Overview of epilepsy in context to its genetic basis, etiology, diagnosis and the possible treatments

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Abstract
Epilepsy is a neurological problem occurs due to the seizures formed in brain. It produces jerking in the whole body for short or for long time period. Epilepsy originated from a word Akkadian. Physical injuries and accidents can cause seizures. Brain tumor, injuries and brain infection are involved in causing isolated epilepsy. Abnormal activity in brain cortex can cause epileptic seizures. Fever also induces seizures in children’s. EEG helps to recognize the epileptic seizures. Brain tumor and stroke can cause death sooner in epileptic patient. Epilepsy can also cause changes in female, male hormones and arrhythmia. Adenosine is a chemical in body cells that lower down the risk of seizures. Many types of epilepsy have no cure but there are some surgeries present for the treatment of epilepsy.

Keywords: Anti-epileptic drugs; Epilepsy; Magnetic resonance imaging (MRI); Seizures; Sudden Unexpected death in epileptic patient (SUDEP); Vagus nerve simulation (VNS).

Introduction
Epilepsy is defined as in which neurological problems occur due to the seizures. Seizures are formed in result of epilepsy and produces jerking in the whole body for short or for long time period. Physical injuries and accidents are also involved in causing seizures. Brain injury, stroke and brain tumor are involved in causing isolated epilepsy [¹, ²]. Many epileptic drugs are present to treat Epilepsy. Treatments of epilepsy are different in different countries around the world. Main cause of epilepsy is not known. Epilepsy caused by stroke, any injury in brain, brain infection and genetically, this process also known as epileptogenesis. [³]. Abnormal activity in brain cortex can cause epileptic seizures [⁴]. Fainting and electrolyte imbalance also cause seizures in brain. Electroencephalogram helps in diagnosing the seizures and Epilepsy. Normal testing is not useful for the diagnoses of epilepsy [⁵]. 70% epilepsy is treated by drugs [⁶]. Epileptic drugs are in expensive and anti-seizures. Surgery also helpful for those patient who not get treated with drugs [⁷]. Many people recover from epilepsy. A study reported that 39 million people faced epilepsy in 2015 [⁸]. In developing countries, around 80 percent cases occurred. Another study reported that 1lac, 25 thousand deaths occur due to epilepsy in 2015 [⁹]. Epilepsy is more in old people and newborn in developing countries [¹⁰]. Old people will
face 5-10% of unprovoked seizures [11]. In many countries, there is restriction of driving by epileptic people until they become seizures free [12]. Disturbance in neuronal activity in brain is known as epileptic seizures. Epileptic seizure is defined as when seizures are formed in the brain and occur again and again. Epileptic seizures diagnosed when a person having unprovoked seizures [13]. Epileptic seizures diagnosed by EEG or imaging of brain [14]. According to previous studies, it has been observed that epilepsy is a spiritual state [15]. World's past explanation on the seizures due to epilepsy, originated from a word Akkadian, Akkadian was a language used in oldest Mesopotamia in 2000BC.

**Genetic bases**

In many epilepsy cases heredity plays a key role. Person having head injury doesn't mean he/she will get this disease. The person has more chances to develop epilepsy who having cases of epilepsy in his family. People with genetic history of epilepsy, has more chances to develop this disease than those who don't have any genetic history of epilepsy. Generalized epilepsy is known as when seizures start from both sides of the brain. This type of epilepsy is more due to genetic factors than focal and partial epilepsy. Many types of partial epilepsy which have been found in past years create link with genetics. More chances in developing epilepsy in brothers and sisters. Epilepsy will not also develop in some brothers and sisters. More chances of developing epilepsy in a brother or sister if the child suffering with generalized seizures. Remember, this disease is not communicable and people get it like cold. People with epilepsy, their children's didn't get it but if the genes are forwarded in families the chances will raise. In 100, less than 2 percent people get this disease at any point during the whole lifetime period. If mother has epilepsy and father doesn't, risk of epilepsy in children is less than 5 out of 100 and if father having epilepsy, the chances of epilepsy in children in higher. Many children will not get epilepsy from their parents, however chances of inheriting some kind of this disease is higher and if both parents suffering with this disease, chances is more higher of developing epilepsy in children [16].

