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Biomarkers in Epilepsy: Emerging Tools for Diagnosis, Prognosis and Therapeutic Strategies

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Abstract

Epilepsy is one of the most prevalent neurological disorders, affecting nearly 50 million individuals worldwide and contributing significantly to the global burden of disease. Despite advances in antiepileptic drug development, approximately 30% of patients remain drug-resistant, underscoring the urgent need for precision-based diagnostic and therapeutic strategies. Biomarkers have emerged as promising tools to improve epilepsy diagnosis, prognosis, and treatment response. Genetic biomarkers, including ion channel mutations and mTOR pathway genes, aid in identifying epilepsy subtypes and guiding personalized therapy. Molecular biomarkers such as cytokines, oxidative stress indicators, and neurotransmitter imbalances provide insights into disease mechanisms and epileptogenesis. Imaging biomarkers, particularly MRI and advanced neuroimaging modalities, enhance lesion detection and disease monitoring. Novel candidates such as microRNAs, proteins, and amino acids further expand the biomarker landscape, reflecting underlying pathophysiological processes. Collectively, these advances highlight the importance of integrating biomarker research with clinical practice to enable early detection, individualized management, and improved therapeutic outcomes in epilepsy.

Keywords: Epilepsy; Genetic biomarker; Molecular biomarker; Drug resistant; Epileptogenesis

1. Introduction

Epilepsy is a common brain disorder affecting 50 million people worldwide, accounting for 1% of the global burden of disease. It has been known since antiquity, with the term "epilepsy" derived from the Greek verb "epilamvanein." Epilepsy is a broad category of symptom complexes arising from disordered brain functions that may be secondary to a variety of pathologic issues. The battle between prejudice and acceptance, ignorance and knowledge, myth and science, and charlatanism and rational therapy has been long and difficult, and even today, it has not yet been fully won. The first step, attributed to Hippocrates in about 400 BC, that epilepsy is a brain disease that must be treated by diet and drugs, is crucial in understanding the clinical aspects of epilepsy [1]. Epilepsy is a complex disease with diverse clinical characteristics, making it difficult to understand its mechanisms. It consists of seizures, epileptogenesis, and recurrent unprovoked seizures. Understanding seizures in individuals with epilepsy is challenging due to the altered nervous system and diverse environment. Genes, developmental mechanisms, and neuronal plasticity play major roles in creating hyperexcitability in temporal lobe epilepsy. However, the critical control points for chronic seizures and their persistence, frequency, and severity remain unresolved [2].

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1.1. Importance of biomarkers in epilepsy diagnosis and treatment

Epilepsy affects over 50 million people globally, with 30% uncontrolled despite over 20 antiepileptic drugs. Despite understanding the disease's molecular pathways, no treatments exist for those at risk. Biomarkers, which can be diagnostic or prognostic, are needed to develop targeted treatments for epilepsy. These biomarkers can help identify patients who may benefit from preventive treatments and improve management, leading to better prevention in the right person at the right time [3]. Diagnostic biomarkers of epilepsy, including genetic, serological, neuroimaging, and electrophysiological variables, are measurable variables associated with seizures. These biomarkers can help identify subtle lesions and support differential diagnosis. Short non-coding RNAs, advanced imaging techniques, and electrophysiological biomarkers like transcranial magnetic stimulation and high-frequency oscillations are promising diagnostic biomarkers. Serological biomarkers may also aid in distinguishing between epileptic seizures and non-epileptic events [4]. Identifying reliable biomarkers for epilepsy could improve differential diagnosis, pharmacotherapy, presurgical evaluation, and cost-effectiveness. Advances in electrophysiology, neuroimaging, molecular biology, and genetics could reveal clinically useful biomarkers in the near future [5]. Epilepsy is a neurological condition that cannot be prevented by pharmacological interventions. To address this, biomarkers of epileptogenesis are being investigated to identify patients at high risk and determine the effectiveness of therapeutic interventions. These biomarkers could include genetic, molecular, cellular, imaging, and electrophysiological measures. Ideal biomarkers should be noninvasive and have a profile of multiple biomarkers. Collaborative and multicenter research by neuroscientists with robust animal models and extensive patient populations is expected to be successful [6]. Biomarkers are characteristics that indicate normal biologic processes, pathogenic processes, or responses to exposure or intervention, including therapeutic interventions. The BEST biomarker categories include susceptibility/risk biomarkers, diagnostic biomarkers, monitoring biomarkers, prognostic biomarkers, predictive biomarkers, pharmacodynamic/response biomarkers, and safety biomarkers[7].

2. Potential Biomarkers of Epilepsy

2.1. Genetic Biomarker and Genetic mutations associated with epilepsy

A preliminary literature search has identified 122 genes strongly associated with status epilepticus, primarily found in rare conditions in infants and young children with multiple other handicaps. These genes can be subdivided into those associated with cortical dysplasias, inborn errors of metabolism, mitochondrial disease, epileptic encephalopathies, and childhood syndromes. There are no 'pure status epilepticus genes,' and genetic influences in status epilepticus likely involve development, cerebral energy production, altered biochemical pathways, transmitter and membrane function, and defects in networks or systems [8]. the molecular pathogenic basis for genetic generalized epilepsies linked to mutations in the inhibitory γ-aminobutyric acid (GABAA) receptor γ2 subunit gene, GABRG2. The γ2 subunit is abundantly expressed in the mammalian brain and is assembled into αβγ2 receptors, which play a crucial role in GABAA receptor trafficking and clustering at synapses. These receptors oligomerize with other binding partners and assemble into pentameric receptors. Only correctly assembled receptors can travel beyond the endoplasmic reticulum and reach the cell surface and synapses, where they conduct chloride ion current when activated by GABA. Mutations in GABRG2 have been linked to simple febrile seizures and genetic epilepsy syndromes, including childhood absence epilepsy, generalized epilepsy with febrile seizures plus, and Dravet syndrome, or severe myoclonic epilepsy in infancy. Mutations include missense, nonsense, frameshift, splice-site, and deletion mutations, found in both coding and noncoding sequences. These mutations reduce channel function to different extents and by diverse mechanisms, including nonsense-mediated messenger RNA decay, endoplasmic reticulum–associated protein degradation, dominant negative suppression of partnering subunits, mutant subunit aggregation causing cell stress and cell death, and gating defects. The epilepsy phenotypic heterogeneity associated with GABRG2 mutations may be related to the extent of the reduction of GABAA receptor channel function and differential dominant negative suppression, as well as toxicity related to the metabolism of mutant subunit proteins [9-14].

