

Recent Advances in Epilepsy Syndromes

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Abstract: There are new syndromes of epilepsy are being identified due to progress in the research of epilepsy, as it is being recognized as the most common chronic neurological disorder. Thus, there are additions in the context of classification, etiology, pathophysiology, diagnosis and treatment therapies for epilepsy. Arising of these syndromes is due to *de novo* mutations and hereditary conditions in patients. Epilepsy with the age of onset of infancy or before has a poor prognosis and shown to be highly lethal or else survivors develop severe psychomotor impairments. One of the reasons can be attributed as most of these epileptic seizure episodes are missed or misdiagnosed as nonepileptic seizures because they co-exist with each other and thus, resulting in disabling of epilepsy. Hence, it is important to know nonepileptic seizure episodes that mimic epileptic seizures to avoid worsening of the diseased condition. Therefore, this review article discusses the detailed aspects of epilepsy intending to provide recent advances that would be helpful to epileptologist and researchers in the field of epilepsy in the correct understanding of the syndrome, associated causes, diagnosis and thus for implementing right treatment therapy.

Keywords: Epilepsy, Etiology, Pathophysiology, Diagnosis, Treatment, Nonepileptic seizures.

1. Introduction

Epilepsy is a condition of recurrent seizures which are characterized by brief episodes of involuntary movement. It may involve a part of the body/focal or the entire body/generalized and are sometimes accompanied by loss of consciousness. Seizure episodes are due to excessive electrical discharges in brain cells. Paroxysmal activity, which is due to disturbing in a physiological balance between excitation and inhibition within the central nervous system is the reason behind arising of seizures. This could be either due to an increase in excitatory neurotransmission or a decrease in inhibitory neurotransmission [1-2]. Seizures can be provoked or unprovoked. Those occurring as a result of external factors such as head injury, stroke, uremia, or alcohol detoxification are called provoked seizures. They do not reappear if their cause is treated [3]. If the cause is due to internal factors, then those are called as an unprovoked seizure. Epilepsy affects about 1% of the population, regarded as the fourth most serious neurological disorder and 90% of cases are from developing countries (WHO). According to the International league against epilepsy, individuals are considered as epileptic, if they had any one of the following conditions 1. One unprovoked or reflex seizure and 60% probability of recurrence risk after two unprovoked seizures, occurring over the next 10 y. 2. Or two unprovoked seizures taking place >24 h apart.

2. Classification

2.1 Generalized seizures

These seizures affect both the cerebral hemispheres (Table 1). Absence Seizures (Petitmal) involve staring, unresponsiveness to external verbal stimuli and automatisms like chewing, lip-smacking, rubbing fingers together, eye fluttering or other repetitive hand motions that start and stop gradually. Seizure begin and end suddenly [4]. They are two types depending upon the duration involved. Atypical absence seizures are longer (5-30 sec) than typical absence seizures (5-20 sec). Patients show cognitive impairment in atypical seizure whereas it is normal in typical seizure [2]. Generalized tonic-clonic (GTC) (grand mal) are characterized by a sudden loss of consciousness, muscles in arms, legs, back, and chest becomes stiff (Tonic phase) and jerking and twitching muscles (Clonic phase). Myoclonic seizures are brief, shock-like jerks of muscles. The term "Myo" means muscle and "clonus" means rapidly alternating contraction and relaxation (jerking and twitching) of muscles. Atonic seizures involve the loss of body tone and sometimes accompanied by a head drop or fall.

2.2 Focal (partial) seizures

These Seizures are limited to a part of one cerebral hemisphere. The clinical manifestations of a focal seizure depend on the area involved. E.g. A focal seizure involving occipital lobe may present with visual disturbances; blindness, visual illusions, palinopsia, nystagmus and focal seizure involving the temporal lobe shows the sudden sense of fear or anxiety, anger, sadness, joy, stomach upset. If there is no loss of consciousness, seizures are called as simple partial and when consciousness is impaired during a focal seizure, the seizure is called as dyscognitive (complex partial); seizures arising from the temporal lobe are often dyscognitive. Seizures are preceded by an aura, which is a focal seizure manifestation wherein a patient retains awareness and describes motor, sensory, autonomic, or psychic symptoms [4].

2.3. Combined generalized and focal epilepsy

Certain patients show both generalized and focal seizures. EEG of such patients shows both generalized and focal spike-waves.

2.4. Epileptic spasms

The origin of this seizure is unknown. Epileptic spasm shows by sudden extension or flexion of extremities for several seconds and then recur in clusters. Epileptic spasms occur at any age and if they begin in the first year of life, it is known as infantile spasms.

2.5 Rigidity and multifocal seizure syndrome, lethal neonatal (RMFSL)

RMFSL is a newly diagnosed epilepsy in neonates. Seizures (drug-resistant) appear in the womb (intrauterine) or the first few d of birth. Clinical features are rigidity, myoclonic seizures, jerks, apnea, reduced head circumference, hypertonicity that may persist throughout life. All patients died in early infancy. Infants show development and neurological delay. Ictal EEG shows bilateral frontotemporal sharp waves and 4–6 Hz theta background activity. Antiepileptic drugs (AEDs) are not effective [5].

2.6 Benign familial neonatal epilepsy (BFNE)

BFNE is a condition characterized by recurrent seizures in neonates. The seizures begin around 3rd day of life and remit within 1 to 4 mo. Seizures (usually tonic or clonic) can occur one side or both sides of the body, often accompanied by apnea. They are frequent and sometimes several times in a day leading to status epilepticus [4, 6]. EEG shows theta pointu alternate (rhythmic activity in theta of 4-7 Hz, sometimes with sharp waves), which may persist even after the seizure stops or focal discharges or spikes. The prognosis is good and development is normal. Some neonates continue to have seizures in adulthood. GABA agonists, phenobarbital and valproate should be avoided. No medications have been approved [7]. Recently, retigabine has shown to be effective in mice, but further studies are needed to confirm in human beings [8].

2.7 Early myoclonic encephalopathy (EME)

EME and Ohtahara syndrome are considered as epileptic encephalopathy according to ILAE. This term describes the epileptic syndrome in which seizures are intractable and progress to severe cerebral dysfunction over time, often leading to an early death. EME presents within the first 3 mo of age or a few hours after birth. Initially, the appearance of erratic focal myoclonus of the face or extremities or only of a small area, such as a finger is seen. Focal seizures and tonic spasms are very frequent. The jerks are described as erratic or fragmentary because they are not continuous and shift to another body part. The EEG shows "burst suppression pattern" which is not continuous and is more distinct during sleep and burst to burst interval is longer than Ohtahara syndrome [9, 10]. The suppression burst pattern can progress into hypsarrhythmia of West syndrome (infantile spasms). Metabolic and genetic etiologies have been identified. The prognosis is very poor. Infants may die within 2 y of life (50%) or else develop severe cerebral dysfunction [9]. A study reported where a female patient showed the transition of EME into malignant migrating partial seizures of infancy [11]. Recent data shows lidocaine, carbamazepine [12], ketogenic diet [13] and a high dose of Phenobarbital [14] were effective in treating this syndrome.

2.8 Benign familial neonatal-infantile epilepsy (BFNIE)

An autosomal dominant epilepsy disorder with an intermediate variant between benign familial neonatal seizures and benign familial infantile seizures. The onset is in between 2 d to 6 mo. Seizures occur in clusters of afebrile or febrile (rarely) secondarily generalized partial seizures. Psychomotor development is normal. Interictal EEG is normal and ictal EEG shows rhythmic bilateral spikes or spike-wave discharges arising from the posterior region. The prognosis is good; remission of seizures before 12 mo. Phenobarbital and carbamazepine work in subsiding seizures [15].

2.9 Ohtahara syndrome

It is also known as early infantile epileptic encephalopathy (EIEE). Seizures begin before 3 months (mo) of age. Infants show severe developmental and neurological abnormalities, even before seizures start. Tonic spasms can occur, but not frequent. These seizures last only for few sec and can occur alone or in clusters, more commonly to one side of the body. Seizures occur anytime. The EEG is very abnormal with a burst suppression alternating with a flat pattern. The pattern typically remains unchanged during both wakefulness and sleep, unlike early myoclonic encephalopathy where the burst suppression pattern is discontinuous and distinct during sleep. This syndrome can transition into West syndrome, which is characterized by transition from burst suppression pattern to hypsarrhythmic pattern and can further evolve into Lennox-Gastaut syndrome, which is accompanied by generalized slow wake spikes. Several etiologies have been suggested for Ohtahara syndrome including; structural, metabolic and genetic. The prognosis of Ohtahara syndrome is generally very poor. Patients frequently die during infancy and survivors show severe psychomotor impairments. The ketogenic diet was found to be effective [9].

2.10 Jamuar syndrome

A new recognized autosomal recessive epilepsy arises in the first few mo after birth. Seizures are refractory to medications. Seizure types include infantile spasms (more often), myoclonic jerks, GTC and sometimes with a fever. Affected infants show severe developmental and intellectual delay, feeding difficulties, dystonia, axial hypotonia, impaired motor skills (absent speech and language), chorea and sometimes tremors. EEG was found to be different at different stages; burst suppression pattern in the neonatal period, hypsarrhythmia in the infancy stage and generalized spike waves in childhood. Patients die in childhood or survivors develop cognition impairments [16].

2.11 Benign familial infantile epilepsy (BFIE)

BFIE is an idiopathic infantile epilepsy syndrome. The onset of seizures is in between 3 and 12-mo old infant and they are mostly of partial type, some with secondary generalization. Seizures occur in clusters for several d and stop spontaneously at about 18 mo. The interictal EEG is normal, but ictal EEG shows diffuse discharges from the Centro-occipital region. The course of the disease is benign with normal psychomotor development. Patients present with motor arrest, unresponsiveness, head or eye deviation to one side, staring, twitching of eyelids, grunting, cyanosis, hypertonia and unilateral or bilateral clonic jerks. Patients regain full consciousness and activity during the interictal period. A syndrome called familial infantile convulsions and choreoathetosis (ICCA) has been observed in which BFIE patients present in childhood and adolescence with choreoathetotic dyskinetic attacks occurring spontaneously or after a stimulus (e.g. exercise, stress) and in rare cases, familial or sporadic hemiplegic migraine is seen. With anti-epileptic treatment (e.g. carbamazepine, valproate, phenobarbital) symptoms subside fastly [17].

2.12 West syndrome (WS)

WS is characterized by epileptic spasms or infantile spasms (IS) or salaam attacks [10]. The spasms appear within the first year of life; usually, the onset is in between 4 and 6 mo. Males are more affected than females. The duration of an epileptic spasm is intermediate between a myoclonic jerk, which is briefer and a tonic seizure, which is more sustained. Initially, infants show no visual contact [18]. Spasms often occur in clusters of head nods, forceful flexion, or extension of the trunk and limbs during sleep transitions, especially on awakening. The interictal EEG pattern is called hypsarrhythmia, a disorganized, chaotic pattern of high voltage and spikes waves in multiple cortical parts. The classic ictal EEG pattern is a generalized slow wave followed by decrease voltage (electro-decremental response), accompanied by a spasm. Patients show psychomotor impairment and development delay and often evolve into LG syndrome.

Tuberous sclerosis complex (TSC) is responsible for a high incidence of IS, upto 50% of TSC patients show hypsarrhythmic pattern. It is an autosomal dominant genetic condition associated with seizures, eye, heart and kidney tumours and skin findings [4, 19]. Adrenocorticotrophic hormone (ACTH) and corticosteroids are used. Vigabatrin, a GABA transaminase inhibitor is effective for spasms when it is caused by TSC. Pyridoxine and biotin therapy should be tried in refractory seizures [4, 10].

2.13 Malignant migrating partial seizures of infancy (MMPSI)

It is a severe form of epilepsy and described as partial seizures migrate from one region to another, leading to secondarily generalized seizures. Seizure activity may last from sec to several days. The onset of seizures is before 6 mo, but sometimes start within a few weeks of birth. Seizures are often accompanied by sudden flushing, drooling, apnea, movement of the head or eyes, twitches in the eyelids or tongue, chewing motions or jerking [20]. Infants suffer from microcephaly, intellectual impairment and developmental delay. Ictal EEGs display paroxysmal discharges whereas interictal EEGs show diffuse slowing of the background activity with multifocal epileptiform discharge. Seizures are often refractory, but some patients responded to potassium bromide and stiripentol [10].

