Chapter 9
Iron and Epilepsy

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1 Introduction

1.1 Epilepsy- a Neurological Disorder

Epilepsy was theoretically defined as a brain condition characterized by an enduring proclivity for epileptic seizures. This definition is commonly implemented in practice as having two unprovoked seizures separated by more than 18 hours (Fisher et al., 2014). Epilepsy is a term used to describe a group of disorders that all reflect underlying brain malfunction and can be caused by a range of factors. The terms seizure and epilepsy have little in common in terms of definition. Such definitions are critical for communication among medical experts, as well as other stakeholders in law, disability benefits, driving restrictions, workplace safety, education, and a variety of other areas (Fisher et al., 2005). The definitions on this page are intended for a wide range of people, including physicians, educators, researchers, government officials, and epilepsy patients and their families (Blume et al., 2001). Epilepsy is defined as a patient who has had a seizure and whose brain has a pathologic and lasting tendency to suffer recurring seizures for any reason. When compared to people who do not have the disorder, this tendency might be thought of as a pathologic reduction of the seizure threshold. Epileptogenesis is a pathologic process in which the brain undergoes physiological and anatomical changes that increase seizure vulnerability and the chance of spontaneous recurring seizures (SRS) (Pitkänen et al., 2015). Oxidative stress is a significant pathogenic mechanism of

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epileptogenesis in epilepsies of various etiologies (Pauletti et al., 2019; Shekh-Ahmad et al., 2019).

1.2 Epilepsy Prevalence around the World

Epileptic seizures affects 60 million individuals globally, with 4–five million in the United States, eight million in Europe, and at least 50 million in underdeveloped countries (Galanopoulou et al., 2012). Epilepsies affect a large number of children in their early years. People under the age of six and individuals over the age of sixty have the highest age-specific incidences of >50 per 100,000 in the population (Symonds et al., 2021). Drug-resistant seizures develop in a significant number of children with neurological conditions in their first three years of life (40%). These individuals are at an increased risk of neurobehavioral disorder, as well as premature death (Jennum et al., 2017). While it is evident that early initiation, poor seizure management, and neurological disorder are all associated, the cause of these relationships is unknown. Even if it is expected that the fundamental underlying cause will have a significant impact on outcomes, it has never been addressed at the population level utilising modern neuroimaging and genetic technology (Symonds et al., 2021).

1.3 Epilepsy in Adults

One of the most common serious brain disorders is epilepsy. They can affect persons of various ages and manifest themselves in a variety of ways. Although the incidence of juvenile cancer has declined in industrialized countries over the last three decades, this decline has been accompanied by a rise in the number of elderly people (Duncan et al., 2006). Various mutations in the same gene might cause different epileptic syndromes, hence a clinical manifestations could have multiple genetic causes. On the other hand, most epilepsies are most likely complex features involving environmental influences on inherited susceptibility, which are mediated by common polymorphism in specific genes. Epilepsy is diagnosed through clinical examination, with neurophysiological studies assisting in the diagnosis (UK, N.C.G.C, 2012). The application of brain imaging to detect the structural and functional causes and effects of epilepsies is quickly evolving. Antiepileptic medications decrease seizures in 60–70 percent of persons without altering the underlying tendency to have seizures. Pharmacogenetic studies hold the possibility of better individualising medication for each patient, resulting in the greatest likelihood of benefit and the fewest negative effects. For patients with refractory focal epilepsy, neurosurgical excision holds the possibility of a life-changing treatment. Novel treatments include precision seizure prediction and focused therapy with pharmaceutical delivery, brain stimulation, and biological grafts (Kwan & Brodie, 2006).

1.4 Risk Factors of Epilepsy

Risk factors include age, genetics, family history of epilepsy, history of febrile seizures, alcohol consumption, CNS and other infections, brain trauma, head injury, perinatal stroke, preterm birth, and geographic location. Epilepsy induced by a head injury, central nervous system illnesses, and tumours can strike at any age. The most frequent risk factor in people over 65 is cerebrovascular disease (Granger et al., 2002). In adulthood, external non-genetic risk factors such as vascular disease, such as stroke, are increasingly common. Certain types of epilepsy, whether in childhood or adults, may be linked to modifiable risk factors such alcohol use, traumatic brain injuries, or CNS infections (Walsh et al., 2017). Knowing these risk factors could enable for more regular outpatient clinic examinations, warning families about seizures, advising to record video in case of seizure suspicion, and, if necessary, obtaining an early EEG.

1.5 Epilepsy Classification

The seizures and epilepsies classified as per the International League Against Epilepsy's (ILAE) in 2017 is considered as the latest. This classification was aimed to assist the patients and clinicians in deciphering language and distinguishing between seizures with generalized and localized onsets (Sarmast et al., 2020). Seizures and epilepsy are better diagnosed and managed when they are categorized into various medications beneficial for different seizure types. The clinical aspects of epilepsy are divided into three stages by the ILAE: seizures, epilepsies, and epilepsy syndromes. This focus has been on the cause and complications at each stage (Zuberi & Brunklaus, 2018).

