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A COMPREHENSIVE REVIEW ON EPILEPSY

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ABSTRACT

Epilepsy is commonly known as seizure-associated medical conditions either morbid or comorbid altogether. Although many different procedures were determined for diagnosing and treating epilepsy using various methods. It is still very difficult to diagnose the exact causative path for an epilepsy occurrence. Thus, understanding epilepsy with its classifications, different pathophysiologies have helped researcher to target-selective drugs against epilepsy. Thus, this article defines epilepsy with different classes of anti-epileptic drugs describing their advantages and disadvantages of their applications.

KEYWORDS: Epilepsy, Anti-epileptic drugs, Pathophysiology, ILAE

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INTRODUCTION

As per ILAE (International League against Epilepsy), "Epilepsy is short-term event consists of distinct signs and symptoms involving idiosyncratic nerve activities in CNS causing abnormal behaviour and action." It is often identified by transitory tendency of brain causing once or repetitive seizures either involving psychological, neurobiological or social repercussions. Recently, ILAE stated a new definition of epilepsy for clinical use which can be considered if any of the following situations experienced by patients:

(a) Minimum occurring of two outrageous reflective seizures with 24 hours of interval.

(b) At least one unrequited seizure having chances of occurring comparably related seizures following to the two motiveless seizures in the subsequent 10 years.

(c) Diagnostically identification of symptoms of seizures [1].

Helen E. Scharfman explains seizures and epilepsy are often considered same. Although there is difference between them. Epilepsy is stated as unexpected re-occurring seizure while seizure was elicited by different factors and they may not re-occur in patient. Epileptogenesis shows the gradual evolution of epilepsy in neuronal activity of brain.

In other words, various of activities which gradually evolves the conditions to generate seizures into normal brain activity. Thus, pool of neurons was supposed to be highly elevated leading to abnormal discharge of signals to generate seizures [2]. Alternatively, P. A. Dekker reported that seizures are caused by the excess amount of effusion from neurons in central nervous system. It is anticipated as instantaneous

unconventional body activities, commonly involves the conscious disturbance, unwanted muscle functioning or atypical sensitivity [3].

Etiology of Epilepsy

Although, epilepsy identification is mainly based on the symptom studies and remarks in electroencephalography. There are very few notable studies were presented to provide brief of causative agents or conditions to initiate seizure in person. This is mainly regarded due to statement stating that "epilepsy is an initial sign for major yet elemental neurological conditions." Epilepsy was sub-categorized based on their etiology in the recent data provided by ILAE Commission. Thus, Epilepsy was distributed in between genetic, structural/ metabolic, unspecified conditions.

On the basis of many distinct studies of patients, it has been concluded that these seizures were caused due to their genetic mutation as well as their acquired or provoking factors or either of them is found in the patient. In the survey study of Simon D. Shorvon, genetic mutations often resulted either in the pathological pathway disturbance or structural modification in the body. Sometimes, it was found to cause commonly molecular pathological adaptation which also involves the symptom categorized effects.

Alternatively, idiopathic seizures may cause bodily divergences, or adaptation or mutation of synaptic, membrane, neurotransmitter. Apart from this symptomatic epilepsy, there is a seizure without an identified pathologic or structural definition which cannot be distinguished any common clinical examinations like microscopic, histologic or neurological scopy. Thus, it is considered as unpredictable seizures.

Although this classified epilepsy is included recently, they cannot be pinpoint in the commission reports. These unknown causative agents for the generation of epilepsy have indicates that these inducing seizures does not trigger due to any known provoking conditions. Thus, the provoking factors do not cause any of these epilepsies. Excitation for epilepsy was created with either environmental or anatomic or from both factors, which were not majorly acknowledged importantly. This ignorance continues even after the facts found that were stating that many of the drug resistant seizures were occurred due to the provoking factors. Hence, treating or variation of these factors can help in treatment of seizures [4].

Epileptic Pathophysiology

S. Engelborghs in general, seizures occur with an excess of spontaneous or constant ejection of neurotransmitters from nerve cells. The key principle for all seizures is a constant increment in discharge of nerve excitation transmissions. These unwanted neuronal ejections were linked to various factors like trauma, depletion in oxygen level, tumours or lesions, infection and mutation in metabolic process. Although, there is no specified etiology or pathway for the occurrence of epilepsy [5].

Philip A. March Outwardly, in spite of having knowledge about the cerebrocortical physiology, it is still difficult to identify the source of Epileptogenesis process in the body [6]. Berkovic *et al.,* [5] Thus, for proper understanding of the pathophysiology of seizures (genetic & acquired), it is necessary to learn about the adaptive modification of brain processing for the whole life. This understanding of modification of neuronal cell is significant to identify the onset and offset of epilepsy [7].