2.14 Epilepsy and mental retardation limited to females (EFMR)

EFMR is regarded as X-linked chromosomal disorder where only females are affected and males are the carrier, represents a unique inheritance pattern. This mode of inheritance is a key diagnostic feature of this disorder [21]. EFMR is manifested by “stormy” multiple seizures types (often occur in clusters), fever sensitivity, fearful screaming with autism and aggressive behaviour in infancy or early childhood [21-23]. The mean age of seizure onset is 14 mo (range 6–36 mo). Motion arrest, complex movement in the face or extremities, eye deviation, cyanosis, respiratory changes, systemic jerks are also frequent symptoms [22]. More than half of the patients show developmental regression, intellectual difficulties and language delay [23]. EEG studies showed heterogeneous features (generalized spike-wave and polyspike wave activity and/or focal discharges). After infancy, the EEG background may become normal [21]. A study reported the effectiveness of midazolam, phenytoin/fosphenytoin, phenobarbital, methylprednisolone, potassium bromide and clobazam in EFMR [22].

2.15 Dravet syndrome (DS)

DS also called as severe myoclonic epilepsy of infancy (SMEI). It is a rare, catastrophic epilepsy syndrome in which seizures begins before 18 mo of age. The initial seizure often occurs with a fever. Later, other seizure types occur and the child shows developmental regression. Seizures are prolonged, frequent often triggered by high temperature and are resistant to medications (drug-resistant epilepsy) [24]. 15-20% of infants died due to sudden unexpected death in epilepsy (SUDEP) [25]. Mutations have shown in the voltage-gated sodium channels with haploinsufficiency causing non-functional sodium channels. Hence, sodium channel blockers should be avoided. Benzodiazepine, valproate, potassium bromide and clemizole may attenuate seizures [26]. Recently, FDA has approved cannabidiol [27] and a treatment regimen containing fenfluramine with stiripentol [28] in DS.

2.16 Generalized epilepsy with febrile seizures plus (GEFS+)

GEFS+ patients suffer from febrile seizures and stops at the of 5 to 6 y or in some continues into adult life. These children may develop additional afebrile seizure types, including GTC, absence, and myoclonic [4]. Seizures are often more during sleep. Intellect is usually normal or sometimes with speech delay and behavioural problems. EEG is repeatedly normal or sometimes shows slowing of background and polyspikes waves. Treatment depends on the seizure type and patients [29].

2.17 Childhood absence epilepsy (CAE)

CAE is by characterized by staring and diminished responsiveness with peak onset is in between 4 and 10 y of age. The seizures start abruptly last from 5 to 20 sec and the frequency of seizures varies from a few to hundreds per day, almost recur daily. Thus, it is considered as Pyknolepsy [30]. The frequency increases due to stress, fatigue and hyperventilation is a strong activator of seizures. When the seizure ends, the patient resumes the previous activity immediately. EEG shows 3-Hz spike-wave complexes. Although the simple test is required in the clinic to diagnose absence seizures and assess treatment effectiveness, these seizures can be easily missed or misdiagnosed because absence seizures are nonconvulsive and brief. Mutations in calcium channel dysfunction and GABA receptor have been identified which causes altered physiology of thalamocortical circuits with abnormal firing of thalamic neurons. Most children with absence seizures have normal neurologic development and intelligence [4]. Drugs such as ethosuximide and valproate are effective than lamotrigine for treating absence seizures [30].

2.18 Lennox-Gastaut syndrome (LGS)

LGS begins between the ages of 3 and 5 y. Patients develop medically intractable seizures up to hundreds per day, constituting an epileptic encephalopathy. LGS characterized by multiple seizure types such as atonic, tonic (more often), atypical absence, myoclonic, intellectual disability with slow spike and wave pattern (1.5-2.5 Hz) in EEG. Antiepileptic drugs such as valproate, lamotrigine, topiramate, rufinamide, lacosamide, clobazam, clonazepam and felbamate are used in treating LGS [4]. Cannabidiol has also been approved in this disorder [27].

2.19 Landau-Kleffner syndrome (LKS)

LKS (acquired epileptic aphasia) is a rare epilepsy, which is characterized by loss of acquired language abilities. LKS occurs in previously normal children with normal language development who gradually lose the ability to understand spoken language and produce speech (Landau and Kleffner 1957). Besides these, the syndrome has expanded to include behavioural, autistic and cognitive dysfunction. Autism patients also show similar symptoms may or may not accompanying seizures, so the differentiation between LKS and autism sometimes poses a difficulty. The seizures usually respond readily to AEDs (e.g., benzodiazepines, valproate, levetiracetam, ethosuximide) [4].

2.20 Panayiotopoulos syndrome (PS)

PS affects occipital lobe of the brain in early childhood between the ages of 3-6 y. Hence, also known as early-onset childhood occipital epilepsy. Abnormalities that causes seizures can be seen on EEG commonly arising from the occipital lobe. Autonomic status epilepticus usually lasts for >30 min. It does not affect normal physical and cognitive development in children. Patients usually experience autonomic epileptic seizures with emesis and autonomic status epilepticus which are the cardinal manifestations of PS. Two-thirds of seizures occur during bedtime. Other autonomic manifestations include cardiorespiratory and thermoregulatory disturbances, pallor (or sometimes flushing or cyanosis), mydriasis (or sometime miosis), incontinence of urine, hypersalivation and modifications of gut motility. EEG shows multifocal functional spikes. The syndrome is benign that gets resolve into adulthood. However, autonomic seizures with cardiorespiratory arrest are life-threatening. Benzodiazepines are used for nonconvulsive status epilepticus [31].

2.21 Jeavons syndrome (Eyelid myoclonia with absences)

It is defined by the manifestation of the following triad: (1) Occurrence of eyelid myoclonia (EM) with or without brief absences which is triggered by eye closure (not by eye blinking); (2) Seizures induced by eye closure (3) Photosensitivity, typically during childhood at a peak of 6-8 y. It is more prevalent in girls. Sleep deprivation, alcohol abuse, bright sensitivity and television or video-gaming may induce GTCS. Some studies suggest genetic contribution, but further accurate studies are needed for a better knowledge of the syndrome. Ictal paroxysmal activity (PA) is characterized by high-amplitude generalized polyspikes, often followed by brief discharges (3– 6 sec). Hyperventilation promotes and darkness abolishes this activity. This syndrome does not affect mental status and development of children. Levetiracetam [32] and valproate subsides all type of seizures. Overlapping of this syndrome with Juvenile myoclonic epilepsy was found in a few cases [33].

2.22 Doose syndrome

Doose syndrome is also known as epilepsy with myoclonic-atonic seizure or myoclonic-astatic epilepsy, present within the first 5 y of life, usually between 3 mo and 4 y of age. It is more common in males and describes as generalized idiopathic epilepsy with multiple seizure types, but myoclonic and atonic seizures are more common. All seizure types can result in status epilepticus. A family history of are photosensitivity has been found, suggesting hereditary cause. Initially, the EEG is normal, but later shows brief bursts of 2 to 5 Hz polyspikes and wave complexes with background slowing and parietal theta. These may remain even after remission of epilepsy, often during sleep. This helps to distinguish between Doose syndrome and LGS, in which the EEG is more abnormal with no normal background activity and slower (2–2.5Hz) spike-wave. The ketogenic diet or Adrenocorticotrophic hormone is the first-line therapy in Doose syndrome. Ethosuximide, valproic acid, levetiracetam, zonisamide, topiramate are also helpful, but certain drugs like carbamazepine, oxcarbazepine, phenytoin and vigabatrin have been reported to worsen seizures in Doose syndrome [34].

2.23 Rolandic epilepsy

It affects the rolandic area, i.e., face in between 3 and 13 y of children and also known as benign childhood epilepsy with centrotemporal spikes. Seizures begin with clonic movements of the face (grimacing, vocalizations) and often make the child wake up from sleep [35]. Some patients experience headaches or migraines, learning difficulties and behavioural problems during seizure episodes. The EEG shows a pattern of perisylvian spiking [36]. This syndrome resolves spontaneously by early adulthood. Antiepileptic drugs such as carbamazepine are the treatment of choice when seizures are frequent [35].

2.24 Sunflower syndrome

It is another rare photosensitive epileptic disorder characterized by highly stereotyped seizures. The age of onset of this syndrome varies between 3 and 10 y of age, affecting 75% more in girls. Children show unique behaviour during seizures episodes that they get drawn towards the bright source of light and waving one hand in front of their eyes simultaneously and sometimes accompanied by unconsciousness. Absence seizures and generalized tonic-clonic seizures also occur. EEG is abnormal with features of generalized epilepsy. Sunflower syndrome was misinterpreted as self-induced photosensitive epilepsy. However, the self-induced term was proven to be wrong when EEG studies have shown that the excessive depolarization of neurons in the brain start at the same time as the hand waving behaviour occur [37]. A recent study has shown that fenfluramine may be effective in this rare epilepsy [38].

2.25 Idiopathic photosensitive occipital epilepsy (IPOE)

It is the most common forms of reflex epilepsies in which seizures are trigger by environmental photic stimulation (television and video gaming) [39]. IPOE is focal epilepsy appears at puberty. Seizures are characterized by brief visual hallucinations, which may be either positive such as flashes, phosphenes or negative such as scotoma, hemianopia, amaurosis. Other symptoms include eye movement, tinnitus and vertigo; the latter two represent spreading of seizures to the posterior temporoparietal region. If the temporal lobe is affected, automatisms and loss of consciousness may occur. Post-ictal symptoms may include headache; indistinguishable from migraine, nausea, vomiting and less often severe seizures or status epilepticus can occur. Secondly generalized tonic-clonic and febrile convulsions may also occur. Valproate, carbamazepine and phenobarbitone may abolish seizures [40].

2.26 Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)

ADNFLE is also known as sleep-related hypermotor epilepsy (SHE) [41], familial epilepsy with focal seizures characterized by clusters of brief nocturnal motor seizures (stereotyped nightmares, verbalizations, sudden limb movements, parasomnias) during peak childhood. These incidents are often misdiagnosed as nightmares, night terrors, sleepwalking or panic attacks. The mean age of onset 9 y (85% of cases have the onset of seizures by 20 y of age). Development and intellect are usually normal. Ictal EEG may be normal but interictal EEG shows epileptiform discharges during sleep. The condition is lifelong, but not progressive. These attacks become milder and less frequent. Carbamazepine reduces seizure in 70% of individuals. However, it is partially effective in CHRNA4 variants, in such cases, zonisamide is more responsive. Quinidine significantly reduces seizures for KCNT1 variants [42]. Oxcarbazepine, topiramate, fenofibrate, levetiracetam, gabapentin and acetazolamide are used as add-on therapy and nicotine transdermal patches in refractory seizures [43].

2.27 Autosomal dominant partial epilepsy with auditory features (ADEF)

ADEF is also called as lateral temporal epilepsy, genetic focal epilepsy presents autosomal dominant inheritance. The disorder is characterized by focal sensory auditory seizures and receptive aphasia in early adulthood (4-50 y). Auditory seizures include humming, buzzing, or ringing sounds during an episode. Sounds such as ringing telephone may precipitate seizures. Focal seizures may also follow secondarily generalized seizures. Seizures are generally mild and infrequent. Interictal-ictal EEG is often normal. However, sometimes focal epileptiform abnormalities are present in the temporal lobe. The prognosis is usually good and seizures are well controlled by carbamazepine, phenytoin and valproate [44].

2.28 Familial mesial temporal lobe epilepsy (FMTLE)

This is another form of familial focal temporal lobe epilepsy with adolescent or adult-onset. Seizures are manifested as déjà vu, dreamlike state, fear and nausea [45]. Visual and auditory illusions are other symptoms. Hippocampal atrophy is another common characteristic feature [46]. It shows genotype heterogeneity. Ictal EEG shows temporal lobe discharges and interictal EEG usually normal or sometimes mild focal slow waves, sparse sharp arising from the temporal lobe. Sleep deprivation may activate epileptiform abnormalities. Prognosis is excellent with well-controlled to medications [47].

