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COMPARATIVE EVALUATION OF HIPPOCAMPAL SCLEROSIS INMESIAL TEMPORAL LOBE EPILEPSY: ANATOMICALCORRELATES, PATHOPHYSIOLOGY, IMPACT ON ANTIEPILEPTIC DRUG RESPONSE AND CLINICAL OUTCOMES – A REVIEW

Kommana Balaram Kumar[1]*, Kuppala Charan Sai[2], Vasupalli Yojitha[3], Talabathula Varshini[4], Aditi Samantaray[5], Mohsin Akram[6]

[1]*Professor, Department of Pharmaceutical Chemistry Assistant Professor, Visakhapatnam, Andhra Pradesh, India.
[2]Department of Pharmaceutical Sciences, Assistant Professor, Srinivasarao College of Pharmacy, Visakhapatnam, Andhra Pradesh, India.
[3,4,5,6]Pharm D, Department of Pharmaceutical Sciences, Assistant Professor, Srinivasarao College of Pharmacy, Visakhapatnam, Andhra Pradesh, India.

***Corresponding Author: Kommana Balaram Kumar**

Professor, Department of Pharmaceutical Chemistry Assistant Professor, Visakhapatnam, Andhra Pradesh, India.

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ABSTRACT

Hippocampal Sclerosis (HS) is the most common underlying cause of Mesial Temporal Lobe Epilepsy (MTLE), and it's often the reason why many patients don't respond to medication. It involves the loss of specific neurons, an increase in glial cells, and a reshaping of the connections within the hippocampus. Even though there are many Antiepileptic Drugs (AEDs) available, a large number of MTLE-HS patients don't find relief with these medications and often need surgery. This resistance to drugs arises from the combination of structural damage in the hippocampus and intricate molecular processes, such as the increased activity ofdrug transporters that pump drugs out of cells, and ongoing inflammation in the brain. This review brings together the latest findings on the different anatomical and histopathologicaltypes of HS, what we can see using advanced brain imaging, the underlying molecular mechanisms, the cognitive and clinical consequences, and how it significantly affects drug resistance. Additionally, we will explore factors that help predict whether surgery or medication will be moreeffective, and we'll discuss future directions, emphasizing the importance of personalized treatment plans to improve patient results.

KEYWORDS: Hippocampal Sclerosis, Mesial Temporal Lobe Epilepsy, Antiepileptic Drugs, Pharma co resistance, Neuroimaging, P-glycoprotein, Neuro inflammation, Deep Brain Stimulation.

INTRODUCTION

Mesial Temporal Lobe Epilepsy (MTLE), the most common type of focal epilepsy in adults, often involves Hippocampal Sclerosis (HS) as a primary underlying cause. (Engel, 2001) HS involves specific nerve cell loss, an increase in glial cells, and changes in the structure of the hippocampus, which together trigger network changes that perpetuateepilepsy (Blümcke et al., 2013) The International League Against Epilepsy (ILAE)classification offers a consistent way to categorize H S based on its microscopic features. This improves research comparisons and helps link these features more accuratelywith patient outcomes (Thom, 2014).

Studies suggest that HS is present in up to 70% of individuals with MTLE who don't respond to medication, highlighting its importance in diagnosis and treatment

(Téllez-Zenteno et al., 2010). MTLE-HS often begins with seizures at a young age, frequent recurrences, and difficulty controlnlig seizures with drugs over time (Kwan et al., 2011). While Anti-Epileptic Drugs (AEDs) are typicallythe first line of treatment, many with MTLE-HS, about two-thirds, eventually develop resistance to these drugs, making surgery a potential option (Kwan et al., 2009).

Better neuroimaging techniques have become crucial for identifying and understanding HS. Magnetic Resonance Imaging (MRI)can reveal shrinkage of the hippocampus, increased brightness on certain scans, and changes in water diffusion patterns, all of which strongly relate to the severity of HS seen under a microscope (Jackson et al., 1993). Functional MRI and Diffusion Tensor Imaging (DTI) further show broader network disruptions beyond the hippocampus, involving other brain regions in seizure spread and cognitive issues (Bernhardt et al., 2010). Comparing patients with HS-related MTLE to those with other types of MTLEindicates notable differences in seizure characteristics, cognitive abilities, and treatment responses (Wiebe et al., 2001).

