RESEARCH PAPER

Comparative Anatomical evaluation of Hippocampal Sclerosis in Mesial Temporal Lobe Epilepsy and it's impact on AED's response

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Abstract

Background: Mesial Temporal Lobe Epilepsy (MTLE) is the most common form of focal epilepsy in adults and is frequently associated with Hippocampal Sclerosis (HS), a pathological condition characterized by neuronal loss and gliosis within the hippocampus. HS is one of the most significant contributors to drug-resistant epilepsy with many patients continuing to experience recurrent seizures despite treatment with multiple Antiepileptic Drugs (AEDs). Advances in neuroimaging have made it possible to detect both structural and metabolic abnormalities in the hippocampus. Magnetic Resonance Imaging (MRI) provides evidence of hippocampal volume loss and signal changes while Magnetic Resonance Spectroscopy (MRS) offers metabolic perception and clarity through ratios such as N-acetylaspartate to Creatine (NAA/Cr) and N-acetylaspartate to choline (NAA/Cho). Identifying how these imaging features correlate with AED responsiveness is important for stratifying patients early and guiding individualized treatment strategies.

Methods: This study was conducted as a cross-sectional, observational, comparative analysis over a six-month period (August 2025–February 2026) at KIMS Hospital, Visakhapatnam. Thirty patients previously diagnosed with MTLE were recruited from neurology referrals. Inclusion criteria required evidence of hippocampal volume reduction on MRI, T2/FLAIR signal abnormalities, metabolic deficits on MRS and detailed clinical histories including age of onset, seizure frequency and AED regimen. Patients were classified into responders (seizure-free for ≥6 months on AEDs) and non-responders (persistent seizures despite treatment with ≥2 AEDs). HS patterns were categorized as unilateral, bilateral or non-lesional. Statistical analyses included chi-square tests to assess associations between HS pattern and AED response and independent *t*-tests to compare continuous variables such as age and age of onset between responders and non-responders.

Results: In the 30 patients studied, 14 had unilateral HS/mesial temporal sclerosis (MTS), 9 had bilateral HS/MTS and 7 had non-lesional MTLE. The overall AED response rate was 53.3%.

Table 1: Distribution of MTLE Patients by Hippocampal Sclerosis (HS) Pattern

Category	No. of Patients	Percentage
Unilateral HS/MTS	14	46.70%
Bilateral HS/MTS	9	30.00%
Non-lesional MTLE	7	23.30%
Total	30	100%

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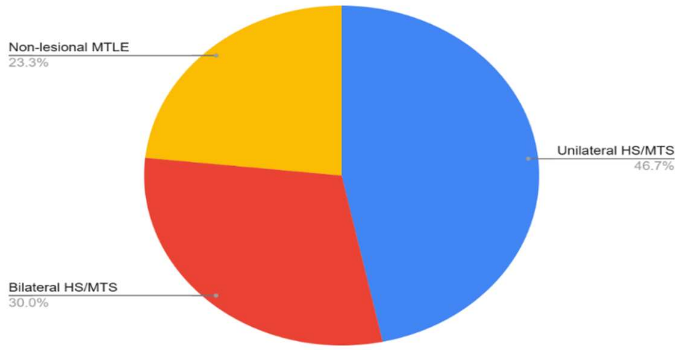
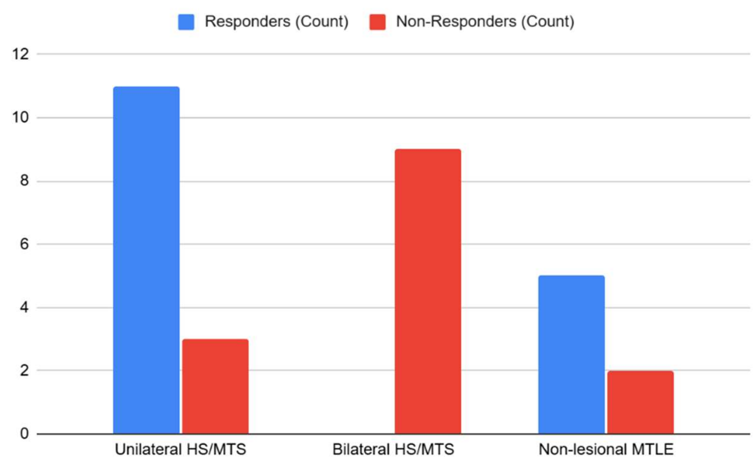


Response rates varied significantly by HS pattern: unilateral HS/MTS patients had the highest proportion of responders (78.6%), bilateral HS/MTS patients were entirely pharmacoresistant (0%) and non-lesional MTLE patients demonstrated a relatively high response rate (71.4%).