2.29 Juvenile myoclonic epilepsy (JME)

JME is an epilepsy syndrome that typically begins in adolescence and consists of myoclonic or 90% of patients shows GTC seizures especially after awakening. A very few patients show absence seizures. The myoclonic jerks may cause the patient to drop or fling objects. Seizures are exacerbated by sleep deprivation, fatigue, alcohol use and photic stimulation. The neurologic examination and intelligence are usually normal in JME [4]. Heterogeneity in JME has been found where some families are linked to EJM1. The gene at the EJM1 locus has now been identified as BRD2, a putative transcriptional regulator [48]. Valproate is the most effective AED and levetiracetam and lamotrigine are preferred in females [49].

2.30 Juvenile absence epilepsy (JAE)

JAE is characterized by absence seizures and sometime GTCS. In an absence seizure, individuals will stare and are unresponsive. Their eyes may roll up briefly or the eyelids may flutter. Some people may have repetitive movements like mouth chewing (automatisms). Some people consider Juvenile absence epilepsy is a synonym of childhood absence epilepsy. However, the former occurs after age 10 y, frequency of absence seizures is less while the latter occurs before 10 y, usually between 6-8 y and frequency of absence seizures are upto 20-40 times per day. Another difference is JAE is a lifelong condition, but seizure in CAE resolves when the child gets older. Valproate and lamotrigine are effective. Ethosuximide can be used, if absence seizures are not controlled [50].

2.31 Familial partial epilepsy with variable foci (FPEVF)

It is an autosomal dominant syndrome with incomplete penetrance and characterized by partial seizures mostly during sleep [51]. The onset of a seizure is highly variable (from infancy to adulthood) [52]. Seizures originate as variable foci that are from frontal or temporal or occipital lobes in different family members. Because of variable foci in different family members, this syndrome is easily misdiagnosed with other epilepsies. Interictal and ictal EEG shows focal epileptic patterns. There are no structural abnormalities and intellect impairments. Common AEDs are effective [51].

3. Etiology

Determining the etiology of seizures assist in determining the right treatment as there are several types of seizures exist. A range of etiology has been recognised; from structural, genetic, infectious, metabolic, immune to an unknown group [53].

3.1 Structural etiology

A structural etiology refers to abnormalities visible on neuroimaging examination where the electroclinical assessment together with the imaging findings lead to a reasonable inference that the imaging abnormality is the likely cause of the patient's seizures. Structural etiologies may be acquired due to stroke, trauma or malformations of cortical development. Despite there being a genetic basis with such malformations, the structural correlate underpins the person's epilepsy. Structural lesions identification requires appropriate MRI imaging.

Structural abnormalities may be genetic or acquired or both. For Example, 1. Polymicrogyria may be secondary to mutations in genes such as GPR56, or acquired, secondary to intrauterine cytomegalovirus infection. 2. Acquired structural causes include trauma, hypoxic-ischemic encephalopathy, infection and stroke. 3. Tuberous sclerosis complex causes non-cancerous tumours in the brain and other body parts which are due to mutations in the genes TSC1 and TSC2 encoding hamartin and tuberin respectively have well-defined structural etiology on a genetic basis. In such cases, both structural and genetic etiologies can be used.

Examples: Hypoxia-ischemia, intracranial haemorrhage, developmental brain anomalies such as cortical dysplasia [4, 19], hypomyelination, hypoplasia of the corpus callosum, cortical atrophy, and atrophy of the brainstem and cerebellum [18] in west syndrome. Hemimegalencephaly, agenesis of the corpus callosum, porencephaly, agenesis of the mamillary bodies and dentatoolivary dysplasia, hypoxic injury, cortical dysplasia in Ohtahara syndrome [9]. Cortical dysplasia, trauma, stroke, perinatal hypoxia in LGS [54].

3.2 Genetic etiology

More than 70% of epilepsies are due to genetic factors. The concept behind genetic epilepsy is that it results directly from a known or presumed mutation in which seizures are the main symptom of the disorder. First, the inference of a genetic etiology can be based solely on a family history of an autosomal dominant disorder. For example, in the syndrome of benign familial neonatal epilepsy, most families have mutations in potassium channel genes, KCNQ2 or KCNQ3 and in some cases, the underlying mutation is found in a small proportion of individuals, such as in autosomal dominant nocturnal frontal lobe epilepsy.

Second, a genetic etiology can be suggested by clinical research studies in patients suffering from childhood absence epilepsy or juvenile myoclonic epilepsy.

Lastly, a molecular basis may have been identified and may implicate a single gene or more. Most of severe and mild epilepsies have genetic etiology and it is important to mention that genetics does not equate with inheritance. This means that the patient has a new mutation that has arisen in him or her which is not found in family members, but this patient may now have a heritable form of epilepsy. For example, if the individual has a *de novo* dominant mutation, their offspring will have a 50% risk of inheriting the mutation. Due to advancements in molecular genetics, the inheritance pattern and *de novo* mutations in epilepsies are being identified.

Examples: Chromosomal abnormalities such as down syndrome, Pallister-Killian syndrome, neurocutaneous disorders such as Sturge weber syndrome, Incontinentia pigmenti and mutation of ARX gene or CDKL5 gene in west syndrome. Tuberous sclerosis complex (TSC) is the most common cause in west syndrome [19] and LGS [54]. A detailed study of genes involved in epilepsy syndromes is discussed in the pathophysiology section.

3.3 Infectious etiology

An infectious etiology refers when a patient with epilepsy in which seizures arises as a result of acute infections such as meningitis, neurocysticercosis, encephalitis, tuberculosis, cerebral malaria, HIV, cerebral toxoplasmosis, subacute sclerosing panencephalitis and congenital infections such as cytomegalovirus and Zika virus. These infections sometimes have a structural correlation such as postinfection due to head injuries and also refer to the postinfectious development of epilepsy such as viral encephalitis leading to seizures in the aftermath of the acute infection. This etiology carries specific treatment implications.

Examples: CNS infections such as encephalitis or meningitis in west syndrome and LGS.

3.4 Metabolic etiology

A wide range of metabolic disorders causes epilepsy. This area is expanding due to a greater understanding of the phenotypic spectrum. The concept in metabolic epilepsy is that it results directly from a known or presumed metabolic disorder in which seizures are the main symptom of the disorder. Metabolic disorders can cause seizures by any one of three ways: dysregulation of intracellular osmolality, deficiency of substances required for cellular metabolism or membrane physiology, accumulation of toxic substances inside the cells. Examples include porphyria, uremia, aminoacidopathies, or pyridoxine-dependent seizures. Most metabolic epilepsies have a genetic basis, but some may be acquired such as cerebral folate deficiency. It is important to identify seizures underlying metabolic causes of epilepsy to specify therapies and to prevent intellectual impairment in patients.

Examples: Non-ketotic hyperglycaemia, pyridoxine deficiency, phenylketonuria, maple syrup urine disorder, biotinidase deficiency, Ohtahara syndrome, early infantile epileptic encephalopathy, mitochondrial encephalopathies in west syndrome [4, 19]. Nonketotic hyperglycinaemia, cytochrome C oxidase deficiency, pyridoxine dependency, carnitine palmitoyl transferase deficiency, biotinidase deficiency, mitochondrial respiratory chain complex I deficiency in Ohtahara syndrome. D-glyceric acidemia, propionic aciduria, molybdenum cofactor deficiency, pyridoxine deficiency, methylmalonic acidemia, sulfite oxidase deficiency, Menkes disease and Zellweger syndrome in early myoclonic encephalopathy [9]. Hypercalcaemia, non-ketotic hyperglycaemia, hypertension, lactic acidosis are the etiologies behind occipital lobe epilepsy [40]. Low levels of zinc in cerebrospinal fluid and B₁₂ in BFNE [7].

3.5 Immune etiology

Immune-mediated epilepsy explains that some immune disorders result in seizures as one of the main symptoms. An immune etiology can be conceptualized as where there is evidence of autoimmune-mediated central nervous system inflammation. Immune epilepsies have been recently recognized in both adults and children. Diagnosis of this autoimmune encephalitis is rapidly increasing, particularly in the field of antibody testing. Examples include anti-LGI encephalitis, anti-NMDA receptor encephalitis [53] and anti-GluR3 in Rasmussen's encephalitis [55]. The emergence of these antibodies makes this etiologic subgroup a specific category and has given the treatment implications with targeted immunotherapies.

3.6 Unknown etiology

There are certain epilepsies whose cause is not yet known. This can be due to the complexity of epilepsy syndrome, unavailability of evaluation tests. The extent to which a cause can be determined depends on the extent of the evaluation available to the patient, health care settings and countries. In poor patients the cost is unaffordable hence etiology remains hidden or unknown. Therefore, deciding treatment for seizures poses difficulty or may fail therapy.

4. Pathophysiology of epilepsy

A seizure can be hypothesized as an imbalance between excitation (E) and inhibition (I) in the brain (Stafstrom 2010). This E/I imbalance results from alteration at many levels of brain function that can be genetic or acquired. Genetic pathologies leading to epilepsy occur anywhere from the circuit level (e.g. hyperpolarization of neurons) to the receptor level (e.g., Gamma-Amino Butyric Acid [GABA] receptor subunits mutations) to abnormal ionic channel function (e.g., Sodium channel mutations). Similarly, acquired cerebral injury can change circuit function (e.g., Physical deformities in the hippocampal region due to head injury or repeated febrile seizures) [4].

4.1 Genetics of epilepsy

Genetic causes contribute to the major proportion of epilepsies. Due to the emergence of molecular genetics, considerable advances in understanding the genetics of mammalian or nonmammalian epilepsy have been made. The genetic causes can be a form of rare Mendelian inheritance pattern (for example, X-chromosomal dominant, X-chromosomal recessive, autosomal dominant, autosomal recessive,) or in a Non-mendelian inheritance (Mitochondrial inheritance chromosomal aberrations) [56]. In most of these disorders, epilepsy is a symptom of disturbances of brain function including cognitive impairment, cerebellar dysfunction and other neuronal dysfunctions. These impairments are maximum at birth or arise in adulthood and are progressive. Each of the mutant genes in epilepsy encodes an ion channel, neurotransmitter, enzyme or receptor. Both polygenic and monogenic mutations can cause epilepsy. However, monogenic epilepsy can become polygenic due to identification of *de novo* mutations.

4.1.1 Ionic channels genes in epilepsy

Mutated voltage or ligand-gated ion channels are a major cause of idiopathic epilepsies. Mutations of ionic channels may lead to following alterations at non-synaptic levels a) Alterations in ionic microenvironment; e.g. increased extracellular K⁺, decreased extracellular Na⁺ or Ca⁺². b) Decreases in size of extracellular space. c) Failure of ion transport: Na⁺-K⁺ pump or Cl⁻-K⁺ co-transport. d) Presynaptic terminal bursting. e) Ephaptic interactions.

4.1.2 Non-ionic channel genes in epilepsy

Non-ion channel genes (genes coding for amino acid or neurotransmitter) play a negligible role in the pathogenesis of epilepsies. Mutations in non-ionic channels may influence following alterations at synaptic cleft; a) Depression of GABA and Glycine-ergic inhibition. b) NMDA receptor activation; voltage-dependent excitatory postsynaptic potentials (EPSPs) c) Frequency potentiation of EPSPs d) Actions of modulators [55].

4.1.3 Neurochemical mechanisms underlying epilepsy

4.1.3.1 GABA

It is a major inhibitory neurotransmitter in the brain. It is reported that desensitization of GABA binding site or decreased levels of GABA and glutamic acid decarboxylase (GAD) or decrease released of GABA from synaptic terminals were found in various animal models and epileptic patients. Hence, increasing GABA levels can prevent seizure activity [55].

4.1.3.2 Glutamate

Glutamate causes excitation of neuronal cells by activation of both ionotropic and metabotropic postsynaptic receptors. Few glutamate gene mutations have been found linked to a human epilepsy syndrome such as Landau-Kleffner syndrome, Ohtahara syndrome and early myoclonic encephalopathy.

4.1.3.3 Catecholamines

Dopamine levels were found to be decreased in the nucleus caudatus in the spontaneous epileptic rat as well as in epilepsy patients. Moreover, seizures were aggravated by dopamine antagonists and alleviated by dopamine agonists in animal models of absence epilepsy [55]. This suggests that elevating dopamine levels can prevent the occurrence of seizures. However, the role of norepinephrine in epilepsy has been controversial in different animal models; prazosin, an α_1 antagonist has shown proconvulsant property in the spontaneous epilepsy mouse model and anticonvulsant in strychnine induced epilepsy in mouse while clonidine, an α_1 agonist acts as both proconvulsant and anticonvulsant in amygdala kindling and electroshock convulsions in rats [57].