On a molecular level, HSinvolves changes in connections between nerve cells, abnormal growth of certain nerve fibers,reduced inhibition by GABA,and ongoing inflammation (Engel, 2012). These factors are believed to contribute to both the development of epilepsy and resistance to drugs. Genetic factors, such as variations in genes affecting drug transport and inflammation, may also influence how patients respond to medication, although their precise roles are still being investigated (Helmstaedter et al., 2003).

The impact of HS extends beyond just seizure control. Patients often experience memory problems, emotional difficulties, and a decreased quality of life, with outcomes varying depending on which side of the braisn Iaffected and the extent of the damage (Baxendale, 1997). Surgical removal of the affected area, particularly anterior temporal lobectomy or selective amygdalohippocampectomy, has shown better seizure control in MTLE- HS compared to continuing with AEDsalone (Jokeit & Ebner, 2002). However, the risk of cognitive decline, variability in long-term results, and challenges in determining who will benefit most from surgery remain important considerations.

This review offers a comparative analysis of HS in MTLE, focusing on how it affects the response to AEDs. It covers anatomical features, microscopic characteristics, neuroimaging findings, molecular mechanisms, clinical and cognitive effects, and treatment outcomes. By bringing together evidence for m various fields, this review aims to clarify how HS contributes to drug resistance and to identify potential strategies for improving treatment in MTLE-HS.

REVIEW

Anatomical Correlates of HS

Hippocampal Sclerosis (HS) is distinguished by specific nerve cell loss, an increase in glial cells,and changes in the organization of the hippocampus. These alterations significantly affect how Mesial Temporal Lobe Epilepsy (MTLE) manifests and how it responds to medication. Nerve cell loss is typicallymost pronounced in the CA1 and CA3 regions of the hippocampus, while CA2 tends to be less affected (Trenerry et al., 1993). The dentate gyrus exhibits mossy fiber sprouting, a characteristic ofepilepsy-relatedreorganization, which amplifies recurrent excitatory circuits (Helmstaedter & Elger, 1996).

The International League Against Epilepsy (ILAE) classificationrefines our understanding of HS by categorizing it into types 1, 2, and 3, based on specific patterns of nerve cellloss (Lee etal., 2002). Type 1, involving cell loss in CA1 and CA4, is the most common and is strongly linked to early-onset epilepsy and resistance to medication. Type 2, mainly characterized by CA1 loss, and type 3, with selective CA4 involvement, seem to have different clinical courses and prognostic implications (Rausch & Babb, 1993). Inchildren, HS often shows more widespread damage throughout the hippocampus compared to adults, suggesting that the developing brain may be particularly vulnerable to epilepsy-related changes (Sutula et al., 1989).

Microscopic studies also reveal an increase in glial cells and changes in inhibitory circuits, especially a reduction in GABAergic interneurons. This diminishes inhibitory control and promotes excessive excitability in thenetwork (Houser, 1990). Furthermore, the presence of long-term epilepsy-associatedtumors and dual pathology (HS combined with focal cortical dysplasia) complicate the anatomical picture, leading topoorer surgical outcomes (Babb & Brown, 1993). Advanced stereological analyses confirmthat nerve cell loss not only correlates with seizure severity but also with cognitive impairments, notably memory dysfunction, underscoring the significant clinical burden of HS (Margerison & Corsellis, 1966).

In conclusion, anatomical changes provide a fundamental explanation for the diverse clinical presentations of MTLE -HS and its resistance to drug treatments (Figure 1 and 2).