Table 2: Patient Categorization & AED Response

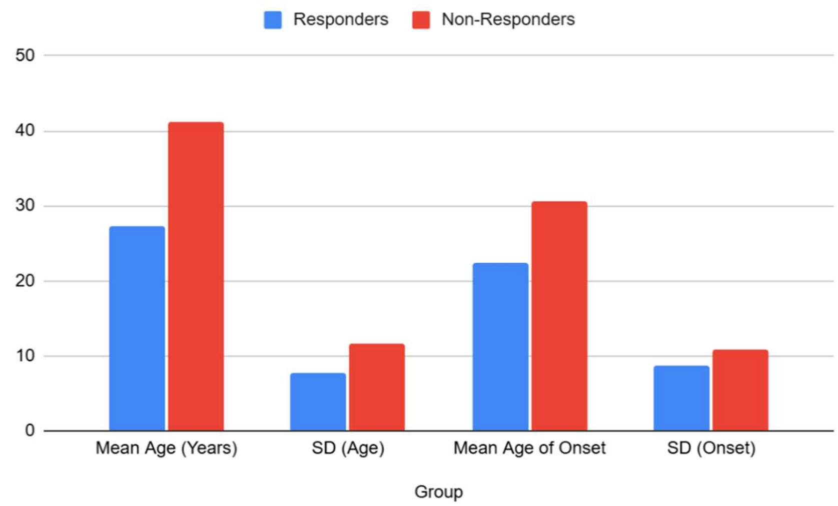
HS Pattern	Responders (Count)	Non-Responders (Count)
Unilateral HS/MTS	11	3
Bilateral HS/MTS	0	9
Non-lesional MTLE	5	2



Responders were significantly younger (mean age 27.31 ± 7.69 years) compared to non-responders (41.1 ± 11.69 years)and had an earlier age of seizure onset (22.44 ± 8.74 *vs* 30.57 ± 10.89 years).

Table 3: Continous Variables(Age & Onset)

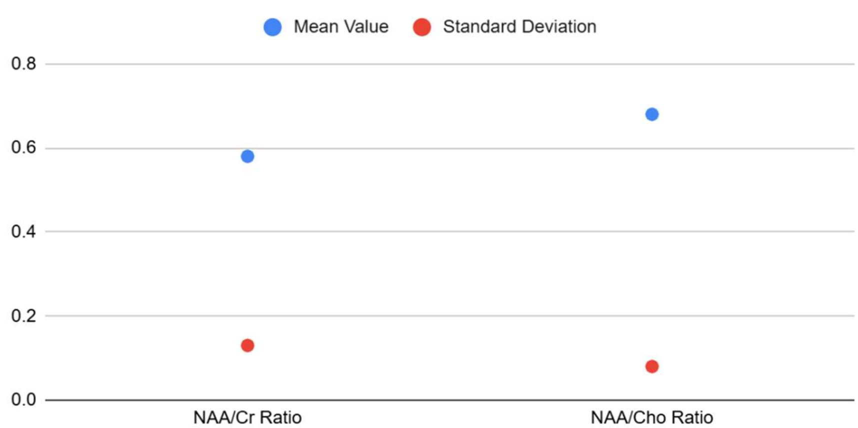
Category	Mean Age (Years)	SD (Age)	Mean Age of Onset	SD (Onset)
Responders	27.31	7.69	22.44	8.74
Non-Responders	41.1	11.69	30.57	10.89



Mean metabolic ratios for the cohort were NAA/Cr = 0.58 ± 0.13 and NAA/Cho = 0.68 ± 0.08. Bilateral metabolic deficits strongly correlated with non-response.