**Seizures classifications**

Two types are involved in this first is basis classification and second is expanded classification. Both are different from one another shown in (Fig. 1). In Focal onset, seizures get starts on the single brain side. The face start spasm and the arm start moving. Person is awake and well aware of everything but didn't in the condition to control the seizures and after this person not remember anything. In Generalized seizures, many parts of brain are involved for developing seizures. Person in this case very less aware, that what is happening in the surrounding. Grand mal seizures also known as generalized tonic clonic seizures which fall in this category. The person didn't respond to anything if you shake or take your hand in his face. The person muscles became rigid and this phase is tonic. Its take few seconds and then gets serious and fast movement of his body, this phase is the clonic phase. It can last for few minutes. The jerking of body stops and the person comes back in his normal state. In generalized seizures person is more toward danger because he didn't well aware what’s happening in the surrounding and the chances of injury due to tonic clonic seizures is more because person can't protect itself [17].
Figure 1. Types of seizures

**Basic classification**
Seizures are also known as Focal which is old word that’s mean partial, generalized mean unchanged, unknown, and unclassified seizures shown in (Fig. 1). Behavior of a person and the EEG tells that when generalized seizures occur both hemispheres are activated. Unknown types of seizures mean when we don't know when seizure starts but other signs are known. Many conditions are not clear in unclassified seizures. Focal seizures are further divided into two types, first one is aware and the second is impaired also known as simple and complex respectively. In the basic classification, after knowing the percentage of awareness in focal seizures and also involvement of explaining the start of motor and non-motor, further classes with numbness leads to expanded classification. Focal to bilateral tonic clonic seizures are now known after the secondary generalized seizures. Tonic clonic or other motor are now classified into generalized motor seizures and beginning of unknown seizures also divided into tonic clonic or other motor.

**Expanded classification**
These types formed the basis of above described basic classification and types of motor and non-motor are further classified and expanded under focal, generalized and unknown seizures shown in (Fig. 2). Focal motor seizures are classified by knowing, and awareness impaired in time of seizures. Next stage of types comes from the symptoms and sign of seizures [18] ILAE classification of epilepsy focuses on the etiology of disease and every step of disease diagnosis that can be implied on every age. Clinician should be directed to recognize the patients’ epilepsy class as well as other syndromes. The patients who not fulfil the criteria of epilepsy classification should be described in seizures type. To identify, in which type of epilepsy a patient fall, he must fulfill the definition of epilepsy which was provided in 2014 [19]. As compared to seizures types, epilepsy types are wider and provide information about
genetic investigation, imaging, tests in laboratory, its prognosis and relationship with other disease. To know in which class the patient falls, use the types of seizures patient having and plot total to one of these 4 types. In Combined Generalized and Focal epilepsy there are epilepsy syndromes i.e. Darvet and Lennox Gastaut syndrome. Epilepsy syndrome is different from epilepsy type, it provides many characteristics like Verdict of EEG, imaging findings, age dependent characteristics, seizures types and prognosis provide more knowledge and information [21].