Schematic: Neuron loss → Gliosis → Mossy Fiber Sprouting → Epileptogenesis

Pharmacoresistance (withI-L1β, TNF-α, P-glycoprotein, cytokines shown as molecular contributors

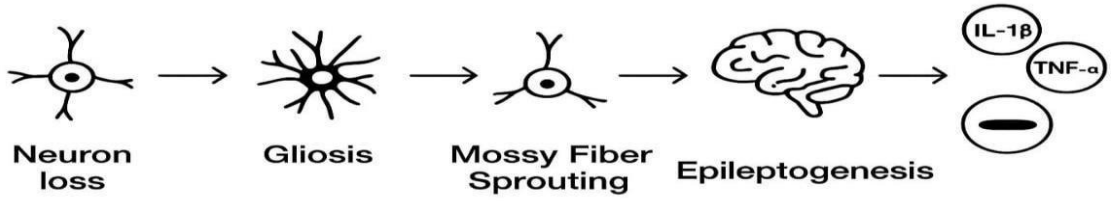

Figure 1– Pathophysiological Cascade of HSin MTLE.

Table 1: ILAE Classification of HS.

Type	Anatomical Involvement	Neuron Loss	Clinical Outcome	Drug Response
Type1	CA1+CA4	Severe	Poor	Pharmaco resistant
Type2	CA1 only	Moderate	Intermediate	Variable
Type3	CA4 only	Mild	Better	Some responsiveness

Diagram comparing normal hippocampal circuitry vs HS with aberrant mossy fiber sprouting

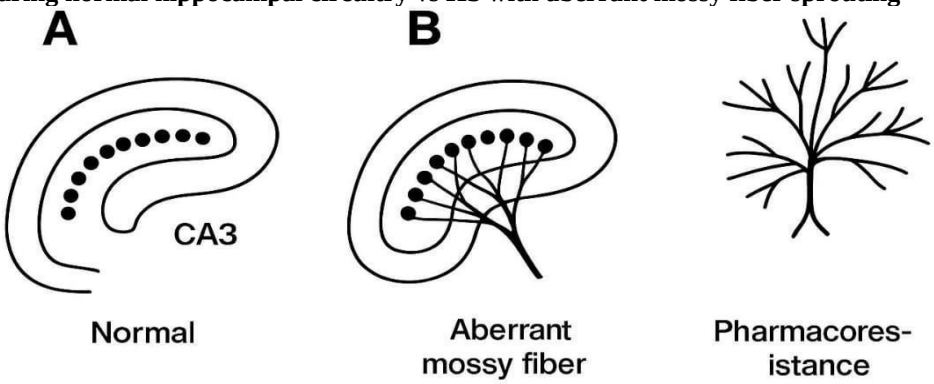

Figure 2: Mossy Fiber Sprouting in HS.

NEUROIMAGING ADVANCES

Magnetic Resonance Imaging (MRI) has revolutionized thein vivo detection of HS. Hippocampal atrophy, increased T2/FLAIR signal intensity, and loss of internal architecture are key radiological markers (Falconer & Serafetinides, 1963). Volumetric MRI shows strong agreement with histopathology, confirming MRI's role as the non-invasive diagnostic gold standard (Mathern et al., 1995). High-resolution imaging now enables assessment of individual hippocampal subfields, revealing that CA1 and subiculum atrophy best predict seizure recurrence and poor surgical outcomes (Swartz et al., 2006).

Diffusion Tensor Imaging (DTI) and tractography studies reveal impaired fractional anisotropy in hippocampal efferent pathways, such as the fornix and cingulum, highlighting network-level disruption in MTLE-HS (Pitkänen & Lukasiuk, 2011). Functional MRI (fMRI) adds complementary insights, showing altered connectivity between the hippocampus and extra-temporal regions, including the default mode network and prefrontal cortex, correlating with seizure frequency and cognitive deficits (Engel et al., 2003).

Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomogarphy (SPECT) further demonstrate hypometabolism and hypoperfusion beyond the hippocampus, reinforcing the concept that MTLE-HS is a network disorder rather than apurely focal pathology (Spencer et al., 1990). It's important to note that MRI-negative HS, where histopathological sclerosis isn't visible radiologically, presents significant diagnostic and therapeutic challenges. Studies reveal that MRI-negative patients often have less favorable surgical outcomes and require multimodal imaging for accurate localization (Engel, 1996).

