IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

"Epilepsy: Recent Advances In Diagnosis, Therapeutic Strategies, And Understanding Of Mechanistic Pathways"

Shivani J. Basniwal, Dr. Rajendra M. Kawade.
Nandkumar Shinde College of pharmacy, Aghur
Ta. Vaijapur Dist. Chh. Sambhaji Nagar, Pin Code: 423701,
State: Maharashtra, Country : India

Abstract

The majority of individuals worldwide suffer from numerous neurological disorders, and people nowadays deal with a variety of stressors in their hectic everyday lives. One of the most prevalent neurologic conditions affecting the brain, epilepsy affects around 50 million people globally, with 90% of those affected living in poorer nations. Epilepsy is caused by a combination of genetic factors, brain infections, strokes, tumors, and high fevers. There are now more than ever identified types of infantile epilepsy disorders. Still, a sizable portion of newborns (those between the ages of 1 and 24 months). Long-term epilepsy is a medical condition that often results in recurrent, unpredictable seizures that impair mental and physical functioning. The clinical appearance of the illness is discussed in the article, along with the kinds and frequency of seizures as well as related symptoms like behavioural and cognitive abnormalities. Together with considerations of genetic predispositions and possible environmental triggers, a thorough review of modern diagnostic techniques is offered, including neuroimaging and EEG. The effectiveness and patient outcomes of various treatment modalities, including medication and surgery, are assessed. The study also emphasizes the difficulties in treating this condition and the continuous investigation into novel treatments meant to enhance the quality of life for those who are impacted. Hemi convulsions-hemiplegic epilepsy, benign myoclonic epilepsy, benign familial/nonfamilial infantile seizures, severe myoclonic epilepsy of infancy, myoclonic-astatic epilepsy, generalized epilepsy with febrile seizures plus, early infantile epileptic encephalopathy, early myoclonic epilepsy, infantile spasms/West syndrome, and malignant migrating partial seizures of infancy.

Keywords: Pathophysiology, anti-epileptic medications, seizures, biomarkers, treatments, history, causes, symptoms, and indicators of epilepsy.

Introduction :

Although it can happen at any age, epilepsy is more common in young children and adults over 65. (1). Although epilepsy is a syndrome characterized by a wide range of symptoms involving aberrant electrical activity in the brain on an episodic basis, it is not a single disorder. Not all epilepsy syndromes are permanent; others only affect a kid during specific developmental phases. The mainstay of conventional epilepsy treatment is anticonvulsant medication. However, even with the finest drugs currently available, over 30% of epileptics are unable to manage their seizures (2,3). Treatment is symptomatic in that there is no effective prophylactic or cure available, however medications do reduce seizures. Due to the side effects of many medications and the prolonged nature of therapy, medication compliance is a significant issue(4). The English word epilepsy comes from the Greek word epilam banein, which meaning "to be seized." This meant both the

illness and the isolated incident. The phrase alludes to the period's magical beliefs, which contributed to the stigma attached to epilepsy because those who had it were viewed as evil or filthy (5). Significant neuropathological changes in the hippocampus, consciousness fluctuations, motor coordination problems, stigma, and other brain processes are common symptoms. Aside from the lack of essential and potent drugs, insufficient drug delivery systems and delayed diagnosis of this illness have seriously impeded the development and improvement of successful treatment. Over half of the cases that are remitted have resistance to medicinal medications (6,7) A person's quality of life may be negatively impacted by epilepsy due to physical harm from seizures, long-term seizure disorders, incapacity to work or attend school, negative treatment outcomes, comorbid conditions, psychosocial damage, the advent of drug-resistant seizures, and early mortality. Epilepsy or a seizure condition is defined as having at least two unprovoked seizures separated by at least 24 hours. Individuals who have one seizure but are more likely to have more, such as those who have seizures linked to primary brain tumors, may be diagnosed with epilepsy and receive treatment accordingly.

