Epilepsy: A brief review

Abdul Waheed*, Swati Pathak, Roohi Mirza
Department of Pharmacology,
Amity Institute of Pharmacy, Amity University, Noida, U.P. India
abdul.waheed2050@gmail.com

ABSTRACT

Epilepsy is a chronic brain disorder characterized by tendency to recurrent seizures or fits. The seizures can leads to loss of consciousness, disturbance of movement, muscle spasms, autonomic and mental functions. Epilepsy is developed because of imbalance in nerve signalling chemical called neurotransmitters. During epilepsy, the level of excitatory neurotransmitter glutamate increases and the level of inhibitory neurotransmitter GABA decrease. These lead to abnormal signalling in brain causes epilepsy. Primary diagnosis of epilepsy includes eye–witness and family history. Electroencephalograph (EEG) is the cornerstone for diagnosis of epilepsy and measures the brain wave activity. Neuroimaging like computed tomography (CT) scan, magnetic resonance imaging (MRI) and positron emission tomography (PET) techniques are used to diagnose abnormalities in structure and function of brain. Video recording is also useful for the monitoring of epileptic events. The most common approach of treatment is to prescribe antiepileptic drugs (AEDs). Three generations of AEDs including phenytoin, valproate, carbamazapine, lamotrigine, Oxcarbazepine, Primidone, Phenobarbitone, Gabapentin, Topiramate, Levetiracetam, Felbamate, Rufinamide, Zonisamide, Tiagabin and Vigabatrin etc. are prescribed. These AEDs have some teratogenic effects on pragnent woman and lactating mother; need precautions. Instead of pharmacological approaches, Non-pharmacological approaches also used for the treatment of epileptic seizures like ketogenic diet, atkins diet, yoga etc. Thr purpose of this review is to update the current knowledge on epilepsy classification, diagnostics, approaches of treatment, pathophysiology, mechanism of epileptogenesis and teratogenic effects.

Key words: Antiepileptic drugs, Diagnosis, Epilepsy, Non-pharmacological approaches, teratogen.

OBJECTIVE

As per WHO epilepsy is one of the most common serious brain disorders that affects not only the individual, but also has impact on family and the society in general. Epilepsy affects all the ages, races, sex, education, economic status and social classes across all geographical boundaries. Hence need to aware about epilepsy.

INTRODUCTION

Epilepsy is a brain disorder that affects at least 12 millions people in India and 65 millions of people worldwide[(1)]. As per WHO epilepsy is one of the most common serious brain disorders that affects not only the individual, but also has impact on family and the society in general. Epilepsy affects all the ages, races, sex, education, economic status and social classes across all geographical boundaries. It is expressed by unpredictable recurrent seizures or fits, which can leads to loss of consciousness, disturbance of movement, muscle spasms, autonomic and mental functions. During the seizure, neurons may fire 500 times faster than normal neurons. Mechanism of epilepsy is believe to be imbalance in neurotransmitter release i.e. abnormally increase the level of excitatory neurotransmitter glutamate while decrease in inhibitory neurotransmitter GABA. Several types of epilepsy have now been linked to defective ion channels that control the flow of ions and regulate neuron signalling. Diagnosis includes eye–witness, family history, electroencephalograph (EEG), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS) techniques. Most common approach to treating epilepsy is to prescribe antiepileptic drugs (AEDs). There are various older and newer AEDs like Gabapentin, Topiramate, Phenytoin, Valproate, Carbamazapine, Lamotrigine, Oxcarbazepine, Levetiracetam, Felbamate, Rufinamide, Zonisamide, Tiagabin, Vigabatrin,

Primidone and Phenobarbitone are used for the treatment of epilepsy. These drugs are use for symptomatic treatment of epilepsy that stops seizure but not cure the epilepsy. About 75—80% of epileptic patients respond to conventional antiepileptic drugs but in 20—25% cases therapeutic failures and refractoriness occur[2]. In society there are many myths about epilepsy like (a) epilepsy is because of possession by evil sprit and hence sorcery is the treatment (b) epilepsy is mental illness (c) people with epilepsy are below normal in their intelligence (d) marriage cure epilepsy (e) seizure can be stopped by giving a key in the hand or making a person to smell onion or shoe. But this is not the fact; epilepsy is treated by giving antiepileptic drugs.