Figure 2. Types of epilepsy

Epilepsy diagnosis and its prevalence

An electroencephalogram helps to recognizing the epileptic seizures, the basic identification is based on the start of seizures. EEG provides pattern of brain waves and neuroimaging which is seen after CT scan or MRI. It helps to see the brain structure, which part of brain is working or not, in difficult cases monitoring of video and EEG may be very helpful [20]. Epilepsy is an endemic conditions effecting 50 million people around the world and it is reported that epilepsy takes important proportion for the world’s disease. The number of epilepsy in common population at a time is between 4 to 10 / 1000 people. 5 million people each year are diagnosed with epilepsy in the entire world. In well developed countries 49 out of 100000 people are recognized with epilepsy every year. In middle or low income class countries 139 out of 100000 people are diagnosed with epilepsy which is very high as compared to high income countries. In Neurocysticercosis, Injuries due to road accidents, birth related injuries; changes in medical infrastructure are involved. 80 percent people who live in middle income countries and low income countries are suffering from epilepsy. Epilepsy is more common in young children and old-age persons while seizures can form in any person of any age. In U.S 1 out of 100 people has been diagnosed with epilepsy. The chances of Epilepsy in the person for lifetime are is 1 out of 26. Seizures may form in many different areas of the world, in different age groups and different races. CDC reported that
3.4 million people in the U.S live with epilepsy and 4lac 70 thousand children suffering from this. This disease affects more that 65 million people throughout the world and it is the 4th common neurological condition. Epilepsy is more common in children of first year of their birth but a person with epilepsy becomes stable after the age of 10. The rate of epilepsy raises after age of 55 and it forms Alzheimer's disease, strokes and brain tumors. All these are caused by epilepsy after the age of 55 [22].

**Epilepsy effects on various part of body**

Memory affected by focal seizures. Common reason of memory issues in people who suffer with epilepsy is deformity in the frontal lobe and temporal lobe of brain. Left temporal lobe is important for verbal memories. If person suffering seizures in left side of brain, it may cause difficulties in remembering names, words etc. Right temporal lobe is important for visualization and for prospective memory frontal lobe plays an important role. The person who has seizures in the frontal lobe can cause many issues like to remember things which you want do in future. This condition is known as post ictal confusion. Anti-epileptic drugs also involved in memory issues. Memory issues also appear due to changes in drugs intake or high intake of medicine [23]. Activity of brain cells changed by epilepsy and these brain cells are known as neurons. In the form of electric impulses, these neurons are involved in message transfer. When any kind of changes in these impulses occur, it can cause seizures. As epilepsy is involved in brain changes, it also affect the body and it’s every part [24]. Arrhythmia will happen due to seizures. Arrhythmia is defined in which heart beat too fast or too slow due to seizures and the seizures also affects the normal rhythm of heart. Irregular heartbeat can be very dangerous and life threatening. Specialist thinks that sudden unexpected deaths in epilepsy are happened due to disturbance in heart rhythm [25]. A hormonal change occurs in the reproductive system of both male and female that has epilepsy. Epilepsy can affect the menstrual cycle of women and can cause irregular periods. Woman suffering with epilepsy has polycystic ovary disease. In women's sexual desire can be lower due to epilepsy and its medications. Level of testosterone, sexual desire, and the production of sperm in 40 % of epileptic man is low. Man's sex derives and sperm count can be reduced due to epilepsy drugs. Breathing regulated by autonomic nervous system. Breathing is temporarily stopped during seizures because seizures can affect the autonomic nervous system. There is low level of oxygen in this state and this can cause SUDEP [26].

Central nervous system is involved in sending messages from brain to the spinal cord and then to body in the form of electrical messages and epilepsy is the disease of central nervous system and if there are any changes in this system occur this can cause seizures. Voluntary and involuntary functions of nervous systems can have affected by epilepsy. Muscles become stretched and droopy due to seizures. Involuntary pull, spasm and rigidity of muscle in tonic seizures occur and unexpected muscle tone loss occurs in atonic seizures. Bones become weak due to intake of drugs during epilepsy. Risk of osteoporosis and fractures of bones is increased when you are suffering with epilepsy. Food movement in the digestive system also affected by seizures and can cause the following symptoms i.e. loss of bowel control, problem in breathing, vomiting, and nausea. Epilepsy can effect very part and system of body. Drugs and surgeries help to control seizures [27]. Different parts of human are affected by epilepsy shown in (Fig. 3).
Figure 3. Effects of epilepsy on different systems of the body

Seizures due to fever
In newborn babies and children, the main type of pathological activities of brain is the febrile seizures. Febrile seizures occur due to fever. 1 out of 20-50 children seizures start due to fever. Febrile seizures are also the main type of PBA (Pathological brain activity). Febrile seizures effects brain development [28]. Intractable epilepsy also associated with focal febrile and prolonged seizures [30]. For pediatricians and physicians who treat those people who suffering with epilepsy, there is area of interest in focusing these types of seizures their mechanisms and its results [31].

