

## Original Research Article

# Neuroimaging in drug resistant epilepsy

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### ABSTRACT

**Background:** Epilepsy is a common serious neurological condition and 30 to 40 % of people with epilepsy have seizures that are not controlled by medication. Patients are considered to have drug resistant epilepsy if disabling seizures continue despite appropriate trials of two anti-epileptic drugs. Most lesions causing drug resistant epilepsy can be detected by 3T MR Imaging using dedicated epilepsy protocol which is crucial for diagnostic and subsequent therapeutic planning with benefit from surgery. We present a review of the major abnormalities related to drug resistant epilepsy, highlighting the key findings of 3 T MRI.

**Methods:** A Cross-sectional Observational study was done in 30 patients. Patients less than 60 yrs of age of either sex, diagnosed with DRE as per ILAE criteria, were included in the study. 3T MRI was performed using dedicated epilepsy protocol, with additional 3D imaging for manual hippocampal volumetric evaluation.

**Results:** About 77% cases showed an MRI abnormality on visual assessment, with additional 16% cases showing abnormal MRI findings on manual hippocampal volumetry. Nearly 50% of the abnormal MRI cases showed Mesial Temporal Sclerosis, followed by neoplasms as etiology of DRE.

**Conclusions:** MR imaging has significantly improved detection of pathologies related to epilepsy, especially with the advent of epilepsy protocol. The total percentage of MRI abnormalities increased after incorporating manual hippocampal volumetry.

**Keywords:** Drug Resistant Epilepsy, Magnetic Resonance Imaging, Mesial Temporal Sclerosis, LEATs, 3 T

### INTRODUCTION

Epilepsy is a disorder of the brain that is characterized by an enduring predisposition to generate epileptic seizures. It affects approximately 50 million people in the world and every 5 in 1000 in India.

In epilepsy three types of patient response are seen- those with spontaneous remission, remission with anti-epileptic drugs and persistent seizures despite anti-epileptic drugs among which Drug Resistant Epilepsy (DRE) is included. The International League Against Epilepsy defines Drug Resistant Epilepsy as “failure of adequate trials of two

tolerated and appropriately chosen and used anti-epileptic drug schedules to achieve sustained seizure freedom”.<sup>1</sup> It also recommended replacing the term intractable with drug resistant epilepsy. Nearly 30% epilepsy cases are DRE.<sup>2</sup> When adequate seizure control is not achieved, a presurgical evaluation in an epilepsy referral centre is recommended.

These evaluations explore how to resect the epileptogenic zone without causing functional deficits.<sup>3</sup> 3T MRI offers major advances in structural and functional neuroimaging.

### **Structural causes of drug resistant epilepsy identified on MRI**

- Mesial temporal sclerosis (MTS),
- Malformations of cortical development-microcephaly, megalencephaly, focal cortical dysplasia, heterotopia, lissencephaly, schizencephaly and polymicrogyria,
- Neoplasms-ganglioglioma, astrocytoma, dnet, hypothalamic hamartoma,
- Vascular malformations,
- Neurocutaneous syndromes-tuberous sclerosis and Sturge Weber syndrome.

### **Risk factors for DRE**

No single risk factor has been found for DRE. Rather, a combination of two or more risk factors help to define it.<sup>4</sup> These include response to first antiepileptic drug, high number of seizures prior to diagnosis and treatment, underlying etiology and seizure classification. Certain paediatric epilepsy syndromes are almost invariably intractable like early neonatal myoclonic encephalopathy and Rasmussen encephalitis.<sup>5</sup>

### **Role of imaging**

CT imaging in DRE is helpful in acute situations to exclude other underlying neurological conditions, which may trigger acute seizures such as stroke, intracranial haemorrhage and encephalitis. However, in non-acute imaging of epilepsy, dedicated epilepsy MRI is the first choice.<sup>6</sup>

MRI evaluation in DRE patients includes (i) identification and delineation of epileptogenic focus with up to 80% of patients with DRE having structural abnormalities evident on MRI (ii) detection of residual lesion (iii) prognosis. Dedicated MRI protocols can detect epileptogenic abnormalities with great sensitivity and specificity, with standard MRI failing to detect 57% of focal epileptogenic lesions.<sup>7</sup> Dedicated epilepsy protocol for evaluation of cases with epilepsy is the “essential 6” sequences: T1 axial and coronal; T2 axial and coronal FLAIR and axial susceptibility weighted sequence. Recommended slice thickness is 3mm for T2, FLAIR and susceptibility weighted, and 1mm slices for T1. Oblique coronal plane, perpendicular to the long axis of hippocampus is best for medial temporal lobe structures.<sup>6</sup>