This work reviews the current knowledge on Classification, diagnostics, medications, Non-Pharmacological approaches, pathophysiology, mechanism of epileptogenesis and teratogenic effects.

PATHOPHYSIOLOGY OF EPILEPSY [3,4]

The first visible symptom of epilepsy is repeated seizure; generated due to malfunction of ion channels on synapses during neurotransmission. Primarily seizures are as result of hypoactivity of inhibitory neurotransmitter or hyperactivity of excitatory neurotransmitter. A persistent increase of neuronal hyperactivity or excitation is a single characteristic in most of the epileptic syndrome. The anomalous behaviour of neurons is associated with causative factors which are mainly categorized into two groups: Chemical Imbalance and Brain Injuries. Chemical imbalance includes low blood level of sodium, calcium, sugar and oxygen. Brain injuries include intercranial haemorrhage, brain oxygen deficiency, infection, trauma, tumour meningitis, stroke, and other neurological disorders. Other factors such as Genetic Factors and inflammation factors like Cytokines & tumour necrosis factor (TNF) are also involved. Neurological firing during seizure and pathophysiology of epilepsy are represented in fig 1. Role of neurotransmitter, ion channels and genetic factors in epilepsy are listed in table 1, 2 &3 respectively.

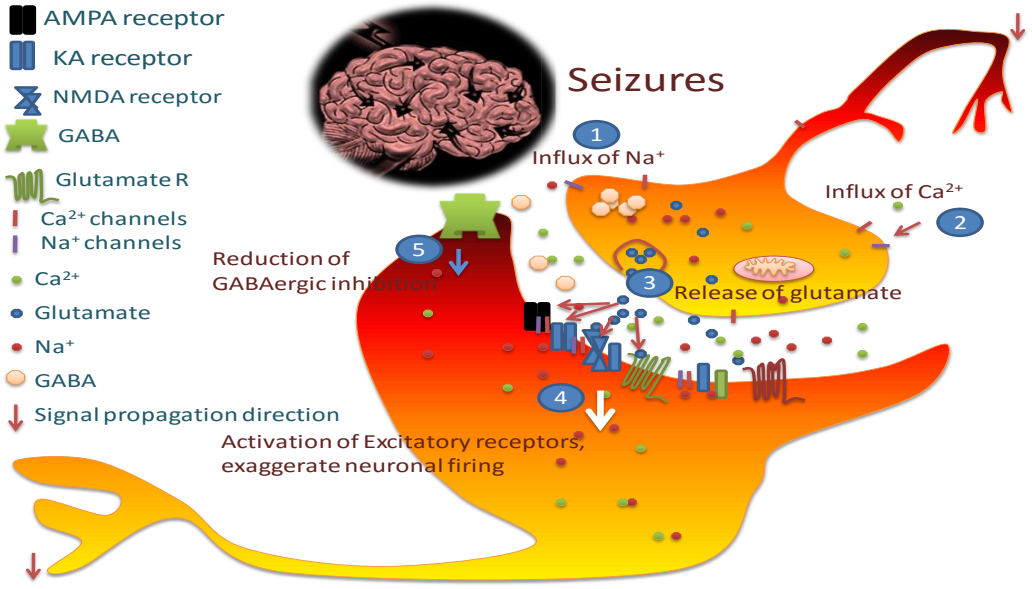

Figure 1: Neuronal firing during seizures. Neuronal firing is triggered by altered signal propagation. This may be the result of abnormalities in neuronal membrane stability or in the connections among neurons. Epileptic bursts consist of sodium dependent action potentials (1) and a calcium-dependent depolarizing potential (2). The opening of voltage activated Ca^{2+} channels and results in the flood of neurotransmitter (glutamate) into the synaptic cleft (3). Increased the accumulation of glutamate activate N-methyl-D-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate receptors with consequent influx of Na^{+} and Ca^{2+} ions through the channels gated by these receptors leads to Neuronal hyper-excitability (4). Uncontrolled increase in Disinhibition is also one of the key events in the generation of epileptic seizures, since a reduction of GABAergic inhibition is necessary to produce the synchronous burst discharges in groups of cells (5).

