Journal of PharmaSciTech
2012; 1(2):20-26
Review Article

Epilepsy and its Management: A Review

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Abstract

Now-a-days, people are facing various kind of stress in the fast daily life and most of the people in the world are suffering from various neurological disorder. Epilepsy is one of the most common neurologic disorders of the brain, affecting about 50 million individuals worldwide and 90% of them are from developing countries. Genetic factors as well as infection in brain, stroke, tumor and high fever cause epilepsy. It imposes a large economic burden on health care systems of countries associated with stigma and discrimination against the patient and even his/her family in the community, workplace, and school and home. Many patients with epilepsy suffer severe emotional distress, behavioural disorders and extreme social isolation. There are many seizure types and different mechanisms by which the brain generates seizures. The two hallmarks of seizure generation are hyperexcitability of neurons and hypersynchrony of neural circuits. A large variety of mechanisms alters the balance between excitation and inhibition to predispose a local or widespread region of the brain to hyperexcitability and hypersynchrony. The objective of the review is to discuss history, epidemiology, etiology, pathophysiology, classification of epilepsy, symtomps, diagnosis, management of epilepsy and its future trends.

Keywords: Anti-epileptic drugs, pathophysiology, seizures, epidemiology, hypersynchrony

Introduction

Epilepsy affects up to 1% of the population, making it second to stroke as one of the most common serious neurologic disorders.[1] About 50 million people world wide have epilepsy and 90% of them are from developing countries.[2] In the past several years, our understanding of epilepsy has increased in several respects. It is a common chronic neurological disorder in which the balance between cerebral excitability and inhibition is tipped toward uncontrolled excitability and characterized by recurrent unprovoked seizures.[3-5] There is now clear evidence that there are distinct differences between the immature and mature brain in the pathophysiology and consequences of seizures. It is a collection of many different types of seizures that vary widely in severity, appearance, cause, consequence and management.[6] The seizures are associated with characteristic signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain.[7] Epileptic seizures often cause transient impairment of consciousness leaving the individual at risk of bodily harm and often interfering with education and employment. It is universal, with no age, sex, geographical, social class or racial boundaries[8]. Epilepsy is more likely to occur in young children or people above 65 years of age; however it can occur at any time.[9] Epilepsy is not a single disorder but a syndrome with vastly divergent symptoms, involving episodic abnormal electrical activity in the brain. All epilepsy syndromes are not life long-some forms are confined to particular stages of childhood. Conventional treatment of epilepsy consists primarily of anticonvulsant medications. However, over 30% of people with epilepsy do not have seizure control even with the best available medications.[10-11] Although these drugs often control or reduce the frequency of seizures, some patients show little or no improvement and therefore surgery may be considered in difficult cases. Therapy is symptomatic in that available drugs inhibit seizure but neither effective prophylaxis nor cure is available. Compliance with medication is a major problem because of the long term therapy together with unwanted effects of many drugs.[12] The purpose of this overview is to provide general considerations and management of epilepsy.

History of epilepsy

The word epilepsy derived from the Greek work 'epilepsia' which means 'to take hold of'[13] which in turn was combined form 'epi' means upon and 'lambanein' means to take. In-ancient time's epilepsy was connected with religions faint or ever a possession by a demon. In the past epilepsy was considered as the sacred disease in support of this view a large number of people believed that epilepsy affected people who to some extent taken hold of by demons or that the visions experienced by the epileptic people were sent by the Gods. Even among the animist Hmong generations, for instance, epilepsy was considered as an attack by a demonic spirit, but the affected person could become revered as a shaman through there explicit experiences.

Reference may be made that in most cultures peoples having

epilepsy have been looked down upon and even they were kept confined to jail; in the Salpetriere, the birth place of modern neurology, Jean-Martin Charcot observed that the epileptic people all nothing but mentally retarded, as they affected by chronic syphilis or criminally insane. As with other parts of Africa, in Tanzania, even to day people believed that epilepsy is connected with evil spirits, witchcraft or poisoning or to be contagious.[14] Roman people believed that epilepsy was god sent curse and was known as Morbus comitialis (disease of the assembly hall).

