

Utility of Magnetic Resonance Imaging Brain Epilepsy Protocol in New-Onset Seizures: How is it Different in Developing Countries?

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INTRODUCTION

Seizures are symptoms of abnormal brain function and due to a diverse etiology. Western studies have shown that about 4% of the population will have an unprovoked seizure by the age of 80, and treatment may reduce the chance of a second one by as much as 50%.^[1] According to the World Health Organization, of the 50 million people with epilepsy worldwide, 80% reside in developing countries.^[2]

ABSTRACT

Introduction: Magnetic resonance imaging (MRI) is the current imaging tool of choice in the investigation of patients with seizures. The advent of high-resolution MRI with a dedicated seizure protocol has significantly increased the chances of identifying a cause, resulting in a positive clinical impact on the management of these patients. **Aims:** The aims of this study were to evaluate the diagnostic efficacy of standard MRI, identify whether there is an increase in the diagnostic yield with the addition of dedicated seizure protocol, and compare the diagnostic yields of MRI and electroencephalogram (EEG) individually and in combination. **Subjects and Methods:** This is a prospective study of 129 consecutive patients who presented with new-onset seizures over an 18-month period. The MRI scans performed on 1.5T were reviewed for their diagnostic yield and their association with abnormal electrical activity on EEG. Chi-square test of significance ($P < 0.05$) was used to test for the difference in proportion. The correlation between MRI brain and EEG was studied using McNemer test. **Results:** MRI detected potentially epileptogenic lesions in 59 patients (47%). The frequency of epileptogenic lesions was highest in patients who had focal-onset seizures (81%). The most common lesion type was infection and inflammation (28%), with neurocysticercosis being the most common, followed by mesial temporal sclerosis, ischemia, and tumor. About 37% of epileptogenic lesions were missed by standard protocol, which were detected on a dedicated seizure protocol MRI. The diagnostic yield of EEG was 31%. Abnormal MRI and EEG were concordant in 18% of patients, with EEG being normal in 37% of patients with epileptogenic lesions. **Conclusions:** MRI detects epileptogenic lesions in almost one half who presented with new-onset seizures and of these, more than third of them were detected using a “dedicated seizure protocol.” While almost 50% with seizures will have a cause identified on MRI, the sensitivity can be substantially improved by utilizing a dedicated seizure protocol.

KEYWORDS: *Dedicated seizure protocol, electroencephalography, magnetic resonance imaging, new-onset seizures*

Epilepsy is a chronic condition characterized by recurrent seizures unprovoked by an acute systemic or

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neurologic insult.^[3] An epileptic seizure is a clinical manifestation of abnormal, excessive neuronal activity arising in the gray matter of the cerebral cortex.^[4]

The histologic substrates of epilepsy can be divided into five major categories as follows: tumor, disorders of neuronal migration and cortical organization, vascular malformation, mesial temporal sclerosis, and neocortical sclerosis secondary to brain injury. Magnetic resonance imaging (MRI) is the most sensitive and specific imaging technique for the noninvasive identification of each of these epileptogenic substrates.^[5]

The American Academy of Neurology and the American Epilepsy Society reported that the diagnostic yield of neuroimaging for revealing epileptogenic lesions in patients with new-onset seizures ranges from 1% to 47%^[6] that was based on six studies of computed tomography (CT) scan abnormalities. Another study of epileptogenic lesions using only MRI reported diagnostic yields between 14% and 48%.^[7] However, the studies were limited by including patients with acute symptomatic seizures and preexisting epilepsy, low patient numbers, and uncertain diagnostic process.

Here, we studied a large, prospective, consecutively acquired cohort of individuals who presented to the emergency room with potential new-onset seizures. Our aims were:

1. To evaluate the diagnostic efficacy of a standard MRI of the brain in patients with first-onset seizures
2. To identify whether there is an increase in the diagnostic yield with the addition of high-resolution sequences with a dedicated seizure protocol
3. To compare the diagnostic yields of MRI and electroencephalogram (EEG) individually and in combination.

SUBJECTS AND METHODS

It is a hospital-based prospective study where 129 patients presenting with a history of new-onset seizures for 18 months underwent both MRI of the brain and EEG.

Inclusion criteria

1. All patients aged 5 years or more presenting with first-onset seizures
2. Five years of age was taken as cutoff value to exclude all children presenting with febrile seizures from the study data.