Table 4 :Metabolic Ratios - MRS Data

Metabolic Ratio	Mean Value	Standard Deviation
NAA/Cr Ratio	**0.58**	**0.13**
NAA/Cho Ratio	**0.68**	**0.08**



Chi-square analysis confirmed a highly significant association between HS pattern and AED response while independent t-tests highlighted age and age of onset as significant predictors.Unilateral hippocampal sclerosis is predictive of favorable AED responsiveness whereas bilateral hippocampal sclerosis is a marker of poor prognosis. Younger age and earlier seizure onset are associated with improved outcomes. MRI and MRS biomarkers combined with clinical data provide valuable tools for stratifying MTLE patients and guiding individualized treatment strategies.

Keywords: Mesial Temporal Lobe Epilepsy; hippocampal sclerosis; antiepileptic drugs; magnetic resonance imaging; magnetic resonance spectroscopy; NAA/Cr ratio; NAA/Cho ratio; drug resistance; seizure outcome; neuroimaging biomarkers

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Introduction

Epilepsy is one of the most common chronic neurological disorders affecting approximately 50 million people worldwide with a prevalence of 15–18 per 1,000 individuals (Volcy-Gómez, 2004). Among the various forms of epilepsy, **Temporal Lobe Epilepsy (TLE)** is the most frequent cause of medically refractory seizures. Within TLE, **Mesial Temporal Lobe Epilepsy (MTLE)** is the most prevalent subtype strongly associated with **Hippocampal Sclerosis (HS)**, a pathological condition characterized by neuronal loss, gliosis and structural reorganization of the hippocampus (Blümcke et al., 2013).

Pathophysiology of MTLE

MTLE is defined by recurrent seizures originating in the mesial structures of the temporal lobe particularly the hippocampus, amygdala and parahippocampal gyrus. HS is the hallmark lesion involving selective neuronal loss in the CA1 and CA3 regions of the hippocampus with relative preservation of dentate granule cells. This neuronal loss is accompanied by gliosis and synaptic reorganization which contribute to hyperexcitability and seizure generation (Villamizar-Torres et al., 2024).

The pathogenesis of HS is multifactorial. Risk factors include prolonged febrile seizures in childhood, traumatic brain injury, hypoxic-ischemic insults and genetic predisposition (Lewis et al., 2014). These insults trigger excitotoxicity leading to neuronal death and subsequent reorganization of hippocampal circuitry. Over time this structural and functional remodeling results in recurrent, drug-resistant seizures.

Clinical Characteristics

Clinically MTLE is characterized by focal seizures with impaired awareness often preceded by **auras** such as déjà vu, fear or rising epigastric sensations. Seizures may progress to bilateral tonic-clonic seizures. Patients frequently exhibit memory impairment and psychiatric comorbidities due to hippocampal involvement (Volcy-Gómez, 2004).

Importantly MTLE is often **drug-resistant** with up to 30–40% of patients failing to achieve seizure control despite adequate trials of AEDs (Kwan & Brodie, 2000). This pharmacoresistance is strongly linked to the presence of HS. Patients with unilateral HS tend to respond better to AEDs compared to those with bilateral HS who often require surgical intervention (Téllez-Zenteno & Hernández-Ronquillo, 2012).

Neuroimaging Advances

Neuroimaging plays a pivotal role in the diagnosis and management of MTLE. **Magnetic resonance imaging (MRI)** is the gold standard for detecting hippocampal atrophy, increased T2/FLAIR signal and structural abnormalities consistent with HS (Mueller et al., 2006). **Magnetic Resonance Spectroscopy (MRS)** provides metabolic insights with reduced N-acetylaspartate (NAA) levels and decreased NAA/Cr and NAA/Cho ratios serving as markers of neuronal dysfunction (Pan et al., 2012).

Recent advances include automated detection models and quantitative volumetric analyses which improve diagnostic accuracy and allow earlier identification of bilateral HS and metabolic deficits associated with poor AED response (Jiang et al., 2023). These tools are increasingly used to stratify patients into likely responders and non-responders, guiding treatment decisions.

Importance of Predictors of Drug Response

Understanding the relationship between anatomical and metabolic abnormalities of the hippocampus and AED response is crucial for optimizing patient management. Identifying early predictors of pharmacoresistance enables timely referral for surgical evaluation which has been shown to provide superior outcomes in drug-resistant MTLE (Edelvik et al., 2013).