The common definition of epilepsy is the experience of recurring, repeated events. Due to the difficulty in diagnosing epilepsy, studies addressing the epidemiology of seizures or epilepsy can contain errors(8,9). Consequently, epilepsy is defined as a brain disease characterized by any combination of the following symptoms: a diagnosis of epilepsy syndrome; at least two unprovoked (or reflex) seizures that happen more than 24 hours apart; two unprovoked (or reflex) seizures; one unprovoked (or reflex) seizure; and a probability of future seizures equal to the overall recurrence risk (at least 60%) following two unprovoked seizures that happen within the next ten years (10).The word "epilepsy" describes a group of neurological conditions characterized by recurrent, unpredictable disturbances of normal brain function called epileptic seizures. The term "epilepsy" refers to a collection of conditions that can have multiple causes and indicate underlying brain dysfunction. It is not one illness at a time. There isn't much agreement among experts on what seizures and epilepsy actually mean. Communication between medical experts and those involved in lawmaking, disability

benefits, driving laws, workplace safety, education, and many other areas depends on these kinds of descriptions.

History of epilepsy:

Epilepsy can be efficiently and economically treated using low-cost medication, such as conventional antiepileptic drugs: phenobarbital, phenytoin, carbamazepine, valproic acid, and benzodiazepines. Most new drugs benefit these patients' medical care more through tolerance than through actual improvement. These can sometimes have a major effect on the outcome and lead to a seizure-free state because of improved compliance. Refractory seizures affect about one-third of patients with epilepsy who receive a new diagnosis. (10,11) The name "epilepsy" comes from the Greek word "epilepsia," which means "to take hold of." Epi was derived from the word "lambanein," which means to take, and meaning "upon." (12) Epilepsy used to be associated with faint faiths or being possessed by a demon. Epilepsy was formerly thought of as the sacred disease. Many people held the belief that epilepsy afflicted those who had been partially captured by demons or that epileptics' experiences with visions were delivered by the gods. For example, epilepsy was regarded as an attack by a demonic spirit even among the Hmong animist generations, but the afflicted individual could become respected as a shaman via their personal experiences. (13) About 900 BC, a man named Punarvasu Atreya described epilepsy as a loss of consciousness. However, the ancient Greeks had differing views on this phrase. They linked epilepsy to genius and the divine, insisting it was a form of spirit possession. The Greeks believed Julius Caesar and Hercules were two famous people who suffered from the illness. The Greeks had no ill will towards epileptics in general since they thought that some of them were intelligent people (15,16). We don't know the cause of epilepsy at all. The term "epilepsy" does not describe the kind or severity of a person's seizures; epilepsy can be brought on by genetics in certain situations, but it can also be brought on by head trauma, strokes, infections, high fevers, or tumors. (17)

Etiology :

Gamma amino butyric acid (GABA) and glutamate are the primary inhibitory and excitatory neurotransmitters, respectively, that mediate the majority of synaptic transmission in the mammalian brain. The primary inhibitory amino acid neurotransmitter in the central nervous system of mammals is GABA. There are two primary categories of its receptors: The more common subtype, GABAA, is a ligand-gated Cl^- ion channel that opens when presynaptic neurons release GABA. Due to its enormous abundance and involvement in nearly all neuronal circuits, the GABAA receptor protein has been well described. A member of the G-protein coupled receptor family, GABAB is connected to ion channel control as well as metabolic pathways. (3)

Risk factor of epilepsy:

There are many different risk factors for epilepsy that can raise the chance of getting the disorder. Among the major risk factors are:

1. Genetics: Since some types of epilepsy have a hereditary component, a family history of the disorder or other genetic disorders may raise the risk.

2. Head Trauma: Epilepsy may occur as a result of traumatic brain damage sustained in falls or accidents.

3. Brain Infections: Infections that induce inflammation in the brain, like meningitis, encephalitis, or neurocysticercosis, raise the risk of epilepsy.

4. Stroke and Vascular Diseases: Epilepsy may develop as a result of brain damage caused by conditions like stroke that impair blood flow to the brain.

5. Developmental Disorders: Neurofibromatosis and autism spectrum disorder are two conditions that can raise the risk of epilepsy.

6. Prenatal Brain Injury: Epilepsy can develop later in life as a result of brain damage that occurs before birth and is frequently brought on by the mother's illnesses, inadequate nourishment, or oxygen shortage.

7. Age: Although epilepsy can strike at any age, children and older adults are more likely to experience its beginning.

8. Dementia: Epilepsy risk may be elevated in older persons with dementia and associated neurodegenerative disorders.

9. Substance Abuse: Excessive use of drugs or alcohol, particularly during withdrawal, might raise the risk of epilepsy and cause seizures.