4.1.3.4 Serotonin (5-HT)

Gerber *et al* reported that 5-OH DPAT, an agonist of 5-HT_{1A} receptor increases epileptic discharges in a genetic model of absence epilepsy in rat [58]. In contrast, another study has shown 5-OH DPAT [59] and other 5-HT agonists as a potent suppressor of epilepsy [60]. Though there are no mutations associated with epilepsy syndromes have been identified until now, but animal models suggested that decreased serotonin levels resulted in epileptogenesis [58]. Thus, increasing serotonin levels can be another approach to treat epilepsy. Considering this approach, recently 5-HT agonist fenfluramine has been approved as an anticonvulsant in Dravet syndrome by US FDA [61].

4.1.3.4 Glycine

It is an inhibitory neurotransmitter in the brainstem and spinal cord. Low concentration of glycine (10 μ M) activates presynaptic glycine receptors which promote proconvulsant mechanism. In patients with temporal lobe epilepsy changes in glycine receptor expression in the hippocampus region of the brain have been reported, suggesting the role of glycinergic signalling in epilepsy. It is also reported that glycine terminates neuronal excitation and reduced the firing of action potentials in hippocampal neurons in in-vitro studies [62].

4.1.4 Genes that are involved in epilepsy syndromes

4.1.4.1 RMFSL

There are only a few cases of RMFSL, all of them reported to have a mutation in *BRAT1* (breast-cancer-1(BRCA1)-associated ataxia telangiectasia mutated activator-1) [5] (Chromosome 7p22.3) gene. The protein encoded by this gene is thought to play a role in preventing apoptosis and sensing damaged DNA.

4.1.4.2 BFNE

This is inherited in an autosomal dominant pattern which arises due to mutations of two distinct, but related to novel voltage-gated potassium channel genes *KCNQ2* (chromosome 20q13.3, most commonly) and *KCNQ3* (chromosome 8q24) [6, 63]. Above two genes encode potassium channels subfamily Q member 2 (Kv7.2) and 3 (Kv7.3) respectively. These channels transport potassium into and out of cells which plays a key role in generation and conduction of electrical currents. These channels also generate a particular type of electrical signal 'M-current' which ensures that the neurons are not constantly active or excitable. A very few patients have shown mutation in *SCN2A* gene [6]. *SCN2A* gene encodes voltage-gated sodium channel alpha 2 subunits.

4.1.4.3 EME

Almost all patients of EME reported spiny neurons in the white matter which was later found to be v-erb-a erythroblastic leukaemia viral oncogene homologue 4 (ErbB4) protein. *ErbB4* gene (2q34) produces an enzyme called receptor tyrosine-protein kinase erbB-4, which have a role in the migration of interneurons [9]. Mutation of this gene disturbs interneuron migration and GABA-ergic interneurons in the postnatal cortex [64]. Few mutations in *AMT* [65], *CDKL5* [66], *STXBPI*, *SPTANI* [67], *SLC25A22* [68] have also been reported. *AMT* gene (3p21.31) is responsible for producing amino methyltransferase enzyme, which together with other enzymes involved in glycine cleavage system in mitochondria. Breakdown of excess glycine is needed for normal functioning and development of CNS.

4.1.4.4 BFNE

Mutations in the voltage-gated sodium channel subunit gene *SCN2A*, located on chromosome 2q24.3 [15].

4.1.4.5 EIEE

A wide number of mutations such as in *ARX*, *ARHGEF9*, *BRAT1*, *CDKL5*, *KCNQ2*, *PCDH19*, *PNKP*, *PLC- β 1*, *STXBPI*, *SLC25A22*, *SPTANI*, *SCN2A*, *SCN8A*, *ST3GAL3* and *TBC1D24* genes have been identified in EIEE [69]. The protein produced from *Aristaless* related homeobox (*ARX*) gene plays a role in the differentiation, proliferation of neurons and migration of interneuron to the developing cortex that contribute to brain development during the early embryonic stage. This protein also acts as a transcription factor (regulate other genes) for the development of the brain during embryonic development. Dysfunctional differentiation may also lead to a deficiency of inhibitory interneurons, partly accounting for the intractable seizures [9, 64]. A few patients also reported manifesting syntaxin binding protein 1 (*STXBPI*) gene and solute carrier family 25 (*SLC25A22*) gene mutations. The former gene (9q34.11) regulates the synaptic vesicular release of GABA and glutamate as well as differentiation and migration of neurons while the latter gene (11p15.5) is involved in mitochondrial glutamate transport. Dysfunction of this transport could lead to energy reduction during development leading to neuronal cell death [9]. Cell division cycle 42 guanine nucleotide exchange factor (GEF)-9 gene, *ARHGEF9* (Xq11.1) encodes collybistin (a brain-specific protein form during development) which is responsible for cell signalling transduction pathways and activation of Rho-family GTPases [70]. *PNKP* gene (19q13.33) codes for polynucleotide kinase-phosphatase enzyme which is responsible for repairing of damaged DNA. Thus, damaged DNA disrupts the neural function. *SCN8A* (12q13.13) codes for Na_v1.6 channel which is highly expressed in the central nervous system. This subunit forms the pores of sodium channel, which allow the influx of sodium ions during depolarization of neurons. *ST3GAL3* (1p34.1) produces a beta-galactoside alpha-2,3-sialyltransferase 3, a protein found in Golgi apparatus which is involved in cellular recognition. *TBC1*

domain family member 24 protein is produced by *TBC1D24* gene (16p13.3) whose clear function is not yet known. It has been suggested that this protein is associated with synaptic vesicles transport and respond to oxidative stress.

4.1.4.6 JS

This newly diagnosed epilepsy shown to have a mutation in *UGDH* gene (4p14). This gene codes for UDP-glucose 6-dehydrogenase that is responsible for conversion of UDP-Glucose to UDP-Gluconate which is involved in intoxication and a precursor of glycosaminoglycans (GAGs). GAGs are involved in neuronal development, plasticity, neuronal migration and make up the important part of extracellular matrix [16].

4.1.4.7 BFIE

Mutations in *PRRT2* gene (16p11.2) encoding for proline-rich transmembrane protein 2 has been found. It interacts with another protein called SNAP25 which helps in controlling the release of neurotransmitters. Other mutations are associated with *SCN2A*, *KCNQ2* and *KCNQ3* [17].

4.1.4.8 WS

Mutations in *CDKL-5*, *MeCP-2*, *ARX*, *STXBP-1*, *SPTAN1*, and *PLC-β1* genes have been involved in west syndrome [10]. *CDKL-5* gene (Xp22.13) makes an enzyme called cyclin-dependent kinase which is highly expressed in the brain. This enzyme is responsible for movements, growth and formation of neurons. *MeCP-2* gene (Xq28) produces methyl-CpG binding protein 2 (MeCP-2) which are thought to regulate gene expression. It maintains alternating splicing of proteins in the brain which is required for maintenance of synapses. Spectrin alpha, non-erythrocytic 1 (*SPTAN1*) gene located on chromosome 9q34.11 is responsible for producing spectrins that are expressed in non-erythrocytic cells. Spectrins maintain cellular functions such as DNA repair and cell division. A recent mutation in *ALG13* gene has been found in infantile spasms [71].

4.1.4.9 MMPSI

Mutations in the *KCNT1* [72], *SCN8A* [68], *SCN1A* and phospholipase *Cβ1* (*PLCB1*) [10] gene mutations have been described in few patients. *PLCB1* gene (20p12.3) provides instruction for phosphatidylinositol-specific phospholipase C which produces secondary messengers like diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). These secondary messengers regulate the intracellular transduction mechanisms. *PLCB1* affects neuronal cell proliferation by inhibiting cyclin Y-dependent kinase (*CDK16*) [73] which is required for neuronal development. Recently, a rare *BRAT1* mutation was found in MMPSI patients. Mutation of this gene is associated with the appearance of seizures within the few the first few d of life or in utero and high lethality rate [74].

4.1.4.10 EFMR

Mutations of *PCDH19* (Xq22.1) [75] gene have been reported in affected female patients. This gene encodes protocadherin 19 which is a calcium-dependent, cell adhesion protein. The reason for mutation only in females and the exact physiology of this protein is not known yet.

4.1.4.11 SMEI

Mutations in the *SCN1A* (more than 70%), *SCN2A*, *SCN1B*, *SCN8A*, *STXBPI*, *GABRA1*, *GABRG2* and *PCDH19* [25] genes have also been identified in patients with SMEI as found in GEFS⁺. Mutation of *SCN9A* (2q24) encoding Na_v1.7 [76] channel causes febrile seizures and temporal lobe epilepsy has also been reported.

4.1.4.12 GEFS+

Mutations underlying this epilepsy are in the α and β-subunit of a voltage-gated Na⁺ channel (*SCN1A*, *SCN2A*, *SCN1B*, *SCN2B*), GABA_A receptor γ2 subunit gene *GABRG2* (Chromosome 5q34) and δ-2 subunit gene *GABRD* (chromosome 1p36.33) [77] and *SCN9A* [76] have been identified. These *SCN* genes provide instructions for making sodium channels which help in conduction of electrical circuits. Recently few de novo mutation of *STX1B* gene (16p11.2) [78] codes for syntaxin 1B. A presynaptic protein thought to involve in the release of presynaptic vesicles into the plasma membrane. Its precise function is yet to be known. Marini et al have also reported a de novo mutation in *HCN1* gene. *HCN1* gene (5p12) [79] encodes a hyperpolarization-activated, cyclic nucleotide-gated channel which is permeable to potassium and slightly to sodium. This channel gets activated during hyperpolarization and conducts hyperpolarization-activated current (I_h) in the brain.

4.1.4.13 CAE

Mutations in *CACNA1H*, *CLCN2*, *GABRA1* (5q34), *GABRB3* (15q12), *GABRG2* (5Q34), *JRK*, *NIPA2*, *SLC2A1* [80] genes have been identified. *CACNA1H* (16p13.3) gene provides instruction for T-type calcium channel; Ca_v3.2 triggers sodium-dependent action potential leading to depolarization of thalamic neurons [81]. *CLCN2* (3q26) gene shows locus heterogeneity in case of CAE [82]. Inactivation of *JRK* (8q24.3) gene resulted in epileptic seizures in mice, but the exact of this gene is not known in epilepsy [83]. Solute carrier family 2 member 1 (*SLC2A1*) (1p34.2) produces glucose transporter protein type 1 (*GLUT1*) which transport glucose molecules across the blood-brain barrier into the brain. Disruption in glucose transport could lead to energy deficiency and causes neurological abnormalities. *NIPA2* (15q11.2) instructs to produce non-imprinted in Prader-Willi/Angelman syndrome region protein 2 which is a magnesium transporter. Mutation of this gene causes extracellular accumulation of Mg⁺² ions and decreased intracellularly. This alteration was found to cause NMDA activation, thus leading to excitation of neurons [84].

4.1.4.14 LGS

Few children reported a mutation in *ALG13* gene (Xq23) [71]. This gene encodes a subunit of UDP-N-acetylglucosamine transferase which is involved in N-glycosylation of protein in the endoplasmic reticulum. The exact role of N-glycosylation in arising seizures is still unknown but it is suggested that this process is required for neuronal cells during embryonic development.

4.1.4.15 LKS

GRIN2A gene (16p13.2) mutations are known to cause LKS. Glutamate ionotropic receptor NMDA type subunit 2A (*GRIN2A*) encodes GluN2A (NR2A) protein, a highly expressed protein involved in speech and language region of the brain. GluN2A is a subunit of NMDA

receptors and regulate glutamate and glycine binding to NMDA receptors. Few patients had reported mutation in *RELN*, *EPHB2* and *NID2* [85]. *RELN* genes (7q22.1) produces a protein called “Reelin” which triggers neurons to migrate their proper locations. *EPHB2* (1p36.12) encodes Eph receptor to which Ephrin ligand binds and maintain cellular processes like motility and differentiation. *NID2* (14q22.1) provides instructions to make nidogen-2 protein (cell adhesion protein) that binds to collagen I and IV and laminin and involved in maintaining the structure of the basement membrane.

4.1.4.16 Jeavons syndrome

KIAA2022 gene mutation was found very recently in this syndrome [86].