Exclusion criteria

1. Any previously diagnosed noncentral nervous system disorders liable to cause seizures
2. Patients with known contraindications to MRI

3. Syncopal and hypoglycemic attacks, pseudo-seizures, or drug-induced seizures
4. Patients presenting with head injury.

Statistical analysis

Quantitative variables were expressed in terms of mean, standard deviation, or median interquartile range with confidence interval of 95%. The entire qualitative variable was expressed in terms of proportion. Chi-square test of significance ($P < 0.05$) was used to test for the difference in proportion. The correlation between MRI brain and EEG was studied using McNemer test.

Patient selection criteria for the study

The patients selected for the study were clinically diagnosed cases of seizures as per the criteria laid down by the International League Against Epilepsy (ILAE) 1981.

A detailed history was taken and clinical examination was done. The points noted were duration of illness, type of seizures, and any associated illness. Detailed clinical and neurological examination was done to find any neurological deficit. Based on the history and examination, a clinico-etiological diagnosis was made.

Investigations

All the patients underwent MRI brain scanning on 1.5T (Magnetom Avanto TIM, 18 channel; Siemens, Erlangen, Germany) within 7 days from the onset of seizures. The procedure was briefly explained to the patients including the risks of contrast examination. A routine EEG is recorded from the scalp electrodes obtained 3 days before or after the MRI and as soon as practical after presentation with the index seizure, preferably within 48 h.

Magnetic resonance imaging protocol

All patients underwent both “standard protocol” and “dedicated epilepsy protocol.”

- Standard protocol includes T1-weighted sagittal, T2-weighted axial, fluid-attenuated inversion recovery (FLAIR) axial, and diffusion weighted imaging/apparent diffusion coefficient
- Dedicated epilepsy protocol includes T2-weighted and FLAIR coronal oblique plane perpendicular to the long axis of hippocampus [Figure 1], T1-weighted inversion recovery coronal oblique, magnetization prepared rapid gradient echo, susceptibility-weighted imaging, and contrast-enhanced MRI if required. Table 1 shows the MRI seizure protocol used in our institute.

For the purposes of the study, the MRI findings were then classified into three major categories as follows:

1. Patients who had structural lesions causally or

potentially related to epilepsy were classified as having an “epileptogenic lesion”

- Those who had structural lesions unlikely to be causally related to epilepsy or had nonspecific lesions were categorized as having a “nonepileptogenic lesion”
- Those who had no lesion on MRI were categorized as “normal.”

The epileptogenic lesion group was subdivided broadly into eight categories as follows: infection and inflammation (including neurocysticercosis, tuberculoma, and calcified granuloma), hippocampal sclerosis, ischemia, gliosis, malformation of cortical development, tumor and tumor-like lesions, metabolic disorders, and vascular malformations based on previous publications on neuroimaging in epilepsy.^[8-10]

For the purpose of investigating the association of MRI lesions with abnormal electrical activity on EEG, the EEG results were coded as “focal or generalized epileptiform,” “focal or generalized slowing,” or “normal.”

Electroencephalogram protocol

Routine scalp video EEG recordings were performed as soon as practical after presentation with the index seizure, preferably within 24 h. The recordings were acquired with digital EEG systems (Galileo Mizar 40, EBNEURO, Italy) using 29 electrodes according to the international 10–20 system.

RESULTS

We studied 129 consecutive patients who presented with clinical diagnosis of first-onset seizure as per criteria laid done by the ILAE 1981.

Out of 129 patients, the EEG recording of three patients showed artifacts and were inconclusive, and hence excluded from the study.

Patient characteristics

Out of the 126 cases, the age of the cohort was between 5 and 82 years, with the mean age of 33.9 years. There were 71 males (56%) and 55 females (44%).

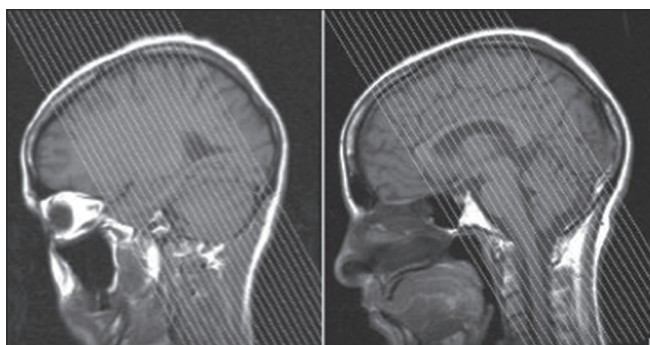


Figure 1: Magnetic resonance imaging sections taken in coronal oblique plane perpendicular to the long axis of the hippocampus.

