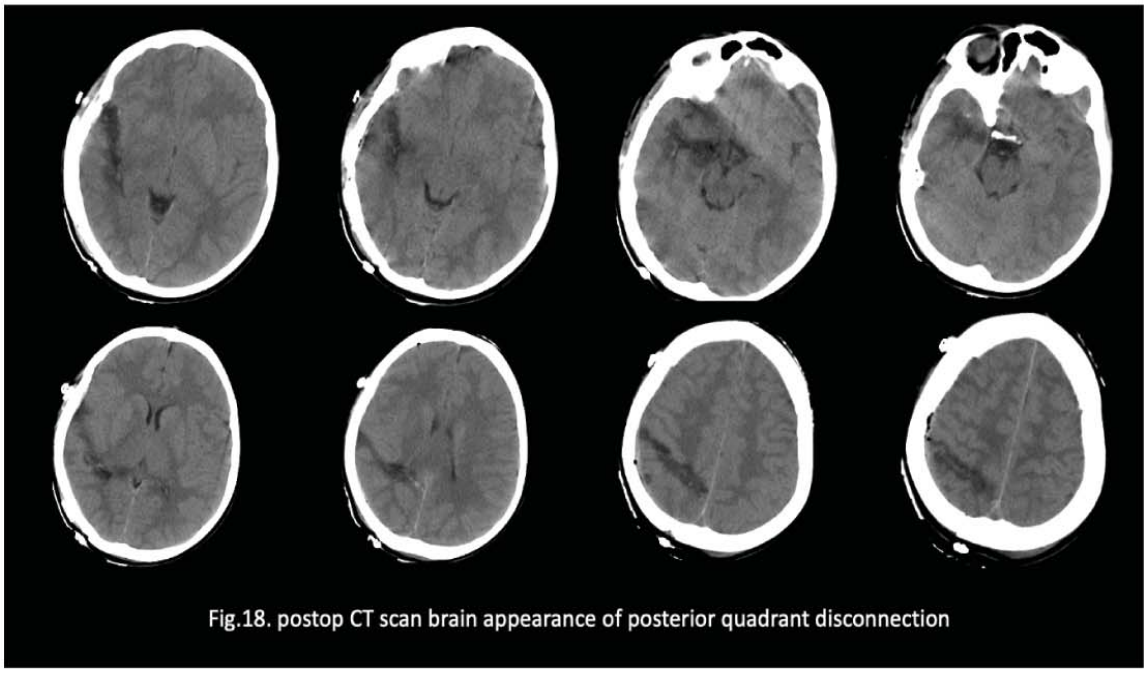

Fig.18. postop CT scan brain appearance of posterior quadrant disconnection

Follow-up of 8 years post-surgery, the child is seizure free and is off anticonvulsants.

planned and a fronto-temporo-parietal craniotomy (fig.16) was done. Motor cortex was identified with Ojemann's electrical stimulation of the brain

Intraoperative view of left posterior quadrant disconnection from left frontal lobe and right hemisphere which cured the medically refractory epilepsy.

CT scan(fig18) showing posterior quadrant disconnection in another patient

Follow-up of 8 years post-surgery, the child is seizure free and is off anticonvulsants.

# Refractory Epilepsy

**Dr. Ashutosh. N Shetty**

## INTRODUCTION

Epilepsy is one of the serious, disabling neurological ailment with around 20-40% of people with epilepsy being refractory. This leads to interference in school ,work attendance and interpersonal relationship causing difficulty in acquiring vocational and social skills.

## DEFINITION

As per ILAE disabling seizures continuing despite being on two tolerated, appropriately chosen and used antiepileptic drugs ,either alone or in combination.

## OTHER NAMES

Drug resistant, Intractable

## RISK FACTORS

Age group – Later childhood or adolescence

Response to first Antiepileptic drugs (AED) – 50% of patients respond to first AED, 10% respond to the second AED, and only 3% respond to a third drug or multiple drugs. Around 30-40% of patients may be resistant to first AED which can lead to having refractory epilepsy.

High number, longer duration of seizures or status epilepticus prior to diagnosis

Underlying aetiology and seizure classification - most significant factors associated wih developing Drug Resistant Epilepsy include younger age at the diagnosis and longer time of evolution of epilepsy, the presence of Complex Partial Seizures, high frequency of seizures, Mesial Temporal Sclerosis on MRI, and bitemporal epilepsy.

Family history of epilepsy

History of febrile seizures

Paediatric epilepsy syndromes such as Early neonatal myoclonic encephalopathy, Early infantile epileptic encephalopathy, Lennox Gastaut syndrome, West syndrome, Rasmussen's encephalitis.

Abnormal EEG, neurological examination and developmental delay.

## CAUSES OF PSEUDORESISTANCE

Noncompliance

Nonepileptic seizures

Misdiagnosis of seizure type or epilepsy syndromes.