Even to day stigma continues but the people understand that it is gradually decreasing with time at least in developed countries. Hippocrates remarked that it will not take much time to eradicate the menace of epilepsy as it is not divine.[15]

Epidemiology

Epilepsy is one of the most common of the serious neurological disorders.[16] It is estimated that there are 55 lacks persons with epilepsy in India, 20 lacks in USA and 3 lacks in UK.[17] Each year 120 per 100,000 people in the United States come to medical attention because of a newly recognized seizure. At least 8% of the general population will have at least one seizure and not have epilepsy. The rate of recurrence of a first unprovoked seizure with in 5 years ranges between 23% and 80%.6 The age adjusted incidence of epilepsy is 44 per 100,000 people in a year. Each year about 125,000 new epilepsy cases occur; of these, 30 % are in people younger than age 18 at the time of diagnosis. The relatively high frequency of epilepsy in the elderly is now being recognized. At least 10 % of patients in long- term care facilities are taking at least one antiepileptic drug (AED).[6]

The National Sentinel Audit of Epilepsy-Related Deaths led by 'Epilepsy Bereaved' drew attention to this important problem. The Audit revealed; "1,000 deaths occur every year in the U.K. as a result of epilepsy" and most of them are associated with seizure and 42% of deaths were potentially avoidable.[18]

Causes of epilepsy

The cause of epilepsy is completely unknown. The word epilepsy does not indicate anything about the cause or severity of the person's seizures, some cases of epilepsy are induced by genetic factors, but it can also result form brain injuries caused by blows to the head, stroke, infections, high fever or tumors.[19] It has been observed that heredity (genetics) play an important role in many causes of epilepsy in very young children, but it can be a factor for people of any age. For instances, not everyone who has a serious head injury (a clear cause of seizures) will develop epilepsy.[7]

Certain epilepsy syndromes termed as reflex epilepsy need specific precipitants or trigger for seizures to occur like reading, flashing lights and precipitants like emotional stress, sleep deprivation sleep it self, heat stress, alcohol and febrile illness are examples of precipitants cited by patients with epilepsy. Notably the influence of various precipitants varies with the epilepsy syndrome.[20] The menstrual cycle in epileptic women can influence patterns of seizure recurrence, catamenial epilepsy in the seizure linked to the menstrual cycle.[21] There are different causes of epilepsy that are common in different age groups;

1. In neonatal period and early infancy, the most common causes are hypoxic–ischemic encephalopathy, CNS infections, trauma, congenital CNS abnormalities and metabolic disorder.

2. In late infancy and early childhood, the most common febrile seizures may be caused by CNS infections and trauma.

3. In child hood well defined epilepsy syndromes are generally observed.

4. In adolescence and adult hood the causes are more likely to be secondary to any CNS lesion.

5. In old persons, cerebrovascular disease is the most common cause, the other causes, includes CNS tumors, head trauma and other degenerative diseases like dementia.[22]

Pathophysiology of epilepsy

Seizures are paroxysmal manifestations of the cerebral cortex. A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces with in the network of cortical neurons. The basic physiology of a seizure episode is detected to in an unstable cell membrane or its surrounding/adjacent supportive cells. The seizure originates from the gray matter of any cortical or subcortical area. Initially a small number of neurons fire abnormally. Normal membrane conductance and inhibitory synaptic current breakdown and excess excitability spread either locally to produce a focal seizure or more widely to produce a generalized seizure. This onset propagates by physiologic pathways to involve adjacent to remote areas.

As abnormality of potassium conductance, a defect in the voltage-activated ion channels, or a deficiency in the membrane ATPases linked to ion transport may cause neuronal membrane unstable and cause a seizure. Certain neurotransmitters (e.g. glutamate, aspartate, acetyl choline, norepinephrine, histamine, corticotropin releasing factor, purines, peptides, cytokines and steroid hormones) enhance the excitability and propagation of neuronal activity, whereas γ-amino butyric acid (GABA) and dopamine inhibit neuronal activity and propagation.

During a seizure, the demand for blood flow to the brain increases to carry off CO_2 and to bring substrate for metabolic activity of the neurons, as the seizure prolongs, the brain suffers more from ischemia that may result in neuronal destruction and brain damage.[6]

Mutation in several genes may be linked to some types of epilepsy. Genes that code for protein subunits of voltage-sensitive and ligand-activated ion channels have been associated with the generalized epilepsy and infantile seizure syndromes.[23]

One speculated mechanism for some forms of inherited epilepsy are mutation of the genes which code for sodium channel proteins; these defective sodium channels remain open for long time and causing the neurons hyper excitable as a result glutamate an excitatory neurotransmitter may be released in large amount form the neurons which by binding with nearby glutamanergic neurons-triggers excessive calcium (Ca^2+) release in the post synaptic cells which may be neurotoxin to the affected cells.[16]

Seizures

Table 1: International classification of epileptic seizures [24-25]

Types	Description
I. Partial Seizures (seizures begin locally)	A. Simple (without impairment of consciousness)
	1. with motor symptoms.
	2. with special sensory or soma to sensory symptoms.
	3. with psychic symptoms
	B. Complex (with impairment of consciousness)
	1. Simple partial onset followed by impairment of consciousness with or without automatisms.
	2. Impaired consciousness at onset – with or without automatisms.
	C. Secondarily Generalized (partial onset evolving to generalized tonic clonic seizures)
II. Generalized seizures (bilaterally symmetrical and without local onset)	
III. Unclassified Seizures	
IV. Status epileptics	

The different types of seizures are given in Table 1 and here is the brief description of the seizures.