Various neurobiological pathophysiological paths were identified as the key feature for the improper functioning of neurons. On studying these dysfunctioning, several specific biomarkers were identified which claim to be causing death at last. Thus, these condition diagnoses indicate that these biomarkers were responsible for causing health problems and mortality in the patients. Few of these mode actions were acknowledged to understand the pathophysiology of epilepsy.

Chronic Systemic Inflammation

These long-term inflammations were often caused due to the liberation of proinflammatory cytokines which were interconnected to the immune-related cells along with chronic stimulation of intrinsic immune system. These systemic inflammations are different from those acute inflammations. In this, serum C-reactive protein (CRP) is identified as biomarker for this inflammation. These systemic inflammations have shown their activities in the generation of epileptogenesis. Various CNS injuries like trauma, stroke, viral infection, febrile or status epilepticus created the probability for developing seizures. Occurrence of these type of

inflammation might create the proinflammatory conditions which might generate ictogenesis in the body. Theoretical data of causing epilepsy due to systemic inflammation can be considered due to the following incidence:

(i) Constant proinflammatory stimulus increment during epilepsy in epileptic foci.

(ii) Clinically specific targeting proinflammatory mechanical path after indications of epilepsy for more than few minutes or identifying the activity of antiepileptic drugs [7].

The initiation of epilepsy due to excitation caused by stimulation signalling from proinflammatory conditions or factors includes the gamma-aminobutyric acid (GABA) and glutamate receptors and by stimulus effect of different gene responsible for activity in synaptic plasticity. On some of studies, astrocytes and microglia have shown activities indicating their direct involvement in the developing epileptogenesis.

Oxidative Stress

During cellular metabolism process, many oxygen reactive species ejects chemicals like superoxide radical, hydrogen peroxide, hydroxyl radical and singlet oxygen. Discharge of these chemicals might show significant effects in between the epileptic process. Otherwise, it might be one of the factors which is indirectly contributing to molecular pathology of epilepsy. This oxidative stress is deliberated for causing hindrance in intracellular calcium homeostasis which resulted in enhanced excitation in nerve activity, vulnerability for seizures, susceptibility for unwanted stress and degeneration of nerve cells. On study, it has been observed that disruption in mitochondria activity is directly connected for creating oxidative stress which is responsible for the generation of acquired chronic epilepsy.

Methylation Capacity

Methylation is biochemical process for the transformation of methyl group i.e., CH_3 to targeted organic molecules in the body. This process is essential for the nucleic acid synthesis, deoxyribonucleic acid methylation, neurotransmitter formation, protein methylation, metabolism of homocysteine and for detoxification of liver occurring in the body. In different case study, it has been observed that unrequired alteration in methylation capacity specifically caused by homocysteine is defined as one of the factors in many distinct ill conditions which involves congenital birth defects, late pregnancy complications, neurodegenerative and psychiatric diseases, osteoporosis, and cancer [8].

Stages of Seizures

Generally, Seizures different phases were defined on the basis of duration of seizure occurrence in the body. In different articles, phrase ictal has been applied for determining seizure durations in the body. Thus, different stages of seizures can be explained as per the following:

Preictal or Prodrome Stage

This interval timing is before the seizure occurred in the body. This stage can last long from minutes to days resulting in abnormal behaviour of person. People who are able to identify this stage, often consider it as a warning signs for preparing counter measure over seizures. Although it makes the person dizzy and causes abnormal behaviour (smell, taste differently, ringing in the ear, feeling weird in stomach etc.) in the body. It is not helpful in defining accurate time of occurrence for seizure.

Ictal Stage

Ictal is defined as the undeniable seizure durations. During this phase, there is a definite alteration in the body. These seizures are basically created by the excess discharge of neuro-transmitters in the central nervous system. These ictal often causes a severe changes or movement which leads to dangerous conditions. On observation of these person with different medical devices during the ictal phase, various alterations in cardiovascular, metabolic and electro-encephalogram will be visible. Many of these diagnostic results during this stage help in determination of type and origin source of seizures which will be significant in treatment of epilepsy [9].

Interictal Stage

This phase involved the time interval in between the seizures. Many peoples having seizures, mostly involved temporal lobe epilepsy, have emotional agitations in the middle of seizures. These disruption ranges from slight fear to pathologically identified anxiety and depressions. Moreover, complication occurs within this phase are mainly causing more

problems and hard to control rather than seizures themselves.

Co/Interictal Stage

This is the final or end phase of epilepsy. It is described as the duration in which recovery process is loosed after the seizures. Its duration varies from minutes to hours depending on the category of seizure, experienced and intensity of seizures and time span taken by the seizure. In this stage, person experiencing seizures might feel tired and confused between different activities and also have the change in their emotional and conscious level. In few cases, signs and symptoms of this phase can guide the doctor to diagnose or identify the section of the brain responsible for seizure occurrence.