4.1.4.17 Doose syndrome

This syndrome is considered as a part of GEFS+ because of mutations in sodium channel (*SCN1A*, *SCN2A*, *SCN1B*) and GABA (*GABRG2*) [87] genes and few patients of Doose syndrome reported to have a family history of GEFS+. However, this is not found in all cases [34]. Recent mutation in the *SLC2A1* gene, *SYNGAP1*, *KIAA2022* and *CHD2* gene have been reported [87]. *CHD2* (15q26) gene produces chromodomain DNA helicase protein 2 that help in gene expression. The exact mechanism of this protein in the brain is not known. *SYNGAP1* (6p21.32) encodes synaptic Ras GTPase activating protein 1 which is required for cognition during early brain development. This protein is found in synapse and regulate synapse adaptations. *KIAA2022* (Xq13.3) encodes neurite extension and migration factor (NEXMIF) protein [88] which is expressed during early development of life. This protein involved in neuronal migration into the hippocampus, entorhinal and piriform cortices region of the brain [89].

4.1.4.18 Rolandic Epilepsy

Mutations in *ELP4*, *KCNQ2* and *GRIN2A* genes are found to be involved in this disorder. *ELP4* gene (elongator acetyltransferase complex subunit 4) located on 11p13 chromosome encodes a complex, histone acetyltransferase (HAT) which binds to RNA polymerase II to regulate transcription during transcription elongation. Chromosome 15 (15q14) mutation are also identified, but the specific gene involved is not yet determined [36].

4.1.4.19 ADNFLE

Unlike other epilepsies which are due mutations in voltage-gated ion channel, mutations causing this frontal-lobe epilepsy is encoded by ligand-gated [63]alpha and beta subunits of neuronal nicotinic acetylcholine receptor (nAChR), namely the *CHRNA2* (8p21.2), *CHRNA4* (20q13.33) and *CHRNA2* (1q21.3). When a neurotransmitter called acetylcholine attach to nAChR in the brain, it acts as a channel and allows sodium, calcium and potassium ions to cross the cell that plays an important role in chemical signalling between nerve cells. Other genes such as *KCNT1* (9q34.3), *DEPDC5* (22q12.3), *CRH* (8q13), *CABP4* (11q13.2) [43], *NPRL2* (3p21.31), *NPRL3* (16p13.3) and *PRIMA1* (14q32.12)[90]. *KCNT1* encodes a voltage-dependent and intracellular sodium/calcium-activated potassium channel, $K_{Ca4.1}$. This is a member of the Slo-type subfamily of potassium channel genes, also known as Slack, which causes hyperpolarisation after repetitive neuronal excitability [72]. *CRH* gene releases a corticotropin-releasing hormone which is released by synapse and has excitatory potential. Increased expression of CRH was found in both animal models and epilepsy patients [91]. ADNFLE shows autosomal recessive inheritance pattern when *PRIMA1* gene mutation occurs. This gene encodes Proline-rich membrane anchor 1 (PRiMA1) which anchors Acetylcholinesterase. This enzyme hydrolyses acetylcholine in the neuron. Mutation of this gene leads to accumulation of ACh; causing the excitatory potential to generate [90]. *CABP4* encodes $Ca_v1.4$; a voltage-gated calcium channel [92].

4.1.4.20 ADPEAF

Mutations in the *LGII*, *MICAL1* and *RELN* gene are a cause of ADPEAF [44]. *LGII* gene (10q23.33) encodes leucine-rich glioma inactivated 1 (Lgi1) or epitempin protein which maintains physiology of K^+ channels in the neurons. It is needed in post-natal maturation and dendritic thinning of glutamatergic synapses and found to be a Nogo receptor 1 ligand, which antagonizes myelin-based growth inhibition [45]. Microtubule-associated monooxygenase, calponin and LIM domain containing 1, *MICAL1* (6q21) encode for monooxygenase enzyme which prevents repolymerization of F-actin by oxidation of methionine residues on the actin filament.

4.1.4.21 JME

This epilepsy has a complex inheritance pattern. When the disorder is caused by a mutation in the *GABRA* gene, it is inherited in an autosomal dominant pattern. The *GABRA1* gene is located on chromosome 5q34-q35, which provide instructions for synthesizing α -1 subunit of the GABA_A receptor, the principal receptor that mediates the inhibitory synaptic transmission in the mammalian brain. Other gene mutations which cause JME are *CACNB4* (2q22-q23) and *CLCN2* (3q26). The *CACNB4* gene provides instructions for synthesizing β -4 subunit of L-type calcium channel, this subunit is most often associated with coordinating movements, which is the function of the cerebellum whereas *CLCN2* gene provides instructions for synthesizing a chloride channel called CLC-2. It is predicted that the loss of function of this gene causes neuronal excitability and this channel regulates the volume of neurons by playing a role in osmoregulation [56].

4.1.4.22 EJM1

When juvenile myoclonic epilepsy shows mutations in the *EFHC1* gene (6p12.2) [57, 82], then it is regarded as juvenile myoclonic epilepsy type 1. It provides instruction for making a protein called EF-hand domain which function as a calcium-binding protein (EFHC1). The role of the EFHC1 protein is not completely understood, although it is thought to help regulate calcium homeostasis by interacting with another protein that acts as a calcium channel, allowing calcium ions to move across the cell. The movement of these ions is critical for normal signalling between neurons in the brain and other parts of the nervous system. It has also shown to stimulate apoptosis of cells.

4.1.4.23 JAE

CAE and JAE also share genomic similarity i.e., *CLCN2* gene mutation apart from clinical features of seizures [94].

4.1.4.24 FPEVF

Several cases have shown mutation in *DEPDC5* gene (22q12.3) and few mutations in *NPRL2* gene (3p21.31) and *NPRL3* gene (16p13.3). *DEPDC5* gene provides instruction for a complex called GATOR1. This complex regulates mTOR pathway, which plays an important role

in growth and development and plasticity of nerve cells. Few mutations in *NPRL2* gene and *NPRL3* gene have also been reported. These two genes have a similar function as *DEPDC5* mentioned above [95].

4.2 Acquired causes of epilepsy

Acquired causes of epilepsy arise after injury of the cerebral cortex by traumatic, vascular, infectious and other insults, but there is no clear understanding of the cellular and molecular events initiated by the injury that causes cortical excitability. Injection of a foreign antigen into monkey cortex evoked an immune attack and triggered epileptic seizures, suggesting the role of an autoimmune mechanism may be responsible after brain infection or injury (Kopeloff et al., 1942). Almost 5 decades later, evidence has arisen demonstrating an autoimmune mechanism in epilepsy, Rasmussen's encephalitis (RE). RE is a rare progressive neurodegenerative illness of unknown cause that typically affects children in the first decade of life. This disease destroys the cortex of a single cerebral hemisphere and manifests as loss of motor, sensory, visual and language functions, dementia and severe seizures that are refractory to medication. Rabbits immunized with glutamate receptor subunit 3 (GluR3) protein developed epilepsy and cerebral changes characteristic of RE. Successful Plasma exchanges therapy for RE led to the discovery of anti-GluR3 antibodies in RE patients [55, 63].

5. Epilepsy Imitators

There are certain conditions in which epileptic and non-epileptic events co-exist and may imitate and misdiagnosed as epilepsies or vice versa. They are called as epileptic imitators [96], nonepileptic seizures, psychogenic seizures or pseudoseizures [4]. Because of the similarity between these two, many epileptic seizures were considered as tics [34, 86], night terrors, sleepwalking or any other attacks [42]. Hence, it is important to know the list (Table 3) of diseased conditions for a correct diagnosis of epilepsy events from non-epilepsy events [96].

6. Diagnosis

To diagnose epilepsy, a doctor should be able to differentiate between an epileptic seizure and nonepileptic seizure. This can involve a neurological examination, neuroimaging, genetic testing, metabolic evaluation, lumbar puncture test and other tests.

6.1 Neurological test/Neuro-psychological Assessment

A neurological test includes various methods of detecting abnormalities within the brain. This test starts with some simple questions and mental evaluation tests. For instance: A test of memory, including how well a person can remember words, a test of the ability to name and recall certain objects, simple calculations, muscle function testing by walking a few steps, reflex tests, sense test (to know which part of the brain is affected) [97]. This assessment also helps in determining the type of epilepsy; impaired memory indicates temporal lobe epilepsy [98].

6.2 Neuroimaging techniques

6.2.1 Electroencephalogram (EEG)

It is the most common neuroimaging technique that can detect abnormal electrical activity in the brain such as unilateral spikes (focal epilepsy), or diffuse bilateral spikes (generalized epilepsy). The activation procedure is performed to increase the yield of epileptic activity during EEG by hyperventilation and photic stimulation.

Hyperventilation for 3 min has a seizure-provoking effect (absence seizure) and photic stimulation helps in obtaining paroxysmal epileptiform discharges or generalized seizure in a person susceptible to generalized epilepsy. Simultaneous video-EEG recording can be done over several days to increase the diagnostic yield and to differentiate an epileptic seizure from a nonepileptic event. The EEG can be repeatedly normal or complex in patients with epilepsy, especially in frontal and temporal lobe epilepsy. In such cases, intracranial EEG monitoring, an invasive technique using strips or depth electrodes placed under the skull is performed to define a seizure focus [98].

6.2.2 Amplitude-integrated EEG (aEEG)

Cerebral seizure activity, surveillance of antiepileptic drug treatment and prediction of cerebral outcome after birth asphyxia in preterm and term infants has been widely used in neonatal intensive care units (NICU). In such cases, an aEEG is an accessible, safe method and provides easily interpretable data for continuous cerebral function monitoring. It is recorded with two or four scalp electrodes, like EEG. This method is complementary to the existing techniques such as EEG, MRI and other techniques [99].

6.2.3 Magnetic resonance imaging (MRI)

This uses a magnetic field and radio waves to give a finer image of the brain. It can figure out structural brain abnormalities, lesions that cause seizures and changes in the white matter of the brain. Hence, it is considered the best imaging technique for epilepsy because it is especially sensitive to detecting a variety of seizure causes [100]. Functional MRI analyses blood flow by using blood oxygen level-dependent (BOLD) and detect changes in brain electrical activity which cannot be determined by other imaging techniques [101]. Another method called magnetic resonance spectroscopy measures the concentrations of neurochemicals in different brain regions and sometimes can assist in recognizing a seizure focus [102].

6.2.4 Magnetoencephalography (MEG)

MEG uses magnetic coils and sensors that can detect the electromagnetic field produced by neurons. It is non-invasive, painless like an EEG. But it is more accurate than EEG because the skull and the tissue surrounding brain do not interfere with the readings whereas they affect EEG's readings. This is often done with EEG or magnetic resonance imaging (MRI), which helps to pinpoint the area of the brain that seizures are arising from [100].

6.2.5 Computerized Tomography (CT) Scan

A computerized tomography (CT) or computerized axial tomography (CAT) scan utilizes X-rays and can detect problems in the brain. It is considered as less sensitive because of its lower resolution compared to MRI. But a CT scan is preferred over MRI in emergency conditions to rule out immediate treatment.

6.2.6 Positron emission tomography (PET)

This scan is usually helpful in detecting focal seizures. A low dose of radioactive material is injected into the patient's vein to record how the brain uses sugar in between seizures to identify any areas in the brain that aren't metabolized sugar properly, which is an indicator of the seizure's origin.

6.2.7 Single-photon emission computerized tomography (SPECT)

This is a specialized test that is used only if other tests failed to locate seizure origin. It is same as a CT scan except that like a PET scan, a low dose of radioactive material is injected, which shows the blood flow activity in the brain helping to pinpoint the origin of seizures [100].

6.2.8 Intraoperative electrocorticography (ECoG)

In 1954, Penfield and Jasper at the Montreal Neurological Institute discovered a brain monitoring technique called electrocorticography (ECoG) intending to identify seizure foci and facilitate epilepsy surgery more precisely. In ECoG, the electrode leads are placed directly over a surgically-exposed cortical surface that can be performed in the operating room for a relatively short duration at the time of surgery; intraoperative ECoG (acute) or can be performed outside the operating room (after surgical electrode implantation) or extra-operative ECoG for a longer time (chronic) to record abnormal electric signals in the brain. It was found in a survey in 1992 that ECoG to be used by over 80% by surgeons around the globe [103].

6.3 Genetic testing

The genetic tests most commonly utilized in the evaluation of patients with epilepsy include chromosomal microarray, epilepsy gene panels, and whole-exome sequencing. Each test has its specific benefits and limitations. The diagnostic yield is variable for all tests [104].