I. Partial seizures

In simple partial seizures (cortical focal epilepsy) the seizure focus in the motor context results in attacks consisting of repetitive convulsion of particular muscle group. The patients lose voluntary control of the affected parts of the body without losing consciousness.

In complex partial seizure, discharge begins locally and often remains localized. The symptoms include involuntary muscle contractions, abnormal sensory experiences or autonomic discharge or effects on mood and behavior, often termed psychomotor epilepsy. The seizure focus is located in the temporal lobe.[26]

Secondarily generalized attack, in which a partial seizure immediately precedes a generalized tonic-clonic (grandmal) seizure.

II. Generalized seizures

Generalized seizures involve the whole brain, including the reticular system and thereby produce abnormal electrical activity throughout both hemispheres. Immediate loss of consciousness is characteristic of generalized seizures.[27] Absence seizure (petitmal) is prevalent in children associated with momentary loss of consciousness but no muscular component or little bilateral jerking (from eye lid blinking to more extensive clonic body movement.[28] It is usually characterized by 3 to 30 seconds of unconsciousness or diminished consciousness.[29] Myoclonic seizures are epileptic seizures in which the motor manifestation is myoclonus. Clonic seizures are characterized by loss of consciousness, autonomic symptoms and rhythmic clonic characters of all muscles. Tonic seizures are associated with loss of consciousness and autonomic symptoms accompanied by tonic contractions of the limbs.[30] Tonic-clonic seizure (grandmal) consists of an initial strong contraction of the whole body muscles causing a tonic spasm. Respiration stops and defecation, micturation and salivation often occur this tonic phase lasts for one minute and is followed by a series of violent, synchronous convulsion. The patient remains unconscious for few minutes and then gradually recovers, feeling ill and confused.[27] Atonic seizure (akinetic) is associated with unconsciousness with relaxation of all muscles due to excessive inhibitory discharges, patient may fall down.[30] Infantile Spasm (hypsarhythmia) related to intermittent muscle spasm and progressive mental deterioration.

III. Unclassified category

A third unclassified category covers undetermined epilepsy and epileptic syndromes. Special syndromes include conditions such as febrile convulsion in which seizures are related to specific situations. Around 2 to 4% of children experience a convulsion associated with a fabric illness. Only 2 to 3% of these children become epileptic in later years. This is a six fold increase in risk compared with general population. Several factors are associated with an increased risk of developing epilepsy-pre-existing neurological disorder or developmental delay, a family history of epilepsy or a complicated febrile seizure. For children at high risk of developing recurrent febrile seizures and epilepsy, rectally administered diazepam at the time of fever may prevent recurrent seizures and avoid side effects of chronic therapy.[12]

IV. Status epilepticus

Status epilepticus may be defined as a prolong seizure , or a period of repeated seizure with out restoration of normal consciousness in between, lasting for more than 30 minutes, although the

prolonged and repeated seizure activity lasting more than 5 to 10 minutes can be considered as status epilepticus and requires treatment. Any type of seizure can lead to status epilepticus but generalized tonic clonic status epilepticus is the most common and dangerous type.

Initial treatment consists of supporting respiration and maintaining blood pressure. Then antiepileptic treatment may status with diazepam I.V. or as rectal solution followed by phenytoin (or alternatively phenobarbitone clomethearate or paraldehyde) to prevent recurrence. Once seizure is controlled phenytoin sodium may be given I.V. with monitoring of blood pressure and ECG. If the measures do not control seizure, anesthetics, like short acting barbiturate, such as thiopental should be given and the patient should be ventilated. Children may exhibit behaviors similar to epileptic seizures but are not caused by epilepsy. These include:

1. In attentive staring.

2. Benign shudders (children below age 2 years, usually when they are tired or excited).

3. Self gratification behaviors (nodding, rocking, head banging).

4. Conversion disorder (flailing and jerking of the head). Conversion disorder can be differentiated from epilepsy because the episodes never occur during sleep and do not involve incontinence or self injury.

