Original Article

EPIDEMIOLOGICAL INVESTIGATION AND CLINICAL MANAGEMENT FOR THE TREATMENT OF EPILEPSY

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DOI: 10.47750/pnr.2022.13.S09.765

Abstract

The aim of this review is to understand the factors that cause epilepsy, diagnosis and its management. Epilepsies are among the most prevalent severe brain disorders. The prevalence of epilepsy is widespread across the world, affecting people of all ages and genders. Although childhood prevalence has decreased over the past three decades in wealthy nations, this decrease is mirrored by a rise in the senior population. Because stroke, neurological disorders, and tumors are more common in older people, both the prevalence and incidence of epilepsy are slightly greater in males than in women and tend to peak in this age range. Both in children and adults, focal seizures occur more frequently than widespread ones. To determine epilepsy's cause the electroencephalogram (EEG), a test that detects and records brain activity, is frequently used in the identification and evaluation of epileptic seizures. Formulating mechanistic theories that may be tested to propel the development of innovative therapies requires an understanding of the natural history of pharmacoresistant epilepsy and the variables associated with it. Epilepsy prediction with high accuracy, targeted therapy using medication delivery, surgery, and brain stimulation are potential novel therapies. But despite these treatments, comorbidities continue to have a significant negative impact on quality of life and are insufficiently controlling seizures in one-third of those who are afflicted.

Keywords: Electroencephalogram, seizures, Neurostimulation, Clinical Management, Epilepsy.

Introduction

A set of neurological illnesses known as epilepsy are non-communicable and are characterized by recurring epileptic episodes. Due to abnormal electrical activity in the brain, epileptic seizures can range in length from short, hardly perceptible bursts to prolonged, violent shaking. These incidents have the potential to cause accidents also as physical damage, like broken bones. Seizures in brain disorder often repeat and should not have a right away underlying cause. It is not thought to exist in cases of isolated seizures brought on by a particular cause, such as poisoning. Due to the frightening nature of their symptoms, people with epilepsy may receive diverse treatments around the world and face varying degrees of societal stigma. [1]

The electroencephalogram (EEG) of a person can show excessive and abnormal neuronal activity in the cortex of the brain, which is the fundamental mechanism of epileptic seizures. Most epilepsy cases are idiopathic, meaning they have no known cause. However, epileptogenesis, a process that can develop from brain trauma, stroke, brain tumors, infections of the brain, or birth defects, can also cause some cases. Only a small percentage of cases have been explicitly connected to known genetic alterations. In order to make a diagnosis, it is necessary to rule out other illnesses that might result in symptoms similar to fainting, as well as to look for additional seizure triggers, including alcohol withdrawal or electrolyte imbalances. Blood testing and brain imaging may also be used to partially achieve this. A normal test does not rule out epilepsy, but an EEG can frequently confirm the diagnosis. [2]

It may be possible to avoid epilepsy that develops as a result of other problems. About 69% of the time, seizures may be controlled with medicine, as well as frequently affordable anti-seizure options. When medicine is ineffective in controlling seizures, surgery, neurostimulation, or dietary changes may be considered. Not all epilepsy instances are permanent, and many people get better to the point where they no longer require medication. [3]

Causes of epilepsy

Recurrent epileptic seizures are a long-term risk factor for epilepsy. Depending on the areas of the brain affected and the person's age, these seizures may manifest in a variety of ways. Both inherited and acquired factors can contribute to epilepsy, and frequently these variables interact to generate the condition. Known acquired causes include severe brain injuries, strokes, tumors, and brain issues brought on by an earlier infection. About 60% of the time, there is no recognized cause. While brain tumors and strokes are more common in older people, epilepsies brought on by genetic, congenital, or developmental disorders are more common in younger people. [4].