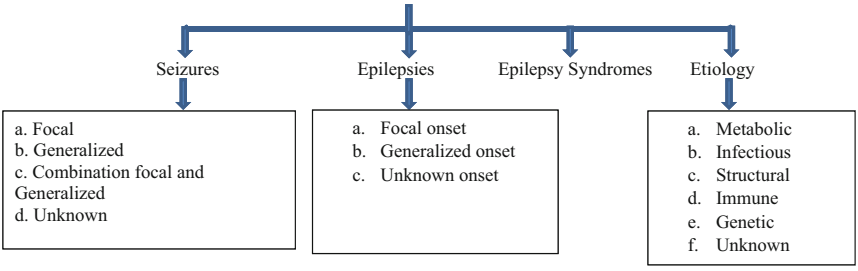
1.6 Seizure

Seizures are symptoms and signs that occur when a group of neurons in the brain experience unusually intense or concurrent neural excitation. While epilepsy is characterized as a severe neurological ailment marked by a persistent proclivity for unprovoked seizures as well as the neurological, intellectual, and psychosocial implications of the condition (Brodie et al., 2018). At least two uncontrolled seizures that occur more than 24 hours apart are required to diagnose epilepsy. A syndrome is characterized as a recurring seizure that is accompanied by abnormal examinations in a predictable pattern. It frequently comprises several different types of epilepsy (Sarmast et al., 2020).

When diagnosing epilepsy, factors such as the model and incidence, seizure type, genetic predisposition, Electrophysiological, and Magnetic resonance imaging abnormalities are all considered (Aaberg et al., 2017).

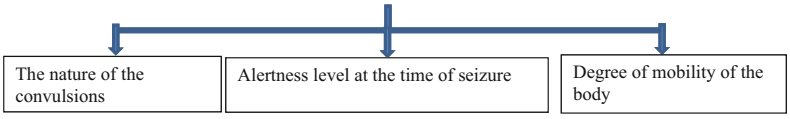
1.6.1 The Structure of Classification

The new classification has four components in general which is as follows: (Sarmast et al., 2020).

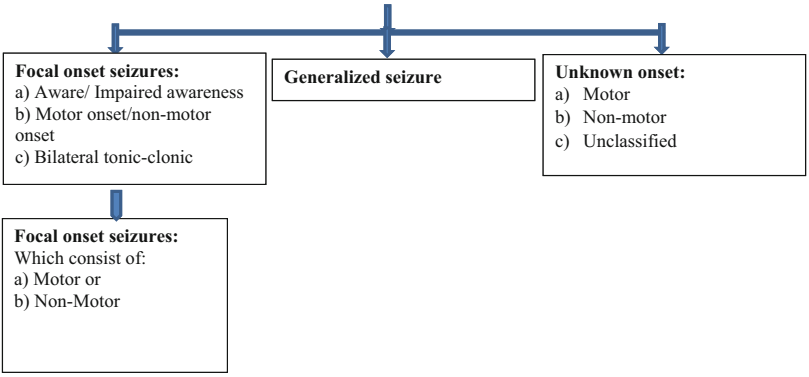


1.6.2 Classification of Seizure

Seizures are divided into three categories based on the following characteristics (Falco-Walter et al., 2018):



1.6.3 Seizures Are further Classified into Three Based on the Onset (Auvin, 2018)



FOCAL SEIZURES WITH MOTOR SYMPTOMS	
TYPES OF SEIZURE	**INTERPRETATION**
1. Focal Akinetic Seizure	In this type, the seizures represent rapid loss of muscle tone on one limb and one side of the body that lasts only a few seconds. The majority of the time, consciousness is sustained.
2. Focal Stereotyped Seizure	Recurrent actions, such as repeating something again and again, lip-smacking, kneading, or strolling, are examples of recurring motor activity. It's a common sign of a seizure that causes localized loss of awareness.
3. Focal Grand Mal Seizures	A sustained rise in muscle tension that persists for a few seconds or minutes causing the patient's extremities or neck rigidity.
4. Clonic Seizures	A symmetrical syncopated twitching of a muscle group happens over time.
5. Focal Epileptic Spasms	Muscle spasms that are uncontrollable and occasionally painful, which are prevalent in youngsters. Video-EEG is commonly used to diagnose it. Infantile spasm is the name given to it when it happens in infants.
6. Hyperkinetic Seizures	Characterized by excessive and frequently uncontrollable muscle movements such as frenzied kicking, thrashing, and pedaling.
7. Myoclonic Seizures	It's related to a complex partial seizure in that it's characterized by fast twitching in one portion of the body and face, as well as brief, un-sustained muscle spasms.
NON-MOTOR FOCAL SEIZURES	
TYPES OF SEIZURE	**INTERPRETATION**
1. Focal Autonomic Non-Motor Seizures	This type of convulsions that affect the sympathetic nervous system, resulting in symptoms such as increasing gastrointestinal pressure, hot and chilly sensations.
2. Focal Behavior Arrest Non-Motor Seizures	These seizures are characterized by the halt of all activities and the inability to respond for the duration of the seizure.