Majority of the patients experienced seizures when they were awake (87.3%) and majority (80%) presented with single episode of seizure. Nearly 47% of the patients who presented with single episode of seizure showed epileptogenic lesions.

Almost 78% of the patients presented with generalized tonic-clonic seizures and the rest (21%) with partial seizure, out of which 12% were with simple partial seizure.

Majority of the patients (83%) did not give any significant past history of other abnormalities.

Magnetic resonance imaging diagnostic yield

Of the 126 patients who underwent MRI, 85 (67%) had positive findings. Of these, a potentially epileptogenic lesion was detected in 59 (47%) and a nonepileptogenic abnormality in 26 (21%) patients [Table 2a].

The diagnostic yield of MRI in detecting epileptogenic lesion was 47% in our study. Table 2b shows the diagnostic yield of MRI in different studies.

Among the potentially epileptogenic lesions, infection and inflammation were the most common (28%). Table 3 shows the etiology and frequency of epileptogenic lesions.

Of patients in the infection and inflammation groups, eight patients had neurocysticercosis [Figure 2] followed by five patients with tuberculoma [Figure 3] – hippocampal sclerosis [Figure 4] was a frequent finding in our

Table 1: Magnetic resonance imaging seizure protocol used in our institute

Sequence	TR in ms	TE in ms	Slice thickness in mm	Field of view in mm	Slices
FLAIR Axial	9000	92	5.0	230	20
T2 Axial	4500	97	5.0	230	20
T1 Sagittal	450	9	5.0	240	20
T2 Coronal	7340	110	5.0	230	25
DWI	3600	102	5.0	230	20
MPRAGE	1920	3.5	1.0	240	-
SWI	49	40	2.5	230	-
T1 IR coronal	7000	72	4.0	230	20
FLAIR coronal	9000	92	4.0	230	20
T1 Axial	480	8.7	5.0	230	20

Table 2a: Magnetic resonance imaging diagnostic yield

MRI	Number of patients (n=126)	Percentage
Normal	41	32.5
Abnormal		
Epileptogenic lesions	59	67.5
Non epileptogenic abnormalities	26	
Total	85	

MRI: Magnetic resonance imaging

study with 11 patients (19%) followed by ischemia 10 (17%) [Figure 5].

Tumors [Figure 6] were relatively uncommon (10%), of which majority were gliomas and one was meningioma.

Malformation of cortical development [Figure 7] group had three (5%) patients, of which all the three had focal cortical dysplasia.

Arteriovenous malformation was seen in 2 patients [classified into the vascular malformation group] who presented with first onset seizure [Figure 8].

Standard magnetic resonance imaging versus epilepsy protocol magnetic resonance imaging

Of the 59 patients with potential epileptogenic lesions in our study, 37 (63%) epileptogenic lesions were detected using “standard protocol” MRI and the remaining 22 (37%) lesions were detected using “dedicated epilepsy protocol” MRI [Table 4]. Two 10-year experienced radiologists who were unaware of clinical data or information evaluated both “standard protocol” MRI and “dedicated epilepsy protocol” MRI. Analysis of interobserver agreement between the two reviewers demonstrated a kappa value of 0.908, indicating excellent agreement. We found significant abnormalities on using “dedicated epilepsy protocol” MRI scans in 37% of patients whose results of “standard protocol” MRI were normal. Our study showed that there was an increase in diagnostic yield (37%) in finding epileptogenic lesions in patients who presented with first-onset seizure by adding “dedicated epilepsy protocol.”

Of the epileptogenic lesions, all the 11 patients (100%) with hippocampal sclerosis were detected by using “epilepsy protocol” MRI which would have been missed if only “standard protocol” MRI was done.

Magnetic resonance imaging in focal-onset seizures

Patients who presented with focal-onset seizures (27) had a higher proportion of potentially

epileptogenic lesions (22 [81%]) compared with the patients with generalized tonic-clonic seizures.

Among the nonepileptogenic abnormalities, 12 (46%) had nonspecific white matter hyperintensities followed by small vessel disease in 10 patients.