Inadequate medication doses or drug-drug interaction

Alcohol binging, drug abuse, stress

Sleep deprivation

## PATHOGENESIS

1. Target hypothesis – AEDs work by targeting specific pathways and receptors in the brain. This hypothesis states that changes in these targets reduce the effects of drugs.
2. Transporter hypothesis – Overexpression of multidrug efflux transporters causing a decrease in intracerebral drug concentration.
3. Morphological hypothesis – Medial temporal sclerosis is a progressive process leading to alteration in neural circuits.

4. Genetic hypothesis – polymorphism in drug transporter gene (ABCB1,MDR1,DRE)

**IMPACT OF REFRACTORY EPILEPSY**

Can cause significant morbidity due to head injuries, burns, fractures. It can lead to scholastic decline, Unemployment, social isolation, inability to drive, depression ,psychosis.

Can progress to refractory or super-refractory status epilepticus thus leading to prolonged hospital stay, economic burden and dependency care

Super-refractory status epilepticus is a status epilepticus that continues for >24hrs despite anesthetic treatment,or recurs on attempting to wean of the anesthetic regimen with causative etiology being autoimmune or genetic.

Risk of Sudden unexpected death in epileptic patient (SUDEP).

**EVALUATION OF REFRACTORY EPILEPSY :**

Patients usually need a prolonged Video Electroencephalopraphy(EEG) to understand the semiology of seizures and localisation. Use of Grid electrodes and Electrocorticography are advanced invasive tests which help in further localisation of focal epilepsy syndromes. Magnetoencephalography as a supportive tool has been efficacious in evaluation of intractable epilepsy.

MRI Brain with epilepsy protocols focussing on volumetry, thin sections of desired focus help in diagnosing the structural causes of Refractory epilepsy syndromes.

Fluorodeoxyglucose (FDG) Positron emission tomography ( PET) and Single photon emission computer tomography (SPECT) scans play a role in Magnetic resonance imaging (MRI) Brain negative patients as well as in supportive evidence to Video eeg evaluation.

A detailed neuropsychological evaluation and Psychiatrist evaluation is done before subjecting any patient to surgical treatment.

**TREATMENT OF REFRACTORY EPILEPSY:**

1. Choose a AED which is effective for the seizure type at appropriate dosage with less side effect profile, less drug interactions, as per comorbid conditions like hepatic, renal impairment, obesity, gender, child bearing age, cost effectiveness.

2. Focal Epilepsy patients with well localised lesions in non eloquent areas with less risk of cognitive impairment should be offered surgical treatment.

3. The various surgical treatment that can be offered are anterior temporal lobectomy,amygdalohippocampectomy,lesionectomy such as in hypothalamic hamartomas, Corpus callosotomy for drop attacks, multiple subpial resections.

4. The relative non invasive treatment options are Gamma knife surgeries though they take a longer period to show its effectiveness, Laser ablation therapy to localised lesions.

5. Ketogenic diet (4F+1C+1P) offers a 50% seizure reduction in nearly 38% percent patients of any type of refractory epilepsy.The other diet protocols are Modified Atkin's diet and Glycemic Index diet.

6. The other treatment modalities which can be offered are Vagus nerve stimulation (VNS) which help even for drop attacks, Deep Brain stimulation (DBS), Responsive Nerve stimulation (RNS), Transcranial Magnetic stimulation (TMS).

7. Cannabinoids have been useful in reducing seizure frequency .

**SUMMARY :**

There are 20-40% patients with refractory epilepsy with multifactorial aetiologies with failure of first AED trial being the most important risk factor who are at increased risk of morbidity and mortality. These patients need to be evaluated with Video EEG,MRI Brain ,PET,SPECT scans for deciding

further course of action with surgery offering a gold standard treatment for Focal Refractory epilepsy. For patients who are not candidates for surgery ,recommended other options are VNS, DBS, RNS, TMS. Ketogenic diet offers a ancillary treatment guide for these patients thus helping these subjects in having fruitful years of life.

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Risk factors associated with drug resistant focal epilepsy in adults: A case control study

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# Seizure Mimics

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**Introduction:**

About 50 million people are affected with epilepsy worldwide, of which a large number are in developing countries. About 70 -80 % of these people will be able to lead a productive life with appropriate treatment with antiepileptic drugs. The rest suffer from "Medically Refractory Epilepsy". [1] It is thus imperative to have a proper diagnosis of Seizures and Epilepsy.

An epileptic seizure has been defined as "a transient occurrence of signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain. This can manifest in the form of motor, sensory, autonomic, experiential and other phenomena and can be due to various reasons.

"Epilepsy" has been defined by the ILAE task force in 2014, as "at least two unprovoked (or reflex) seizures occurring >24 h apart or one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years or the diagnosis of an epilepsy syndrome.