Genetics

The majority of instances are thought to involve genetics, either directly or indirectly. Only 1-2 % of epilepsies are caused by a single gene deficiency; the majority is brought on by the interaction of many genes and environmental variables. There are fewer than 200 single gene abnormalities known, and they are all rare. Most implicated genes have an indirect or direct impact on ion channels. Ion channel genes, enzyme genes, GABA genes, and G protein-coupled receptor genes are a few of them. [5]

If one twin has the condition, there is a 50–60% probability that the other will have it as well in identical twins. 15% of non-identical twins are at risk. This hazard is higher in people who have widespread seizures as opposed to localized ones. Many times (70–90%), if both twins are ill, they have the same epileptic syndrome. The risk for other close relatives of someone with epilepsy is five times higher than it is for the general population. 90% of people with Angelman syndrome and 1–10% of people with Down syndrome suffer from epilepsy. [6]

Phakomatoses

Phakomatoses are a class of multisystemic diseases that primarily affect the skin and central nervous system. They are often referred to as neurocutaneous disorders. They are brought on by abnormal embryonic ectodermal tissue development, which is often the result of a single genetic mutation. Defective development can lead to epilepsy as well as other indications like autism and intellectual incapacity because the brain, other neural tissue, and skin are all derived from the ectoderm. Compared to other phakomatoses, including neurofibromatosis type 1, others, like tuberous sclerosis complex and Sturge-Weber syndrome, have a higher rate of epilepsy. [7]

About 1 in 6,000–10,000 live births are affected by tuberous sclerosis complex, an autosomal dominant condition that results from mutations in either the TSC1 or TSC2 gene. These mutations cause the mTOR (mechanistic target of rapamycin) pathway to be activated, which promotes the formation of tumors in a variety of organs, including the kidneys, skin, heart, and brain. Additionally, it is thought that aberrant mTOR activity modifies neuronal excitability. mTOR inhibitors, cannabidiol, and vigabatrin are new advances for the treatment of epilepsy in TSC patients. Epilepsy surgery is often pursued. [8]

Acquired

Tumors, strokes, head trauma, prior infections of the central nervous system, genetic abnormalities, and birth-related brain injury are a few more disorders that might result in epilepsy. Almost 30% of people with brain tumors also have epilepsy, which accounts for about 4% of cases. Temporal lobe tumors and slow-growing tumors carry the highest risk. Risks for other mass lesions, like arteriovenous and cerebral cavernous malformations, can range from 40 to 60%. 6–10% of stroke survivors go on to develop epilepsy. The severity of the stroke, cortical involvement, bleeding, and early seizures are risk factors for post-stroke epilepsy. [9]

There is conflicting information regarding the relationship between epilepsy, non-celiac gluten sensitivity, and celiac disease. Coeliac disease, epilepsy, and brain calcifications appear to be part of a distinct illness. According to a review from 2012, celiac disease affects 1% of the general population but between 1% and 6% of those with epilepsy. In regions of the world where the parasite is prevalent, neurocysticercosis, a type of infection with the pork tapeworm (cysticercoids) in the brain, is the cause of up to half of epilepsy cases. Other types of brain infections, such as cerebral malaria, toxoplasmosis, and toxocariasis, can also result in epilepsy. [10]

Mechanism of epilepsy

Since many neurons do not typically fire at the same time when signals move through the brain, brain electrical activity is typically non-synchronous. Numerous elements in the cell's environment as well as within the neuron itself control neuron activity. The type, quantity, and distribution of ion channels inside the neuron, alterations to receptors, and changes in gene expression are all factors. Ion concentrations, synaptic plasticity, and glial cell control of transmitter breakdown are some of the factors that surround the neuron [11].