Table 1: Role of neurotransmitters in epilepsy

Neurotransmitters	Role in epilepsy
GABA (γ amino butyric acid)	Reduced GABA in microgyric cortex Reduced benzodiazepine receptor binding in medial thalamic nucleus (mesial temporal lobe epilepsy) Reduced benzodiazepine receptor density in CA1 region Reduced GABA levels and GAD activity (epileptic foci) Auto-antibodies to GAD (Stiff-man syndrome)
Glutamate	Up regulation of hippocampal ionotropic glutamate receptors (temporal lobe epilepsy) Anti-gluR3 antibodies (Rasmussen encephalitis) Increased plasma glutamate levels (absence seizures)

Table 2: Role of Ions channels in epilepsy

Ions Channel	Role in epilepsy
Na^+	Mutation voltage-gated Na^+ channel (generalized epilepsy with febrile seizures)
K^+	Mutation voltage-gated K^+ channel (benign familial neonatal convulsions)
Ca^{++}	Reduced ACh-mediated Ca flux (nocturnal frontal lobe epilepsy)

Table 3: Genetic factors of Epilepsies [5]

Epilepsy syndrome	Genetic cause
Generalized epilepsy with febril seizure type I &II	Type I: Point mutation in B_1 subunit of a voltage gated sodium channel. Type II: Point mutation in A_1 subunit of a voltage gated sodium channel.
Benign Familial neonatal convulsions	Genes KCNQ2 & KCNQ3 at 20q & 8q chromosomes respectively of voltage gated potassium channel.
Autosomal dominant nocturnal frontal lobe epilepsy	Point mutation in the A_4 subunit of neuronal nicotinic acetylcholine receptor on chromosomes 20q (CHRNA4) gene. This lead to reduce in GABA.
Episodic ataxia Type I	Point mutation on chromosome 12p13 of human voltage gated potassium channel gene.

CAUSES OF SEIZURES AND EPILEPSY

Mechanisms of seizures are not clearly known but assumed to be a genetic factor that code for the Na^+/ca^{++} ion channel protein; disturbance in inhibitory neurotransmitter GABA and excitatory amino acid Glutamate; brain injuries like stroke, infection, blow of head, high fever and tumor. Causes of seizures vary by age of person. One-third of children with autism spectrum disorder may have seizures. Seizures commonly begin in people over age of 60. Common causes of seizures are listed in table 4.

Table 4: Common causes of seizures by age [6]

Age	Causes
Newborn	Brain malformations Lack of oxygen during birth Low levels of blood sugar, calcium, magnesium and other electrolytes Inborn errors of metabolism Intercranial haemorrhage Maternal drug use
Infants and Children	Fever (febrile seizures) Brain tumour (rarely) Infections
Children and Adults	Congenital conditions (Down's syndrome; Angelman's syndrome; tuberous sclerosis and neurofibromatosis) Genetic factors Progressive brain disease (rare) Head trauma

CLASSIFICATION OF EPILEPSY

Classification of epilepsy is essential for understanding of epileptic seizure, correct diagnosis and first step towards correct treatment. It is helpful

for both clinician and researcher. The International League Against Epilepsy (ILAE) published the last official update for the epilepsies in 1989. A report in 2010 by the ILAE Commission on Classification and Terminology recommended that changes be made in the current conceptualization, terminology, and definitions of seizures and epilepsy. Classification of epilepsy and syndromes are listed billow.