Many different conditions may present like seizures and the differential diagnosis presents a formidable problem. Syncope and PNES (paroxysmal non epileptic seizures) are frequently diagnosed as epilepsy and treated for several years. These and other conditions mentioned later in this chapter, are considered to be Seizure mimics. In his classical book, Gowers considered sleep disorders, and migralepsy as related to epilepsy but in the borderland. These form a separate group similar to seizure mimics. Further there are atypical presentations of seizures themselves which resemble Seizure mimics and these must be considered under a separate entity called "Seizure chameleon". [3,4]. Further a mimic of one condition may be a chameleon of another condition. These concepts are depicted pictorially in Figure 1. This review will proceed to explain various conditions under mimics, borderland and chameleons of seizures and the relationships they share with each other. This in turn, should throw light on the differential diagnosis of seizures.

**Seizure mimics:**

Syncope and PNES are common causes of Seizure mimics. Others are listed in table 1. A careful history can usually differentiate between the various types of Mimics.

**Syncope:**

It has been defined as a transient loss of consciousness secondary to acute global hypoperfusion of the cerebrum. There are 3 types of syncope, Vasaovagal or reflex, orthostatic hypotension and cardiac

**Neurally mediated or vasovagal syncope:**

It usually results from a failure of neurally mediated vasopressor reflexes which maintain the blood pressure and cerebral perfusion in different conditions such as dehydration, emotional stress, and standing posture. It is commonly accompanied by premonitory symptoms such as light headedness, dizziness (related to hypotension) and autonomic activation such as diaphoresis, pallor, palpitations, nausea, hyperventilation, and yawning. There may be accompanying myoclonic jerks, uprolling of eye

balls, grunting, and urinary incontinence, raising the spectre of epilepsy. However, post ictal confusion is rare.

**Orthostatic Hypotension:**

It has been defined as drop in systolic blood pressure greater than 20 mmHg or diastolic blood pressure greater than 10 mm Hg, within 3 minutes of standing or in the head up tilt table test. Some times delayed hypotension can also occur beyond 3 minutes. It reflects a failure of the sympathetic vasoconstrictor system.

Symptoms premonitory to the syncope such as light headedness, dizziness may be seen. Further visual blurring reflecting occipital ischemia, neck pain, orthostatic dyspnea, and angina are all reported. Supine hypertension is frequently seen. Many drugs are also known to cause orthostatic hypertension, such as alpha blockers, tricyclic antidepressants and Phenothiazines. Hence a drug history is also essential. [5]

Degenerative disorders such as multiple system atrophy, advanced parkinson's disease, diffuse Lewy body disease are known to be associated with autonomic failure and orthostatic hypotension. Peripheral neuropathies such as diabetes mellitus, amyloid, immune-mediated neuropathies, and hereditary sensory and autonomic neuropathies are also associated with autonomic dysfunction.

**Cardiac Syncope:**

It is usually caused by arrythmias or structural heart disorders causing reduced cardiac output and cerebral hypoperfusion. Sinus or Atrioventricular node dysfunction may cause brady arrythmias and cardiac syncope. Ventricular tachyarrhythmias and disorders of cardiac electrophysiologic instability such as e long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia may also predispose to cardiac syncope. Structural diseases like hypertrophic obstructive and other cardiomyopathies, myocardial ischemia, cardiac tumours such as left atrial myxoma also can cause cardiac syncope. It is important to recognize this entity as it can frequently cause sudden cardiac death.

**Psychogenic Non epileptic Seizures (PNES):**

**Epidemiology:**

Estimated prevalence of PNES is 33/100,00 general population in developed countries. It co exists with true seizures in about 10 percent patients. Many people with PNES have co morbidities like anxiety and depression. PNES also leads to loss of working days and quality of life, thereby making its diagnosis imperative.

**Clinical features:**

Several features help to distinguish PNES from true seizures such as a long duration, a variable course, asynchronous or side to-side movements, ictal eye closure at onset, ictal crying and post-ictal memory of ictal information presented. Tongue bite and urinary incontinence may occur in PNES too. Another study pointed out that video-EEG preserved awareness, eye fluttering, and the modulation of event intensity by bystanders were more common with PNES, while acute onset, ictal eye-opening and post-ictal confusion/sleep reliably predicted Seizures. [6]

The gold standard to differentiate PNES from seizures is by Video EEG, showing lack of ictal activity during the seizure. If the clinical features are also suggestive of PNES, one may make a diagnosis with certainty.[7]

Structural MRI changes have also been noted both in terms of cortical atrophy, with cortical thickness and voxel based morphometric analyses in the anterior cingulate cortex, supplementary motor area, pre and post central cortices.

**Other seizure mimics:**

Other rarer seizure mimics are outlined in table 1

**Seizure borderland:**

Although Sleep disorders, migralepsy and syncope were included in the initial description by Gowers, syncope is now firmly placed under seizure mimics. Others, however remain firmly

under borderland group, as they are "near it but not of it".