2.2. Role of genetic testing in epilepsy diagnosis

A study of children with newly diagnosed epilepsy at less than 3 years of age in 17 US pediatric hospitals found that genetic testing is crucial for initial evaluation. Out of the 775 patients, 12.3% had brain injuries. Of the remaining 680 patients, 48.1% underwent genetic testing, identifying pathogenic variants in 40.4% of them. The highest yields were found in children with tuberous sclerosis complex, metabolic diseases, and brain malformations. A total of 180 of 446 children (40.4%) underwent some testing, with pathogenic variants identified in 48 of 180 children. Diagnostic yields were greater than 15% regardless of delay, spasms, and young age. The study suggests that genetic investigations, particularly broad sequencing methods, have high diagnostic yields in newly diagnosed early-life epilepsies, regardless of key clinical features. Thorough genetic investigation emphasizing sequencing tests should be incorporated into the initial evaluation of newly presenting epilepsies, not just for those with severe presentations and poor outcomes [15].

Genetic testing in epilepsy patients has become widespread due to next-generation sequencing and the discovery of new causative genes. Pathologic variants resulting in epilepsy cause syndromic disorders, metabolic disorders, brain malformations, and abnormal cellular signaling. This article reviews available genetic testing, common genetic causes of epilepsy, data behind genetic epilepsies, and discusses results with patients. It proposes an algorithm for testing patients with epilepsy to maximize yield and limit costs based on phenotype, age of seizure onset, and presence of other neurologic comorbidities. Modern neurologists must be able to accurately interpret results and order appropriate genetic testing for targeted and cost-effective patient care [16]. Epilepsy management is challenging due to the numerous syndromes and seizure types, as well as the variable response to therapies. In the last two decades, genetic etiology has been revealed in over half of all epilepsies, with single gene defects in ion channels or neurotransmitter receptors associated with most inherited forms. Several genetic tests are now available, including targeted assays and revolutionary tools that allow sequencing of all coding and non-coding regions of the human genome[17-19].

3. Molecular Biomarkers

3.1. Inflammatory markers (e.g., cytokines, chemokines)

A review of 83 studies on CSF cytokines and chemokines revealed that while our understanding of neuroinflammatory disorders is improving, our biomarker repertoire for monitoring inflammation remains limited. B-cell markers like CXCL13 and BAFF are found to be elevated in autoantibody-associated disorders, while interferon gamma is mainly elevated in viral encephalitis. Th2 and Th17 cytokines are frequently elevated in ADM and NMO, while Th1 and Th17 cytokines are more common in multiple sclerosis. Cytokine/chemokine profiling could provide new insights into disease pathogenesis and improve our ability to monitor inflammation and treatment response. [20] Seizure generation and recurrence are the focus of extensive preclinical and clinical investigations to develop novel treatments for epileptic seizures, especially for pharmacoresistant epilepsies, which affect around 30% of patients. Neuroinflammation is a common activation in epileptogenic brain regions in humans and is also involved in animal models of epilepsy. Inflammatory mediators in the blood and molecular imaging of neuroinflammation could provide diagnostic, prognostic, and predictive biomarkers for epilepsy, aiding patient stratification in future clinical studies. The review focuses on the IL-1 receptor-Toll-like receptor 4 axis, the arachidonic acid-prostaglandin cascade, oxidative stress, and transforming growth factor-β signaling associated with blood-brain barrier dysfunction [21-22].

3.2. Oxidative stress markers (e.g., ROS, COX-2)

Epileptogenesis is a process involving structural modifications in the brain that lead to seizures. The etiopathogenesis of epilepsy can be attributed to various factors, including neurodegeneration, disturbance of the brain-blood barrier, amygdala dysregulation, alterations of the glutamatergic system, oxidative stress, hypoxia, and epigenetic modification of DNA. Inflammation markers play a crucial role in epileptogenesis through cytokine balance in the CNS or through the complement pathway[24]. The basal ganglia (BBB) in the brain regulate the entry of plasma-born substances and immune cells into the nervous tissue. However, it undergoes transient changes during events like seizures, traumatic and ischemic CNS injuries, or pathogenic infections. Epileptic seizures also provoke inflammatory responses that enhance calcium influx into neurons and activate glial cells, leading to a decrease in seizure threshold and neuronal hyperexcitability. Various pathways are identified in the hippocampal during the epileptic process, including disruption of the BBB, COX-2 signaling pathway, classical cytokines, and TLRs [25]. Neuroinflammation and oxidative stress are interconnected in epilepsy, with neuroinflammation activating transcriptional regulators NF-KB and Nrf2, leading to increased NADPH oxidase activity and a highly oxidative environment. These factors also affect mitochondrial function and the metabolic status of neurons and glia, which are already metabolically stressed in epilepsy. This review explores the mechanisms by which neuroinflammation and oxidative stress influence each other in epilepsy and examines the efficacy of treatments targeting oxidative stress and redox regulation in animal and human epilepsies [27-28].

3.3. Neurotransmitter-related markers (e.g., glutamate, GABA)

Neurotransmitter disorders are inherited neurometabolic diseases caused by disturbances in neurotransmitter metabolism, including amino acids like GABA, cholinergic transmission, and biogenic amines like dopamine, serotonin, noradrenaline, and adrenaline. These disorders are primarily characterized by biogenic amines, GABA, and cofactor defects. New disorders involving synaptic architecture, metabolism defects, and choline metabolism deficiencies are also reviewed. Biogenic amines regulate brain functions like movement, behavior, emotions, and blood pressure. Disorders of biogenic amines include levodopa-related movement disorders and early complex encephalopathies. GABAergic transmission regulates epileptic mechanisms, cognition, behavior, and arousal levels. Some neurotransmitter disorders are treatable [29]. Neurotransmitter deficiencies are rare neurological disorders causing clinical onset during childhood due to genetic defects in enzymes involved in the synthesis, degradation, or transport of neurotransmitters or defects in cofactor biosynthesis. The new DNAJC12 deficiency broadens the pathophysiological

spectrum. These deficiencies result in a lack of monoamine neurotransmitters, especially dopamine and its products, leading to decreased serotonin levels. Symptoms can occur in the neonatal period, with classic signs including hypotonia, movement disorders, autonomous dysregulations, and impaired development. Diagnosis relies on quantitative neurotransmitter detection in cerebrospinal fluid, while treatment involves supplementation of missing neurotransmitter precursors or restoring deficient cofactors for endogenous enzymatic synthesis. This review aims to enhance understanding of neurotransmitter disorders and help clinicians choose useful diagnostic steps for valid diagnosis [30]. Studies suggest that gamma-aminobutyric acid (GAGA), a major inhibitory amino acid neurotransmitter, is involved in the pathogensis of many neurologic diseases and psychiatric disorders. GABA is primarily degraded to succinic semialdehyde by the enzyme GABA-transaminase (GABA-T), which inhibits this enzyme, leading to an elevation of GABA contents in the brain. This elevation correlates with pharmacologic and behavioral effects. The activity of GABA-T in the brain and blood platelets is correlated with certain neuropsychiatric disorders like alcoholism, epilepsy, and Alzheimer's disease. Platelet GABA-T has similar kinetic and inhibitor characteristics to the brain, allowing for studies on the enzyme's activity in relation to neuropsychiatric disorders to understand, diagnose, and treat GABA-related central nervous system disorders [31-33].