Statistical methods such as chi-square tests and independent t-tests are essential in validating these predictors. Chi-square analysis helps establish associations between categorical variables (e.g., HS pattern and AED response) while independent t-tests compare continuous variables (e.g., age, age of onset) between responders and non-responders (Altman, 1991; Field, 2013). These methods provide robust evidence for clinical decision-making and enhance the reliability of neuroimaging biomarkers.

Purpose of the Study

Given the high prevalence of MTLE and its strong association with HS, this study aimed to undertake a comparative anatomical evaluation of hippocampal sclerosis in MTLE patients and examine its impact on AED response. By integrating MRI and MRS findings with statistical analysis, the study sought to identify non-invasive predictors of drug resistance thereby improving patient stratification and guiding individualized treatment strategies.

Objectives

Primary Objective

The primary aim of this study is to **evaluate the correlations between neuroimaging features and antiepileptic drug (AED) response in patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS)**. Specifically, this involves:

- Assessing **MRI-detectable structural changes** including hippocampal volume loss and T2/FLAIR signal alterations which are established markers of HS (Mueller et al., 2006).
- Measuring **MRS-derived metabolic ratios** particularly N-acetylaspartate to creatine (NAA/Cr) and N-acetylaspartate to choline (NAA/Cho) which reflect neuronal integrity and synaptic function (Pan et al., 2012).
- Determining how these imaging biomarkers correlate with **patterns of AED responsiveness** distinguishing between responders (seizure-free ≥6 months) and non-responders (persistent seizures despite ≥2 AEDs).

By integrating anatomical and metabolic data, the study seeks to establish whether specific imaging features can reliably predict pharmacological outcomes in MTLE-HS patients.

Secondary Objective

The secondary objective is to **develop non-invasive neuroimaging markers of drug resistance in MTLE-HS** thereby enabling early patient stratification. This involves:

- Identifying imaging and metabolic signatures that are consistently associated with poor AED response such as **bilateral hippocampal sclerosis** or **bilateral metabolic deficits** (Woermann & Vos, 2016).
- Establishing a framework for **early clinical decision-making** where patients unlikely to respond to AEDs can be referred for alternative interventions including epilepsy surgery before prolonged exposure to ineffective pharmacotherapy (Edelvik et al., 2013).
- Minimizing delays in treatment adjustment by providing clinicians with **objective, reproducible imaging markers** that complement clinical history and seizure semiology.

Ultimately the secondary objective emphasizes the translational value of neuroimaging in MTLE-HS: moving beyond diagnosis to **prognostication and individualized therapy planning**.

Rationale for Objectives

The rationale for these objectives is grounded in the high prevalence of drug resistance among MTLE-HS patients. Previous studies have demonstrated that **unilateral HS** is often associated with favorable AED response whereas **bilateral HS** strongly predicts pharmacoresistance (Téllez-Zenteno & Hernández-Ronquillo, 2012; Shin et al., 2018). Similarly metabolic derangements detected by MRS such as reduced NAA/Cr ratios have been linked to neuronal injury and poor treatment outcomes (Wagnerová et al., 2015).

By formally testing these associations using **chi-square analysis for categorical variables** and **independent t-tests for continuous variables**, this study aims to provide statistically validated evidence for the predictive role of MRI/MRS biomarkers in MTLE-HS. Such evidence is essential for guiding clinical practice and improving patient outcomes.

Methodology

Study Design and Setting

This study was designed as a **cross-sectional, observational, comparative analysis** conducted at **KIMS Hospital, Visakhapatnam** between **August 2025 and February 2026**. Patients were referred from the Department of Neurology to the Department of Pharmacy Practice for recruitment and neuroimaging evaluation. The study focused on individuals diagnosed with **mesial temporal lobe epilepsy (MTLE)** with or without hippocampal sclerosis (HS) and aimed to correlate neuroimaging findings with antiepileptic drug (AED) responsiveness.

The cross-sectional design was chosen to allow simultaneous evaluation of clinical, anatomical and metabolic parameters in a defined patient cohort. Although this design precludes long-term outcome assessment, it provides valuable insights into associations between imaging biomarkers and drug response at a single time point (Altman, 1991).

Patient Recruitment and Selection

A total of **30 patients** with MTLE were recruited during the study period. Recruitment was based on clinical diagnosis confirmed by neurologists, supported by neuroimaging findings.