Symptoms of seizure

The seizure is the characteristic event in epilepsy associated with the episodic high frequency discharge of impulses by a group of neurons in the brain. The clinical signs and symptoms of seizure depend on the location of the epileptic discharges in the cortex and the extent and pattern of the propagation of the epileptic discharge in the brain. e.g. involvement of the motor cortex causes convulsions, hypothalamus causes peripheral autonomic discharge and the involvement of the reticular formation of the upper brain stem leads to the loss of consciousness [(27)].

Diagnosis

A number of different tests have been developed to determine the epilepsy in an individual and its type.

EEG Monitoring: Electron encephalogram is very useful in the diagnosis of various seizure disorders. The EEG may be normal in some patients who still have the clinical diagnosis of epilepsy even many people having no epilepsy show some unusual brain activity on EEG video monitoring is often used in conjunction with EEG to determine the nature of a person's seizures.

Brain Scan

It is an important diagnostic tool, which is useful for identifying brain tumors, cysts, and other structural abnormalities in brain. The most commonly used brain scans include CT (computed tomography), PET (positron emission tomography) and MRI (magnetic resonance imaging) SPECT (single photon emission computed tomography) MRS (magnetic resonance spectroscopy). CT & MRI scans reveal the structure of the brain. PET and MRI can be used to monitor brain's activity and detect abnormalities. SPECT used to locate seizure foci in the brain.

MEG (magneto encephalogram) detects the magnetic signals generated by neurons. MRS can detect abnormalities in the brain's biochemical processes.

Medical History

Medical history including symptoms and duration of the seizures helps in determining epilepsy and kind of seizures present in the person.

Blood Tests

Seizures are occasionally causes by an acute underlining toxic or metabolic disorders in which case appropriate therapy should be directed the specific abnormality e.g. hypocalcaemia. Blood samples are often screened for metabolic or genetic disorders that may be associated with the seizures. Blood samples are also tested for the problems such as infections, lead poisoning, anemia and diabetes that may be causing or triggering the seizure.[31]

Management of Epilepsy

The terms anticonvulsant and antiepileptic are used inter changeably. An anticonvulsant is an agent that blocks experimentally produced seizures in laboratory animals and antiepileptic drug is a drug used medically to control the epilepsies.[32]

Principles of management [33]

1.Any causative factors of epilepsy must be treated, e.g. cerebral neoplasm.

2.The patients should be educated about the disease, duration of treatment and need for compliance.

3.Precipitating factors should be avoided, e.g. alcohol, sleep deprivation, emotional stress.

4.Natural variation should be anticipated, e.g. fits may occur particularly or exclusively around periods in women.

5.Antiepileptic drug should be given only if seizure type and frequency require it, i.e. more than one fit every 6-12 months.

The antiepileptic drugs have been classified as follows in Table 2 and Table 3 and the important pharmacokinetic parameters are tabulated below (Table 4):

Table 2: Classification of drugs used in the therapy of epilepsies[34]

Seizure type	Conventional anti-seizure drug	Recently developed anti-seizure drug
I. Partial seizures		
(i) Simple partial	Carbamazepine Phenytoin Phenobarbital	Gabapentin Lamotrigine

Seizure type	Conventional anti-seizure drug	Recently developed anti-seizure drug
	Primidone Valproate	
(ii) Complex partial	Carbamazepine Phenobarbital Phenytoin Primidone Valproate	Gabapentin Lamotrigine
(iii) Partial with secondly generalized tonic clonic seizure	Carbamazepine Phenobarbital Phenytoin Primidone Valproate	Gabapentin Lamotrigine
II. Generalized seizure		
(I) Absence Seizures	Clonazepam Ethosuximide Valproate	
(ii) Myoclonic Seizure	Valproate	
(iii) Tonic-clonic Seizure	Carbamazepine Phenobarbital Phenytoin Primidone Valproate	

Table 3: Chemical classification of antiepileptic drug[28]

Chemical Class	Examples of antiepileptic drug
Barbiturates	Phenobarbitone, Mephobarbitone, Primidone
Hydantoins	Phonations, Mephenytoin
Iminostilbene	Carbamazepine
Oxazolidinedione	Trimethadione (Troxidone)
Succinimide	Ethosuximide
Aliphatic Carboxylic acid	Valproic acid (Sodium valproate)
Benzodiazepines	Clonazepam, Diazepam
Acetyl urea	Phenacemide
Newer drugs	Progabide, Vigabatrin, Gabapentin Lamotrigine, Felbamate, Topiramate, Tiagabine
Miscellaneous	Acetazolamide, Dexamphetamine