(continued)

3. Focal Cognitive Non-Motor Seizures	If the individual has delusions, hallucinations, short-term memory loss, or mental confusion during the episode.
4. Focal Emotional Non-Motor Seizures	Anxiety, nervousness, fright, exhilaration, grief, sadness, or other sensation can trigger these seizures, which are non-motor seizures.
5. Focal Sensory Non-Motor Seizures	Can cause ocular, nasal, perceptual, gastronomic, somatic delusion, or disorientation.

MOTOR GENERALIZED SEIZURE	
TYPES OF SEIZURE	**INTERPRETATION**
1. Tonic-Clonic-Myoclonic seizures	Individuals with juvenile myoclonic epilepsy are more likely to experience this episode.
2. Myoclonic-atonic seizures	This type was previously known as myoclonic Astatic seizures and is typically found in people with Doose syndrome.

GENERALIZED NON-MOTOR SEIZURES	
TYPES OF SEIZURE	**INTERPRETATION**
1. Petit Mal Seizures	Seizures like this are distinguished by abrupt cessation in activities, accompanied by a blank look and, on rare occasions, eye deviation, followed by fast recovery. It may be linked to eyelid fluttering.
2. Atypical Absence Seizures	It begins gradually, with more significant reductions in muscle tone than in normal absence.
3. A myoclonic-absence seizure	A sequence of syncopated jerks precedes this seizure, accompanied by a period of gazing.
4. Jeavons Syndrome	It's a rare type of epilepsy in which seizure includes a sudden upward twitching of the eyelids, which could be related to the gazing phase (absence seizure). It is frequently triggered by closing one's eyes.

2 Mortality in Epilepsy

Epilepsy patients are at a higher risk of dying young. Epilepsy with symptoms might cut your life short by up to 19 years. Early death, trauma, homicide, infections, and epileptic seizures are all more common in epilepsy patients than in the general population (Gaitatzis & Sander, 2004). Although little is documented about fatalities in resource-poor nations, research suggests it is higher than other countries, which could help to explain why impoverished countries have an increased prevalence and decreased incidence of active epilepsy (Sander, 2003). Although the pharmacological causes of early unexplainable mortality in epileptic seizures remain unclear, cardiovascular arrhythmias, notably asystole connected to convulsions, have been identified in methodology to achieve and are thought to occur only in rare cases (Duncan et al., 2006). Protracted Electrocardiogram tracking is required to discover

patterns that indicate a high probability of ventricular contraction and advise myocardial synchronization as a preventive measure.

3 Neuropathology of Epileptic Seizures

A brief episode of clinical manifestations, or both, in the brain caused by abnormally high or synchronised neuronal activity is known as a seizure activity. A transient synchronised discharge of a network of neurons that lasts less than 70 milliseconds and is distinct from a seizure is known as an interictal spike (De Curtis & Avanzini, 2001). The paroxysmal surging region can, in fact, be distinguished from the seizure onset zone. Seizures are thought to be triggered by a disruption in the brain's usual balance of excitation and inhibition, however this is now regarded an oversimplification. Communication among dissimilar circuits is required for the brain's function, which is most likely mediated through waves among these circuits. The creation of oscillations in cortical networks is dependent on interneurons, neural transmission (e.g., synaptic transmission), and inherent neuronal properties (Ward, 2003). The emergence of epileptic discharge as an epiphenomenon of such asynchronous circuits is possible. Greater spread and neuronal recruitment, as a result of a combination of greater connection, increased excitatory transmission, a failure of inhibitory mechanisms, and changes in intrinsic neuronal properties, are thought to be the beginning of the transition from normal to epileptiform behaviour. In human studies, the electroencephalogram (EEG) becomes less chaotic in large areas of the cortex before a seizure, indicating extensive synchronisation (Litt & Echauz, 2002).

In localized epileptic seizures, focal cognitive interruption related to focal clinical abnormalities (i.e., tumours) or, less typically, a hereditary diathesis results in seizures that start small and grow as more brain areas are recruited. The location of the focal, as well as the speed and degree of spread, influence the seizure's clinical manifestation (Duncan et al., 2006).

Seizures occur across the cortex due to a broad decrease of the seizure threshold in global epilepsies, which are mainly genetically based (Duncan et al., 2006).