Table 2b: Diagnostic yield of magnetic resonance imaging in different studies

Different studies	Epileptogenic lesions on MRI (%)
Ponnatapura et al.	47
American Academy of Neurology ^[6]	1-47
American Epilepsy society ^[6]	5-47
Liu et al. ^[7]	14-48

MRI: Magnetic resonance imaging

Table 3: Etiology and frequency of epileptogenic lesions

MRI epileptogenic lesions	Number of patients (n=59)	Percentage
Infection and Inflammation	17	28.8
Hippocampal sclerosis	11	18.6
Ischemia	10	16.9
Gliosis	6	10.1
Malformation of cortical development	3	5.0
Tumor and tumor like lesions	6	10.1
Metabolic disorder	4	6.7
Vascular malformation	2	3.3

MRI: Magnetic resonance imaging

Table 4: Standard magnetic resonance imaging versus epilepsy protocol magnetic resonance imaging

Epileptogenic lesions	Number of patients (n=59)	Percentage
Diagnosed using Standard protocol MRI	37	62.7
Diagnosed using Epilepsy protocol MRI	22	37.3
Total	59	100

MRI: Magnetic resonance imaging

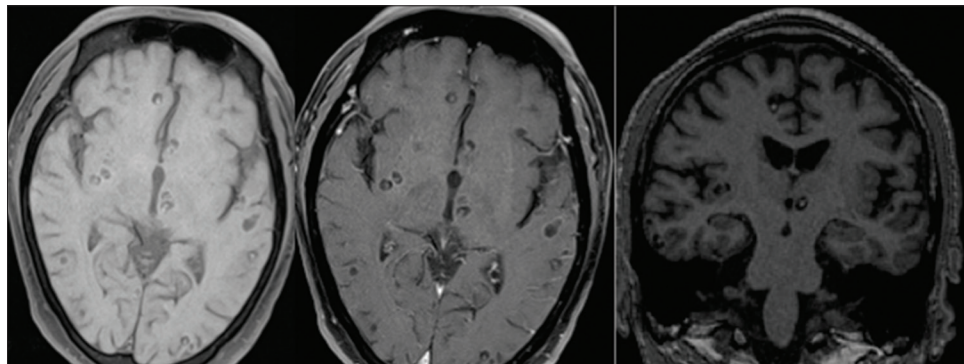


Figure 2: A 60-year-old male patient who presented with serial episodes of complex partial seizures. Axial pre- and post-contrast T1 and magnetization prepared rapid gradient echo sequence show multiple well-defined round ring-enhancing lesions scattered in cerebral hemisphere suggestive of neurocysticercosis. Electroencephalogram was normal in this patient.

Electroencephalogram diagnostic yield

Of the 126 patients who underwent EEG, 39 (31%) showed abnormal recordings and 87 (69%) showed normal recordings. The diagnostic yield of EEG in patients presenting with first-onset seizure was 31% in our study. Out of the 39 abnormal recordings, 12 (31%) showed generalized slowing and 18 (46%) showed epileptic discharges [Table 5].

Nine patients showed idiopathic generalized epileptic discharges (GEDs) and EEG and MRI helped to confirm the diagnosis. Of nine patients (23%) with GED, MRI should abnormalities in two (22%), however,

no potential epileptogenic lesions were detected on MRI (seven were normal; two showed nonspecific white matter hyperintensities).

Our study showed only 5 (18.5%) abnormal EEG recordings in patients who presented with focal-onset seizures.

Magnetic resonance imaging and electroencephalogram correlation

There were 22 patients (18%) with an abnormality on both MRI and EEG. So, abnormal MRI and EEG were concordant in 18% of patients in our study [Table 6].