Mechanism of febrile seizures occurrence caused by fever as well as having genetic bases
Febrile seizures spread into the families and formed unpredictably epilepsy that’s why involvement of genetics for their initiate is also important to discuss. In a study, experiments were done in rodents and rodent produced seizures due to hypothermia [32]. In humans and rodent models, mutation in many ion channels were susceptible due to febrile seizures [33, 34]. Together, these mutation in chlorine and sodium channels have been well known. In an individual, single mutations of a gene also contribute to febrile seizures and various genes interconnection might involve in seizures occurrence [35]. Many cellular processes like neurons electrical activity affected by
temperature [36]. Many neuronal ion channels functioning depend upon temperature and also regulates the ionic currents. Raise in temperature could also increase the neuronal firing that can cause seizures. Condition of temperature rise is called hyperthermia and it can be produced due to hot baths and anticholinergic drugs. In children, measurement of temperature is not achievable. In rodents models it is confirmed that increased in brain temperature can starts the seizures. Hyperthermia inhibit changes in many mutated ion channels and increased the excitability of the circuits [37].

**Sudden Unexpected death in epileptic patient**

As compared to common population, risk of death in people with epilepsy is 1.6-3 [38]. The risk is more in children with epilepsy. Death may cause sooner in a person whose epilepsy is due to brain tumor, stroke or any other thing. The most common cause of death in epileptic patients is SUDEP. Sudden Unexpected death in epileptic patient is known as SUDEP. Death due to SUDEP is not linked with any kind of accidents. 1 person with epilepsy out of 1000 can experience this. More chances of SUDEP in those epileptic patients who have poor control on epilepsy. Surgery of SUDEP can cause 9 deaths out of 1000, mostly in children. Many cases report that SUDEP is seen at the time of death but the death causes are not known. Problem in breathing, irregularities in the rhythm of heart, brain conditions and any other problem in body parts [39].

**Epileptic patient’s life expectancy**

Oxford University and college U.K in 2013 reported that premature death as compared to whole community is 11 times high in epileptic patients. Due to mental health issues rate of death is more. By giving complete treatment for seizures 6 /10 patients recovered from seizures after few years of treatment and did suffer with seizures again. First medication for seizures will help 50 to 60 percent people to become seizures free and 11 to 30 people from 100 will be seizures free after 2nd medication for seizures. Uncontrolled epilepsy will remain in 25 people out of 100. Within 2 years, 74 out of 100 will be seizures free including children having onset seizures [40].

**Adenosine to control seizures**

It has been proposed that adenosine plays an important role in controlling of seizures [41]. It is also confirmed by many studies that adenosine reacts on different seizures models i.e. *in vivo* and *in vitro* and help in controlling seizures. A study done in which action of adenosine observed on the models of acute seizures. In these seizures models the adenosine linked with a receptor which is adenosine (Ado) type 1 receptors (A1Rs) [42]. In seizure models, which may be electrically or chemically induced, the insertion of adenosine in it produces an anticonvulsant action and stops seizures [43]. In the animals which are immature these actions are also seen and in the brain A1R linked anticonvulsant effects occur [44]. Anticonvulsant activities dismiss gradually due to repeated A1Rs activation. In the seizures suppression adenosine plays an important role and involved in the conversion of patterns of seizures into epileptics [45]. Adenosine is also involved in stopping events of seizure which is present already as well in the seizures prevention. In different models of epileptic seizures, actions of adenosine occur. In brain for the reduction of adenosine action, the intracranial A1R activation occurs in the specific parts of brain which is involved and responsible for the initiation of seizures [46].