Absence seizures, a type of generalised seizure, are caused by the thalamocortical loops. Subcortically, absences were assumed to be caused by thalamic neurons driving neocortical neuron recruitment (McCormick & Contreras, 2001).

4 Iron in Brain

Despite the fact that iron is required for appropriate brain function as a component of cellular proteins, iron-sulfur complexes, haemoglobin, and neurotransmitter, triglyceride, and genetic synthesis, too much iron can be neurotoxic. The brain's ability to store a quickly available source of iron is crucial for appropriate neurologic function, despite the fact that both insufficiency and excess have substantial neurological

consequences (Connor et al., 2001). Because of the blood-brain barrier, getting iron to the brain in a timely and adequate manner is difficult. The regional differentiation of cerebral activity and the complexity of cellular processes add to the complexities. Age and geography have an impact on iron-dependent processes in the central nervous system (CNS). As a result, the procedures that keep the CNS iron level under control must be examined by region and age. In addition to ageing and regional requirements, dietary variables and disease are confounding factors that affect brain iron uptake (Beard et al., 1993). The role of iron in a number of CNS activities, as well as the consequences of altered iron metabolism in a variety of neurotoxic disorders, highlight the need for further research into various aspects of iron homeostasis. Iron is in high demand in the brain, which correlates to its high energy needs (Piñero & Connor, 2000). Adenosine Triphosphate (ATP) is required by the brain to sustain membrane electrochemical gradients, synaptic transmission, and axonal transport (Beal, 1998). Iron is required for the creation of lipids and cholesterol, which are crucial substrates for myelin synthesis, as well as metabolic enzymes found in oligodendrocytes. Iron is also suggested to play a role in the action of the GABAergic system. As a result, it's expected that variations in iron availability to the brain and iron metabolism in the central nervous system will have a negative impact on a number of neurologic activities. Intelligence, motor function, endorphin activities, and myelination are the most typically observed problems associated with CNS iron deficiency (Shinobu & Beal, 1997). Iron levels in the brain fluctuate with age and disease, and they decline when the diet is deficient in iron. Low brain iron levels in neonates and children have been related to behavioural and cognitive difficulties, as well as an iron-deficient diet. Pantothenate kinase-associated neurodegeneration, vascular dementia, Parkinson's disease, and corticospinal dementia have all been connected to abnormal iron accumulation and, in some cases, changes in iron-related components in sick brain circuits (Fleming et al., 1998). Iron-mediated oxidation appears to play a role in apoptosis in a number of disorders, according to a growing body of research. When it comes to iron availability, multiple sclerosis and other demyelinating diseases demand special consideration (Gunshin et al., 1997). Oligodendrocytes require a steady supply of iron because axonal management and implementation necessitate a large amount of it (Vulpe et al., 1999). On the other hand, higher oxygen consumption, lipid concentration, and white matter mineral content all contribute to an increased risk of oxidative injury. This article discusses the present state of knowledge about iron homeostasis in the brain, as well as its probable role in neurotoxicity (Piñero & Connor, 2000). Iron is essential for cognitive function, as evidenced by the presence of integrins transporters on brain vascular endothelial cells (Moos, 2002). The transmission of iron into the central nervous system from the vascular system is governed when the brain's iron requirement is significant, such as in circumstances of micronutrient deficiencies or during neurodevelopment, so that in iron-replete conditions, the excavation of iron by frontal cortex endocytosed is low, and the opposite is true when the brain's iron requirement is high. While it is widely accepted that iron is taken up at the brain's borders via receptor-mediated iron-transferrin absorption (Moos, 2002).

5 Modulation of Erythropoiesis in the Blood-Brain Barrier (BBB)

Because of its high metabolic rate, the central nervous system contains a lot of non-heme iron. The majority of the iron is found in the ventral striatum, with the latter reaching levels comparable to the liver. The BBB protects the brain from systemic iron variations, and disruptions in iron homeostasis in peripheral organs have little impact on brain iron metabolism. As a result, iron and iron-modifying polypeptides levels in the serum, as well as cerebrospinal fluid (CSF) that surrounds the brain, vary drastically (Moos, 2002). A monolayer of polarized capillary endothelial cells with tight connections forms the BBB, which regulates cargo transfer from the luminal or apical surface of blood to the abluminal or basolateral surface of CSF and brain interstitial fluid (Deane et al., 2004; Rouault et al., 2009).

6 Brain Iron Deposition and Neuronal Death

Neurodegeneration with brain iron accumulation (NBIA), a collection of hereditary neurologic illnesses, is distinguished by excessive iron deposition in the limbic system, substantia nigra, striatum, and cerebellar dentate nuclei (Gregory et al., 2008). The beginning age varies, and most instances present with a wide range of overlapping clinical symptoms, such as progressive extrapyramidal indications with diverse combinations of movement problems, seizures, and visual difficulties, eventually leading to the cognitive deterioration (Kurian et al., 2011; Kruer et al., 2012).