Epilepsy

Although the precise cause of epilepsy is unknown, little is understood about the cellular and network mechanisms that underlie it. However, it is unknown under what conditions the brain's excessive synchronization causes it to change into seizure-like behavior. Changes in the amounts of microRNAs (miRNAs) appear to be the main factor. A family of tiny non-coding RNAs called microRNAs (miRNAs) may be important regulatory mechanisms and therapeutic targets in the treatment of epilepsy because they regulate the expression levels of numerous proteins by reducing mRNA stability and translation. Excitatory neurons are less resistant to fire during this time in epilepsy. This might happen as a result of altered ion channels or malfunctioning inhibitory neurons. [12]

Seizures

There is evidence to suggest that epileptic seizures do not frequently occur at random. Stress, excessive alcohol intake, flashing lights, and lack of sleep are just a few of the factors that can induce seizures. During an epileptic episode, a group of neurons begins firing inappropriately, excessively, and simultaneously. This causes a paroxysmal depolarizing shift, a wave of depolarization. An excitatory neuron often becomes more resistant to firing for a while after it fires. This is caused in part by adenosine's harmful effects, the influence of inhibitory neurons, and electrical alterations inside excitatory neurons. While generalized seizures start in both hemispheres of the brain, focal seizures start in just one. While some seizures seem to have minimal impact, some seizure types have the potential to alter brain structure. Specific brain alterations such as gliosis, neuronal loss, and atrophy are associated with epilepsy. However, it is unclear if epilepsy causes these changes or whether these changes lead to epilepsy. [13]

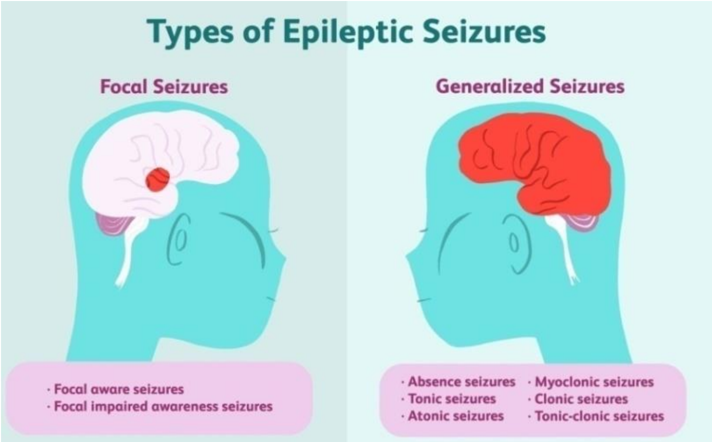
Sign and symptoms

Depending on where in the brain the disturbance initially emerges and how far it progresses, seizures can have a range of features. The limbs constrict, then extend, and the back arches during tonic-clonic seizures, which last 10 to 30 seconds (the tonic phase). A shriek may be heard when the chest muscles tense, followed by a coordinated shaking of the limbs (clonic phase). Muscles contract continuously during tonic seizures. Frequently, when breathing is halted, a person becomes blue. The limbs shake in synchrony during clonic convulsions. People with epilepsy are more likely to experience bodily problems (such as fractures and bruises from injuries brought on by seizures) as well as psychological problems (such as fear and despair). [14]

Types of seizure

According to how and where the aberrant brain activity starts, doctors typically categorize seizures as either focal or generalized.

Figure 1 : Types of seizures



Focal seizures
Seizures are referred to as "focal seizures" when they seem to be caused by abnormal activity in just one part of your brain. These seizures fall into two categories:
• **Focal seizures without loss of consciousness** - These seizures—once known as simple partial seizures—don't result in unconsciousness. They could modify feelings or affect how objects, sound, feel, look, smell, or taste. Déjà vu can happen to certain people.
• **Focal seizures with impaired awareness** - These seizures, which were once known as "complex partial seizures," include a shift or loss of consciousness or awareness. This kind of seizure could make you feel like you're dreaming. You could look off into space, not react normally to your surroundings, or make repeated actions like rubbing your hands together.

Generalized seizures

Generalized seizures are defined as seizures that seem to affect every part of the brain. six types of generalized seizures exist.
1. **Absence seizures** - Petit mal seizures, sometimes referred to as absence seizures, usually affect young children. They only endure for 5 to 10 seconds and are characterized by blank stares, with or without slight body movements like eye blinking or lip smacking. These seizures could happen up to 100 times each day in clusters.