Longitudinal imaging studies have also demonstrated progressive atrophy of the contralateral hippocampus and neocortical regions, supporting the hypothesis that uncontrolled seizures drive structural remodeling and worsen prognosis (D. D. Spencer et al., 1984). Collectively, imaging biomarkers not only aid in diagnosis but also serve as predictors of surgical outcome andcognitive decline (Figure 3).

Illustration of coronal MRI slices: normal hippocampus vs HS with atrophy + T2 hyperintensity

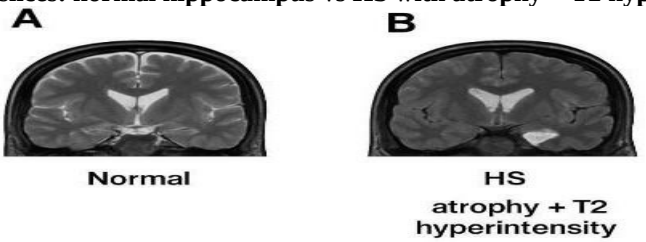

Figure 3: MRI Findings in HS.

Table 2: MRI and Advanced Imaging Markers of HS Imaging.

Technique	Key Finding	Clinical Relevance
T2/FLAIR MRI	Hyperintensity	Indicates gliosis
Volumetry	Hippocampal atrophy	Correlates with duration
DTI	FA reduction	Network damage
7T MRI	Subsfield resolution	Early HS Detection

MOLECULAR PREDICTORS

The molecular pathways of drug resistance in MTLE-HS have been extensively studied, with evidence supporting structural and molecular contributors.One prominent hypothesis involves overexpression of multidrug efflux transporters like P-glycoprotein (encoded by ABCB1). These actively remove AEDs from the epileptogenic focus, reducing local drug concentrations (Wieser, 1991). Studies show increased P-glycoprotein expression in sclerotic hippocampi, strongly correlating with drug resistance (Téllez-Zenteno et al., 2005).

Neuroinflammatory processes, including the upregulation of interleuki-n1β, tumor necrosis facto-rα, and cyclooxygenase-2, contribute to hyperexcitability and alter AED responsiveness (Wiebe et al., 2001b). Chronic gliosis sustains an inflammatory environment and impairs blood-brain barrier integrity, facilitating abnormal molecular trafficking (Helmstaedter & Elger, 1996b). Furthermore, alterations in GABA-A receptor subunit composition and NMDA receptor upregulation havebeen reported in HS, suggesting synaptic reorganization modifiespharmacological sensitivity (S. Baxendale et al., 2006).

Apoptotic and neurodegenerative pathways also play a role. Increased expression of caspases and pr-o apoptotic proteins in HS contributes to progressive neuronal loss and altered network properties (Jokeit & Ebner, 1999). Epigenetic modifications, including DNA methylation changes ingenes regulating neuronal excitability and inflammation, are emerging as contributors to variable drug response (Bernhardt et al., 2010b).

Collectively, these molecular alterations highlight why standard AED regimens frequently fail in MTLE-HS patients, underscoring the need for novel therapies targeting transporter proteins, inflammatory mediators, or epigenetic regulators (Figure 1).

Table 3: PharmacoresistanceMechanisms in HS.

Mechanism	Example	Impact on AEDs
Transporter overexpression	P-glycoprotein (ABCB1)	↓ Brain AED levels
Inflammation	IL-1β, TNF-α	↑ Excitability
Ion channel mutations	SCN1A, GABRA1	Altered drug sensitivity
Epigenetics	DNA methylation	Persistent resistance

CLINICAL OUTCOMES

Clinically, MTLE-HS is strongly associated withpoor seizure control under pharmacological therapy. Epidemiological studies suggest that up to two-thirds of patients with HS fail to achieve long-term seizure freedom with AEDs (Bernasconi, 2003). Early epilepsy onset, prolonged seizure duration before treatment, and the presence of dual pathology are consistent predictors of poor medical outcomes (Keller et al., 2002).

Comparative outcome studies have consistently demonstrated superior seizure freedom rates following surgical intervention compared to continued pharmacotherapy. Landmark randomized controlleditarls, such as the one conducted by Wiebe et al., have indicated that around58% of surgical patients achieved seizure freedom after one year, compared to only 8% of those treated with medication (Mueller et al., 2011). Lon-g term studies reveal that a considerable number of surgically treated HS patients experience lasting seizure remission, although therisk of relapse remains for many years (Bonilha et al., 2006).