7 Iron in Epilepsy

Iron is a trace element that is necessary for human development and growth. Many redox events, including oxidative metabolism, the electron transport chain, the pentose phosphate pathway, and DNA transcription, require iron molecules (Thirupathi & Chang, 2019; Abbina et al., 2020). Iron, on the other hand, is involved in the creation of myelin and the metabolism of epinephrine, norepinephrine, and dopamine in the nervous system, as well as intellectual development and neurodegenerative illnesses (Thirupathi & Chang, 2019).

As a result, the human body's iron metabolism should be closely monitored. Abnormal iron metabolism has been associated with several depressive illnesses, including ischemic post-stroke and posttraumatic epilepsy (PTE) (Yokoi et al., 1995; Mori et al., 2004).

8 Epilepsy Induced by Iron

Among the most common causes of intractable epilepsy in ischemic stroke patients is iron overload. Blood extravasates and erythrocytes and hemoglobin are destroyed when a brain injury or acute cortical infarction occurs. Hemoglobin and iron produced by hemoglobin are linked to reactive oxygen species(ROS) and nitrogen species(RNS). ROS as well as RNS, on the other hand, have been linked to iron-induced epileptic convulsions in mice (Chen et al., 2020). In recent studies, injections of ferric chloride into the cortex of rats were shown to cause protracted epileptic episodes in rats (Chen et al., 2020). O2 and OH are produced after ferric chloride is injected into the cerebral cortex of rats. These hydroxyl radicals may cause epilepsy by promoting reactive oxygen species (ROS) in neuronal membranes and an increase in guanidine molecule production in the brain.

9 Iron Metabolic Process in Epilepsy

Hemosiderin is formed when hemoglobin is broken down in the brain. Hemosiderin is one of the most frequent types of accumulated iron in the nervous system, and it has been connected to degenerative disorders including epilepsy (Zhang et al., 2018). The human body accumulates chelating ferrous, which is then metabolized into transition metals in the bloodstream via ceruloplasmin (Mukhopadhyay, 2018; Naito et al., 2021). This finding demonstrated that iron controls inflammation in the epileptic brain, which serves a role in the initiation and progression of epilepsy. Finally, abnormal iron oxidation and transport in epileptic patients' brains could be one of the factors of epilepsy's origin and recurrence. Although iron injections into the brain cause seizures, the link between epilepsy and iron metabolism is yet unknown and requires further research. Imaging technologies can be used to diagnose and evaluate epilepsy based on the abnormal distribution of iron in the epileptic brain (Chen et al., 2020).

10 Histopathological Changes in the Epileptic Brain Tissue

Gliosis, neuronal degeneration, vascular malformation, Hippocampal sclerosis, Ganglioglioma Tumor, Focal cortical dysplasia, Glial scar, Cavernous angioma were found in the routinely processed biopsy specimens collected from brain resections utilising the peroxidase-antiperoxidase technique (Kallioinen et al., 1987).

Hippocampal sclerosis is more common in patients with status epilepticus. The Cornu Ammonis (CA) 1 field of the hippocampus is characterised by cellular infiltration and neurodegeneration, followed by the hilus, Cornu Ammonis 4, and Cornu Ammonis 3 fields. The dentate granular cell layer and neurons in the CA2

field are relatively undamaged. The dentate granular cell layer is also commonly scattered, with ectopic neurons found in the molecular layer. Neuronal loss is accompanied by axonal reconfiguration, which includes both excitatory and inhibitory neurons (Mathern et al., 1995).

The mechanisms that link seizures to hippocampal damage or changes in excitatory and inhibitory pathways remain a mystery. One of the primary theories for explaining the hyperexcitability of hippocampal principal cells and seizure activity is GABA-mediated inhibition. GABAergic neurons innervate a varied range of morphological and neurochemical types of primary cells. The somata (and proximal dendrites) and axon beginning segment (AIS) of main cells, respectively, receive a considerable GABAergic input from huge basket cells and chandelier cells (DeFelipe, 1999).

11 Histopathological Changes in the Iron Induced Epileptic Brain Tissue

Serial sections stained with Nissl, hematoxylin, and eosin, as well as Methylene blue, indicated delamination, neuronal pyknosis and loss, and astrogliosis in untreated animals (Willmore & Rubin, 1981). Golgi-Cox and Cresyl violet stain methods revealed (i) desecration of Golgi-stained neurons, (ii) astrocytosis, (iii) dendritic spine loss, (iv) reduced dendritic branching, and (v) excitotoxic injury of dendrites.