Classification of Epilepsy and syndromes [7] :

1. Localisation-Related (Focal, Local, Partial)

1.1. Idiopathic with age related onset

- Benign childhood epilepsy with centrotemporal spikes
- Childhood epilepsy with occipital paroxysms

1.2. Symptomatic

- Comprises syndromes of great individual variability, mainly based on:
- Anatomical localisation
- Clinical features
- Seizure types
- Etiological factors

(Epileptic syndromes of unknown etiology are classified as cryptogenic)

2. Generalised Epilepsies and Syndromes

2.1 Idiopathic, with age related onset, listed in order of age

- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy
- Childhood absence epilepsy (pyknolepsy)
- Juvenile myoclonic epilepsy
- Epilepsy with tonic-clonic seizures on awakening

Other generalised idiopathic epilepsies, if they do not belong to one of the above syndromes can still be classified as generalised idiopathic epilepsies

2.2 Idiopathic and/or symptomatic, in order of age of appearance

- West's syndrome (infantile spasms)
- Lennox-Gastaut syndrome
- Epilepsy with myoclonic-astatic seizures
- Epilepsy with myoclonic absences

2.3 Symptomatic

2.3.1 Nonspecific etiology

- Early myclonic encephalopathy

2.3.2 Specific syndromes

- Epileptic seizures may complicate many disease states
- Included under this heading are those diseases in which seizures are a presenting or predominant feature

3. Epilepsies and Syndromes Undetermined as to Whether They Are Focal or Generalised

3.1 With both generalised and focal seizures

- Neonatal seizures
- Severe myoclonic epilepsy in infancy
- Epilepsy with continuous spike waves during slow wave sleep
- Acquired epileptic aphasia (Landau-Kleffner syndrome)

3.2 Without unequivocal generalised or focal features

- This heading covers all cases where clinical and EEG findings do not permit classification as clearly generalised or localisation-related, such as in many cases of sleep tonic-clonic seizures

4. Special Syndromes

4.1 Situation-related seizures

- Febrile convulsions
- Seizures related to other identifiable situations such as
    - Stress
    - Hormonal changes
    - Drugs
    - Alcohol
    - Sleep deprivation

4.2 Isolated, apparently unprovoked epileptic events

4.3 Epilepsies characterised by specific modes of seizure precipitation

4.4 Chronic progressive epilepsia partialis continua of childhood

Classification of AEDs:

Anti-epileptic drugs are one of the most commonly used approaches for the treatment of epilepsy. There are three generations of anti epileptic drugs listed in table 5.

Table 5: Classification of AEDs:

Generations	Drugs
First generation	Carbamazepin, Phenytoin, Phenobarbital, Primidone, Clobazam, Clonazapam, Ethosuximide, Valproate.
Second generation[8]	Felbamate, Oxcarbazepine, Rufinamide, Topiramate, Stiripentol, Gabapentin, Lamotrigine, Levetiracetam, Pregabalin, Tiagabaline, Vigabaterin, Zonisamide.
Third generation[9]	Eslicarbazepine, Lacosamide, Brivaracetam, Carabersat, Carisbamate, DP-velproic acid, Fluorofelbamate, Fosphenytoin, Ganaxolone, Losogamone, Remacemide, Retigabine, Safinamide, Seletracetam, Soretolide, Stiripenol, Talampanol, Valrocemide.

Mechanisms of Antiepileptic Drug

AEDs are use for the treatment of seizures; each AEDs have different mechanism of action and listed in table 6. They are categorized as follows:

A. **GABA- Glutamate dependent**: There are many AEDs that enhance inhibitory events of GABA (γ-aminobutyric acid). GABA is an inhibitory neurotransmitter and glutamate is an excitatory amino acid. Enhancing GABAnergic event, balance the excitatory Glutamate event; resulting treatment of seizure. (e.g. Benzodiazepines, Gabapentins, Phenobarbital, Tiagabline, Topiramate, Vigabatrin, Valproic acid).