10. Childhood Febrile Seizures: Although the majority of children who experience febrile seizures may not go on to develop epilepsy, the risk may be marginally increased if the seizures are lengthy or complex. Although they can raise a person's risk, these factors do not ensure that epilepsy will occur.

Diagnosis:

A variety of tests have been created to identify the type of epilepsy a person has. Electron encephalograms, or EEGs, are a valuable diagnostic tool for a number of seizure diseases.

Even while many people without epilepsy exhibit some a typical brain activity on EEG, some patients may still have normal EEGs. Video monitoring is frequently used in conjunction with EEG to assess the type of seizures a person is experiencing.

Brain scan:

Brain scan is a crucial diagnostic procedure that can be used to find brain tumors, cysts, and other structural anomalies. Computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) are the three most often used brain scans. MR S (magnetic resonance imaging) and SPECT (single photon emission computed tomography) The structure of the brain is shown by CT and MRI studies. Brain activity can be tracked and abnormalities can be found using PET and MRI. Finding seizure foci in the brain is done using SPECT.

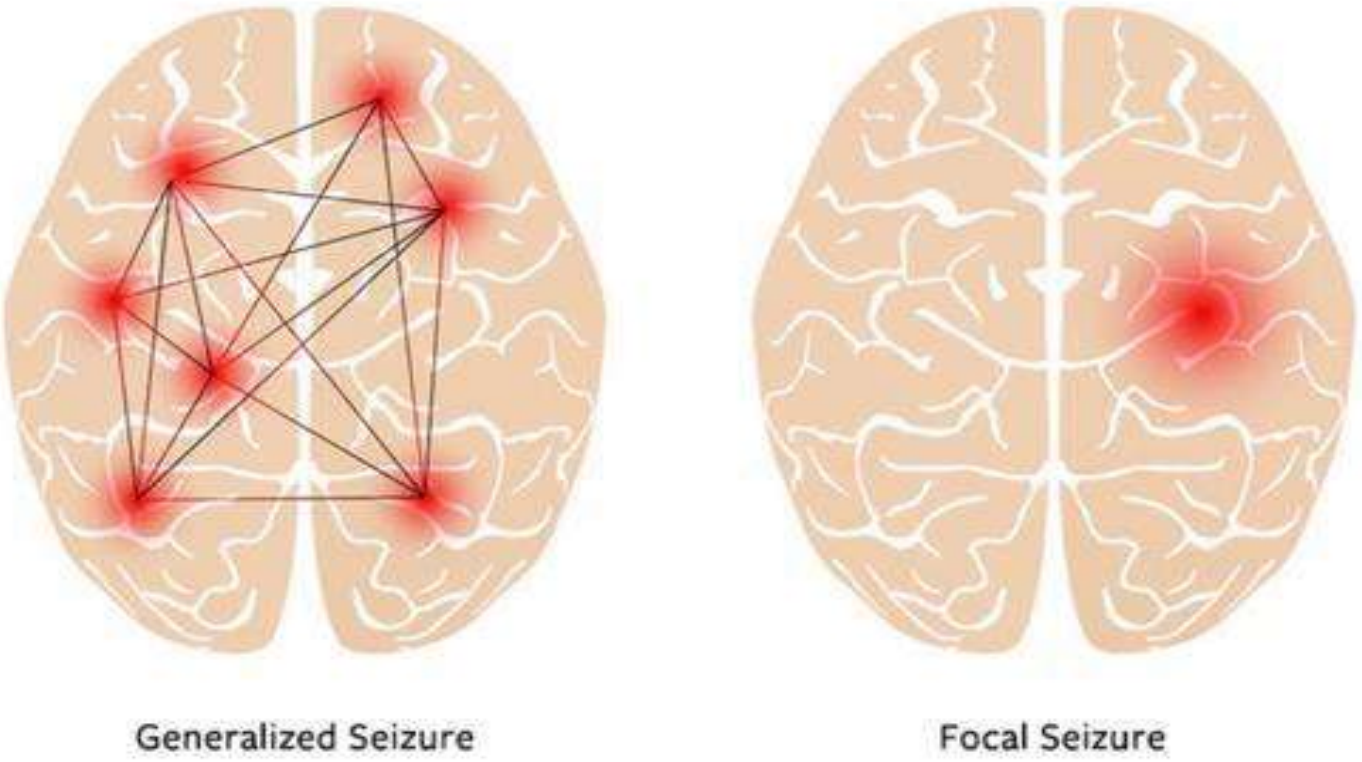
Blood Tests:

In certain cases, acute underlying toxic or metabolic diseases might produce seizures. In these cases, the proper therapy should be addressed against the specific anomaly, such as hypocalcaemia. Blood samples are frequently examined for genetic or metabolic conditions that could be linked to the seizures. Blood samples

are also examined for conditions that could be causing or precipitating the seizure, such as infections, lead poisoning, anemia, and diabetes. (24)

Type of seizure:

1. Partial seizures.
2. Generalized seizures.



PARTIAL:

Without a noticeable change in consciousness, simple partial seizures result in motor, sensory, autonomic, or psychological symptoms. alterations in somatic feeling (such as paresthesias or tingling), vision, balance, autonomic function, olfactory alterations, and hearing are additional ways that these seizures may present. Focused seizure activity and a temporary impairment in the patient's capacity to maintain regular touch with the surroundings are characteristics of complex partial seizures. Both cerebral seizures, typically of the tonic-clonic type, can be affected by partial seizures. Simple partial seizures, particularly those with a frontal lobe emphasis, are frequently followed by secondary generalization (6).

GENERALIZED:

Both cerebral hemispheres can cause generalized seizures at the same time. The hallmark of absence seizures (petit mal) is abrupt, fleeting unconsciousness without a loss of postural control. Usually, the seizure lasts only a few seconds; there is no postictal confusion and consciousness returns as abruptly as it was lost. The clinical and electrophysiological characteristics of atypical absence seizures differ from those of ordinary absence seizures. A momentary clouding of the sensorium, or loss of consciousness, coupled with specific generalized epileptic discharges and no other discernible clinical indications is known as a simple absence seizure. A complicated absence seizure suggests the presence of additional symptoms. About 20% of people with epilepsy have generalized, tonic-clonic seizures, formerly known as grand mal seizures. (6)

A tonic spasm is caused by a severe contraction of the entire body muscles at the beginning of a tonic-clonic seizure (grandmal). Defecation, micturation, and salivation frequently occur during this one-minute tonic phase, which is followed by a series of severe, synchronized convulsions. After a few minutes of unconsciousness, the patient slowly regains consciousness, feeling unwell and disoriented. (15). When all

muscles relax during an atonic seizure (akinetic seizure), the patient may lose consciousness and collapse as a result of excessive inhibitory discharges. (30).

Medical Treatment of epilepsy:

Antiepileptic drug (AED) therapy, the most popular type of treatment for the majority of patients, aims to prevent seizures or minimize their frequency, prevent long-term treatment side effects, assist patients in maintaining or returning to their regular psychosocial and occupational activities, and assist patients in leading normal lives. A careful assessment of the risk of seizure recurrence, the effects of persistent seizures on the patient, and the benefits and drawbacks of the chosen pharmaceutical agent should all be taken into consideration before starting AED therapy (33, 34).

Early AED use may be preferable in order to prevent further seizures. For people who have to drive, go to work, or care for other family members, having seizures in the future could be distressing. The risk of seizure recurrence varies from patient to patient and is dependent on the kind of epilepsy and any associated neurological and medical conditions. Nevertheless, the risk of adverse effects from pharmacotherapy rises by around 30% after the first course of treatment.4. Treating children who use drugs frequently presents additional challenges, especially in the areas of behavior, learning, and brain development (39, 33, 35, 36).

Whether to begin therapy with a patient who has experienced only one seizure is up for debate. Treatment should be given if there is unmistakable proof that a single seizure was caused by an identified lesion that is epileptogenic, such as a CNS tumor, an infection, or trauma. Eliminating seizures completely is the main goal of AED treatment. The proportional risk of epilepsy recurrence can vary depending on the kind or range of seizures. The likelihood of recurrence is high (almost 90%) for those with congenital neurological abnormalities or epileptiform discharges on an EEG. The viewpoints of the patient and their family should also be considered while beginning AED therapy.