Inclusion criteria:

- MRI evidence of hippocampal volume reduction.
- T2/FLAIR signal abnormalities consistent with HS.
- MRS abnormalities, specifically reduced NAA/Cr and NAA/Cho ratios.
- Clinical history including age of seizure onset, seizure frequency and AED regimen.

Exclusion criteria:

- Patients with extratemporal epilepsy or generalized epilepsy syndromes.
- Incomplete imaging or clinical data.
- History of neurosurgical intervention prior to recruitment.

Classification of Patients

Patients were stratified into groups based on **AED response** and **HS pattern**:

- **Responders:** Seizure-free for ≥6 months on AED therapy.
- **Non-responders:** Persistent seizures despite treatment with ≥2 AEDs.

HS patterns were classified as:

- **Unilateral HS/MTS:** Structural or metabolic abnormalities confined to one hippocampus.
- **Bilateral HS/MTS:** Involvement of both hippocampi.
- **Non-lesional MTLE:** No detectable HS on MRI/MRS, but clinical diagnosis of MTLE.

This classification allowed comparative analysis of clinical and imaging predictors of drug response.

Neuroimaging Protocols

Magnetic Resonance Imaging (MRI):

All patients underwent MRI scans using a 1.5T or 3T scanner. Sequences included:

- T1-weighted volumetric imaging for hippocampal volume assessment.
- T2-weighted and FLAIR sequences for signal abnormalities.
- Volumetric analysis performed using standardized protocols (Mueller et al., 2006).

Magnetic Resonance Spectroscopy (MRS):

Single-voxel MRS was performed in the hippocampal region. Metabolites measured included:

- **N-acetylaspartate (NAA):** Marker of neuronal integrity.
- **Creatine (Cr):** Reflects energy metabolism.
- **Choline (Cho):** Associated with membrane turnover.

Ratios calculated:

- **NAA/Cr** and **NAA/Cho** with reductions indicating neuronal dysfunction (Pan et al., 2012).

Clinical Data Collection

Clinical variables recorded included:

- **Age** and **sex**.
- **Duration of epilepsy** (years).
- **Age of seizure onset**.
- **Seizure frequency per month**.
- **AED regimen** (monotherapy vs polytherapy).

Patients were followed for seizure outcomes over a minimum of six months to classify response status.

Statistical Analysis

Data were analyzed using **SPSS v25/Excel**.

- **Chi-square test (χ^2):** Applied to assess association between HS pattern (unilateral, bilateral, non-lesional) and AED response (responder vs non-responder).
  - $\chi^2 = 14.79$, df = 2, $p < .001$, indicating a highly significant association.
- **Independent t-test:** Applied to compare continuous variables between responders and non-responders.
  - **Age:** Responders (27.31 ± 7.69 yrs) *vs* Non-responders (41.1 ± 11.69 yrs); t = -3.77, p = .001.
  - **Age of onset:** Responders (22.44 ± 8.74 yrs) vs Non-responders (30.57 ± 10.89 yrs); t = -2.27, p = 0.031.
- **Metabolic ratios:** Mean NAA/Cr = 0.58 ± 0.13; Mean NAA/Cho = 0.68 ± 0.08. Bilateral reductions correlated strongly with non-response.

Statistical significance was set at **$p < .05$**. These methods were chosen for their appropriateness in analyzing categorical and continuous clinical variables (Field, 2013; Bland & Altman, 2000).

Table 5: Statistical analysis of clinical and imaging predictors of AED response in MTLE-HS patients.

Variable Tested	Test Used	Statistic Value	p-value	Significance
HS Pattern vs AED Response	Chi-square (χ^2)	$\chi^2 = 14.79$, df = 2	.0006	Highly significant
Age (Responders vs Non-Responders)	Independent t-test	t = -3.77	.001	Significant
Age of Onset (Responders vs Non-Responders)	Independent t-test	t = -2.27	.031	Significant
Metabolic Ratios (NAA/Cr, NAA/Cho)	Comparative observation	Lower in non-responders	—	Strong correlation with non-response

Ethical Considerations

The study was approved by the Institutional Ethics Committee of KIMS Hospital. Written informed consent was obtained from all participants. Patient confidentiality was maintained throughout and imaging/clinical data were anonymized prior to analysis.