6.3.1 Chromosomal microarray (CMA)

CMA is designed to detect missing or additional pieces of genetic material also known as copy number variants (CNVs). This is recommended as the first-tier test for children with developmental delay, intellectual disability and autism. The diagnostic yield for CMA in patients with epilepsy is estimated to be approximately between 4-17%.

6.3.2 Epilepsy gene panels

This technique makes use of next-generation sequencing (NGS) technology to analyse multiple genes associated with epilepsy. The diagnostic yield of epilepsy gene panels is estimated to be approximately 23%, though this may vary based on additional factors such as the age of seizure onset, clinical indication and family history.

6.3.3 Whole-exome sequencing (WES)

Like gene panel, WES utilizes NGS to sequence all of the exons of protein-coding regions (genome-scale genetic testing) in the patient's DNA. The estimated diagnostic yield is approximately 32% for proband only testing (patient) or even higher when testing is performed using a trio-based analysis (i.e. child and both parents). There is also the possibility for genetic variants to be identified in genes unrelated to epilepsy (secondary findings) because this testing analyses the entire exome. It has therefore been recommended by the American College of Genetics and Genomics (ACMG) that patients undergoing genome-scale genetic testing should provide written informed consent that is obtained by qualified genetics professional and patients should be offered the option to opt-out of receiving secondary findings after receiving appropriate counselling.

6.4 Metabolic evaluation
Evaluation of cerebrospinal fluid (CSF), urine, blood, serum helps in elucidating the etiology and type of epilepsy since many metabolic disorders lead to epilepsy. In neonatal seizures, metabolic evaluation is mandatory because of inborn errors of metabolism (IBMs) accounts for 1-7 % of all cases in the United States. A blood test can also look at infections that might explain seizure cause [105].

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6.5 Lumbar puncture (spinal tap)

In this test, CSF collected from the lumbar region of the spinal is analyzed to diagnose infections, bleeds, inflammatory conditions and cancers of the brain and spinal cord [106] and performed in children (under 18 mo) with febrile seizures and old patients [107].

6.6 Electrocardiogram (ECG)

It is possible to be misdiagnosed nonepileptic seizures with epileptic seizures when patients have a condition called syncope. In such cases, a neurologist may want to do an ECG to check the heart [100].

6.7 Wada test

It is officially known as the intracarotid sodium amobarbital procedure (ISAP). In this test, angiography is performed by injecting an X-ray dye through a catheter, while the X-ray machine records pictures of the flow of the dye. Then, a medication is injected to temporarily anesthetize on one side of the body. Memory, language, thinking and other functions are tested while keeping that side anesthetized. The Wada test can help the epilepsy team to evaluate how important each side of the brain is for language and memory functions and to determine the type of surgery for seizures while preserving areas of the brain connected to speech and memory [108].

7. Treatment of epilepsy

Epilepsy is usually treated with prescription drugs to control seizures, but it may also involve surgery, nerve stimulation devices, or special diets, depending on the situation. Regardless of the treatment course, the end goals are the same: to help the patients to live the fullest life, prevent seizures and minimize the effects of the disorder.

7.1 Antiepileptic drugs (AEDs)

Epilepsy treatment with AEDs would become seizure-free provided appropriate medications used. According to WHO, 70% of cases can be treated with medications and 30% are drug-resistant. Drug resistant epilepsy (has the risk of mortality) should initially be tried with a combination of AEDs and if remain untreated, then epilepsy surgery and other therapies should be used. Mechanisms of AEDs [55-56, 97], side effects [27] with their pharmacokinetic profile (Drug bank) are listed in Table 4.

7.2 Surgeries

Antiepileptic drugs fail to control seizures in about 30% of people with epilepsy. This is known as drug-resistant or intractable or refractory epilepsy. Surgery is recommended only when the brain has a tumor or lesion that causes seizures and in focal seizures. The right surgery will depend on the type of epilepsy as well as the results of pre-surgical evaluation and testing. After surgery, patients either become seizure-free or fewer seizure episodes. If medication is still needed, it is usually a lower dose. Four types of surgeries are used to treat epilepsy [27].

7.2.1 Lobectomy

This is the most common type of epilepsy surgery recommended only for focal seizures. It is two types: temporal and frontal. In temporal lobectomy, a part of the temporal lobe is removed. It has a high success rate. Many patients have fewer seizures or become seizure-free after surgery, whereas in frontal lobectomy, a part of the frontal lobe is removed. It has a lower success rate than temporal lobectomy.

7.2.2 Multiple Subpial Transection

It is performed when an area of the brain cannot be removed. It involves making shallow cuts in the cerebral cortex. It was found to be temporarily successful for Landau-Kleffner syndrome.

7.2.3 Corpus Callosotomy

Corpus callosum connects and facilitates communication between the right and left cerebral hemispheres, but it is not necessary to survive. The corpus callosum is removed either small portion or completely so that it can stop spreading epileptic discharges between hemispheres.

7.2.4 Hemispherectomy

It is one of the oldest surgical techniques for epilepsy. It is only performed if one hemisphere is not functioning due to damage from injury or seizures such as RE. The success rate is 70%. The two most common types of hemispherectomy include; Anatomical hemispherectomy: Frontal, parietal, temporal, and occipital lobes are removed from the hemisphere while leaving the brain stem, basal ganglia, and thalamus intact. It is the most extreme form, which may cause some loss of abilities. People who underwent this surgery are often able to function well. Functional hemispherectomy: Seizures arising region are removed from the hemisphere as well as disconnecting the corpus callosum.

7.3 Specialist-Driven Therapies

Specialist-driven therapies are usually adjunctive to antiepileptic treatments.

7.3.1 Vagus Nerve Stimulation (VNS therapy)

It is FDA-approved therapy to treat refractory epilepsy in adults and children over 4 y old. A vagus nerve stimulator, similar to a pacemaker is implanted under the skin on the chest which delivers regular electrical pulses and a wire runs to the left vagus nerve near the neck region. The electrical signals can lessen the severity and frequency of seizures. Up to 20 to 40% reduction in seizures [27]. The device is switched on after 4 weeks of implantation and stimulated 30 sec for every 5 min. A special magnet can be passed over the stimulator to control the aura. Usually, it takes 2 y to control seizures [110].

7.3.2 Responsive Neurostimulation

Similar to VNS therapy, responsive neurostimulation is like a pacemaker for the brain and FDA-approved for adults with drug-resistant focal epilepsy. It works by continuously monitoring brain waves and analyses patterns to detect abnormalities, then it responds with electrical stimulation that returns brainwaves to normal, preventing the seizure onset.

7.3.3 Deep Brain Stimulation (DBS)

In DBS, electrodes are placed in the thalamus. They are connected to a device that is implanted under the skin in the chest that sends electrical impulses to the brain. This can lessen or even stop seizures. DBS has been approved in adults with partial epilepsy by FDA [27].

7.3.4 Trigeminal nerve stimulation (TNS)

It is a novel non-invasive neuromodulatory device, which contains a pulse generator attached to a single-use electric patch. Low level electric signals are sent to patches that are placed on the patient's forehead, which stimulate trigeminal nerve fibers and send therapeutic signals to seizure arising areas of the brain. The data from the long-term study showed TNS to be a promising treatment for drug-resistant epilepsy [111].

7.4 Nutritional therapy/Diet

It is an economical and promising option with minimal adverse effects for the treatment of epileptic patients and important adjunct to the available antiepileptic drugs (AEDs) [112].

7.4.1 Amino acids

7.4.1.1 Threonine

Gietzen et al. demonstrated that deficiency of threonine induces increased latency, duration and severity of seizures in Pentylentetrazole induced and Maximal electroshock induced seizures in rats. Its deficiency thought to alter numerous gene transcripts of receptors, ion channels, transporters and structural proteins in the anterior piriform cortex. This alteration causes decreased synthesis of GABA and potentiates glutamate released [113].

7.4.1.2 Leucine

L-leucine has excitatory activity in the brain because it is the source of amination for glutamate synthesis [114]. In contrast, even very low concentration of D-leucine alleviate seizures even after the onset of seizure activity in mice as potent as diazepam without any sedative effects. It works by inhibiting long term potentiation in the hippocampal CA1 region [115].

7.4.1.3 Carnosine

It is a precursor to a key inhibitory neurotransmitter in the brain (GABA), neuroprotective against metal-mediated neurotoxicity and antioxidant by scavenging reactive oxygen species (ROS), nitric oxide and carbonyl species. Carnosine and its derivatives found to show reduced lipid peroxidation, increased antioxidant levels and anticonvulsant activity against PTZ induced seizure in animals, but further studies are required to confirm the role of carnosine and its derivatives in humans [116].

7.4.1.4 Histidine

It is a precursor of histamine and neurotransmitter in the brain. Brain histamine levels might play an important role in epileptogenesis. It is thought to increase carbamazepine levels as well as improves memory in the kindling model in rats. Therefore, it serves as a beneficial adjuvant for AEDs for the treatment of epilepsy associated with impairment of spatial memory [117].

7.4.1.5 Carnitine

Carnitine deficiency can lead to seizures as a side effect. Low nutritional intake of carnitine, metabolic disorders, and use of AEDs (polytherapy) lead to its deficiency. L-carnitine was found to be effective against ammonium acetate induced seizures in mice [118] and has some ameliorative effect against PTZ-kindled mice [119].

7.4.1.6 Taurine

An inhibitory amino acid in the brain acts by causing hyperpolarization of neurons. Taurine treatment found to show a reduction in seizures in 30% of patients. However, the efficacy decreases with time due to its excretion through urine. The possible mechanisms by which taurine can decrease seizures are; by decreasing the intracellular level of Ca^{+2} , inhibiting the release of D-aspartate (analogue of L-glutamate) and activating GABA_A receptors [112].

7.4.2 Minerals

7.4.2.1 Magnesium

Magnesium is the fourth most common mineral in the human body and has a role in enzyme activities, utilization of vitamin B6 (a cofactor required for GABA synthesis) and inhibits NMDA receptor. It is reported that people with epilepsy have lower Mg levels [112]. Mutations in Mg²⁺ transporter causes decreased cellular levels of Mg²⁺ in CAE have been identified [84].

7.4.2.2 Manganese

It is an essential element required in low concentration for proper development and functioning of the brain and for the activity of glutamine synthetase which converts glutamate to glutamine. Deficiency of manganese causes accumulation of glutamate (excitotoxicity). However, at the same time overdose of manganese causes toxicity, which is associated with tremors and seizures. Therefore, a low concentration of manganese is recommended in people with epilepsy [112].

7.4.2.3 Zinc and Copper

These elements play an important role in several cellular functions and found in the hypothalamus, hippocampus and olfactory bulb. They accumulate in the synaptic vesicles and co-released with neurotransmitters (glutamate). Zinc supplementation for 4 weeks significantly improved seizures by increasing seizure threshold, weight and cognition against status epilepticus in rats. Serum Cu/Zn levels were significantly elevated in epileptic patients. It is hypothesized that lowering zinc levels augments GABA, an inhibitory neurotransmitter [120].

7.4.2.4 Calcium

Hypocalcemia causes increased neuronal irritability due to reduced extracellular concentration of calcium and elevated intracellular levels, resulting in calcium deposition (brain calcinosis) mainly in the periventricular regions because calcium is responsible for the initiation of neuromuscular irritability mediated through acetylcholine [121]. Hypocalcemia can lead to GTC or focal seizures. Hypercalcemia is much more common than hypocalcemia, but is less frequently associated with acute seizures. Hence, treatment should be based on the biological gradient of calcium [122].

7.4.2.5 Sodium

Hyponatremia (<135 mEq/L) was the only detectable cause of seizures in 70% of infants younger than 6 mo and adults reported in several retrospective studies. While hyponatremia is the cause of seizures, hypernatremia (>145 mEq/L) is likely to be after the onset of seizures, especially generalized tonic-clonic seizures. During seizures, intracellular glycogen is metabolized to lactate, which increases the intracellular osmolality of muscle fibers and influx of water, thus causes hypernatremia. Immediately after this, the loss of water from brain cells leads to the shrinkage of the brain [122].