12 Management of Epilepsy

12.1 Initial Management of Epilepsy

Main and foremost, with any seizing patient, the first concern is to guarantee the patient's safety while awaiting for emergency services (Biazzo-Ashnault et al., 2001). To avoid falls or mishaps, anything that will lead to serious injuries should be put out of the way, and the patient should be moved to the floor or another flat surface if at all possible. The patient's airway, breathing, and circulation should all be assessed (Petit, 2005). When a patient is suffering a seizure, fingers or other objects should not be inserted into their mouth because this can induce aspiration or further injury (Shuster, 1994).

12.2 Diagnosis of Epilepsy

Epilepsy diagnosis is still made clinically, with neurophysiological tests confirming the diagnosis. Many structural causes of epilepsies can be identified via brain imaging. Antiepileptic medicines (AEDs) that are presently accessible stop epilepsy without altering the existing susceptibility to cause them in 60–70 percentage points of individuals. Numerous modern drugs are just as effective as ancient therapies, yet they come with substantial advantages such less drug interactions interactions and increased inflammation (Kutlubaev et al., 2018).

Epilepsy is associated to a higher diagnosis and treatment of mental mental illnesses such as depression, stress, and homicidal ideation (Dunn et al., 2018). The proper therapy of persons with epilepsy requires an awareness of the psychological correlates of epilepsy. It's critical to anticipate typical errors in epilepsy diagnosis and treatment. Early diagnosis errors include non-epileptic psychosomatic convulsions, dizziness with muscle twitching, wandering leg dysfunction, and REM behavioural abnormalities, the latter of which is more common in elderly men (Lin et al., 2020).

It is important to prevent overtreatment with too rapid gradation, excessively high doses, or too many AEDs. Vagus nerve stimulation is a palliative treatment with the potential for mood improvement for persons with refractory focal epilepsy, whereas neurosurgical excision is a life-changing cure (Sartori et al., 2019).

12.3 Pharmaceutical Intervention

Antiepileptic drugs are the cornerstone of treatment (AEDs). Even though "antiepileptic" is a far more precise term, "antiseizure" is a better fit as these medications target the symptoms (epilepsy) rather than the core cause (Kaal et al., 2020). The target of AED therapy is to provide the best feasible seizure control while limiting drug toxicity, resulting in the best possible quality of life. Approximately multiple of epilepsy patients benefit from AEDs, with outcome varying based on a range of factors such as epileptic condition, aetiology, and also before the seizure frequency (Perucca & Tomson, 2011).

12.4 Few Common Antiepileptic Drugs (AEDs)

Monotherapy with antiseizure medicine is the first step in treating epilepsy. For effective epilepsy treatment, understanding the efficacy range, pharmaceutical actions, and modalities of administration for specific antiepileptic medicines is critical.

Cenobamate as well as fenfluramine, two new anti-seizure medications, have been approved in the United States Drug Administration (FDA). Anti-seizure medications from the past were effective, but they had concerns with tolerance and pharmacokinetics. Several modern antiseizure medications have shown efficacy and tolerability that are at least equivalent to or better than previous antiseizure medications as first-line therapy for focal epilepsy as compared to older antiseizure medications. Among the medications on the list are topiramate, levetiracetam, zonisamide, oxcarbazepine, lacosamide and lamotrigine. When compared to lamotrigine, pregabalin was found to be ineffective. Lacosamide, pregabalin, and eslicarbazepine have all been successfully converted to monotherapy for focal epilepsy (Abou-Khalil, 2022). Additional therapeutic options include newer antiseizure medicines with a variety of modes of action. Since 2016, antiseizure medications have benefited from an FDA regulation that allows for the extrapolation of a drug's efficacy as supplementary therapy in adults to monotherapy efficacy (Cardoso-Vera et al., 2021). Additionally, efficacy in adults can be extrapolated to children aged 4 and higher. For both extrapolations, data demonstrating that an antiseizure medication's pharmacokinetics are equal between its initial approved use and its extrapolated use is required. Negative pharmacokinetic or pharmacodynamic interactions linked to mechanism of action should be avoided in anti-seizure medication combinations (Asconapé, 2002).

12.5 Common Basic Issues Using Anti-Epileptic Drugs

By using newer AEDs, chronic toxicity associated with previous AEDs, such as osteoporosis, gingival hyperplasia, and alterations in reproductive endocrine function, can be avoided. Hyponatremia appears to be more prevalent with oxcarbazepine than with carbamazepine. Because felbamate has been connected to a high prevalence of aplastic anaemia and liver failure, it should be used only in exceptional circumstances. Acute angle closure glaucoma has been connected to the use of topiramate. This side effect occurs early in the course of therapy and is promptly reversed when the drug is stopped, therefore physician and patient awareness is crucial (Asconapé, 2002). By reducing serum immunoglobulin levels, anticonvulsant drugs can cause secondary immunodeficiency. Patients using these medications should have their serum immunoglobulin levels tested by their doctors on a regular basis (Kalantari et al., 2022).