B. **Reduce excitatory Glutamate event**: Glutamate is an excitatory amino acid that balance the inhibitory event of GABA neurotransmitter; resulting treatment of seizure (e.g. Felbamate, Phenobarbital, Topiramate).

C. **Blockage of Voltage dependent sodium or calcium channels**: e.g. Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin, Gabapentin, Topiramate, Valproate, lamotrigine

D. **Blocks T-type Calcium channel**: e.g. Ethosuximide, Zonisamide

Table 6: Mechanism of Action of AEDs [10, 2]

Drug	Na^+/Ca^{++} channel blocker	T-type Ca^{++} channel blocker	GABA enhancer	Glutamate inhibitor
Benzodiazepines	---	---	+++	---
Gabapentin	+++	---	+++	---
Phenobarbital	+++	---	+++	+++
Tiagabline	---	---	+++	---
Topiramate	+++	---	+++	+++
Vigabatrin	---	---	+++	---
Valproic acid	+++	---	+++	---
Felbamate	---	---	---	+++
Carbamazepine	+++	---	---	---
Oxcarbazepine	+++	---	---	---
Lamotrigine	+++	---	---	---
Phenytoin	+++	---	---	---
Ethosuximide	---	+++	---	---
Zonisamide	---	+++	---	---
Rufinamide	+++	---	---	---

"+++" documented; "---" not documented mechanism of action.

NON-PHARMACOLOGICAL APPROACHES FOR THE TREATMENT OF EPILEPSY

A number of different non-pharmacological approaches used to prevent seizure or provide epileptic health. This approach includes ketogenic diet, Atkins diet, dietary modifications, nutritional supplements, yoga, vagal nerve

stimulation, music therapy, acupuncture, transcranial magnetic stimulation, aromatherapy, homeopathy and hormones[11].

Therapies including yoga, music therapy, massage and decapitation; all these techniques are stress-reduction techniques that help people to better control seizures. Acupuncture used to stimulate nerve endings that help to improve physical, mental and emotional health.

The ketogenic diet is calorie-restricted and provides a ratio of fat to (carbohydrate + protein) ranging from 2:1 to 5:1. Ketogenic diet is an effective non-pharmacological treatment recommended since 1921. The diet induces ketosis that control seizures. But its use is risky because of its highly restrictive nature and potential to cause significant adverse effects like vomiting, hypoglycemia, dehydration, severe hypoproteinemia, Fanconi's renal tubular acidosis, or marked abnormalities on liver function tests[12]. A less restrictive form of the ketogenic diet may use; the Atkins diet, has shown less adverse effect. The Atkins diet is a low-carbohydrate, high fat diet; it also induce ketosis. Several other nutrients like vitamin B6, vitamin E, magnesium, manganese, dimethylglycine, taurin, thiamine, folic acid, biotin, vitamin D, vitamin K, essential fatty acids, carnitine, and hormone like melatonin & progesterone are used to reduce seizures and improve epileptic health[13].

EFFECT OF ANTI-EPILEPTIC DRUG IN PREGNANT WOMEN AND LACTATION

As epilepsy is a neurological disorder leads to uncontrolled neurological discharge & seizure, in a pregnant woman it is a serious potentially life threatening condition for both woman and child. So it is necessary to take at least one AED to achieve the goal of seizure free women and healthy child. Before taking AEDs it is necessary to know about specific epileptic syndrome, pharmacokinetic and adverse drug reaction of AEDs to avoid adverse effect on pregnancy and lactation.

Woman with epilepsy taking monotherapy is safer in comparison to the polytherapy of AEDs. Taking more than one AEDs carries high risk such as congenital disease, neural tube defect, urogenital defect and facial cleft, hypospadias, growth retardation, Psychomotor and mental retardation[14]. All the old AED like Barbiturates, Phenytoin, Carbamazepin and valproate have higher risk foetal abnormalities in comparison of new AEDs such as Gabapentin, Levetiracetam, Topiramate, Oxcarbazepine, Pregabalin, Tiababin, & Zonisamde. Exposure of AEDs to the pregnant woman and lactation are listed in table 7.