7.4.3 Vitamins

7.4.3.1 Vitamin B₆

Vitamin B₆ is a coenzyme necessary for the functioning of glutamate decarboxylase, which converts glutamate to GABA. The active form of Vitamin B₆ used by the human being is pyridoxal 5'-phosphate (PLP). Deficiency of B₆ increases the risk of seizures (pyridoxine dependent seizures). Vitamin B₆ deficiency causes a rare genetic disorder resulting in severe neonatal seizures and mental disability, which requires a lifelong intake of Vitamin B₆. However, the excessive intake of B₆ causes damage to sensory nerves that may lead to numbness of hands and feet. Therefore, the dose should be adjusted to reach the therapeutic efficacy in the treatment of epilepsy [112].

7.4.4 Ketogenic Diet (KD)

In 1911, a pair of physicians named Gulep and Marie were the first to use starvation in 20 patients for treatment of epilepsy and reported that seizures were less severe during treatment. A decade later, the appearance of acetone and beta-hydroxybutyrate (BHB) was observed in normal subjects by starvation or a diet containing a high proportion of fat and very low proportion of carbohydrates (Woodyatt, 1921). Simultaneous observations were made by Dr Wilder at the Mayo Clinic and reported that ketonemia is the benefit of fasting. Wilder proposed a diet as effective as fasting and could be maintained for a longer period and coined the term “Ketogenic Diet” [123]. KD is a calorie-restricted diet rich in fats with sufficient protein (1 g/kg) and limited carbohydrates (5-10 g/day) that mimic starvation and has beneficial effects on the seizures. The “classic” ketogenic diet, developed at John Hopkins Institute contains a 4:1 ratio of fats to carbohydrates and proteins combined. KD was well tolerated as effective as ACTH in the long term and less severe adverse effects in drug-resistant Infantile spasms [124].

The mechanisms by which this diet works [112] in seizures are 1. Acetyl CoA produced from ketone bodies gets utilized along with oxaloacetate in the citrate synthetase step in the TCA cycle. Thus, there is no availability of oxaloacetate for the conversion of glutamate to aspartate and more glutamate is available and less production of aspartate. The available glutamate is utilized for the synthesis of GABA using glutamic acid decarboxylase. 2. The ketone bodies, which are produced through metabolism hyperpolarize cell membranes and reduces excitability by activating K_{2p} potassium channels in the brain. 3. Calorie (glucose) restriction decreases the energy release through glycolysis, which reduces the high level of synaptic activity. As a result, neuronal firing gets reduced or stopped. Another proposed mechanism suggests that the release of ATP through pannexin hemichannels in neurons due to glucose restriction. This extracellular ATP degraded to adenosine (by ectonucleotidases) and activates A1 receptors, which in turn activates ATP sensitive potassium (K_{ATP}) channels. 4. KD mainly includes polyunsaturated fatty acids (PUFAs) (e.g., Docosahexaenoic acid, Arachidonic acid, Eicosapentaenoic acid) that are involved in inhibition of fast voltage-gated Na channels, L-type Ca channels and activate K_{2p} potassium channels, thus diminishes neuronal excitability. The PUFAs also is shown to trigger peroxisome proliferator-activated receptors (PPARs) which are known to inhibit the proinflammatory transcription factors, as the inflammation is considered as one of the contributors to seizure generation. 5. KD also enhances the release of norepinephrine and leptin both of which has an anticonvulsant effect.

7.4.5 Atkins Diet

In 1970, Dr Rober Atkins prepared a diet named as “Atkins Diet” to combat obesity and consists of 60% fat, 30% protein and 10% carbohydrate, whereas KD comprises of 80% fat, 15% protein and 5% carbohydrate. Hence, it is an alternative to the ketogenic diet for treating epilepsy. It is reported that the efficacy of the Atkins diet in seizure reduction is upto 50-90% in 45% of patients and >90% in 28% of patients which is very much similar to that of the ketogenic diet [112].

7.4.6 Antioxidant therapies

Oxidative stress is regarded as a possible mechanism in the pathogenesis of epilepsy. This condition occurs when the steady-state balance of prooxidants and antioxidants is altered. Prooxidants are free radicals, or atoms with an unpaired electron such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). The harmful effects of free radicals in the organism induce several defense mechanisms (antioxidants), such mechanisms include; removal of free radicals by enzymatic antioxidants such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and non-enzymatic antioxidants. The use of antioxidants for the treatment of epilepsy has gained considerable importance. Several studies have demonstrated oxidative damage to protein, lipids, DNA and RNA caused by an increase in ROS or RNS production in persistent seizures (status epilepticus) induced by Pilocarpine and kainic acid.

7.4.6.1 Enzymatic antioxidants

7.4.6.1.1 SOD

SOD protects cells from superoxide ($O_2^{\bullet-}$) action. It is responsible for superoxide dismutation reaction into H_2O_2 and O_2 . There are three types of SODs: Copper-Zinc SOD, Manganese SOD and Extracellular SOD. Copper-zinc SOD is present mainly in the cytoplasm and peroxisomes. Manganese SOD is present in mitochondria. These enzymes have antitumor activity. Extracellular SOD also contains copper and zinc in its structure and it is synthesized in the cells and secreted into the extracellular matrix.

7.4.6.1.2. CAT and GPx

They protect cells against H_2O_2 by converting into H_2O and O_2 .

7.4.6.2 Nonenzymatic Antioxidants

Vitamin C is a hydrosoluble antioxidant with some prooxidant activity. Its antioxidant potential is due to the removal of $O_2^{\bullet-}$ and HO^{\bullet} and regenerates oxidized vitamin E. Vitamin E (α -tocopherol) is another potent antioxidant, which scavenges peroxy radicals rapidly and interrupts the free radical chain propagation. During this reaction, vitamin E becomes tocopheryl, which is less reactive than the lipid radical and transformed again into tocopherol through the action of Vit C. β -carotene is a hydrophilic precursor of vitamin A. Its antioxidant activity is related to the removal of $O_2^{\bullet-}$ and other free radicals formed during lipid peroxidation. Endogenous pineal gland hormone “Melatonin” is another free radical scavenger. Melatonin has been shown to be an antiepileptic agent in animal models of epilepsy-induced by KA, PTZ and Pilocarpine.

Flavonoids are more efficient antioxidants than vitamins C and E. Their antioxidant activity depends on its structure. Sequestering activity is directly related to the oxidation potential of flavonoids and the species to be scavenged. The smaller the oxidation potential, the greater its activity as a free radical scavenger [125].

8. Conclusion

It is concluded from this review article that the clinical features of epilepsy syndromes vary according to the affected part of the brain involved and age of onset of epilepsy. Genes that have undergone mutations determines the affected part and age. Thus, genetics play an important role in the arising of these syndromes. It is also observed that most of the mutations are of ionic channels and among all, neonatal and infantile seizures are found to be severe and progressive compared to childhood and adulthood onset epilepsy. Nevertheless, these terms

cannot remain the same because with the advent in the discovery of new drugs and other therapies would make changes in these disorders into less severe.

Declaration of competing interest

The author declares no conflict of interest. The author alone is responsible for the content and writing of this article.

Tables

Table 1. Classification of epilepsy syndromes

I) Based on the affected area
a) Generalized seizures Absence Tonic-Clonic Myoclonic Atonic
b) Focal Seizures
c) Combined Focal-Generalized seizures
d) Epileptic spasms
II) Based on the age of onset
a) Neonatal Rigidity and multifocal seizure syndrome, lethal neonatal Benign familial neonatal epilepsy
b) Neonatal-Infantile Early myoclonic encephalopathy Benign familial neonatal-infantile epilepsy
c) Infancy Ohtahara syndrome Jamuar syndrome Benign familial infantile epilepsy West syndrome Malignant migrating partial seizures of infancy Epilepsy and mental retardation limited to females Dravet syndrome
d) Childhood Generalized epilepsy with febrile seizures plus Childhood absence epilepsy Lennox-Gastaut syndrome Landau-Kleffner syndrome Panayiotopoulos syndrome Jeavons syndrome Doose syndrome Rolandic epilepsy

<p>Photosensitive occipital lobe epilepsy</p> <p>Sunflower syndrome</p> <p>Idiopathic photosensitive occipital epilepsy</p> <p>Autosomal dominant nocturnal frontal lobe epilepsy</p>
<p>e) Adolescence and adulthood</p> <p>Autosomal dominant partial epilepsy with auditory features</p> <p>Familial mesial temporal lobe epilepsy</p> <p>Juvenile myoclonic epilepsy</p> <p>Juvenile absence epilepsy</p>
<p>f) Any age</p> <p>Familial partial epilepsy with variable foci</p>

Table 2. Genes involved in epilepsy syndromes

Abbreviation	Syndrome	Channel/Receptor	Gene(s)	Chromosome
RMFSL	Rigidity and Multifocal Seizure Syndrome, Lethal Neonatal	BRAT1	<i>BRAT1</i>	7p22.3 5
BFNE	Benign Familial Neonatal Epilepsy	Kv7.2 Kv7.3 K _{Ca} 4.1 Na _v α1.2 Nicotinic acetylcholine receptor	<i>KCNQ2</i> <i>KCNQ3</i> <i>KCNQ5</i> <i>SCN2A</i> <i>CHRNA4</i>	20q13.33 8q24 6q13 2q24.3 20q13.33
EME	Early Myoclonic Encephalopathy	ErbB4 AMT CDK STXBP1 Spectrins Mitochondrial Glutamate Transport	<i>ErbB4</i> <i>AMT</i> <i>CDKL5</i> <i>STXBP1</i> <i>SPTAN1</i> <i>SLC25A22</i>	2q34 3p21.31 Xp22.13 9q34.11 9q34.11 11p15.5
BFNIE	Benign Familial Neonatal-Infantile Epilepsy	Na _v α1.2	<i>SCN2A</i>	2q24.3
EIEE	Early Infantile Epileptic Encephalopathy (Ohtahara syndrome)	ARX Collybistin BRAT1 CDK STXBP1	<i>ARX</i> <i>ARHGEF9</i> <i>BRAT1</i> <i>CDKL5</i> <i>STXBP1</i>	Xp21.3 Xq11.1 7p22.3 5 Xp22.13 9q34.11

		Mitochondrial- Glutamate Transport Spectrins Na _v 1.6 ST3GAL3 Kv7.2 PCDH19 PNKP Phospholipase-C and CDK-16 TBC1D24	<i>SLC25A22</i> <i>SPTAN1</i> <i>SCN8A</i> <i>ST3GAL3</i> <i>KCNQ2</i> <i>PCDH19</i> <i>PNKP</i> <i>PLC-β1</i> <i>TBC1D24</i>	11p15.5 9q34.11 12q13.13 1p34.1 20q13.33 Xq22.1 19q13.33 20p12.3 16p13.3
JS	Jamuar Syndrome	UGDH	<i>UGDH</i>	4p14
BFIE	Benign Familial Infantile Epilepsy	SNAP25 Na _v α1.2 Kv7.2 Kv7.3	<i>PRRT2</i> <i>SCN2A</i> <i>KCNQ2</i> <i>KCNQ3</i>	16p11.2 2q24.3 20q13.33 8q24
WS	West Syndrome	CDK MeCP-2 ARX STXBP1 Spectrins Phospholipase-C and CDK-16 UDP-N-acetylglucosamine transferase	<i>CDKL-5</i> <i>MeCP-2</i> <i>ARX</i> <i>STXBP-1</i> <i>SPTAN1</i> <i>PLC-β1</i> <i>ALG13</i>	Xp22.13 Xq28 Xp21.3 9q34.11 9q34.11 20p12.3 Xq23
MMPSI	Malignant Migrating Partial Seizures of Infancy	K _{Ca} 4.1 Na _v 1.1 Na _v 1.6 Phospholipase-C and CDK-16 BRAT1	<i>KCNT1</i> <i>SCN1A</i> <i>SCN8A</i> <i>PLC-β1</i> <i>BRAT1</i>	9q34.3 2q24.3 12q13.13 20p12.3 7p22.3 5
EFMR	Epilepsy and Mental Retardation Limited to Females	PCDH19	<i>PCDH19</i>	Xq22.1
SMEI/DS	Severe Myoclonic Epilepsy of Infancy (Dravet Syndrome)	Na _v 1.1	<i>SCN1A</i>	2q24.3