International Classification of Seizures

According to the ILAE commission, classification of seizures can be done as the following:

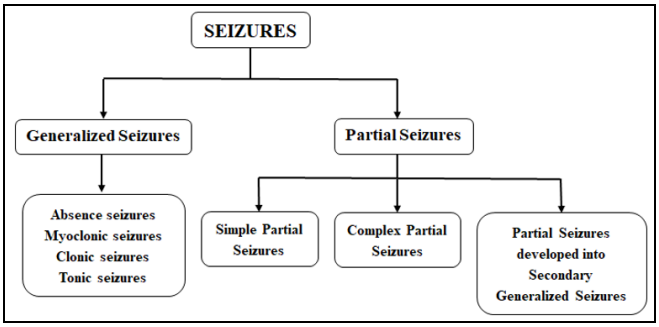

Figure 1: International classification of seizures

Apart from international classification, several other classifications of seizures depending on different factors like part of the brain involved in the epileptic process. People might observe single type of seizure or more than one type of seizure depending on the part of brain working for the generation of epilepsy. The seizure is generally differentiated in the following categories:

1. Generalized Seizures, influencing the whole section of the CNS.

2. Partial Seizures, influencing the specific section of the brain.

3. Non-Epileptic Seizures, provoked by the different factors (glycaemia, fever, stress, etc.) which are not related to epileptic generation.

4. Status Epilepticus, identified as continuous seizure which requires immediate attention for clinical treatments.

Generalized Seizure

Generalized seizure usually includes both section of central nervous system which can be sub-categorized into absence, atonic, tonic clonic and myoclonic seizures. These classified seizures were described below.

Absence Seizures

It is also known as petit mal seizure. These seizures generally occur more than one time a day with a time interval of 2 to 15 seconds. Sometimes. It was observed to happen around 100 times a day. They cause nondescript gazing by person having seizures. This absence seizure might be mistaken as daydreaming, anatomical automatism (lip spanking, limberness), during picking clothes or facial and body jerky movement. These seizures generally occurred in children within the age of 4 to 12-year-old and seldomly found at person more than 20 year of age.

Generalized Tonic-Clonic Seizure

This seizure is also identified as seizures or convulsive seizures or grand mal seizure. Mostly people think of this type of seizure, when discussing epilepsy or seizures. A person having seizures having tonic clonic seizures, he or she observed with spasmic condition in their arms and legs which is defines as tonic stage. While in clonic stage, person will be observed with limbs and head jerky movements. These stages might vary themselves on the basis of tonic-clonic phase experiencing by the person. At the time of seizure occurrence, person might be seen biting their tongues, ceasing or decrement in their breathing, sudden unrestrained movements. Depending on the person health condition, it can take minutes to hours for full recovery of the person.

Myoclonic Seizures

This seizure can be defined by the jerky movement of the body like twitching of arms or legs. These jerky movements were mostly observed during night time, when a person is asleep. Person having these seizures might feel them as the clumsy behaviour. Although requirement of first aid for this type of seizures is not necessary, person might need to visit the doctor for the identification the cause of seizure.

Atonic seizures

These seizures were also identified as drop attacks or astatic seizures or akinetic

seizures. Persons having seizures might experience shuffle behaviour during their body movements which cause the person to drop spontaneously or either to make the flop down or might collapse the person totally [6]. Due to the unique body movement in this type of seizures, it is considered dangerous for the person having it. Most important difficulty in this type is that they generally didn't respond to the epileptic drugs.

Partial Seizure

This type of seizures is mostly found in maximum quantity of people diagnosed for epilepsy. It generally affected a particular part of central nervous system which causes the seizures in the body. Commonly, it affected the single part of the brain which sometimes transfer to the other part of the brain. This type of seizure acted in altering the function of the body which is linked to epileptic causing part of the brain. Partial seizure usually affects the specific part of the brain. However, if this partial seizure develops which includes the whole part of the brain, then it can be diagnosed as partial secondarily generalized seizure.

During the ictal phase of partial seizure, person remains conscious. In few cases, person was observed having conversation and might remember the things occurred with them during seizure. Furthermore, partial seizure was sub-classified into the following categorization:

Simple Partial Seizure

In simple partial seizure, person will remain conscious and alert during the whole process of epilepsy. Although, he or she will not have any capacity to move and/ or to speak until that stage is completed. Part of body on which seizure occurs depend on the part of the brain involved. Depending the CNS part involved, person might experience either twitching, uncontrolled eye movement, hands or feets jerky movement or fast-continuous blinking. Most of the times, this seizure increases simultaneously depending on the intensity of seizures. This often initiated by the up-down of movement of hands which will developed into the movement of the arm. It might also involve the half section of the body movement in a definite pattern. If perception ability of the person is affected than person starts having hallucinations or illusions. Person begin to see or hear things which are not happening at that moment. These seizures start showing mild effects initially which gradually increases in their intensive effects.