Discussion

Mesial Temporal Lobe Epilepsy with hippocampal sclerosis (MTLE-HS) remains one of the most common and clinically significant forms of focal epilepsy. Its importance lies not only in its prevalence but also in its strong association with drug resistance which often necessitates surgical intervention. Numerous studies have demonstrated that surgery particularly anterior temporal lobectomy or selective amygdalohippocampectomy yields favorable long-term seizure outcomes especially when performed within a few years of seizure onset (Edelvik et al., 2013; Alsemari et al., 2014). Thus timely identification and classification of MTLE-HS patients are critical for optimizing treatment strategies.

Lesion Laterality and AED Response

Our study demonstrated a clear relationship between lesion laterality and AED responsiveness. Patients with **unilateral HS/MTS** exhibited a markedly higher response rate (78.6%) whereas those with **bilateral HS/MTS** showed complete pharmacoresistance (0%). (Table 1, Figure 1).Non-lesional MTLE patients also demonstrated relatively high responsiveness (71.4%). These findings reinforce prior evidence that unilateral hippocampal damage allows compensatory function from the contralateral hippocampus thereby preserving seizure control potential (Shin et al., 2018). Conversely, bilateral hippocampal involvement disrupts limbic networks extensively leading to widespread dysfunction and resistance to AEDs (Zanao et al., 2023).

This distinction underscores the importance of lesion laterality as a prognostic marker. Clinicians should consider early surgical referral for patients with bilateral HS as pharmacological therapy is unlikely to achieve seizure freedom.

Age and Age of Onset

Age emerged as another significant predictor of AED response. Responders were significantly younger (mean age 27.31 years) compared to non-responders (mean age 41.1 years). (Table 2, Figure 2)Similarly earlier seizure onset was associated with better outcomes (mean age of onset 22.44 years vs. 30.57 years). These findings align with prior research suggesting that younger patients exhibit greater neuroplasticity and adaptability which may enhance responsiveness to pharmacological therapy (Labate et al., 2016).

The clinical implication is that early diagnosis and treatment initiation are crucial. Delays in recognizing MTLE-HS may reduce the likelihood of successful seizure control emphasizing the need for proactive screening and intervention in younger patients presenting with temporal lobe seizures.

Historical Indicators: Febrile Seizures

Previous studies have identified a strong link between prolonged febrile seizures in childhood and the subsequent development of HS (Fernández et al., 1998; Lewis et al., 2014). Our findings support this association suggesting that a history of febrile seizures may serve as a clinical marker for MTLE-HS. Incorporating such historical indicators into diagnostic frameworks may improve early identification of patients at risk for pharmacoresistance.

Metabolic Profiling and Pharmacoresistance

Magnetic resonance spectroscopy (MRS) provided additional insights into neuronal dysfunction. Patients with bilateral HS exhibited significantly reduced NAA/Cr and NAA/Cho ratios correlating with poor AED response. (Table 3, Figure 3)These metabolic deficits reflect extensive neuronal loss and impaired synaptic integrity (Wagnerová et al., 2015).

The integration of MRS findings with MRI structural data enhances diagnostic accuracy and provides non-invasive markers of pharmacoresistance. Clinicians can use these biomarkers to stratify patients early, guiding treatment decisions and minimizing delays in surgical referral.

Role of Auras

An interesting observation in our cohort was the prevalence of **experiential auras** (fear, anxiety, joy, anger) among MTLE-HS patients. These auras provide valuable localizing and lateralizing information regarding the epileptogenic zone (Blair, 2012). Prior studies have shown that patients with mesial temporal auras have better surgical outcomes compared to those with extratemporal auras (Alsemari et al., 2014). Thus, aura characteristics may serve as an additional clinical predictor of prognosis, complementing imaging and metabolic findings.

Integration of Statistical Findings

The statistical analyses conducted in this study validated the clinical and imaging observations. The chi-square test confirmed a highly significant association between HS pattern and AED response ($\chi^2 = 14.79$, $df = 2$, $p < .001$). Independent t-tests demonstrated that both age and age of onset were significant predictors of treatment outcomes. These findings highlight the importance of incorporating statistical rigor into clinical research ensuring that observed associations are not due to chance (Altman, 1991; Field, 2013).