Quality of life (QoL) studies demonstrate that uncontrolled seizures significantly affect a person's ability to work, learn, and function socially. Interestingly, surgical patients not only have better seizure control but also report improved QoL, even if

they don't become completely seizure-free (Hermann et al., 2002). However, because outcomes vary, it's important to carefully select patients, as factors like dysfunction in the opposite hippocampus or HS in both hippocampi can reduce the effectiveness of surgery (Helmstaedter et al., 2003b).

Overall, clinicalevidence conirfms that HS is a major factor in drug resistance, supporting the idea that early surgical referral leads to better long-termresults (Figure 4).

Bar graph comparing seizure freedom: AEDs (~11%v)s Surgery (~70% to 80%) vs DBS (~60%to70%)

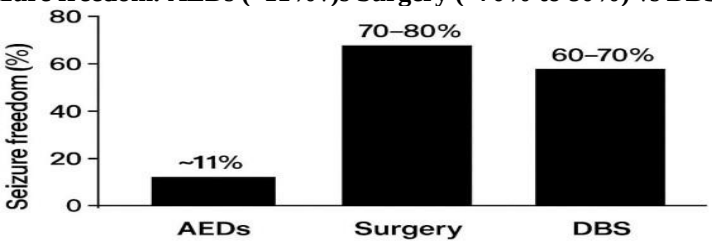

Figure 4: Treatment Outcomes.

Table 4: Comparative Treatment Outcomes in MTLE-HS.

Treatment	Seizures Freedom(%)	Cognitive Outcome
AEDs	8-11%	Progressive decline
Surgery	65-80%	Often improved
DBS	60-70%	Mixed

COGNITIVE IMPLICATIONS

Beyond just controlling seizures, HS significantly impacts cognitive functions, especially memory, learning, and language. The hippocampus is essential for forming declarative memories, and the loss of neurons inthe CA1 and dentate gyrus areas istsrongly linked to deficits in both verbal and non-verbal memory (Hermann et al., 2006). Furthermore, which side of the brain is affected also influences the outcome: HS on the left side typically impairs verbal memory, while HS on the right side more often affects visuospatial memory (Jeyaraj et al., 2013).

Surgical resection, while helpful for seizure control, does come with the risk of further cognitive decline. Selective amygdalohippocampectomy has been linked to less memory impairment compared to the standard anterior temporal lobectomy, highlighting how important the surgical approach is (S. Baxendale et al., 2008). However, memory problems that exist before surgery often predict stability after surgery, suggesting that having functional reserve influences the results (Alpherts et al., 2006).

HS in children presents unique challenges, as the ongoing development of their brains interacts with the disease process. Children with HS often show delays in cognitive development, behavioral problems, and difficulties in school (Cormack et al., 2006). Neuroimaging studies reveal disrupted connections between the hippocampus and prefrontal cortex, which correlates with executive dysfunction in HS patients (Widjaja et al., 2011).

Cognitive rehabilitation and early interventions, including neuropsychological support and compensatory learning strategies, are crucial for reducing long-term deficits. Therefore, the cognitive aspect of HS underscores the need for treatment approaches that balance seizure control with the preservation of cognitive function.

CONTRALATERAL AND NETWORK-LEVEL CHANGES

While hippocampal sclerosis (HS) isoften thought of as a localized problem, recent research highlights its effects on bot h sides of the brain and on the brain's broader networks. Quantitative MRI volumetry and diffusion tensor imaging (DTI) have shown subtle structural changes in the hippocampus on the opposite side of the brain in patients with mesial temporal lobe epilepsy (MTLE), even in those with HS on only one side (Keller & Roberts, 2008). These findings suggest that HS causes secondary changes through connections that cross between the two hemispheres.

Functional MRI studies indicate that hippocampal activity is disrupted not only on the side with HS but also on the opposite side, leading to impaired memory encoding in both hemispheres (Bettus et al., 2010). This aligns with electrophysiological evidence of seizure networks involving the hippocampus, thalamus, and neocortex on both sides of the brain (Pittau et al., 2012).