4. Imaging Biomarkers

4.1. MRI and other imaging modalities for epilepsy diagnosis

Glial cells are crucial for brain function and may be responsible for some epileptic disease states. Neuroimaging of glial cells is desirable, but there are no clear methods to assess their function or localization. Magnetic resonance imaging (MRI) is now part of a standardized epilepsy imaging protocol, with structural volumetric and T2-weighted imaging changes aiding in diagnosis. MR spectroscopy for myo-inositol is being pursued to identify glial alterations and neuronal markers. Diffusion weighted imaging (DWI) is ideal for acute epileptiform events but is not sensitive to glial cells or neuronal long-term changes found in epilepsy. PET radioligands, including those targeting glial cells, hold promise for imaging glial cells. As glial function/dysfunction in epilepsy becomes more apparent, neuroimaging methods will evolve to assist clinicians and researchers in visualizing their location and function [34]. Neuroimaging is a technique used to identify neuropathological changes in epileptogenesis and monitor its progression after injury. It has improved our understanding of epilepsy, including hippocampus sclerosis. Animal models are effective in differentiating epileptogenesis stages. In vivo biomarkers are used to characterize neuronal loss, inflammation, blood-brain barrier alterations, neurotransmitter density, neurovascular coupling, cerebral blood flow, network connectivity, and metabolic activity. Magnetic resonance imaging (MRI) detects structural and functional changes in the brain, particularly in region-specific neuronal damage patterns. Positron emission tomography (PET) and single-photon emission computed tomography help elucidate key functional alterations and monitor epileptic disorders. Validated biomarkers are needed for early identification and monitoring medical interventions [35].

This review explores the application of MRI techniques to the epileptic brain and the search for potential biomarkers of epileptogenicity and/or epileptogenesis in rodents. Diffusion-weighted imaging reveals early changes in water movements, while T2-weighted hypersignal indicates edema or gliosis within brain regions. 31P spectroscopy measures tissue energy reserve, 1H spectroscopy assesses neuronal loss and mitochondrial dysfunction, and 13C spectroscopy analyzes neuronal and astrocytic metabolism and interactions. Diffusion tensor imaging and tractography show good coherence with circuit changes assessed by Timm staining. However, the potential of these techniques as reliable biomarkers of epileptogenesis is still disputed. One study predicts epileptogenesis in 100% of cases, and further imaging approaches are needed to identify potential early imaging biomarkers [36-38].

Neuroimaging techniques, including MRI, are crucial for determining the etiology of epilepsy. Recent advancements in data acquisition and analysis have increased the detection of underlying structural pathologies, which are now classified as "cryptogenic" epilepsy. This type of epilepsy is often refractory to anti-epileptic drug treatment, making surgery the only treatment for drug-resistant patients with structural or consistent functional lesions related to the epilepsy syndrome. Pre-operative detection of the underlying structural condition increases the chances of successful surgical treatment for pharmacoresistant epilepsy [39-40].

4.2. Role of imaging in monitoring epilepsy progression

MRI has been used for 12 years to investigate epilepsy, primarily focusing on defining structural abnormalities that underlie seizure disorders. It can reliably identify hippocampal sclerosis and malformations of cortical development (MCD) in 85% of cases, with subtle MCD or gliosis accounting for most. Functional MRI is used to identify cerebral areas responsible for specific cognitive processes and is crucial for planning resections near eloquent cortical areas. Magnetic resonance spectroscopy (MRS) can investigate cerebral metabolites and neurotransmitters non-invasively. Carbon-13

spectroscopy is a useful method for investigating cerebral metabolism in vivo. PET can provide data on regional cerebral blood flow (rCBF), glucose metabolism, and the binding of specific ligands to receptors. SPECT is the main use of SPECT to produce images reflecting rCBF, but interictal studies alone are not reliable. Spect scans need to be considered in comparison to interictal scans and MRI. Interpretation must be cautious, but SPECT may yield useful data for investigating patients for possible surgical treatment [41]. Epilepsies are brain-related serious diseases with a prevalence of 4-8/1000 and an annual incidence of 20-50/100000 in developed countries. Modern neuroimaging has improved management, with magnetic resonance imaging (MRI) being a key tool. MRI can identify underlying causes of epilepsy and guide clinicians in treatment and prognosis. Epilepsies and epileptic syndromes are classified into focal and generalised. Focal epilepsies account for 40-60% of newly diagnosed cases, with up to 30% developing intractable epilepsy despite antiepileptic drug treatment. Intractable temporal lobe epilepsy requires surgical treatment, while extratemporal results are less favourable [42-43].

5. Recent Advances in Epilepsy Biomarkers Research

5.1. MicroRNAs as Biomarkers

MicroRNA (miRNA) is a non-coding RNA that plays a crucial role in post-transcriptional regulation and gene expression in advanced eukaryotes. It inhibits mRNA expression by identifying a complementary ribonucleotide sequence in the 3′-untranslated region (UTR) of the target messenger RNA (mRNA). Each miRNA may correspond to mRNAs encoded by hundreds of genes simultaneously. Most miRNAs exhibit strictly regulated expression patterns, highlighting their importance in the time, space, and development stages of specific gene expression patterns. The nervous system contains a complex gene regulatory network, which contains both physiological and neurobiological information related to neurological diseases. The emergence of gene chip technology has further explored the relationship between miRNA and epilepsy, as well as the treatment and prognosis of epilepsy. MiRNAs are small single-stranded RNAs of about 22 nucleotides in length and are highly conserved in evolution. They can regulate up to 30% of protein expression after transcription. Epilepsy's exact cause is still debated, but it may be linked to neuronal cell apoptosis, circuit reformation, glial fibroblast proliferation, and inflammatory response. MiRNAs may regulate these processes, potentially contributing to epilepsy occurrence and development. MiRNA imbalance mechanisms and their roles in epilepsy pathogenesis are discussed, highlighting potential biomarkers and therapeutic developments. This highlights the importance of understanding the role of miRNAs in epilepsy.