Table-7: AEDs exposure to the pregnant woman and lactation(15)

Drugs	Teratogenic risk	Effect on lactation
Valproate	High teratogenic risk of valproate including spina bifida	Valproate concentrations in breastfed babies are low.
Lamotrigine	High risk of facial cleft	Lamotrigine is excreted in considerable amounts into breast milk.
Carbamazepine	increased risk of structural birth defects including spina bifida	compatible with breast feeding in the full term infant
Phenytoin	Less use due to increase in malformations in epileptic women.	Breastfeeding is acceptable with phenytoin
Levetiracetam	Its teratogenic risk is unknown	levetiracetam is secreted into breast milk, recent data suggest that the neonatal concentrations are low.
Clonazepam	No particular pregnancy risks have been associated	It may cause drowsiness in the breastfed neonate
Oxcarbazepine, Topiramate, Ethosuximide	Teratogenic risks of these drugs are unknown	These drugs are excreted in breast milk, Breastfeeding is probably acceptable with clinical monitoring
Phenobarbitone	It may carry a significant teratogenic risk	Phenobarbitone in breast milk may cause neonatal drowsiness and apathy

DIAGNOSTICS OF EPILEPSY

Accurate diagnosis of different type of epilepsy is necessary to approaches the treatment of particular type of epilepsy; misdiagnosis can leads to serious consequences including inappropriate treatment. Diagnosis includes eye witness, family history, video recording, EEG, CT scan, MRI, PET and Single photon emission computerised tomography (SPECT) scan.

Eye witness, family history and video recording help in accurate diagnosis as they provide information; what happened before, during and after the seizure. Among these video recording can be very useful for the evidence and diagnosis of epilepsy; it reduces the chance of misdiagnosis.

Electroencephalograph (EEG) is the most commonly recommended method to define brain electrical activity via electrode placed on scalp and identifies disruption [16]. CT scans use X-rays of the brain to provide cross section images of the brain that are stored on a computer. If contrast scan is necessary than only a dye is injected into a vein under consideration of patient allergic history. For the diagnosis of epilepsy Magnetic resonance imaging (MRI) is the most sensitive brain scanning method. It uses magnetic fields and radio waves to penetrate the brain in a non-invasive and painless way, to identify very small lesions and scars in the brain. MRI scan become necessary when there is a possibility of surgery. PET is a non-invasive process and useful to create 3-dimensional images of the brain and uses a tracer to analyse brain function. The most common tracer used analyses glucose in the brain. This test is usually performed between seizures. Single photon emission computed tomography (SPECT) scan may be used when people are being assessed for epilepsy surgery. It is similar to a PET scan, and the most common tracer used measures flow. The injection of the dye into the vein is usually done during seizures, when video-EEG telemetry is taking place. The scan (which takes about 20 minutes) occurs soon after, and it highlights "hot spots" of seizure activity [17].

IMPERIL OF EPILEPSY

People with different sex and age may suffer from epilepsy; epileptic people should avoid some activity like swimming, going out alone, driving, cooking and sleeping alone because they may causes injury or accident, sometimes death. Especially epileptic pregnant women should avoid walking alone; may leads to fall or injury to the pregnancy. Hence need great care to the epileptic patient.

CONCLUSION

As epilepsy is a severe neurological disorder among all the Geographical and economical barriers of population, may leads to death; so it is necessary to correctly diagnose the episode of seizures. All the AEDs have the mechanism of action based on pathophysiology of epilepsy hence accurate diagnosis leads to correct approaches of treatment among all the people including pregnant woman and lactating mothers. Non-pharmacological approaches are also helpful to treat and maintain epileptic health.

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