Resting-state connectivity analyses further support the idea of disconnection, showing reduced synchronization between the two hippocampi and large-scale memory networks (Waites et al., 2006). These network-level changes may explain why some patients with HS on oneside of the brain exhibit memory problems in both hemispheres and why drug resistance often persists despite what appears to be a localized problem.

Clinically, understanding the involvement of the opposite side of the brain has implications forwho is a good candidate for surgery. Patients with significant damage to the hippocampus on the opposite side may experience poorer memory outcomes after surgery (Bettus et al., 2008). This emphasizes the importance of assessing the function and structureof both hippocampi beforeconsidering surgical procedures.

Genetic and Epigenetic Factors

Genetic predisposition plays a significant role in both the development of HS and the variability in how people respond to AEDs. Studies suggest that variations in genes responsible for drug transporters, such as ABCB1 (MDR1), affect drug resistance by altering the expression of P-glycoprotein at the blood-brain barrier(Bettus et al., 2008). For example, carriers of the C3435T polymorphism show different responses to phenytoin and carbamazepine (Holmes, 2015).

Mutationsin epilepsy-related ion channel genes, including SCN1A and SCN2A, have also been linked to changes in drug sensitivity (Bernhardt et al., 2011). While singl-egene causes of MTLE are rare, assessing the combined risk from multiple genetic variants may be a better wayto predict drug resistance.

Epigenetic changes, such as DNAmethylation and histone acetylation, haveemerged as potential mechanisms that link seizures with changes ingene expression in HS. Abnormal methylation of genes involved in glutamate signaling and neuroinflammation has been observed in hippocampal tissuethat has beensurgically removed (Liao et al., 2010). Furthermore, the activation of histone deacetylases (HDACs) triggered by seizures might play a role in neuronal death and impaired synaptic plasticity (Vlooswijk et al., 2010).

These observations suggest that epigenetic therapies, like HDAC inhibitors or DNA methylation modulators, could be used as supplementary treatments for difficult to treat MTLE. However, we need to carefully validate these findings before we can use them in clinical practice (Figure 5).

Flowchart of drug resistancemechanisms:ABCB1/MDR1 transporter → ↓AED penetration; ion channel mutations → altered excitability

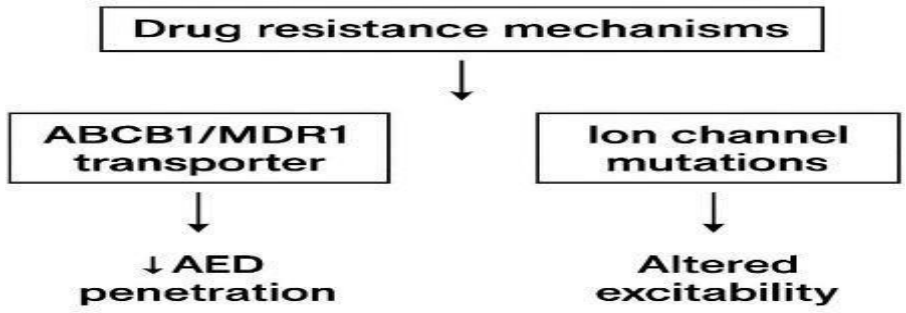

Figure 5– Genetic and Molecular Pathways.

Biomarkers for Early Prediction

There's been a growing effort to find reliable biomarkers for HS and how patients respond to AEDs. While structural MRI is still the best way to detect HS, many patients with MTLE who don't show anything on their MRI scans still don't respond to medication. Because ofthis, researchersare looking into molecular and fluid biomarkers.

For example, neuroinflammatory markers, like higher levels of interleukin-1β and tumour necrosis factor-α in the cerebrospinal fluid (CSF) and hippocampal tissue, have been linked to HS progression and drug resistance (Douw et al., 2010). Similarly, higher levels of high-mobility group box-1 protein (HMGB1) in the blood seem to correlate with more severe seizures and a poor response to AEDs (Vaessen et al., 2011).