Management of epilepsy:

The phrases antiepileptic and anticonvulsant are synonymous. An antiepileptic medication is one that is administered to treat the 32 epilepsies, whereas an anticonvulsant is a drug that stops lab animals from having seizures during tests (31). Principles of Management Treatment is required for any epilepsy triggers, such as brain tumors. The condition, the duration of treatment, and the importance of adherence must all be explained to patients. Avoiding triggering factors like alcohol, sleep deprivation, and emotional stress is advised. It is reasonable to anticipate natural variation; for instance, women may experience fits more frequently or exclusively during their periods. An antiepileptic medication should only be administered if the type and frequency of the seizures, such as more than one fit per six to twelve months, warrant treatment. (27).

The ideal AED should not cause any negative side effects while preventing all seizures. Unfortunately, some patients treated with currently available AEDs frequently develop adverse effects that can range in severity from mild CNS impairment to deadly aplastic anemia or liver failure, in addition to uncontrollable seizure activity. The treating physician or practitioner must choose the AED or medication combination that effectively manages seizures with a manageable amount of side effects. Up to 50% of patients are known to achieve complete seizure control, while another 25% report notable improvements. The type of seizure, family history, and severity of the underlying neurological abnormalities all affect treatment success rates (40, 37).

Antiepileptic drugs may work through one of three primary mechanisms: Inhibiting GABA transaminase or drugs with direct GABA agonist properties can improve GABA-mediated synaptic inhibition by

(i) decreasing the electrical excitability of cell membranes, especially (by blocking) the voltage-dependent sodium channels that control the inward current that produces an action potential;
(ii) increasing membrane permeability to chloride ions, which reduces cell excitability; and
(iii) blocking T-type molecules like glutamate (32, 27).

Oral contraceptives and epilepsy:

Certain antiepileptic medications (such as carbamazepine, phenytoin, barbiturates, topiramate, and oxcarbazipine) might cause hormonal contraception to fail by inducing steroid metabolizing enzymes. As a result, patients on antiepileptic medications need to take an oral contraceptive with a greater amount of estrogen (50 mg per day). (25)

Epilepsy and pregnancy:

Managing epilepsy during pregnancy can cause issues for the fetus as well as the mother. Women with epilepsy are more likely to have stillbirths and spontaneous abortions.

Because of the potential for anoxia and metabolic disorders, patients with seizure disorders should have their conditions appropriately investigated and treated prior to pregnancy using the lowest dosage possible for the growing fetus. It is not necessary to eliminate minor seizures because they are most likely harmless. Patients should be encouraged to take vitamin K and folic acid supplements orally. as folic acid deficiency is a risk factor for neural tube abnormalities and certain antiepilertic medications alter folic acid metabolism. Antiepileptic medications that cause hepatic enzymes reduce the mother's vitamin K levels, which can exacerbate any postpartum haemorrhage.(25)

Surgical treatment of epilepsy:

Surgery should be taken into consideration when seizures interfere with daily living and cannot be managed with the finest medical care. It has been difficult to quantify these problems, though, which is somewhat understandable considering that intractability entails more than just ongoing seizures. Some individuals with refractory seizures only experience moderate impairment, whereas others discover that few episodes have a major influence on their lives. Even after receiving surgery that completely cures them, some people may nevertheless be disabled and unable to work. Few persons benefit from further medical treatment if seizures remain uncontrolled after two trials of high-dose monotherapy with two appropriate AEDs and one trial of combination therapy. At the moment, there aren't many strict restrictions on epilepsy surgery. (36, 42)

When determining whether to begin AED treatment, factors such as the likelihood of a seizure recurrence, the consequences of continuing seizures, and the advantages and disadvantages of the medication in preventing a recurrence can all be taken into account. The proportionate chance of recurrence may vary depending on the type of seizure or seizure condition. Recurrence risk is high (up to 90%) for patients with congenital neurological disorders or epileptiform discharges on an EEG. Furthermore, recurrence risks are increased for patients with brain abnormalities, a history of symptomatic seizures, and Todd's paralysis, which is a brief, temporary paralysis that occurs after a seizure (41, 38).

Conclusion:

As a result, the main factor in choosing an anticonvulsant medication is how well it works for particular kinds of seizures and epilepsy. Despite early treatment and an appropriate daily dosage of an anticonvulsant medication, a considerable percentage of epileptic patients have intractable or drug-resistant epilepsy, even if seizure control is normally satisfactory in the majority of patients. Therefore, there is a need for novel medications that are more beneficial than the current antiepileptic agents in terms of adverse effects and tolerance, even if this means sacrificing efficacy.

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