Complex Partial Seizures

These type of seizures affects more than one part of the central nervous system which can show effects on the responsive behaviour of the person. They mostly commonly show pathological effects only on either one part of the temporal lobes present in the CNS. Thus, people who are vulnerable to this complex partial seizure is also known as temporal lobe epilepsy (TLE). Generally, when a person having seizures, he or she will be standing vacantly or thoughtlessly. They will not have any capacity to have interaction their surrounding work. These people might be chewing, unexplained mumbling, specific monotonous movements. They might also have combined basic or unsystematic movements[9].

Drug Therapy Treatment for Epilepsy

Bazil and Pedley [4] in spite of having neurological effects in CNS resulting in epilepsy, it has affected high number of populations. For the past many decades, with the help of understanding and acknowledgement of neurobiology and molecular pathophysiology of epilepsy, discovery of many advanced and improved antiepileptic agents is in applications. Recently, many discovery and identification of new epileptic drugs are showing effective results in treatment processes [10]. Thus, the following **Table 1** describes the various of drugs in applications against epilepsy.

Table 1: Structural Classification of AEDs Defining Their Targeted Type of Epilepsy and Their Adverse Effects [11]

Classes of Drugs	Drugs	Against for	Cons
Barbiturate	Phenobarbitone	Generalized tonic-clonic seizure (GTCS), Simple partial seizures (SPS), Complex partial seizure (CPS)	Causes sedations, Chronic administration creates abnormal behaviours, disturbance in memory and other psychological problems
Deoxy-barbiturate	Primidone	GTCS, Partial epilepsy	Might cause anaemia, leukopenia, unwanted psychotic reflections and increase size of lymph nodes.
Hydantoin	Phenytoin	GTCS, SPS and CPS	Causes foetal hydantoin syndrome, gum

			hypertrophy, disrupted behaviour, hallucinations, thrombosis, etc.
Iminostilbene	Fosphenytoin Carbamazepine Oxcarbazepine	GTCS, SPS and CPS	Causes vascular complications, damage in intima. Sedations, dizziness, vertigo, diplopia, ataxia. Hyponatraemia, hepatotoxicity
Succinimide	Ethosuximide	Absence seizures	GIT intolerance, tiredness, concentration disturbance, mood swings, drowsiness, headache
Aliphatic carboxylic acid	Valproic acid	Partial seizures, GTCS, absence seizures	Anorexia, alopecia, increase of weight and bleeding intensity, thrombocytopenia
	Divalproex		Hair loss, drowsiness, weight alterations, mood swings
Benzodiazepines	Clonazepam	Absence seizures, myoclonic seizures and akinetic seizures.	Sedations, dullness, loss of concentration, behaviour alterations, motor disturbance, ataxia.
	Clobazam	Partial seizures, Secondarily generalized tonic-clonic seizures, absence, and atonic seizures.	Sedations, lack of concentration, behaviour changes, motor functioning disturbance.
	Diazepam	Status epilepticus, febrile convulsions.	Sedation, psychomotor retardation, resistance tolerance development in chronic use
	Lorazepam	Status epilepticus, convulsions.	Less but local thrombophlebitis complications
Phenyl triazine	Lamotrigine	Absence seizure, myoclonic seizure, akinetic seizure, partial seizure, GTCS.	Dizziness, diplopia, ataxia, vomiting, rashes in children
Cyclic GABA analogues	Gabapentin	Refractory partial seizure with or without generalized, SPS and CPS.	Tiredness, dizziness, mild sedations, irregular functioning of body

CONCLUSION

Epilepsy is a common neurological disease characterised by irregular synchronous neuronal movements in the brain that are excessive. With or without a loss of consciousness, it is seen. In high income countries, the prevalence of epilepsy is 5-8 per 1000 population and 10 per 1000 population in low-income countries and even higher in rural areas. Epilepsy is a universal condition caused by sleep loss, systemic infection, possible external sensory stimuli and predisposed to all ages. Epilepsy is characterised by excessive excitatory neurotransmitter firing and reduced inhibitory neurotransmitter functionality. For the treatment of epilepsy, benzodiazepines, barbiturates, and ion channel modulators are favoured. If monotherapy does not control seizures, then polytherapy is recommended.

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CONFLICT OF INTEREST

None

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