2. **Tonic seizures** - Muscles become tight during tonic seizures, and consciousness may be impacted. Your back, arms, and legs are typically affected by these seizures, which might make you lose your balance and fall to the ground.

3. **Atonic seizures** - Muscle control is lost during atonic seizures, commonly referred to as "drop seizures." You frequently collapse or drop to the ground as a result of this, since it most frequently affects the legs.
4. Clonic seizures - Muscle rigidity results from tonic seizures. Muscle jerking, repetition, or rhythmicity are hallmarks of clonic seizures. These convulsions often affect the arms, face, and neck and can impair consciousness.
5. **myoclonic seizures** - The upper torso, arms, and legs are typically affected by myoclonic seizures, which typically present as quick, short jerks or twitches

6. Tonic – clonic Seizures - The most severe kind of epileptic seizures are tonic-clonic seizures, sometimes referred to as "grand mal" seizures. They may also cause the body to jerk, twitch, or shake, as well as an abrupt loss of consciousness. Sometimes they make you lose control of your bladder or start biting your tongue. [15]

Diagnosis of epilepsy

The diagnosis of epilepsy is often determined based on observation of the seizure onset and the underlying cause. An electroencephalogram (EEG) to search for aberrant patterns of brain waves and neuroimaging (CT scan or MRI) to look at the anatomy of the brain are also frequently part of the early examinations. It is not always feasible to identify a distinct epileptic diagnosis, despite many attempts. In complex situations, Video and EEG monitoring may be beneficial in difficult circumstances. [16]

Electroencephalography can be used to determine the sort of seizure or condition that is occurring while determining the epilepsy diagnosis. Unless otherwise directed by a professional, it is normally only required in children after a second seizure. It can't be used to rule out a diagnosis and might result in false-positive results in healthy people. In some circumstances, it may be beneficial to do the EEG when the afflicted person is dozing off or otherwise sleep-deprived. After a first non-febrile seizure, diagnostic imaging by CT scan and MRI is advised to look for structural issues in and around the brain. Except for situations when bleeding is suspected, in which case CT is more sensitive and accessible, MRI is typically a better imaging technique. Imaging tests could be performed later if someone has a seizure and goes to the ER but soon gets well. [17]

Genetic testing is quickly overtaking EEG and neuroimaging as one of the most crucial epilepsy diagnostic methods since it can reliably diagnose a significant fraction of people with severe epilepsies, such as adults. After 2-3 years, it can be crucial to revisit or re-analyze earlier genetic investigations for patients whose genetic testing came out negative. Epilepsy diagnosis might be challenging. Syncope, hyperventilation, migraines, narcolepsy, panic attacks, and psychogenic non-epileptic seizures are a few additional illnesses that might exhibit symptoms and indications that are extremely similar to those of seizures (PNES). [18]

Treatment of epilepsy

Although there is typically no cure for epilepsy, medicine can effectively manage seizures in roughly 70% of patients. More than 80% of people with generalized seizures can be adequately managed with medication, compared to just 50% of those with focal seizures. The quantity of seizures that take place within the first six months is one indicator of long-term results. Generalized seizures, a family history of epilepsy, psychological issues, and waves on the EEG that suggest generalized epileptiform activity are additional variables raising the chance of a bad result. [19]

First aid

It is a medical emergency known as status epilepticus if a seizure lasts longer than five minutes or if there are more than two seizures in an hour without restoration to a normal level of awareness in between them. A nasopharyngeal airway may be necessary for this situation to keep the airway open and safeguarded. At home, midazolam given orally is advised as the first treatment for prolonged seizures. Using diazepam rectally is another option. Intravenous lorazepam is favored in hospitals. Other drugs like phenytoin are advised if two doses of benzodiazepines are ineffective. [20]

Medications

Anticonvulsant drugs are the cornerstone of epilepsy therapy, sometimes for the rest of the patient's life. The kind of seizure, epilepsy syndrome, other drugs used, other health issues, age, and lifestyle of the patient are all taken into consideration when selecting an anticonvulsant. The first agent is successful in around half of cases; a second single agent is helpful in about 13% of cases, and a third or two agents working together may be helpful in another 4% of cases. About 30% of patients still experience seizures after receiving anticonvulsant medication. [21]