Epilepsy patients often experience cerebral tissue injury, leading to the release of inflammatory factors that can cause damage to the nervous system and excite neurons, causing repeated seizures. In drug-resistant epilepsy, miR-34c-5p is downregulated, potentially upregulating HMGB1 and IL-1β expression. This could exacerbate neuroinflammation and hippocampal neuron loss in epileptogenesis. Toll-like receptor 4 (TLR4) is involved in the development of epileptic inflammation by regulating the expression of nuclear factor-κB, tumor necrosis factor receptor-related factor 6, and IL-1 receptor-related kinase 1. Elevated expression of IL-1, IL-6, and INF-α in epileptic foci indicates that inflammation is closely related to epilepsy. MiR-146a, an immune receptor, regulates the expression of NF-κB, IL-1, and INF-α and affects the inflammatory reaction after an epileptic seizure. Increased miR-146a levels in the epileptic brain may alleviate inflammation, suggesting it may be a target for disease treatment [46].

5.2. Role of microRNAs in epilepsy diagnosis and treatment

In preclinical models of epilepsy, miR-146a plays an important role in the TLR4 signaling pathway, which can suppress the activity of NF-κB, reducing the production of IL-1 and INF-α and the inflammatory reaction caused by epilepsy. In the refractory temporal lobe epilepsy (TLE) rat model, miR-146a increased epilepsy susceptibility by reducing complement factor H. Modulating the miR-146a-complement factor H-IL-1β loop circuit might be a novel therapeutic strategy for TLE.MiR-155 and TNF-α are associated with the regulation of inflammatory pathways in epilepsy, with increased levels in children with chronic TLE. These two molecules interact to mediate the inflammatory process, with miR-155 increasing TNF-α expression to enhance the inflammatory response. MiR-27a-3p expression is significantly increased in the hippocampus of epileptic rats, with an inhibitor effectively reducing IL-1β, IL-6, and TNF-α levels and neuronal apoptosis. Conversely, miR-125a-5p is downregulated in the hippocampus of pentylenetetrazol-induced epileptic rats, suggesting that miR-125a-5p might represent a novel treatment for epilepsy. Dysregulated miRNA expression may be involved in epilepsy pathogenesis by regulating the expression of inflammatory factors. MiR-146a may not only regulate inflammatory factors involved in the onset of epilepsy but may also be a biomarker for diagnosing epilepsy and an important therapeutic target. Recurrent epileptic seizures can cause neuronal apoptosis, which can reorganize synapses between neurons and form abnormal synaptic loops that promote epilepsy recurrence. MiR-21 can inhibit cell apoptosis, with miR-21 expression in the hippocampus increasing several hours after a seizure [46].

5.3. Potential microRNA biomarkers for epilepsy

The study aims to identify blood-based molecular biomarkers for temporal lobe epilepsy (TLE) to support clinical diagnosis. MicroRNAs, short noncoding RNAs with strong biomarker potential, have been reported in human epilepsy, but most studies collect samples from one clinical site, use a single profiling platform, or conduct minimal validation. The researchers collected plasma samples from adult TLE patients in two countries, performed genome-wide PCR-based and RNA sequencing, and validated findings in a large cohort of patients with psychogenic non-epileptic seizures (PNES). They identified three microRNAs with biomarker potential, which were also found to be altered in plasma levels in a mouse model of TLE but not in PNES patients. The study demonstrated rapid detection using an electrochemical RNA microfluidic disk as a prototype point-of-care device [47].

MicroRNAs are potential biomarkers for pathological changes and therapeutic targets in epileptic brains. Recent studies have focused on microRNA profiling in body fluids and brain tissues, with many microRNAs being dysregulated compared to healthy controls. Possible biomarkers include miR-199a-3p in blood plasma and miR-142-5p in blood plasma and blood serum in adults with temporal lobe epilepsy, and miR-153 in blood plasma and miR-145-3p in blood serum in adults with mesial temporal lobe epilepsy. However, the influence of anti-epileptic drugs on microRNA expression in body fluids and brain tissues is largely unknown. Further research is needed with children with temporal lobe epilepsy and using mouse, rat, and non-human primate models to confirm microRNA findings and test the effects of targeting specific microRNAs on disease progression and behaviour [48].

Epilepsy is a complex biological disorder involving various pathways, some of which are regulated by microRNAs (miRNAs), small non-coding RNAs. MiRNAs regulate the stability of several mRNAs by binding to their complementary sequence at the 3′ UTR of a coding mRNA. Studies have focused on the regulation of miRNA on its target genes and analyzed the effects of altered expression of single miRNA, increasing or decreasing miRNA levels in mouse and rat models, and observing the amelioration of pathological features of epilepsy. SNPs in miRNA genes (miRNA-SNPs) are an example of a point mutation that could affect miRNA function in three possible ways: altering transcription of the primary miRNA transcript, processing primary miRNA (pri-miRNA) and precursor miRNA (pre-miRNA), and modulating miRNA-mRNA interactions. These miRNA-SNPs have been associated with the pathogenesis of human disease, including epilepsy. MiRNAs can be detected in blood serum, making them suitable candidates for biomarkers to assess disease risk and treatment responses. Circulating miRNAs have potential applications in aging and neurological diseases. Altered miRNA profiles in biofluids may be useful biomarkers of epileptogenesis [49].

5.4. Proteins and Amino Acids as Biomarkers in epilepsy

Proteins and amino acids have emerged as important biomarkers in epilepsy, reflecting both neuronal injury and altered neurotransmitter dynamics. Protein biomarkers such as S100B, GFAP, IL-1β, TNF-α, IL-6, BDNF, HMGB1, and tau protein are strongly linked to neuroinflammation, gliosis, axonal degeneration, and excitotoxic signaling, processes that underlie seizure generation and progression. Similarly, amino acid biomarkers, including glutamate, GABA, aspartate, glycine, taurine, and D-serine, provide insight into the excitatory–inhibitory balance in epileptic brains. Elevated glutamate and aspartate levels promote excitotoxicity, whereas reduced GABA and taurine compromise inhibitory tone, facilitating recurrent seizures. Clinical and experimental evidence indicate that these biomarkers are not only associated with seizure onset and severity but may also serve as predictors of drug response and disease progression. A combined panel of protein and amino acid biomarkers may therefore improve diagnostic precision and therapeutic monitoring in epilepsy.

5.5. Future Directions in Epilepsy Research and Management:.

It also increases the risk of sudden unexpected death in epilepsy (SUDEP), depression, anxiety, cognitive dysfunction, and developmental delay. Approximately 30% of patients develop drug-resistant epilepsy (DRE). Diagnostic applications include EEG (Electroencephalography), MRI/CT (tumors, hippocampal sclerosis), video-EEG monitoring, neuropsychological testing, and emerging diagnostic tools like blood/CSF biomarkers, genetic testing, functional MRI/PET, and AI/Machine Learning. [49] Conventional treatments include antiepileptic drugs (AEDs) to inhibit neuronal firing, and surgery for both reflexive and disconnective seizures. AI and machine learning can interpret EEG data provide personalized diagnosis. The miRNA sequence is transcribed by RNA polymerase II as a long primary transcript (pri-miRNA), with most miRNAs located in intronic regions of protein-coding mRNA. After splicing, pri-miRNAs emerge as a long hairpin structure, undergo processing to become pre-miRNA and mature miRNA, forming a miRNA duplex. During maturation, miRNA loses part of its sequence, being cut by Drosha in the nucleus and DICER complex in the cytoplasm. The guide strand of the duplex miRNA is recognized and loaded into the RNA-induced silencing complex (RISC), while the passenger strand is usually degraded. Once miRNA recognizes the complementary

sequence on the target mRNA, it binds to it, leading to mRNA degradation or repression. The future direction s in epilepsy presented in Figure: 1.