There were 62 patients (49%) with an abnormal MRI but normal EEG and of these 62 patients, MRI detected 46 (37%) to have a potential epileptogenic lesion. Our

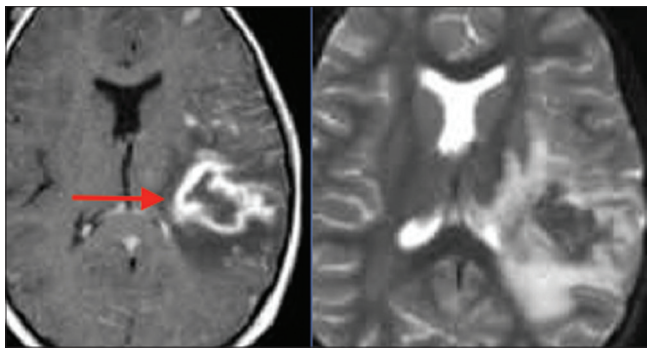


Figure 3: A 24-year-old female patient who presented with single episode of simple partial seizure. Axial postcontrast T1 and axial T2 sequences show conglomerated rim-enhancing lesion in the left parietal lobe suggestive of tuberculoma which was biopsy proven.

Table 5: Electroencephalography diagnostic yield

EEG	Number of patients (n=126)	Percentage
Normal	87	69
Abnormal		
Epileptiform discharges		
Focal	9	7.1
Diffuse	9	7.1
Focal slowing	9	7.1
Diffuse slowing	12	9.5
Total	126	100

MRI: Magnetic resonance imaging

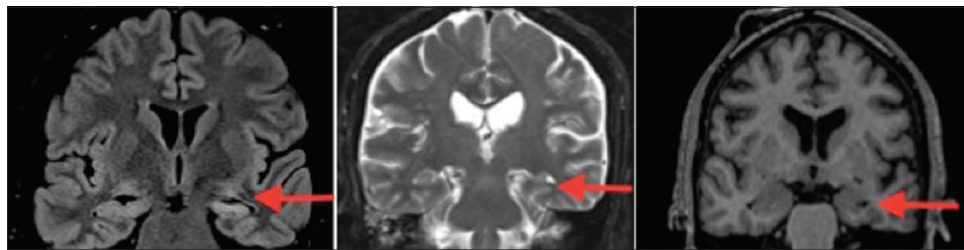


Figure 4: A 23-year-old male patient who presented with complex partial seizure. Coronal oblique T2, fluid-attenuated inversion recovery, and magnetization prepared rapid gradient echo sequence show loss of volume of the left hippocampus with hyperintense signal suggestive of left mesial temporal sclerosis. Electroencephalogram showed left temporal epileptiform discharges.

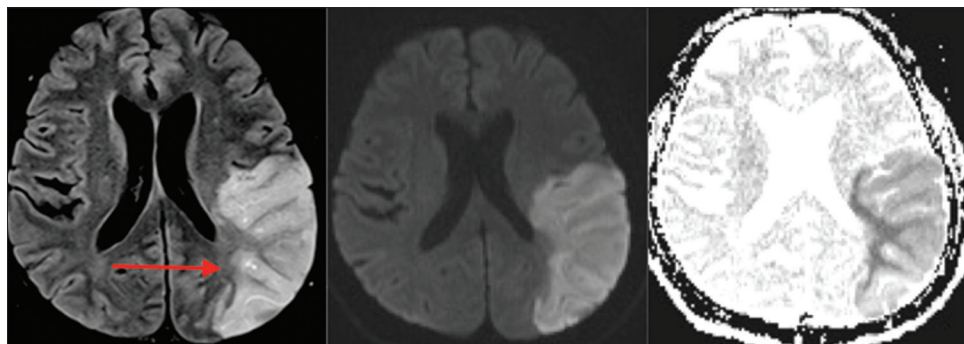


Figure 5: A 57-year-old male patient presented with generalized tonic-clonic seizure and loss of consciousness. Axial fluid-attenuated inversion recovery and diffusion-weighted imaging show wedge hyperintensity in the left parietal cortex with restriction diffusion suggestive of acute-to-subacute left middle cerebral artery territory infarct.

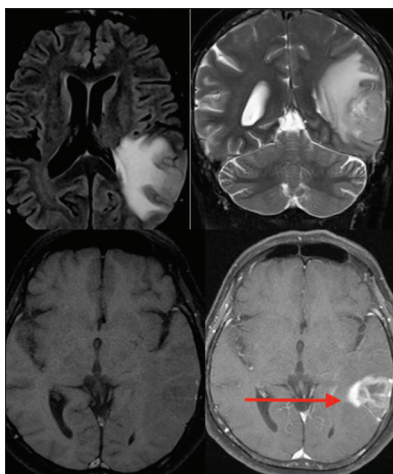


Figure 6: A 56-year-old female patient presented with serial episodes of generalized tonic-clonic seizure. Axial pre- and post-contrast T1 and coronal oblique T2 sequence show enhancing space-occupying lesion in the left temporoparietal lobe which was proven as astrocytoma on biopsy. Electroencephalogram was normal in this patient.

study shows that EEG being normal in 37% of patients with epileptogenic lesions. Furthermore, of these 46 patients, 13 (10%) were detected by using “dedicated epilepsy protocol.”