**Possible treatments to cure epileptic patient**

Many types of epilepsy have no cure but a lot of surgeries are introduced which involve in stopping many types of seizures. Clinician advices the drugs to the epilepsy patient. If a
person doesn’t recover with drugs then surgery is done to get rid of epilepsy or stimulation of vagus nerve or by giving some special diet [47]. Antiepileptic drugs are taken orally and the medicine is prescribed by the doctor according to the condition of patient and its seizures type. In 70 percent cases, AEDs helps to control seizures. Many medicines are involved in the epilepsy treatment i.e. Lamotrigine, sodium valporate, lavetiracetam and carbamazepine [48]. These are some drugs with less side effects: Levetiracetam, Lamotrigine, Tiagabin, Felbamate, Topiramat, Gabapentin, Oxcarbazepine and Tiagabin hydrochloride. These drugs are easy to use with fewer side effects, there mechanism of action described in (Table 1). In 2018, CBD is formed which is cannabidiol, a typed of marijuana and it was approved by drug epidiolex, Cannabidiol is effectively treating severe seizures. 1980s MRI was first time introduced. For the internal structure images technique of MRI (magnetic resonance Ionization) was discovered which gives good images. In this technique, with the help of high resolution 30 ms-1s the brain’s functional activation is attainable [49, 50]. 31P MRS (magnetic resonance spectroscopy) and H are used for assessing metabolites [51]. High contrast images and high resolution also expand with the help of magnetic resonance. In hippocampus this gets an important role in which gray matter of hippocampus is measure as well as the T2 time of relaxation and the abnormalities in hippocampus. Layers of neuron in hippocampus are also disclosed [52]. EEG arrival is also associated with MR that provides vast knowledge and discoveries about epilepsy. GABA in vivo is also measured with the help of MRS [53]. In MR techniques, if there is no lesions of s2 MRI and s3 epilepsy seen, then a lot of imaging quality is also provided which is seen in this lesions [54]. Children with catastrophic epilepsy can cure with ketogenic diet. The anticonvulsant effects of the ketogenic diet on epileptic seizures are shown in (Fig. 4). 1/4 people control their epilepsy with this. This diet is a starvation diet. When a person starving and taking low calories brain starts burning ketones and doesn't burn glucose, when it burns ketones seizure stops, but using this diet growth of children is effected [55]. The advance technique to recognize seizures is SEEG (steroelectroencephlography). This is the safest method where there is sophisticated computer which measures 3-D brain map. In this technique electrodes are placed into specific brain area and record seizures. This technique helps to study deeper in the brain. Laser interstitial thermal therapy in which a laser is passed in the brain with the help of hole in skull that can damage those seizures producing a lot of heat in the tissues of brain.

Table 1. Anti-epileptic drugs and their mechanism of action

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>AEDs Drugs</th>
<th>Mechanism of action</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Cannabidiol</td>
<td>Modulation of neuronal excitability.</td>
</tr>
<tr>
<td>2</td>
<td>Diazepam</td>
<td>Bind to brain receptor &amp; increase the inhibitory effects of GABA.</td>
</tr>
<tr>
<td>3</td>
<td>Carbamazepine</td>
<td>Sodium channel blocker and prevent firing of action potential.</td>
</tr>
<tr>
<td>4</td>
<td>Brivaracetam,</td>
<td>Anticonvulsant effect in brain.</td>
</tr>
<tr>
<td>5</td>
<td>Lorazepam</td>
<td>Bind with benzodiazepine receptor &amp; enhance GABA inhibitory effect.</td>
</tr>
<tr>
<td>6</td>
<td>Ethosuximide</td>
<td>Inhibit sodium-potassium ATPase system.</td>
</tr>
<tr>
<td>7</td>
<td>Lacosamide</td>
<td>Enhance slow activation of voltage-gated sodium channel.</td>
</tr>
<tr>
<td>8</td>
<td>Felbamate</td>
<td>First anticonvulsant drug with inhibitory GABA brain mechanism.</td>
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<tr>
<td>9</td>
<td>Eslicarbazepine</td>
<td>Block voltage-gated sodium channel.</td>
</tr>
<tr>
<td>10</td>
<td>Levetiracetam</td>
<td>Modulate the synaptic neurotransmitter release.</td>
</tr>
<tr>
<td>11</td>
<td>Parampanel</td>
<td>Non-competitive AMPA-glutamate receptor antagonism.</td>
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</tr>
<tr>
<td>12</td>
<td>Phenytoin</td>
<td>Non-specific sodium channel blocker.</td>
</tr>
<tr>
<td>13</td>
<td>Phenobarbital</td>
<td>Act on GABA receptor, increase synaptic inhibition.</td>
</tr>
<tr>
<td>14</td>
<td>Oxcarbazepine</td>
<td>Bind to sodium channel and inhibit neuronal firing.</td>
</tr>
<tr>
<td>15</td>
<td>Tiagabine</td>
<td>Bind with recognition site that associated with GABA uptake carrier.</td>
</tr>
<tr>
<td>16</td>
<td>Valproate</td>
<td>Block voltage-gated channel.</td>
</tr>
<tr>
<td>17</td>
<td>Zonisamide</td>
<td>Block neuronal firing.</td>
</tr>
</tbody>
</table>