Mechanism of action of antiepileptic drugs [27, 33]

Antiepileptic drugs may act mainly by one of three main mechanisms: (i) reducing electrical excitability of cell membranes, particularly (by blocking) the voltage dependent sodium channels which are responsible for the inward current that generates an action potential; (ii) enhancing GABA mediated synaptic inhibition, by inhibiting GABA transaminase or by drugs with direct GABA agonist properties; the result is increased membranes permeability to chloride ion, which reduces cell excitability; (iii) inhibiting T-type calcium channels (important in controlling

Table 4: Pharmacokinetics of commonly used antiepileptic drugs

Drug	T_{max} (h)	Protein binding (%)	t ½ (h)	Therapeutic level (μg/ml)	Active metabolites	Major inactive metabolites
1. Phenobarbitone	1-6	48	96	15.25	None	P-hydroxy Phenobarbitone
2. Carbamazepine	6-12	75	18.7 (Chronic)	4-12	10,11- Epoxite	10,11-transdihydroxy derivative
3. Sodium Valproate	0.5-4	90	7-12	50-100	—	Oxidative derivatives
4. Phenytoin	4-12	92	9-140	10-20	None	P-Hydroxy phenytoin
5. Primidone	0.5-9	15	15.6	4-12	Phenobarbitones & PEMA	P-hydroxy phenobarbitone
6. Clonazepam	1-3	82	30	0.15-0.3	3-hydroxy-clonazepam	7-amino-clonazepam
7. Ethosuccimide	1-2	Negligible	60	50-100	None	Hydroxyderivatives

Note: T_{max} indicates time to reach peak serum level after oral dose, Vd is apparent volume of distribution, $t_{1/2}$ signifies elimination half life of drugs

absence seizures) or by inhibiting excitatory neurotransmitters. e.g. glutamate. Some common contraindications are as follows:

Epilepsy and oral contraceptives[33]

Some antiepileptic drugs (Carbamazepine, phenytoin, barbiturates, topiramate, Oxcarbazipine) induce steroid metabolizing enzymes and can cause hormonal contraception to fail. Therefore the patients taking antiepileptic drugs require a higher dose estrogen–containing oral contraceptive (50mg / day).

Pregnancy and epilepsy[33]

The management of epilepsy during pregnancy may present problems for both the mother and fetus. The incidence of spontaneous abortion and still birth increases in women with epilepsy. Therefore patients should have their seizure disorder properly inves' gate and treated before pregnancy with lowest dose of the developing fetus because of the possibility of anoxio and metabolic disorder. Minor seizures are probably harmless and therefore need not be eradicated; patients should be advised for taking folic acid supplement and vitamin K orally. Because some antiepilertic drugs affect folic acid metabolism and folic acid deficiency is a risk factor for neural tube defects. Hepatic enzyme inducing antiepileptic drugs lower the mother's concentration of vitamin K, which can aggravate any post partum hemorrhage.

Breast feeding[30]

Antiepileptics are generally distributed into breast milk, in low concentration and breast feeding is considered safe when given in usual doses, with the exception of the barbiturates and ethosuximide. Problems of neonatal sedation may occur with the benzodiazepine and barbiturate and ethosuximide is distributed in significant amounts into breast milk and therefore breast feeding should be avoided.

Epilepsy in children[33]

Fits in children are treated as in adults, but children may respond differently and because irritable e.g. with sodium valproate or phenobarbitone. If febrile convulsions have occurred a drug used for major epilepsy may be given continuously (e.g. phenobarbitone 3-4 mg /kg /day) until the child is 5 years old. But prolonged drug therapy e.g. with phynytoin or phenobarbitone may interfere with cognitive development, the drug is withdrawn.

Conclusion

Thus, the selection of an anticonvulsant agent is based primarily on its efficacy for specific types of seizures and epilepsy. Although seizure control is generally good in most patients, a significant proportion of patients with epilepsy suffer from intractable or drug-resistant epilepsy, despite early treatment and an optimum daily dosage of an adequate anticonvulsant agent. There is thus a need for new drugs with a greater benefit as related to side effects and tolerability, even at the expense of efficacy, when compared to the existing antiepileptic agents.

Although many treatments are available, much effort is being devoted to novel approaches. Many of these approaches centre onelucidating the genetic cellular and molecular mechanism of the hyperexcitability, insights that promise to provide specific targets for novel therapy.

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