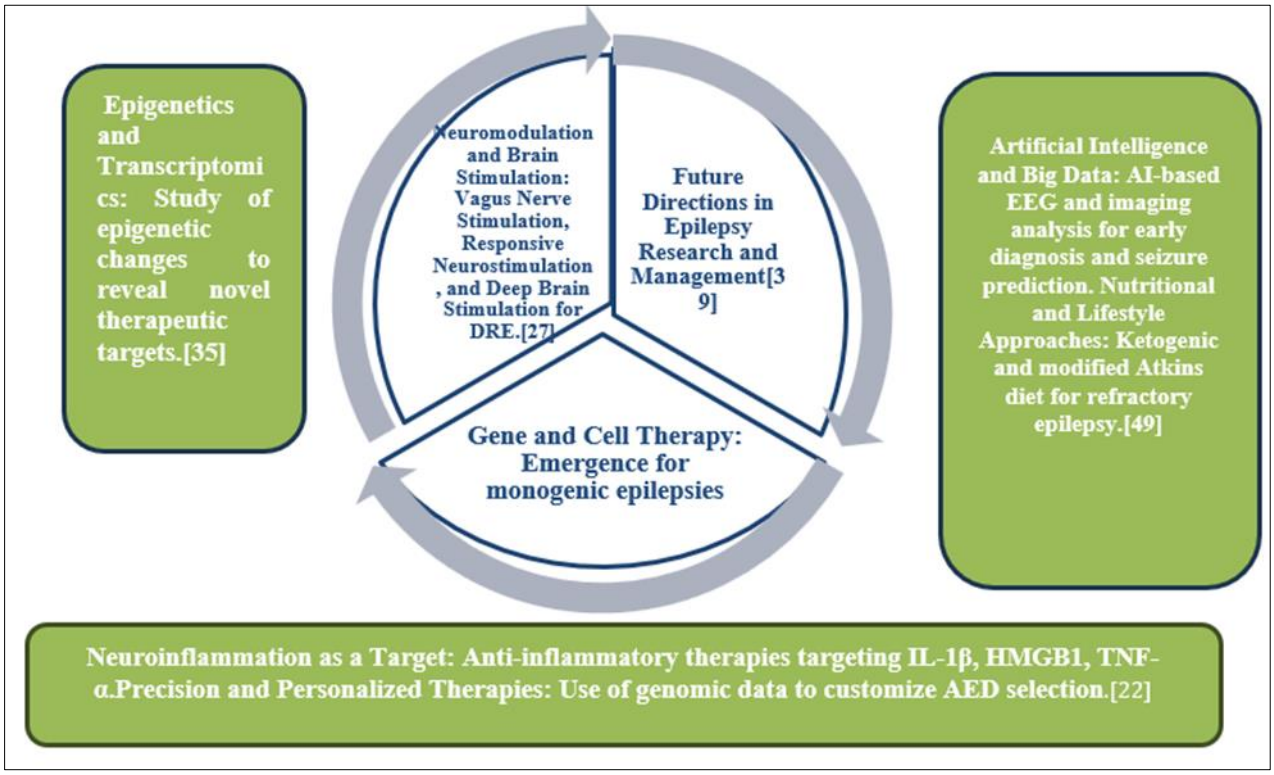

Figure 1 Future Directions in Epilepsy

6. Potential use of biomarkers in epilepsy diagnosis and treatment

6.1. Epilepsy Diagnosis and Prediction

Differentiates epileptic seizures using molecular markers.-Psychogenic nonepileptic seizures (PNES) are often misdiagnosed and mistreated as epileptic seizures, with 70% of cases developing between the second and fourth decades of life. PNES can also affect children and the elderly. At least 10% of patients with PNES have concurrent epileptic seizures or have had epileptic seizures before being diagnosed with PNES. Psychological stress exceeding an individual's coping capacity often precedes PNES. Clinicians find it challenging to differentiate between PNES and epileptic seizures. Some clinical features can help distinguish PNES from epileptic seizures, but other features are nonspecific and occur during both types of seizures. Diagnostic errors often result from overreliance on specific clinical features. Video-EEG is the diagnostic gold standard for PNES when typical seizures can be recorded, and thorough neurological and psychiatric histories can be used to confirm the diagnosis of PNES [50].

The study aimed to determine the serum neurogranin (NGRN) level in epilepsy patients presenting at the Emergency Department with epileptic seizure complaints. The study included patients aged over 18 years who had experienced an epileptic seizure or were experiencing an epileptic seizure proven with EEG. Patients with brain diseases of structural or infectious cause were excluded, and those with traumatic brain injury or severe systemic diseases like sepsis were excluded. A control group of healthy volunteers was also included. The study evaluated 49 patients, with a median serum neurogranin value of 184.16 ng/dl in the patient group and 97.90 ng/dl in the control group. The serum neurogranin value was significantly higher in the patient group than in the control group. The study concluded that the differential diagnosis of epilepsy from Parkinson's disease (PNES) remains a challenging situation for emergency service physicians. The serum NRGN level is high in patients who have experienced an epileptic seizure, making this new biomarker a potential tool for differential diagnosis [51].

The development of human blood biomarkers in epilepsy, highlighting the higher concentrations of brain proteins, neuroinflammatory proteins, and seizure duration in subjects with epilepsy. These biomarkers also show a decrease in levels following antiseizure medication treatment. However, the literature often contains conflicting results due to

differences in study populations, sampling techniques, and epilepsy classification. More studies are needed to focus on epilepsy and seizure types, and standardized reporting could reduce heterogeneity and improve data sharing and subgroup analyses [52].

Identifies epileptogenic zones or biochemical changes before visible changes on MRI or EEG. A retrospective review of clinical and neuroimaging charts of 26 patients diagnosed with seizure-related MR-signal changes found that partial or complete reversibility of these changes was observed. The study ruled out infection or other possible causes of brain damage, but seizure-induced brain-MRI abnormalities remained a diagnosis of exclusion. The results showed unilateral and bilateral abnormalities, with high and low T2-signal, leptomeningeal contrast-enhancement, and restricted diffusion. The abnormalities were found in various areas, including cortical/subcortical, basal ganglia, white matter, corpus callosum, and cerebellum. The reversibility of MRI changes was complete in 15 patients, and with residual gliosis or focal atrophy in 11 patients. Reversibility was noted between 15 and 150 days. Partial simple and complex seizures were associated with hippocampal involvement and status epilepticus with incomplete reversibility of MRI abnormalities. The study concludes that seizure or epileptic status can induce transient, variably reversible MRI brain abnormalities, and increased awareness may reduce the risk of misdiagnosis and unnecessary intervention [53-54].