**Sleep Disorders: Parasomnias:**

They are often difficult to differentiate from frontal lobe epilepsies and pose a diagnostic problem.

**Non- REM parasomnias:**

Confusional arousals, periodic limb movements, rhythmic movement disorder, night terrors and somnambulism are examples of Non- REM parasomnias. Video EEG helps in differentiating these from seizures.

**REM parasomnias:**

This occurs as a result of dissociation of axial atonia during REM sleep. Thus, patients act out their dreams. It is common in the elderly, advanced Parkinson's disease, and with brain stem disease. The parasomnias are responsive to treatment with clonazepam.

**Migraine:**

**Migralepsy:**

International Classification for Headache Disorders (ICHD-II) proposed two diagnostic criteria for migralepsy: (A) migraine fulfilling criteria for migraine with aura and (B) a seizure fulfilling diagnostic criteria for one type of epileptic attack, occurring less than 1 h after a migraine aura. Epilepsy with migraine is a component of some genetic syndromes such as MELAS (mitochondrial encephalo myopathies, lactic acidosis, and stroke) and Familial hemiplegic migraine.

**Migraine syncope:**

This happens in patients with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), wherein they develop loss of consciousness after an episode of migraine.

**Startle syndromes:**

This manifests as an excessive startle response usually seen in babies and young children, to an auditory or tactile stimulus. There are four main types:

**Major Hyperekplexia:**

It presents in the neonatal period with stiffness, startle and startle induced falls. It has been found to be due to a mutation in the alpha subunit of the glycine receptor gene (GLRA1).

**Minor Hyperekplexia:**

This is characterized by excessive startle without stiffness.

**Neuropsychiatric startle disorders:**

These are disorders where startle is accompanied by behavioural features.[4]

**Startle induced epilepsy:**

**Seizure Chameleon:**

Seizures with bizarre or rare phenomena frequently are confused with mimics. These are hence labelled under seizure chameleon. One important point to remember is that chameleons usually have a stereotyped semiology and do not vary. Those seizures which arise from certain parts of the brain and remain localized frequentlt result in bizarre semiologies

**Generalized seizures:**

Certain types such as atonic seizures, absence and myoclonic jerks (especially those that involve individual limbs) are frequently mistaken for seizure mimics.

**Frontal lobe seizures:**

Hypermotor seizures, such as those from the orbitofrontal region are frequently mistaken for PNES. Gelastic seizures accompanied by laughter, can occur from hypothalamic hamartomas, frontal and temporal lobes. These are frequently misdiagnosed as PNES too.

**Temporal lobe seizures:**

Ictal spitting, and cough, which are rare manifestations of nondominant temporal lobe epilepsy are frequently diagnosed as psychogenic. Ictal choking and vomiting can be seen with

insulo- temporal seizures. Experiential phenomena such as Deja (familiarity in unfamiliar surroundings) and jamais vu (unfamiliarity in familiar surroundings) are also well described with neocortical temporal epilepsy. Well formed auditory and visual hallucinations are also seen with posterior temporal neocortical seizures.

**Parietal lobe seizures:**

These may be clinically silent often. However, ictal pain, nonspecific sensory phenomena and perception difficulties are frequently described.

**Occipital lobe seizures:**

Different visual hallucinations formed and unformed, simple and complex have been described, depending on whether the primary visual areas or the association areas and their connections are involved. Ictal blindness and palinopsia (visual persistence after the stimulus has been removed) have also been described. Blinking is frequently seen with temperoparieto occipital junction seizures.

**Non convulsive status epilepticus:**

This is frequently a cause of unexplained loss of consciousness and can be diagnosed by EEG monitoring, showing typical changes.

**Conclusions:**

It is imperative to realize that seizure mimics can frequently be misdiagnosed as seizures. This results in unnecessary loss in quality of life for the person suffering. It is thus important to take careful history of the semiology and look for variability in the history and semiology. Assessment of co-morbid psychiatric and medical conditions is especially important to the diagnosis. Finally, video EEG remains the gold standard, in diagnosisng the spectrum of seizure mimics.

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**Table 1: Seizure Mimics:**

**Types:**

**SyncopeReflex:** Vasovagal, micturition, swallow, carotid sinus, orgasmic and laughingOrthostatic hypotensionCardiac: Arrythmia, Structural heart disease

**PNES**

**Demyelinating disorders:** Multiple sclerosis Devics disease

**Vascular:** Transient ischaemic attack Hemorrhagic strokes: small bleeds, AVMs

**Metabolic disorders:** Hypoglycaemia HyponatremiaUremia

**Movement disorder:** Paroxysmal kinesigenic dystonia/dyskinesia

**Drop attacks:**Colloid cystChiari malformation