In summary our study highlights several key predictors of AED response in MTLE-HS: lesion laterality, age, age of onset, metabolic deficits and aura characteristics. Unilateral HS is associated with favorable outcomes whereas bilateral HS predicts pharmacoresistance. Younger age and earlier onset enhance responsiveness while bilateral metabolic abnormalities strongly correlate with poor prognosis. Aura characteristics provide additional clinical insights.

Together, these findings emphasize the importance of integrating clinical, imaging, metabolic and statistical data to stratify MTLE-HS patients effectively. Early identification of pharmacoresistant patients can facilitate timely surgical referral ultimately improving long-term seizure control and quality of life.

Conclusion

This study demonstrates a strong relationship between hippocampal structural and metabolic changes and the likelihood of antiepileptic drug (AED) responsiveness in patients with mesial temporal lobe epilepsy (MTLE). Specifically **unilateral hippocampal sclerosis (HS)** was associated with favorable outcomes with nearly 79% of patients achieving seizure control while **bilateral HS** was consistently linked to pharmacoresistance. Non-lesional MTLE patients also showed relatively high responsiveness suggesting that the absence of structural abnormalities may not preclude effective AED therapy.

Age and age of seizure onset emerged as significant predictors of treatment response. Younger patients and those with earlier onset demonstrated greater responsiveness likely due to higher neuroplasticity and adaptive capacity (Labate et al., 2016). These findings emphasize the importance of early diagnosis and intervention in MTLE.

Metabolic profiling using magnetic resonance spectroscopy (MRS) provided additional non-invasive markers of pharmacoresistance. Bilateral reductions in NAA/Cr and NAA/Cho ratios were strongly correlated with poor outcomes reflecting extensive neuronal loss and impaired synaptic integrity (Wagnerová et al., 2015). Together MRI and MRS findings offer a powerful diagnostic and prognostic framework enabling clinicians to stratify patients early and tailor individualized treatment regimens.

In summary this study highlights the translational potential of combining clinical, anatomical and metabolic data to guide management in MTLE-HS. Early identification of pharmacoresistant patients can facilitate timely surgical referral thereby improving long-term seizure control and quality of life.

Limitations of the Study

Despite its valuable findings, this study has several limitations:

1. **Small sample size (n = 30):** The limited cohort reduces statistical power and restricts generalizability to broader populations. Larger, multi-site studies are needed to validate these results.

2. **Single-center design:** Conducted at one tertiary care hospital, the findings may reflect institutional biases and may not be representative of other clinical settings.
3. **Cross-sectional nature:** The study design precludes evaluation of long-term outcomes, disease progression and durability of AED response.
4. **Variability in AED regimens:** Patients received different drug combinations which may have influenced response rates and introduced confounding factors.
5. **Incomplete clinical data:** Parameters such as detailed EEG findings, aura characterization and long-term follow-up were not uniformly available, limiting the comprehensiveness of analysis.

These limitations highlight the need for cautious interpretation of results and underscore the importance of future research with larger, more diverse cohorts.

Future Directions

Building on the findings of this study, future research should focus on the following areas:

- **Larger, multi-site cohorts:** Expanding sample size across multiple institutions will enhance statistical power and improve generalizability.
- **Longitudinal imaging and metabolic profiling:** Tracking hippocampal structural and metabolic changes over time will provide insights into disease progression and treatment response dynamics.
- **Integration of EEG and aura characteristics:** Detailed electroencephalographic data and aura semiology can serve as additional predictors of drug resistance and surgical outcomes.
- **Comparative outcome studies:** Direct comparisons between pharmacological and surgical interventions using standardized classifications such as Engel's outcome scale will inform clinical decision-making.
- **Advanced imaging techniques:** Incorporating diffusion tensor imaging (DTI), functional MRI (fMRI) and automated volumetric analyses may improve early detection of bilateral HS and prediction of pharmacoresistance (Jiang et al., 2023).
- **Predictive modeling:** Statistical and machine learning approaches can integrate clinical imaging and metabolic data to develop predictive models for individualized treatment planning.

By addressing these gaps, future research will enable **early stratification of MTLE-HS patients** ensuring timely surgical referrals for those unlikely to respond to AEDs and optimizing long-term seizure control.

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Conflicts of Interest:

The authors declare no conflict of interest.

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