6.2. Predicting Epilepsy Risk

Useful for people at risk after traumatic brain injury, stroke, or febrile seizures. Acute symptomatic and provoked seizures are situational events that occur in proximity to an event. The treatment implications and likelihood of recurrence differ from unprovoked seizures. Patients with acute symptomatic seizures have higher rates of morbidity and mortality in the acute phase of illness. Patients with these seizures in conditions like subdural hemorrhage, traumatic injuries, cortical strokes, neurocysticercosis, venous sinus thrombosis, and viral encephalitis have a higher rate of seizure recurrence, although the rate is less than that of unprovoked seizures. Short-term anti-seizure medication is appropriate for these patients, but longer-term treatment is recommended for those with persistent epileptiform activity on EEG and structural changes on imaging. If a patient has an unprovoked seizure, there is still a higher risk of recurrence and the likelihood of epilepsy development [55]. Post-traumatic epilepsy is a significant concern for those suffering from traumatic brain injury, accounting for 10-20% of cases. Despite seizure prophylaxis preventing early seizures, no treatments effectively prevent late-onset seizures. The progression of neural injury over time contributes to late onset seizure development. This review discusses the epidemiology, risk factors, and current pharmacologic agents used for treatment and limitations of current approaches and suggests solutions.

Pre-clinical models are crucial for investigating mechanistic factors responsible for post-traumatic epilepsy development. New models will be used to explore novel pathways linking acute injury to chronic brain changes, likely mediated by toll-like receptors, neuroinflammation, and tauopathy. Experimental therapies may prove promising in preventing and treating post-traumatic epilepsy. By increasing understanding of post-traumatic epilepsy and injury expansion over time, better treatments with specific molecular targets can be designed to prevent late-onset seizure occurrence following traumatic brain injury [56].

Stroke is the primary cause of seizures and epilepsy in older adults, with patients with larger, more severe strokes, younger age, and acute symptomatic seizures and intracerebral haemorrhage at the highest risk. Prognostic models like SeLECT and CAVE scores help assess epileptogenesis risk. Early electroencephalograms and blood-based biomarkers can provide additional information. Management of acute and remote symptomatic seizures differs, and the choice of antiseizure medication should consider adverse effects, altered pharmacodynamics, and underlying vascular co-morbidity. Drug-drug interactions, particularly between antiseizure medications and anticoagulants or antiplatelets, also influence treatment decisions. This review covers the epidemiology, risk factors, biomarkers, and management of seizures after ischaemic or haemorrhagic strokes [57-58].

The MRC Multicentre trial for Early Epilepsy and Single Seizures (MESS) found a reduced risk of further seizures in patients who received immediate treatment compared to delayed treatment. However, there was no evidence of long-term remission rates. This study aimed to assess the role of patient characteristics and treatment in predicting seizure recurrence. A prognostic model was developed based on individual patient data from MESS to identify patients at low, medium, or high risk of seizure recurrence. The model identified individuals with two or three seizures, a neurological disorder, or an abnormal electroencephalogram (EEG) as the medium-risk group, those with two or more features or more than three seizures as the high-risk group, and those with a single seizure only as the low-risk group. The model showed that immediate treatment had little benefit in patients at low risk of seizure recurrence, but potentially worthwhile benefits were seen in those at medium and high risk [59-60].

6.3. Role of biomarkers in monitoring treatment response

Biomarkers play a crucial role in early detection of treatment response, personalized medicine, and improved patient outcomes. They can detect changes in seizure activity or brain function, allowing for timely adjustments to treatment. Biomarkers play a crucial role in early detection of treatment response, personalized medicine, and improved patient outcomes. They can detect changes in seizure activity or brain function, allowing for timely adjustments to treatment. They can also help tailor treatment strategies to individual patients, improving treatment efficacy and reducing side effects. Molecular biomarkers, such as gene expression or protein levels, can indicate treatment response. Biomarkers can be used in epilepsy treatment monitoring for antiepileptic drugs (AEDs), surgical treatments, and emerging therapies. However, challenges include rigorous validation and standardization, practical integration into clinical practice, and advancements in technology like artificial intelligence and machine learning. By leveraging biomarkers, clinicians can optimize treatment plans, improve patient outcomes, and advance the field of epilepsy care. Future directions include integrating biomarkers into clinical practice and leveraging emerging technologies like artificial intelligence and machine learning for improved analysis and interpretation [61].

7. Conclusion

Epilepsy is a multifaceted disorder with complex etiologies and clinical manifestations, making timely and accurate diagnosis a persistent challenge. Biomarkers represent a transformative approach for addressing these challenges, offering measurable indicators of disease risk, progression, and treatment response. Genetic testing provides valuable guidance for precision medicine, while molecular, imaging, and electrophysiological biomarkers support differential diagnosis and disease monitoring. Emerging tools, such as microRNAs and protein biomarkers, hold significant potential for identifying epileptogenic networks and predicting therapeutic outcomes. However, despite promising developments, biomarker discovery in epilepsy remains in its early stages, requiring large-scale, multicenter studies, standardization, and validation. Future directions should emphasize the development of biomarker panels that combine genetic, molecular, and imaging modalities to achieve greater accuracy and clinical utility. Ultimately, integrating biomarkers into epilepsy research and clinical care may lead to earlier diagnosis, improved patient stratification, targeted treatment strategies, and better long-term management of this complex neurological disorder.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Engel JJ, Pedley TA. Introduction: what is epilepsy? Epilepsy: A comprehensive textbook. 1997;1:1-0.

[2] Scharfman HE. The neurobiology of epilepsy. Current neurology and neuroscience reports. 2007 Jul;7(4):348-54.

[3] Pitkänen A, Löscher W, Vezzani A, Becker AJ, Simonato M, Lukasiuk K, Gröhn O, Bankstahl JP, Friedman A, Aronica E, Gorter JA. Advances in the development of biomarkers for epilepsy. The Lancet Neurology. 2016 Jul 1;15(8):843-56.

[4] Sueri C, Gasparini S, Balestrini S, Labate A, Gambardella A, Russo E, Leo A, Casarotto S, Pittau F, Trimboli M, Cianci V. Diagnostic biomarkers of epilepsy. Current Pharmaceutical Biotechnology. 2018 May 1;19(6):440-50.

[5] Engel Jr., J. Biomarkers in epilepsy: introduction. Biomarkers in medicine. 2011 Oct 1;5(5):537-44.