Table 1: Major advantages and disadvantages of potential first-line antiepileptic drugs

Drug	**Advantages**	**Disadvantages**	**Selected important adverse effects**
Carbamazepine	Efficacious against focal seizures, extensive experience, mood stabilizer, low cost	Enzyme inducer; can aggravate absence and myoclonic seizures	Hypersensitivity reactions, cardiac conduction abnormalities
Gabapentin	Virtually devoid of drug interactions, relatively well tolerated, effective in neuropathic pain	Relatively modest efficacy, restricted to focal seizures; can precipitate myoclonic seizures	Weight gain
Lamotrigine	Efficacious against focal and most generalised seizure types, devoid of enzyme inducing properties, effective in bipolar depression	Requires slow titration; dosing requirements affected by interactions with valproate, enzyme inducers, and oestrogens; can aggravate severe myoclonic epilepsy of infancy	Rash and other hypersensitivity reactions
Levetiracetam	Efficacious against focal, myoclonic, and primarily generalized tonic–clonic seizures; virtually devoid of drug interactions; relatively well tolerated	Higher cost than most other antiepileptic drugs	Irritability, mood changes
Oxcarbazepine	Similar to carbamazepine in efficacy profile, with lower risk of skin rashes and lower enzyme induction potential	Reduces blood levels of oral contraceptives; can aggravate absence and myoclonic seizures	Rash and other hypersensitivity reactions; hyponatraemia more common than with carbamazepine
Phenobarbital	Efficacious against focal and most generalized seizure types, extensive experience, once daily dosing.	Enzyme inducer; can aggravate absence seizures	Cognitive and behavioral adverse effects

Phenytoin	Efficacious against focal seizures, extensive experience, low cost	Enzyme inducer, variable and dose-dependent kinetics; can aggravate absence and myoclonic seizures	Rash and other hypersensitivity reactions; connective tissue and cosmetic adverse effects

There are several medications available, such as phenytoin, carbamazepine, and valproate. According to the available data, valproate, carbamazepine, and phenytoin may all be equally effective in treating both focal and generalized seizures. Compared to rapid-release carbamazepine, controlled-release carbamazepine may have milder side effects.. Recent research has shown that Cicuta virosa and Nux vomica have strong anti-epileptic effects with no harmful side effects. For a sizable portion of the population, this may prove to be highly beneficial. Due to concerns about cost and side effects, levetiracetam and valproate are indicated as second-line therapy for focal seizures in the United Kingdom after carbamazepine or lamotrigine. Lamotrigine is the second-line medication for generalized seizures, with valproate being the first. Valproate is especially helpful in myoclonic seizures and tonic or atonic seizures, hence it is advised for those with absence seizures in addition to ethosuximide. [22]

Numerous commonly prescribed drugs, including phenytoin, carbamazepine, phenobarbital, gabapentin, and valproate, have been linked to an increased risk of birth abnormalities, particularly when used during the first trimester. Despite this, once therapy is effective, it is frequently continued since it is thought that the danger of leaving epilepsy untreated is greater than the risk of the drugs. Levetiracetam and lamotrigine appear to have the lowest risk of passing on birth abnormalities when compared to other antiepileptic drugs. Some people who have not had a seizure in two to four years may be able to gradually cease taking their medications. [23]

Table 2: Branded and generic oral antiepileptic medicines available in market

Sl. No.	**Active moiety**	**Branded**	**Formulation**	**Generic registered**
1	Carbamazepine	Tegretol Tegretol CR	IR, tablet, suspension CR, tablet	Yes Yes
2	Clobazam	Frisium	IR, tablet	No
3	Clonazepam	Rivotril	IR, tablet	No
4	Diazepam	Stesolid, Valium a.o.	IR, tablet	Yes
5	Ethosuximide	Ethymal	EC, capsule, IR, suspension	No
6	Felbamate	Taloxa	IR, tablet, suspension	No
7	Gabapentin	Neurontin	IR, capsule, tablet	Yes
8	Pregabalin	Lyrica	IR, capsule	No
9	Oxcarbazepine	Trileptal	IR, tablet, suspension	Yes
10	Phenobarbital	Luminal, Phenobarbital	IR, tablet	Yes