12.6 Epilepsy that Is Resistant to Medication

After getting additional anti-epileptic drugs, fewer than 20 percentage of individuals who continue to have seizures after two approved AED trials become seizure-free (Brodie et al., 2012). Drug-resistant epilepsy is defined by the failure of two

well-tolerated, carefully chosen, and used AED regimens (as monotherapies or in combination) to achieve persistent seizure-freedom, according to the world organisation named ILAE (Kwan et al., 2010). Drug-resistant epilepsy is associated with increased disability, morbidity, and mortality. When a patient has failed two AEDs, the idea of epilepsy surgery should be considered. For those who are not surgical candidates, alternative anti-epileptic medications may be explored. The advent of a slew of second-generation anti-epileptic drugs, on the other hand, has had minimal impact on overall clinical outcomes, with around a third of patients' seizures remaining uncontrolled (Brodie et al., 2012).

12.7 Surgical Therapy

For drug-resistant epilepsy patients, epileptic resection is the most effective remedy. It entails the removal or resection of epileptic tissue, or, less often, the detachment or removal of epileptic tissue (Ryvlin et al., 2014). To determine surgical candidacy, an array of diagnostics is employed, encompassing skull monitoring systems, structural MRI, wide spectrum of applications single - photon emission, ictal and pre - ictal mono emission magnetic resonance, functional Magnetic resonance imaging, and critical concentration. These studies are attempting to determine the "epileptogenic zone" (the smallest area of cortex that, when resected, disconnected, or destroyed, results in seizure freedom) as well as the risk of post-operative morbidity (Ryvlin et al., 2014). Cranial Electroencephalogram is also necessary in some patients to improve epileptogenic zone localisation, either as intra-operative electrocorticography or chronic extra-operative recordings. When surgical cure is not achievable, palliative epilepsy surgery, such as corpus collostomy, may be performed in selected individuals with the goal of improving quality of life by reducing seizure frequency and severity (Ryvlin et al., 2014).

12.8 Alternative Treatment Options

Vagal nerve stimulation is a non-medicated therapeutic option for those seizure patients who are resistant to drugs. Only 10% of patients become seizure-free, despite the fact that it has been demonstrated to reduce seizures by 40% in half of the patients (Englot et al., 2011). Transcutaneous vagal or trigeminal nerve stimulation are emerging approaches that need to be validated in well-designed trials (DeGiorgio & Krahl, 2013). Some neurotransmission therapeutic approaches that may be used in the epileptic patients who are resistant to AEDs include intracranial stimulation of the anterior dorsal striatum and responsive prefrontal stimulation, which delivers brain impulses when anomalous electrocorticographic movement is detected via a closed-loop system implanted device. Seizures can be minimised with

these treatments, but seizure-free individuals are unusual (Fisher et al., 2010; Morrell, 2011).

12.9 Precision Medicine

Healthcare has long sought to deliver treatments that target the disease's molecular aetiology. The emergence of next-generation sequence analysis has given confidence with a new lease on life, especially in light of successful chemotherapy paradigms. Epilepsy presents a huge opportunity for precision medicine because of several gene discoveries, the availability of experimental in vitro and in vivo models for drug screening, and the possibility of conducting small, cost-effective trials of novel medications (Consortium, E., 2015). Precision medicine is already a reality for some genetic epilepsies. These patients benefit from the low fat diet, which provides an alternative energy substrate for the brain. The discovery of the epileptic seizure's genomic aetiology also allows for the mitigating the impacts of AED side effects. AED medication is the mainstay of epilepsy treatment, with roughly two-thirds of patients experiencing complete seizure control. Despite the availability of second-generation AEDs, the epidemiology of epileptic seizure with drug-resistance, as well as the accompanying risks of impairment, comorbidity, and fatalities, has remained substantially unchanged for decades.

13 Treatment of Epilepsy Induced by Iron

In iron-induced epilepsy, the localized epileptogenic activity spreads across the overall neocortex of both left and right hemispheres (Moriwaki et al., 1990; Moriwaki et al., 1992; Sharma et al., 2007). Various thalamic areas are thought to collaborate in the complexity and worsening of unexpectedly expanded seizures once they begin in the cortical core during this extension of seizure activity (Semple et al., 2020).

Varsha Sharma et al. investigated the antiepileptic impact of ethosuximide in an animal model using epileptic electrographic activity (Sharma et al., 2007). Ethosuximide has been shown to desynchronize the reticulo-thalamocortical circuit's hyper synchronizing electrical activity. This activity of the medicine could be responsible for the medication's anti-absence effect in humans (Pellegrini et al., 1989). Because thalamic and cortical interaction is important in iron-induced cortical focal epilepsy (Sharma & Singh, 1999), It would be interesting to see if ethosuximide can help with iron-induced epileptiform electroencephalographic epileptic seizures. The concept that absence seizures are caused by a subcortical malfunction has recently been proven (Manning et al., 2004; Timofeev & Steriade, 2004), Thus, rather than the diencephalon, it appears that the motor cortex of the cerebrum is a localized seizure origin site for status epilepticus (Sharma et al., 2007).