DISCUSSION

Neuroimaging is central to the evaluation of patients with first-onset seizure, especially in the identification of structural brain lesions that can serve as epileptogenic foci, and that might be surgically resectable if the patient becomes refractory to medical treatment.

In our study, the age of the cohort and gender distribution were similar to the study done by Hakami et al.,^[11] in 2013 where they studied 993 patients with 61% male and 39% females; mean age 42.2 years, range 14.3–94.3 years.

Almost half of the patients who presented with single episode of seizure showed epileptogenic lesions, which is similar to the study done by Wiesmann.^[12]

MRI was abnormal in 67% of patients who presented with first-onset seizures. The diagnostic yield of MRI was high, detecting epileptogenic lesion in approximately half of the patients with epileptic seizures. This finding is within the estimate of diagnostic yields of earlier studies of CT scan and MRI in patients with first-onset seizures.^[13] A study Liu et al., from the United Kingdom reported a comparable diagnostic yield of MRI (35%) in ninety patients with newly diagnosed epilepsy.^[7] However, a Swedish study reported a higher diagnostic yield (48%) of CT and/or MRI in 563 patients presenting after a new-onset seizures.^[13] Similarly, a German study reported a 43% yield of CT and/or MRI in 166 patients.^[14] In contrast, an earlier Australian

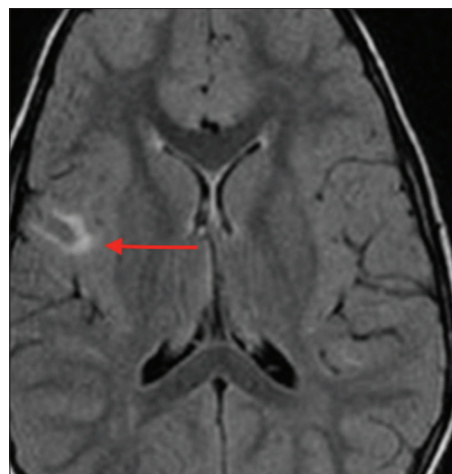


Figure 7: A 10-year-old male child presented with seizure. Axial fluid-attenuated inversion recovery shows focal cortical dysplasia in the right frontal lobe.

Table 6: Magnetic resonance imaging and electroencephalography correlation

MRI	EEG	
	Normal (%)	Abnormal (%)
Normal (%)	25 (19.8%)	17 (13.5%)
Abnormal (%)	62 (49.2%)	22 (17.5%)

EEG: Electroencephalography, MRI: Magnetic resonance imaging

study reported a lower diagnostic yield of CT and/or MRI (14%) in 300 patients.^[15] Another study, which was done in Australia in 2013, showed a significant diagnostic yield (23%) of MRI in detecting potentially epileptogenic lesions in patients with new-onset seizures.^[11]

Among the potentially epileptogenic lesion, infection and inflammation was most common 17 (28%) with eight patients having neurocysticercosis followed by five patients with tuberculoma.

Del Brutto in 2012 concluded that neurocysticercosis is the leading cause of acquired epilepsy worldwide, and the main reason for a higher prevalence of epilepsy in developing countries.^[16]

Another study by Narayanan and Murthy in 2007 concluded that seizures occur in about 50% of children and in 5% of adults with tuberculoma and recurrent seizures are common.^[17]

Our study shows that there is a paradigm shift in the etiology of most common cause of acquired seizure from tuberculoma to neurocysticercosis.

The incidence of mesial temporal sclerosis (19%) is similar to the previous studies, which have reported the incidence from 8% to 30%.^[7,11,12,18] Table 7 shows the incidence of mesial temporal sclerosis in different studies.

Our study shows that there is an increase in diagnostic yield (37%) in finding epileptogenic lesions in patients

who presented with first-onset seizure by adding “dedicated epilepsy protocol” with 100% of mesial temporal sclerosis detected on epilepsy protocol.