11	Phenytoin	Diphantoine	IR, tablet	No

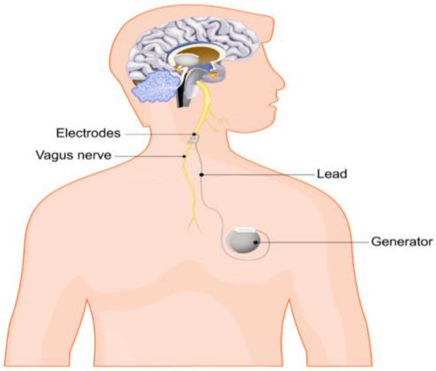
Surgery

For those with focal seizures that persist after prior therapies, epilepsy surgery may be a possibility. At least two or three drugs have been used as part of these additional therapies. Total seizure control is the aim of surgery, and in 60–70% of instances, this is accomplished. Common operations include removing malignancies, removing sections of the neocortex, and removing the hippocampus via an anterior temporal lobe resection. Instead of treating the disorder, some operations, including a corpus callosotomy, are tried to reduce the number of seizures. [24]

Neurostimulation

Patients with drug-resistant epilepsy who are not candidates for respective surgery can use neurostimulation as palliative therapy. With more than 70 000 patients treated globally over the past 15 years using vagus nerve stimulation, it is the most popular method. Consistent outcome statistics across centers and nations demonstrate that more than half of patients treated with this method have a seizure reduction of 50% or more. However, less than 5% of people who get this therapy are seizure-free. The epilepsy therapy known as responsive neurostimulation (RNS) doesn't involve the surgical removal of brain tissue. In a manner similar to how a pacemaker recognizes and manages irregular heart rhythms, RNS employs an implanted device to aid in the prevention of seizures before they start. [25]

Fig 2: Vagus nerve stimulation



Transcutaneous stimulation of the vagus and trigeminal nerves are two novel approaches that have produced good outcomes but need to be confirmed in more studies. Deep brain stimulation is only used in cases of severe epilepsy. Two randomized studies looked at the effects of responsive cortical stimulation, in which a closed-loop implanted device administers an electrical stimulation to detect abnormal electro-corticographic activity and chronic stimulation of the anterior nucleus of the thalamus. [26]

Conclusion

The understanding of the epidemiology of epilepsy has advanced significantly. The projected 6 per 1,000 population median lifetime prevalence rate is lower than that of comparable emerging regions. However, there are a lot of patients in the area who are afflicted, and most of them are either poorly understood or undocumented. There are few statistics available regarding incidence, mortality (especially in the elderly), the lack of effective treatments, public perceptions and attitudes, patient concepts of disease, and help-seeking behavior. Despite significant variation across research, false-positive epilepsy diagnoses are frequent. The strategies for detecting focal and generalized epileptic seizures are highlighted in this comprehensive study. EEG signals may be efficiently used to research brain disorders and mental states. The EEG signal has a number of intrinsic problems due to its complex and subjective visual interpretations as well as the fact that it is very nonlinear in nature. For individuals with medically resistant epilepsy who are not surgical candidates, neurostimulation has emerged as a novel therapy option that may enhance quality of life and occasionally be curative. Pharmacogenetic research holds up the possibility of better individualizing treatment for every patient, with the potential for maximum benefit and the least amount of danger of negative consequences. We think that what goes on daily in the treatment of people with epilepsy deserves the most focus.

Acknowledgements

The authors express their sincere gratitude to Sharad Chandra Pawar College of Pharmacy, Pune for providing facilities to complete this review article.

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