		Na _v α1.2 SCN1B Na _v 1.6 Na _v 1.7 STXBP1 GABA _A GABA _A PCDH19	SCN2A SCN1B SCN8A SCN9A STXBP1 GABRA1 GABRG2 PCDH19	2q24.3 19q13.11 12q13.13 2q24 9q34.11 5q34-q35 5q34 Xq22.1
GEFS ⁺	Generalized Epilepsy with Febrile Seizures Plus	Na _v 1.1 Na _v 1.2 SCN1B SCN2B Na _v 1.7 GABA _A GABA _A Syntaxin HCN1	SCN1A SCN2A SCN1B SCN2B SCN9A GABRD GABRG2 STX1B HCN1	2q24.3 2q24.3 19q13.11 11q23.3 2q24 1p36.33 5q34 16p11.2 5p12
CAE	Childhood Absence Epilepsy	Ca _v 3.2 CLC-2 GABA _A GABA _A GABA _A - NIPA2 GLUT1	CACNA1H CLCN2 GABRA1 GABRB3 GABRG2 JRK NIPA2 SLC2A1	16p13.3 3q26 5q34-q35 15q12 5q34 8q24.3 15q11.2 1p34.2
LGS	Lennox-Gastaut Syndrome	UDP-N-acetylglucosamine transferase	ALG13	Xq23
LKS	Landau Kleffner Syndrome	GluN2A Reelin Eph Nidogen-2	GRIN2A RELN EPHB2 NID ₂	16p13.2 7q22.1 1p36.12 14q22.1
EMA	Eyelid Myoclonic Absences (Jeavons syndrome)	NEXMIF	KIAA2022	Xq13.3
MAS	Myoclonic Atonic Syndrome (Doose)	Na _v 1.1	SCN1A	2q24.3

	Syndrome)	SCN1B GABA _A GLUT1 SynGap1 NEXMIF CHD2	<i>SCN1B</i> <i>GABRG2</i> <i>SLC2A1</i> <i>SYNGAP1</i> <i>KIAA2022</i> <i>CHD2</i>	19q13.11 5q34 1p34.2 6p21.32 Xq13.3 15q26
RS	Rolandic Syndrome	HAT Kv7.2 GluN2A	<i>ELP4</i> <i>KCNQ2</i> <i>GRIN2A</i>	11p13 20q13.33 16p13.2
ADNFLE	Autosomal Dominant Nocturnal Frontal Lobe Epilepsy	Nicotinic-Acetylcholine Receptor CRH Ca _v 1.4 K _{Ca} 4.1 GATOR1 GATOR1 GATOR1 PRiMA1	<i>CHRNA2</i> <i>CHRNA4</i> <i>CHRN2</i> <i>CRH</i> <i>CABP4</i> <i>KCNT1</i> <i>DEPDC5</i> <i>NPRL2</i> <i>NPRL3</i> <i>PRIMA1</i>	8p21.2 20q13.33 1q21.3 8q13 11q13.2 9q34.3 22q12.3 3p21.31 16p13.3 14q32.12
ADPEAF	Autosomal Dominant Partial Epilepsy with Auditory Features	Epitempin Monooxygenase Reelin	<i>LGII</i> <i>MICAL1</i> <i>RELN</i>	10q23.33 6q21 7q22.1
JME	Autosomal Dominant Juvenile Myoclonic Epilepsy	GABA Calcium channel CLC-2	<i>GABRA1</i> <i>CACNB4</i> <i>CLCN2</i>	5q34-q35 2q22-q23 3q26
EJM1	Juvenile Myoclonic Epilepsy Type 1	EFHC1	<i>EFHC1</i>	6p12.2
JAE	Juvenile Absence Epilepsy	CLC-2	<i>CLCN2</i>	3q26
FPEVF	Familial Partial Epilepsy with Variable Foci	GATOR1 GATOR1 GATOR1	<i>DEPDC5</i> <i>NPRL2</i> <i>NPRL3</i>	22q12.3 3p21.31 16p13.3

Table 3. List of Epilepsy Imitators

Epilepsy Imitators	Disease Conditions
1. Sleep-related conditions	a. Parasomnias
	b. Hypnagogic jerks
	c. REM sleep disorders
	d. Benign neonatal sleep myoclonus
	e. Narcolepsy-cataplexy
	f. Periodic leg movements
	g. Sleep-related rhythmic movement disorders
2. Behavioural, psychological and psychiatric disorders	a. Daydreaming /inattention
	b. Eidetic imagery
	c. Self-gratification
	d. Panic attacks
	e. Tantrums and rage reactions
	f. Non-epileptic seizures
	g. Out of body experiences
	h. Dissociative states
	i. Hallucinations in psychiatric disorders
	j. Fabricated / factitious illness
3. Syncope and anoxic seizures	a. Vasovagal syncope
	b. Hyperventilation syncope
	c. Reflex anoxic seizures
	d. Compulsive Valsalva
	e. Breath-holding attacks
	f. Neurological syncope
	g. Long QT and cardiac syncope
	h. Imposed upper airways obstruction
	i. Orthostatic intolerance
	j. Hyper-cyanotic spells
4. Paroxysmal movement disorders	a. Tics
	b. Benign paroxysmal tonic upgaze
	c. Stereotypies
	d. Paroxysmal exercise-induced dyskinesia
	e. Paroxysmal non-kinesigenic dyskinesia
	f. Paroxysmal kinesigenic dyskinesia
	g. Episodic ataxias
	h. Alternating hemiplegia

	i. Opsoclonus-myoclonus syndrome
	j. Hyperekplexia
5. Migraine associated disorders	a. Familial hemiplegic migraine
	b. Cyclical vomiting
	c. Benign paroxysmal vertigo
	d. Benign paroxysmal torticollis
	e. Migraine with visual aura
6. Miscellaneous Events	a. Benign myoclonus of infancy and shuddering attacks
	b. Spinal myoclonus
	c. Jitteriness
	d. Paroxysmal extreme pain disorder
	e. Spasmus nutans
	f. Sandifer syndrome
	g. Non-epileptic head drops
	h. Raised intracranial pressure

Table 4. Pharmacological profile of AEDs

Antiepileptic drugs	Mechanism	Bioavailability (%)	t _{1/2} (h)	Protein binding %	Dose (mg/day)	Side effects
Carbamazepine	Block voltage-dependent Na ⁺ channels, prolongation of inactivated state	75-85	8-24	75	600-1800	Drowsiness, blurred vision, diplopia, disequilibrium, leukopenia, hepatic failure
Oxcarbazepine	Inhibition of voltage-dependent Na ⁺ channels Inhibition of voltage-activated Ca ⁺² currents	100	>2	40	1200-2400	Dizziness, diplopia, headache, blurred vision, somnolence, nausea, reversible hyponatraemia
Eslicarbazepine	Block voltage-dependent Na ⁺ channels, prolongation of inactivated state, regulate channel excitability	94	20-24	30	400-1600	Dizziness, fatigue, headache and diplopia
Phenobarbital	Enhances GABA action, ant glutamate, Ca ⁺² entry reduction	>95	80-120	20-48	90-180	Sedation, depression, loss of concentration, impairment in learning, and memory, mental confusion (older people), and hyperactivity (children)
Phenytoin	Blocks voltage-gated Na ⁺ channels, reduces Ca ⁺² currents	100	12-24	80-90	300-500	Ataxia, dysarthria, gingival hypertrophy, hirsutism, acneiform eruption, hepatic failure, osteomalacia, hyperglycaemia

Fosphenytoin	”	100	15	95-99	150 mg/min	Minor vascular complications
Primidone	Reduces sustained repetitive firing, blocks voltage-dependent Na ⁺ currents	80	6-14	15	750–1250	Sedation, dizziness, nausea, ataxia, depression
Progabide	GABA agonist at A and B sites	60	4	95	19.3–36	Well tolerated, sometimes drowsiness, nausea, vomiting, dysarthria
Diazepam	GABA induced Cl ⁻ influx	>90	30–60	95	4-20	Sedation, dullness
Clonazepam	”	>90	20-40	85	1.5-15 d	Drowsiness, problems with walking and coordination, dizziness.
Clobazam	”	100	>35	80-90	10-60	Confusion, fever hallucinations, chills, cough with yellow or green mucus, feeling shortness of breath, severe drowsiness
Lorazepam	”	90	14	85	2 mg/min at a dose 0.1mg/kg	Drowsiness, dizziness, loss of coordination, headache, nausea, blurred vision, change in sexual interest/ability, constipation, heartburn
Vigabatrin	GABA-Transaminase inhibitor, Inhibits GABA uptake	100	10.5	N	-	Depression, psychosis, behavioural changes, Visual field contraction
Ethosuximide	Reducing T-type Ca ⁺² currents, blocking synchronized thalamic firing	93	60	N	500–1000	Gastrointestinal upset, mood changes, lethargy, hiccups, headache, drowsiness,
Methsuximide	”	-	2.6	N	300-1200	Nausea, vomiting, stomach pain, loss of appetite, diarrhoea, constipation, weight loss, blurred vision
Valproate	Increases GABA levels, blocks T-type Ca ⁺² currents, enhances Na ⁺ channel inactivation	>90	10–20	90	1000–3000	Anorexia, vomiting, loose motions, weight gain, hair loss, thrombocytopenia, tremor, liver failure, pancreatitis
Felbamate	Inhibition of glutamatergic neurotransmission	>90	23	20-36	2400–3600	Nausea, insomnia, headaches, anorexia, aplastic anemia, hepatic failure
Lamotrigine	Reduces glutamate release, inhibits voltage-activated Ca ⁺² currents, blocks voltage-dependent Na ⁺ channels	98	24	55	50-300	Rash, dizziness, diplopia, ataxia, somnolence
Lacosamide	Enhancing Na ⁺ channel inactivation, binding CRMP-2, inhibit glutamate and	100	13	<15	200–400 d	Dizziness, fatigue, ataxia, vertigo rarely, increased PR interval on ECG,

	aspartate release					diplopia and nystagmus
Levetiracetam	Modify the synaptic release of glutamate and GABA by binding to a specific synaptic protein labelled 'SV2A'.	100	6-8	N	1000-3000	Somnolence, infection, headache
Brivaracetam	”	~100	7-8	<20	100	Dizziness, fatigue, somnolence and nausea and vomiting.
Gabapentin	Modulate H-currents, GABA analog but does not bind to GABA receptors, inactivation of Na ⁺ channels	27-60	5-7	<3	1200-2400	Ataxia, dizziness, somnolence, fatigue, nystagmus
Pregabalin	”	>90	6	N	150-600	Weight gain, somnolence, dizziness, irritability
Stiripentol	Increases GABA levels [126]	low	4.5-13	99	50	Somnolence decreased weight, appetite, ataxia
Cannabidiol	Desensitized TRPV1 channel, antagonised GPR55 receptor, adenosine reuptake inhibitor [127]	13-19	18-32	-	20	Generally safe
Tiagabine	Neuronal and glial GABA-uptake inhibitor	>95	7-9	96	32-56	Dizziness, nervousness, abnormal thinking
Topiramate	Na ⁺ channel block, reduction of L-type Ca ⁺² currents, potentiation of GABA at the GABA _A receptor: enhancement of Cl ⁻ flux, Inhibition of glutamatergic neurotransmission: weak block of AMPA/kainate receptors, weak Inhibition of carbonic anhydrase	80	24	15-41	25-400	Fatigue, psychomotor slowing, dizziness, weight loss, renal stones
Zonisamide	Prolongs Na ⁺ channels inactivation blocks T-type Ca ⁺² channels, enhances GABA action, weak inhibition of carbonic anhydrase	Dose Dependent	63	40	25-100	Dizziness, ataxia, confusion, anorexia, nausea, Metabolic acidosis and renal stones
Remacemide	NMDA receptor antagonist, Inactivation of Na ⁺ channels [128]	-	3-4	74	13.5	dizziness, abdominal pain, headache, diplopia, fatigue, dyspepsia, and abnormal vision
Perampanel	Non-competitive selective AMPA inhibitor of postsynaptic glutamate transmission	100	100	96	4-12	Dizziness, somnolence, irritability, headache, ataxia
Retigabine or Ezogabine	Open potassium channels (KCNQ [K _v 7])	60	7.5	80	300	Dizziness, somnolence, impaired concentration, nervousness, headache, fatigue nausea, weakness

						and tremor
Rufinamide	Enhance slow inactivation of sodium channels	70-85	8-12	34	400-3200	Headache, dizziness, fatigue, nausea, somnolence, diplopia nasopharyngitis, tremor

Note: N= Negligible

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