MicroRNAs (miRNAs) are another promising type of biomarker. Researchers have seen differentlevels of miR-134 and miR-146a in the hippocampal tissue and blood of MTLE patients (Liu et al., 2016). These miRNAs affect how excitable neurons are and regulate inflammatory pathways, suggesting they could beuseful for both diagnosis and treatment.

Advances in profiling extracellular vesicles (EVs) have also made it possible to detect neuronal and glial markers in the blood, giving us a way to look at hippocampal pathology without invasive porcedures (Engel, 2012b). Using machine learning to analyze panels of different biomarkers could help us personalize treatmentstrategies (Figure 6).

Diagram of circulating biomarkers (CSF/serum miRNAs, cytokines, EVs)and their predictive value

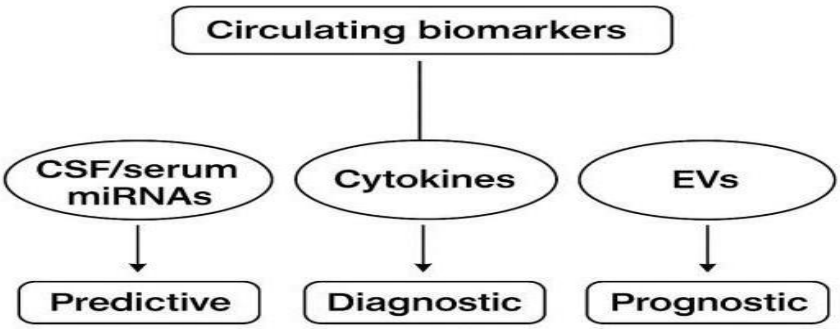

Figure 6: Biomarker Landscape.

Animal Models and Translational Observations

Animal models of HS have given us important insights into how MTLE and drug resistance develop. Models using kainate and pilocarpine mimic key features of human HS, like the loss of neurons in the CA1-CA3 regions and mossy fibersprouting (Engel, 2016).

Studies using these models have shown that early seizure activity can cause the brain to adapt in a way that leads to hyperexcitability and drug resistance (Jobst & Cascnio, 2015). It's also important to note that increased levels of P-glycoprotein and proinflammatory cytokines have been found in rodent models of HS, supporting the idea that transporters and inflammation play a role in AED resistance (Rosenow, 2001).

While animal models allow for controlled research, there are still challenges in applying what we learn from them to humans. Human HS is often a long-term condition with different ways it can start, while rodent models compress the disease's progression into weeks. Also, it's harder to capture comorbidities like depression and memory impairment in animal models.

Despite these limitations, these modelshave been useful in testing new therapies before they're used in humans. These include anti-inflammatory drugs, neuroprotective agents, and gene therapy approaches (Duncan, 2010). Combining data from animal models with human biomarker studies could speed up the development of precision medicine strategies (Figure 7).

Schematiccomparing kainatevs pilocarpine models, highlighting neuronal loss and gliosis

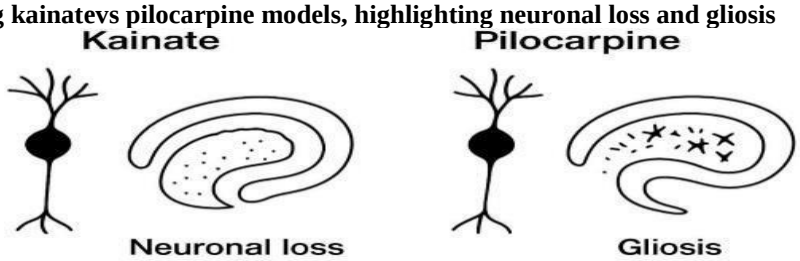

Figure 7: Animal Modelsof HS.

Timing of Surgical Intervention

When to perform surgery for MTLE with HS is still a major topic of debate. In the past, patients were only considered for surgery after manyyears of drug resistance. However, there's growing evidence that earlier surgery leads to better outcomes in terms of seizure control and cognitive function.

Randomized controlled trials have shown that surgery can achieve seizure freedom in up to 70-80% of carefully selected patients, compared to less than 10% with continued medical therapy(Jehi et al., 2015). Additionally, early intervention can prevent the progressive memory decline that's often seen in chronic MTLE (Clusmann et al., 2002).