[6] Engel Jr J, Pitkänen A. Biomarkers for epileptogenesis and its treatment. Neuropharmacology. 2020 May 1;167:107735.

[7] Pitkänen A, Ndode-Ekane XE, Lapinlampi N, Puhakka N. Epilepsy biomarkers—toward etiology and pathology specificity. Neurobiology of disease. 2019 Mar 1;123:42-58.

[8] Bhatnagar M, Shorvon S. Genetic mutations associated with status epilepticus. Epilepsy & Behavior. 2015 Aug 1;49:104-10.

[9] Kang JQ, Macdonald RL. Molecular pathogenic basis for GABRG2 mutations associated with a spectrum of epilepsy syndromes, from generalized absence epilepsy to Dravet syndrome. JAMA neurology. 2016 Aug 1;73(8):1009-16.

[10] Zhou P, He N, Zhang JW, Lin ZJ, Wang J, Yan LM, Meng H, Tang B, Li BM, Liu XR, Shi YW. Novel mutations and phenotypes of epilepsy-associated genes in epileptic encephalopathies. Genes, Brain, and Behavior. 2018 Nov;17(8):e12456.

[11] Escayg A, Heils A, MacDonald BT, Haug K, Sander T, Meisler MH. A novel SCN1A mutation associated with generalized epilepsy with febrile seizures plus—and prevalence of variants in patients with epilepsy. The American Journal of Human Genetics. 2001 Apr 1;68(4):866-73.

[12] Sun Y, Lu L, Li L, Wang J. An advance about the genetic causes of epilepsy. InE3S Web of Conferences 2021 (Vol. 271, p. 03068). EDP Sciences.

[13] Deprez L, Weckhuysen S, Peeters K, Deconinck T, Claeys KG, Claes LR, Suls A, Van Dyck T, Palmini A, Matthijs G, Van Paesschen W. Epilepsy as part of the phenotype associated with ATP1A2 mutations. Epilepsia. 2008 Mar;49(3):500-8.

[14] Shen D, Hernandez CC, Shen W, Hu N, Poduri A, Shiedley B, Rotenberg A, Datta AN, Leiz S, Patzer S, Boor R. De novo GABRG2 mutations associated with epileptic encephalopathies. Brain. 2017 Jan 1;140(1):49-67.

[15] Berg AT, Coryell J, Saneto RP, Grinspan ZM, Alexander JJ, Kekis M, Sullivan JE, Wirrell EC, Shellhaas RA, Mytinger JR, Gaillard WD. Early-life epilepsies and the emerging role of genetic testing. JAMA pediatrics. 2017 Sep 1;171(9):863-71.

[16] Ritter DM, Holland K. Genetic testing in epilepsy. In Seminars in Neurology 2020 Dec (Vol. 40, No. 06, pp. 730-738). Thieme Medical Publishers, Inc.

[17] Striano P, Minassian BA. From genetic testing to precision medicine in epilepsy. Neurotherapeutics. 2020 Apr 1;17(2):609-15.

[18] Sheidley BR, Malinowski J, Bergner AL, Bier L, Gloss DS, Mu W, Mulhern MM, Partack EJ, Poduri A. Genetic testing for the epilepsies: a systematic review. Epilepsia. 2022 Feb;63(2):375-87.

[19] Mefford HC. Clinical genetic testing in epilepsy: clinical genetic testing in epilepsy. Epilepsy currents. 2015 Jul;15(4):197-201.

[20] Kothur K, Wienholt L, Brilot F, Dale RC. CSF cytokines/chemokines as biomarkers in neuroinflammatory CNS disorders: a systematic review. Cytokine. 2016 Jan 1;77:227-37.

[21] Vezzani A, Balosso S, Ravizza T. Neuroinflammatory pathways as treatment targets and biomarkers in epilepsy. Nature Reviews Neurology. 2019 Aug;15(8):459-72.

[22] Vezzani A, Friedman A. Brain inflammation as a biomarker in epilepsy. Biomarkers in medicine. 2011 Oct 1;5(5):607-14.

[23] Kobylarek D, Iwanowski P, Lewandowska Z, Limphaibool N, Szafranek S, Labrzycka A, Kozubski W. Advances in the potential biomarkers of epilepsy. Frontiers in neurology. 2019 Jul 2;10:685.

[24] Rawat C, Kukal S, Dahiya UR, Kukreti R. Cyclooxygenase-2 (COX-2) inhibitors: future therapeutic strategies for epilepsy management. Journal of neuroinflammation. 2019 Oct 30;16(1):197.

[25] Satapathy T, Satapathy A, Satapathy A, Yadav N, Chandrakar M, Chandrakar K. Recent outbreaks of Human Metapneumovirus (HMPV): Prevention, diagnosis and therapeutic insights. *Journal of Drug Delivery & Therapeutics*. 2025 Feb 1;15(2).

[26] Arena A, Zimmer TS, van Scheppingen J, Korotkov A, Anink JJ, Mühlebner A, Jansen FE, van Hecke W, Spliet WG, van Rijen PC, Vezzani A. Oxidative stress and inflammation in a spectrum of epileptogenic cortical malformations: molecular insights into their interdependence. Brain Pathology. 2019 May;29(3):351-65.

[27] Yeligar RR, Sarwa KK, Chandrakar M, Jangde MS. Nanotechnology-based delivery of genistein to overcome physicochemical hindrance and enhance therapeutic response in skin cancer. *BioNanoScience*. 2023 Sep;13(3):1339–1358.

[28] Fabisiak T, Patel M. Crosstalk between neuroinflammation and oxidative stress in epilepsy. Frontiers in cell and developmental biology. 2022 Aug 10;10:976953.

[29] Chandrakar K, Tiwari S, Chandrakar M, Sarwa KK. Pharmacological and toxicity concerns of plant *Prunus armeniaca* including adoptive nanotechnology for precise delivery of their active constituents. *International Journal of Drug Delivery Technology*. 2024 Sep;14(3):1818–1828. doi:10.25258/ijddt.14.3.80.

[30] Rawat V, Chandrakar M, Wahane A, Sahu DK, Sharma N, Chandrakar K. From risk to resilience: The transformative power of welfare programs on liver health. *Issues on Health Science*. 2025 Apr 18;1:117–135. ZenToks.

[31] Sherif FM, Ahmed SS. Basic aspects of GABA-transaminase in neuropsychiatric disorders. Clinical biochemistry. 1995 Apr 1;28(2):145-54.

[32] Zhang T, Yu F, Xu H, Chen M, Chen X, Guo L, Zhou C, Xu Y, Wang F, Yu J, Wu B. Dysregulation of REV-ERBα impairs GABAergic function and promotes epileptic seizures in preclinical models. Nature communications. 2021 Feb 22;12(1):1216.