**Figure 1. Ketogenic diet’s effect on epileptic seizures**

In radiation method CT and MRI is used to measure the main points of seizures. Radiation is passes into the area of seizure and this help in destroying them. In electric stimulation method an electrode is thread in to the skull and then into the thalamus in the anterior thalamic stimulation. In electric stimulation, activity of seizure is recorded with the help of electric device that predict seizure occurrence [56]. The part of brain which is involved in developing seizure is removed with the help of surgery in focal resection. This is the best treatment for those people who suffering from seizures on specific area of brain. Surgery done for those people who having seizures on the brain regions that are critical. Those critical areas are the areas of vision, memory and movement [57]. Part of temporal lobe in the brain is removed with the help of surgery in temporal lobe resection. Anterior temporal lobectomy is the main cause of causing epilepsy in people [58]. Corpus callosotomy is done for generalized epileptic people targeting both brain sides. In this two cerebral hemispheres connection is split [59]. Responsive neuro stimulation records the seizures by using a device known as electrical generator. Activity of seizures from the brain is measured by this device [60]. In deep brain stimulation a device placed under chest skin and electrodes are placed in the skull and this placed through a hole made in skull. For electrodes guidance, MRI is used and the device placed in chest is linked with electrodes in the brain [61, 62]. According to some evidences, balance diet has an effect on seizures and it contains essential nutrients and also helps in keeping energy level balance. It also helps to maintain regular pattern of sleep and good for health Ketogenic diet is good in the treatment for epilepsy shown in (Fig. 4) [63].

**Preventions**

Prevent from traumatic brain injuries because injuries and accidents are also involving in
causing epilepsy. Cysticerosis is also cause epilepsy which is spread by a parasite. To prevent from this parasite, eat good and hygienic food. Lowering down the stress and anxiety also prevent from seizure in epileptic patients. Also epileptic patient needs to take medicine regularly prescribed by doctor to lower down the risk of seizures [64].

Conclusion
Many types of epilepsy have no cure but there are a lot of surgeries present that involves in stopping many seizures types. Anti-epileptic drugs also helpful to control seizures. Many methods are developed now for the treatment of epilepsy like vagus nerve stimulation. All the muscles are under control of nervous system. Muscles become stretched and droopy due to epilepsy. Keto diet is also helpful in preventing seizures. Stem cells implanted in the brain to treat epilepsy when there is no chance of treatment with drugs. Many people live their lives and become seizure free with proper epilepsy treatment.

Authors’ contributions
Conceived and designed the experiments: A Akram & R Waseem, Performed the experiments: F Akram, Analyzed the data: ST Liaqat & A Shahid, Contributed reagents/materials/analysis tools: A Mumtaz & F Akram, Wrote the paper: F Akram & A Arif.

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