Oertzen et al., did similar study in 2002 studying 123 patients by using standard MRI and epilepsy-dedicated MRI and concluded that standard MRI failed to detect 57% of focal epileptogenic lesions.^[19] McBride et al., found significant abnormalities on epilepsy-dedicated protocol MRI scans in 93% of patients whose results of standard MRI performed outside an epilepsy center were reported as normal.^[20]

MRI showed higher proportion of potentially epileptogenic lesions 81% in patients with focal-onset seizures, which is comparable to the study done by Hakami et al.^[11]

It is known that 25%–30% of those who develop focal epilepsy will become drug-resistant, defined as failing at least two first-line anti-epileptic drugs.^[21] This is attributed, at least in part, to the presence of epileptogenic lesions. In patients with drug-resistant epilepsy, surgical treatment is often effective and can control seizures, improve quality of life, and decrease risk of premature death.^[22] The prospect of successful surgery is higher when an epileptogenic lesion is found on MRI.^[23] MRI in first-onset seizure patients allows

the identification of a lesion and earlier consideration of epilepsy surgery.

Partial-onset seizures that secondarily generalize rapidly can be misinterpreted as primary generalized seizures. If, however, the MRI shows a structural lesion that is the likely source of the seizures, then they can be classified as partial.^[23]

The diagnostic yield of EEG in patients presenting with first-onset seizure was 31% in our study with generalized slowing in 31% and epileptic discharges in 46%.

A study by King et al., revealed epileptogenic abnormalities in 39% of adult patients.^[15] In patients with first-onset seizure, Hakami et al., showed EEG abnormality in 31% with slowing in 57% and epileptiform discharges in 42%.^[11] Jha^[24] studied 150 cases of solitary seizures. EEG was done in all patients, and was abnormal in 22% of patients.

In patients with GEDs, there were no potential epileptogenic lesions detected on MRI. However, MRI abnormalities have been reported in up to 24%, while most of these findings were not epileptogenic; potentially epileptogenic lesions were seen in 3%–4% and hence MRI should be warranted.^[25,26]

Abnormal MRI and EEG were concordant in 18% of patients in our study, which is similar to another study.^[11]

Our study also showed that EEG was normal in 37% of patients with epileptogenic lesions, which is similar to EEG being normal in 55% of patients with epileptogenic lesion in a study done by Hakami et al.^[11]

Our study also showed that MRI and EEG were comparable with significant *P* value ($P < 0.01$).

Of note, however, MRI and EEG were discordant in the location of seizure foci where both were abnormal. Hakami et al.,^[11] showed MRI and EEG to be discordant in the location of seizure foci in 8% of patients.

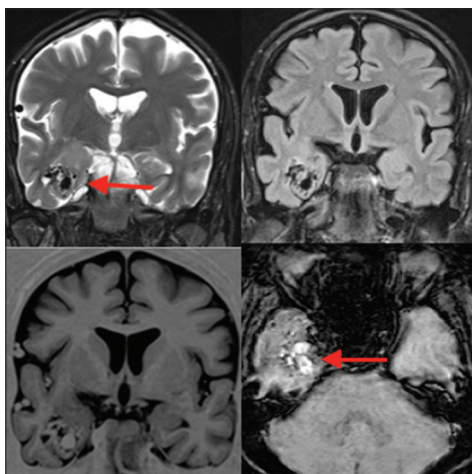


Figure 8: A 40-year-old male patient presented with complex seizure. Coronal oblique T2 and fluid-attenuated inversion recovery, T1 inversion recovery, and axial susceptibility-weighted imaging sequences show arteriovenous malformation involving right temporal cortex.

Table 7: Incidence of mesial temporal sclerosis in different studies

Different studies	Mesial temporal sclerosis (%)
Ponnatapura et al.	19
Wiesmann ^[12]	21
Van Paesschen et al. ^[18]	8
Hakami et al. ^[11]	30
Liu et al. ^[7]	16

CONCLUSIONS

The most common cause of epilepsy in developing country like India is neurocysticercosis and tuberculoma. MRI is doubtlessly the neuroimaging choice in first-onset seizure presentation. A dedicated epilepsy protocol MRI should be done in all patients who presents with first-onset seizures. MRI in first-onset seizure patients allows the identification of a lesion and earlier consideration of epilepsy surgery, especially in patients presenting with focal-onset seizures.

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Conflicts of interest

There are no conflicts of interest.

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