[33] Na JH, Lee H, Lee YM. Clinical Efficacy and Safety of the Ketogenic Diet in Patients with Genetic Confirmation of Drug-Resistant Epilepsy. Nutrients. 2025 Mar 11;17(6):979.

[34] Obenaus A. Neuroimaging biomarkers for epilepsy: advances and relevance to glial cells. Neurochemistry international. 2013 Dec 1;63(7):712-8.

[35] Reddy SD, Younus I, Sridhar V, Reddy DS. Neuroimaging biomarkers of experimental epileptogenesis and refractory epilepsy. International Journal of Molecular Sciences. 2019 Jan 8;20(1):220.

[36] Nehlig A. Hippocampal MRI and other structural biomarkers: experimental approach to epileptogenesis. Biomarkers in Medicine. 2011 Oct 1;5(5):585-97.

[37] Sinha R, Singh R, Chandrakar M, Parihar AKS. Designing of curcumin nanoemulsion by using tamarind gum as natural emulsifying agent. *Research Journal of Pharmacy and Technology*. 2024;17(1):172–178. A & V Publications.

[38] Mito R, Cole JH, Genc S, Jackson GD, Zalesky A. Towards precision MRI biomarkers in epilepsy with normative modelling. Brain. 2025 Mar 5:awaf090.

[39] Desale P, Dhande R, Parihar P, Nimodia D, Bhangale PN, Shinde D, DHANDE R, Shinde D. Navigating neural landscapes: a comprehensive review of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) applications in epilepsy. Cureus. 2024 Mar 25;16(3).

[40] Fitsiori A, Hiremath SB, Boto J, Garibotto V, Vargas MI. Morphological and advanced imaging of epilepsy: beyond the basics. Children. 2019 Mar 11;6(3):43.

[41] Duncan JS. Imaging and epilepsy. Brain: a journal of neurology. 1997 Feb 1;120(2):339-77.

[42] Salmenpera TM, Duncan JS. Imaging in epilepsy. Journal of Neurology, Neurosurgery & Psychiatry. 2005 Sep 1;76(suppl 3):iii2-10.

[43] Duncan JS. Brain imaging in epilepsy. Practical neurology. 2019 Oct 1;19(5):438-43.

[44] Nairismägi J, Gröhn OH, Kettunen MI, Nissinen J, Kauppinen RA, Pitkänen A. Progression of brain damage after status epilepticus and its association with epileptogenesis: a quantitative MRI study in a rat model of temporal lobe epilepsy. Epilepsia. 2004 Sep;45(9):1024-34.

[45] Spencer SS. The relative contributions of MRI, SPECT, and PET imaging in epilepsy. Epilepsia. 1994 Dec;35:S72-89.

[46] Wang J, Zhao J. MicroRNA dysregulation in epilepsy: from pathogenetic involvement to diagnostic biomarker and therapeutic agent development. Frontiers in molecular neuroscience. 2021 Mar 12;14:650372

[47] Raoof R, Bauer S, El Naggar H, Connolly NM, Brennan GP, Brindley E, Hill T, McArdle H, Spain E, Forster RJ, Prehn JH. Dual-center, dual-platform microRNA profiling identifies potential plasma biomarkers of adult temporal lobe epilepsy. EBioMedicine. 2018 Dec 1;38:127-41.

[48] Martinez B, Peplow PV. MicroRNAs as potential biomarkers in temporal lobe epilepsy and mesial temporal lobe epilepsy. Neural Regeneration Research. 2023 Apr 1;18(4):716-26.

[49] Cava C, Manna I, Gambardella A, Bertoli G, Castiglioni I. Potential role of miRNAs as theranostic biomarkers of epilepsy. Molecular therapy Nucleic acids. 2018 Dec 7;13:275-90.

[50] Devinsky O, Gazzola D, LaFrance Jr WC. Differentiating between nonepileptic and epileptic seizures. Nature Reviews Neurology. 2011 Apr;7(4):210-20.

[51] Kalkan A, Demirel A, Atiş ŞE, Karaaslan EB, Ferhatlar ME, Senturk M. A new biomarker in the differential diagnosis of epileptic seizure: Neurogranin. The American Journal of Emergency Medicine. 2022 Apr 1;54:147-50.

[52] Banote RK, Akel S, Zelano J. Blood biomarkers in epilepsy. Acta Neurologica Scandinavica. 2022 Oct;146(4):362-8.

[53] Cianfoni A, Caulo M, Cerase A, Della Marca G, Falcone C, Di Lella GM, Gaudino S, Edwards J, Colosimo C. Seizure-induced brain lesions: a wide spectrum of variably reversible MRI abnormalities. European Journal of Radiology. 2013 Nov 1;82(11):1964-72.

[54] Reddy SD, Younus I, Sridhar V, Reddy DS. Neuroimaging biomarkers of experimental epileptogenesis and refractory epilepsy. International Journal of Molecular Sciences. 2019 Jan 8;20(1):220.

[55] Long-term seizure treatment is considered for these patients, but anti-seizure treatment does not appear to influence long-term seizure remission rates.Gunawardane N, Fields M. Acute symptomatic seizures and provoked seizures: to treat or not to treat?. Current treatment options in neurology. 2018 Oct;20(10):41.

[56] .Lucke-Wold BP, Nguyen L, Turner RC, Logsdon AF, Chen YW, Smith KE, Huber JD, Matsumoto R, Rosen CL, Tucker ES, Richter E. Traumatic brain injury and epilepsy: underlying mechanisms leading to seizure. Seizure. 2015 Dec 1;33:13-23.

[57] Galovic M, Ferreira-Atuesta C, Abraira L, Döhler N, Sinka L, Brigo F, Bentes C, Zelano J, Koepp MJ. Seizures and epilepsy after stroke: epidemiology, biomarkers and management. Drugs & aging. 2021 Apr;38(4):285-99.

[58] Litt B, Echauz J. Prediction of epileptic seizures. The Lancet Neurology. 2002 May 1;1(1):22-30.

[59] Kim LG, Johnson TL, Marson AG, Chadwick DW. Prediction of risk of seizure recurrence after a single seizure and early epilepsy: further results from the MESS trial. The Lancet Neurology. 2006 Apr 1;5(4):317-22.

[60] Smith ZZ, Benison AM, Bercum FM, Dudek FE, Barth DS. Progression of convulsive and nonconvulsive seizures during epileptogenesis after pilocarpine-induced status epilepticus. Journal of Neurophysiology. 2018 May 1;119(5):1818-35

[61] Yang C, Liu Z, Wang Q, Wang Q, Liu Z, Luan G. Epilepsy as a dynamical disorder orchestrated by epileptogenic zone: a review. Nonlinear Dynamics. 2021 May;104(3):1901-16.