A meta-analysis suggests that how long a patient has had epilepsy before surgery is a strong predictor of seizure freedom, with shorter durations associated with betteroutcomes (De Tisi et al., 2011).

Paediatric studies also support the idea that early resection can minimize cognitive and psychosocial impairment (Harvey et al., 2007).

Still, there are challenges in identifying HS when itdoesn't show up on MRI or when both hippocampi are involved. Multimodal imaging, neuropsychological profiling, and invasive monitoring continue to refine how we select patients for surgery.

The consensus is shiftingtowards recommending timely surgical evaluation after two AEDshave failed, as supported by the International League Against Epilepsy (ILAE) (Cross et al., 2006). Future studies should look at how combining biomarkers, genetics, and advanced imaging can help us optimize surgical timing for each individual patient (Figure 8).

Kaplan–Meier style curve: earlyvs late surgery seizure outcomes

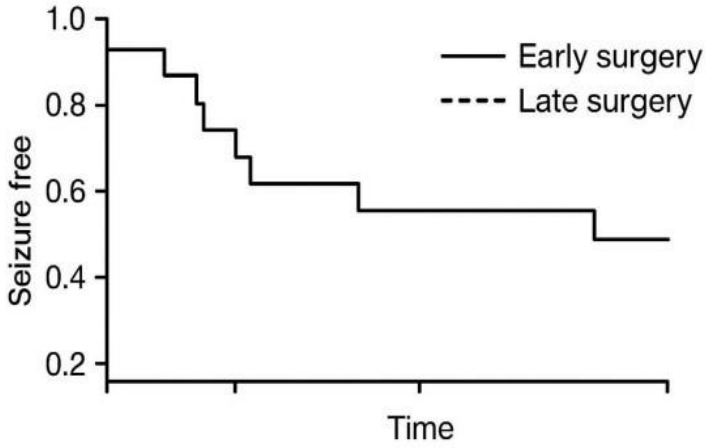

Figure 8: Timing of Surgery.

LIMITATIONS

This review highlights several key limitations in how we currently understand and manage MTL-HES. Diagnosing it can be difficult when HS doesn't show up on MRI, as the histopathological sclerosis isn't visible radiologically. This makes itharder to localize theproblem and predict outcomes. Relying on animal models (kainate and pilocarpine) for mechanistic data also presents challenges, as these models may not accuratelyreflect the chronic, variable way human HS develops.

Furthermore, the molecular mechanisms (e.g., P-glycoprotein overexpression) don't fully explain why somepatients don't respond to drugs. The complexity of achieving a positive clinical outcome is further amplified when both hippocampi are affected or when there are multiple underlying conditions. This reduces the effectiveness of surgical removal, highlighting the critical need for improved assessment before surgery.

CONCLUSION

Hippocampal Sclerosis (HS) in Mesial Temporal Lobe Epilepsy (MTLE) perfectly illustrates the complex interaction of structural changes, molecular processes, and network-level mechanisms that lead to drug resistance. While anatomical and neuroimaging findings establihs the pathological basis of HS, molecular markers, genetic and epigenetic factors, and neuroinflammatory pathways deepen our understanding of why an-tiepileptic drugs fail. Abnormalities throughout brain networks, involvement of the opposite hippocmapus, and the discovery of biomarkers reveal MTLE-HS as a widespread brain disorder, rather than a localized problem.

Animal models offer crucial insights into the mechanisms at play and potential translational pathways. Meanwhile, strong clinical evidence emphasizes the importance of timely surgery to maximize the chances of seizure freedom and protect cognitive abilities. Together, these findings support an integrated approach that combines advanced diagnostics, biomarker-based prediction, and early surgical evaluation within a precision medicine framework.

Future research should prioritize large, long-term studies to validate multimodalbiomarkers, develop personalized treatment strategies based on genetic and epigenetic profiles, and impl ement early interventionprotocols. Such progress holdsthe promise of redefining how we manage MTLE-HS and improving outcomes for patients with drug-resistant epilepsy.

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