The effect of ethosuximide on iron-induced convulsions is of special interest since iron-induced epilepsy is regulated by mitochondrial peroxidation, and ethosuximide, as a calcium channel inhibitor, may have an anti-lipid peroxidative effect (Janero & Burghardt, 1989).

Curcumin is a coloring agent and a primary active polyphenolic component isolated from the Curcuma longa (turmeric) plant's rhizome. It's a crystalline orange-yellow powder that's almost insoluble in water (Ladol & Sharma, 2021). It binds redox-active metal ions and passes the blood-brain barrier. Its antioxidative, anticancer, and anti-inflammatory effects are also well-known (Ladol & Sharma, 2021). Curcumin, given at a dose of 500 ppm, can normalize BDNF and its downstream genes, preventing the cognitive deterioration associated with traumatic brain injury (Wu et al., 2003). Curcumin may also prevent neuronal cell death in kainic acid-induced seizures by blocking the apoptotic cell death signaling pathway and indirectly affecting the blood-brain barrier (Shin et al., 2007).

Gastrodia elata Bl. (GE), an oriental medicine used to treat convulsive disorders and lightheadedness contains vanillyl alcohol (VA) (Hsieh et al., 2000). Iron-induced epileptiform discharge in rats may be prevented by pretreatment with antioxidants such as a-tocopherol and dimethyl sulfoxide (Willmore & Rubin, 1981; Rubin & Willmore, 1980; Willmore & Rubin, 1984), According to the findings, antioxidant therapy may help to avoid the emergence of post-traumatic epilepsy (Hsieh et al., 2000).

Uncaria rhynchophylla (Miq) Jack (UR) is an oriental drug for treating adrenergic disorders such as epilepsy for generations (Hsieh et al., 1999). Both the antiepileptic and inhibitory effects of UR on Kainic acid-induced wet dog tremors and oxidative stress are dose-dependent, according to Ching-Liang et al., implying that the therapeutic action of UR may be attributable to its inhibitory effect on oxidative damage (Hsieh et al., 1999).

Antiepileptic drugs (AEDs) can help with bipolar disorder, migraine, movement problems, myotonia, and neuropathic pain, among other things (Rogawski & Löscher, 2004). Antiepileptic medications are chosen for their effectiveness in treating a certain ailment, differential cytotoxicity and Anticonvulsant compatibility, and vital organ dysfunction (Dichter & Brodie, 1996; Sankar, 2004).

On the pharmaceutical market, there are several anti-epileptic pharmaceuticals for the treatment of epileptic seizures and related diseases. Benzodiazepines, Phenobarbital, Vigabatrin, Tiagabine, Valproate, Topiramate, Gabapentin, Phenytoin, Carbamazepine, Oxcarbazepine, Lamotrigine, Zonisamide, Levetiracetam, Ethosuximide, and Felbamate are only a few of them. Uncaria rhynchophylla, in combination with the medications Ethosuximide, Curcumin, and Vanillyl alcohol (VA), performs a critical function in the treatment of seizures caused by iron.

14 Conclusion

This chapter focuses on improving researchers' and clinicians' knowledge on iron and its role in epilepsy in order to aid in the management and treatment of patients with neurological disorders. Iron is a well-known source of harmful oxidizing agents, demanding complex absorption, use, and retention processes in systemic organs and the central nervous system. Over the last few years, the modulation of erythropoiesis in central organs has become increasingly obvious, providing crucial information on iron transport across the BBB and management inside the brain. Whereas the majority of ferric regulating peptides are generated directly in the brain, their physiological homology has aided in the understanding of the purpose in the brain's dynamic environment. The brain, unlike most other systemic organs, has a region- and mitochondrial ferrous concentration. Additionally, each cell type in the brain has its own mechanism for ion transport, storage, utilization, and sensitivity to changes in the intra- and extracellular environment. Progress toward this goal has been impeded by several limitations in our understanding of brain ion homeostasis. To comprehend the aetiology of iron improper metabolism in hereditary and episodic neuronal diseases linked with ferrous disparity, a thorough understanding of these pathways and their disruption by pathogenic processes implicated in diverse brain disorders is required. Each condition's primary cause of ferrous storage or shortage is likely to be different. The succeeding set of circumstances that leads to the production of free radicals and the accompanying self-enriching multiplier effect is likely to be identical across all brain illnesses. Constant attempts at understanding the nature of ferrous imbalance and seeking for therapies that restore brain iron homeostasis are essential to create therapeutic treatments that can help the rising population suffering from neurological and other illnesses associated to ferrous imbalances.

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