### **Role of hippocampal volumetry**

An important MRI finding in DRE cases is reduced hippocampal volume seen in nearly 50-75% cases.<sup>8</sup> Although most MR imaging studies are sufficient for the detection of gross hippocampal atrophy (HA), subtle HA that may characterize early disease is often missed. To facilitate clinical interpretations, quantitative volumetric methods have been developed, and these methods correlate well with histologically confirmed hippocampal

cell loss. Additionally hippocampal volumetry can guide surgical resection of hippocampus, which is the most successful treatment for drug resistant MTS.<sup>9</sup>

### **METHODS**

This Cross-sectional Observational study was conducted in the Department of Radiodiagnosis, Post Graduate Institute of Medical Education and Research, Dr. Ram Manohar Lohia Hospital. Thirty patients less than 60 years of age with DRE diagnosed as per ILAE criteria referred for MRI brain between November 2015 and March 2017 were recruited in the study. Informed consent was taken from the patients or their legal guardian for inclusion in the study. All the recruited patients underwent MRI Brain using a dedicated Epilepsy Protocol. Approval from hospital and Institutional Ethical Committee was obtained prior to initiation of the study.

### **MRI acquisition protocol**

MRI was performed using Siemens 3.0 Tesla Magnetom Skyra MR system using standard head coil and a dedicated Epilepsy Protocol with the following sequences: T2W and Fluid-attenuated inversion recovery (FLAIR) axial images parallel to long axis of hippocampus, T2W and FLAIR coronal images perpendicular to long axis of hippocampus, Axial Susceptibility weighted imaging (SWI) Sequence, True inversion recovery sequence (IR), Post contrast axial, sagittal and coronal T1 weighted sequences were done as needed. Intravenous contrast (Gd-DTPA) in dose of 0.1 mmol/kg body weight for contrast enhanced scan was given.

### **Manual hippocampal volumetry**

A 3D T1W image was acquired using Fast Low Angle Shot (FLASH) for manual volumetric evaluation. Images perpendicular to the long axis of the hippocampus, oblique coronal section was taken for measurements by outlining the region of interest (ROI) manually on a magnified image. The hippocampus was delineated using anatomical landmarks with the CSF of the temporal horn above, the ambient cistern medially and uncus recess between the hippocampal head and the amygdala. The borders of the hippocampi were manually traced sequentially with a mouse-driven cursor on each slice from the posterior to anterior till the entire length of hippocampus. Hippocampal volume was calculated by summing up the area that had been delineated using the manual cursor. Area thus obtained was multiplied by 0.15 (1mm slice thickness and 0.5mm inter-slice gap), giving values in cubic centimetres.

### **RESULTS**

A total of 30 patients with drug resistant epilepsy were evaluated in the age group of 3 to 65 years, of which 16 were females (53.3 %) and 14 were males (46.7 %).

The mean age of onset of seizures was 10.41+/-9.35 years, ranging from 6 months to 36 years. 21 cases (70%) had seizure onset before 14 years of age.

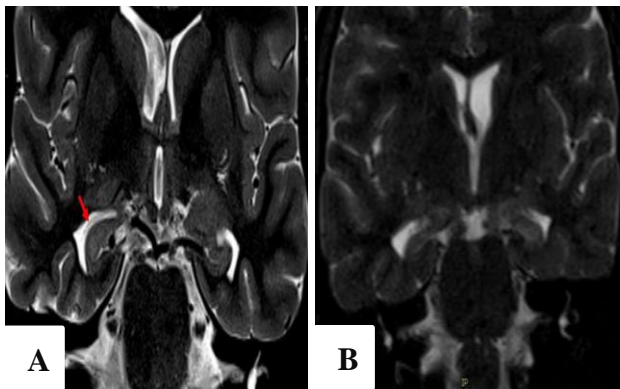
There were 18 cases (60%) with partial seizures, 12 cases (40%) with generalized seizures, and none having myoclonic variety. A total of 12 cases (40%) had clinical history of aura.

EEG was reported as abnormal in 20 cases (66.7%) and normal in 10 cases (33.3%). Abnormal EEG showed epileptogenic focus lateralization in 3 cases (10%).

Of the total 30 patients, 28 cases (93.3%) showed findings on MRI which were seen on visual assessment in 23 (76.7%) cases and 5 (16.7%) cases were detected on manual hippocampal volumetry. The remaining 2 cases (6.6%) did not show any MRI abnormality on visual or hippocampal volumetric assessment.

The distribution of cases based on MRI diagnosis on visual assessment and manual hippocampal volumetry (MHV) was MTS in 14 cases (46.7%), followed by neoplasms in 6 cases (20%), malformations of cortical development in 5 cases (16.7%), vascular malformations in 2 cases (6.6%) and tuberous sclerosis in 1 case (3.3%).

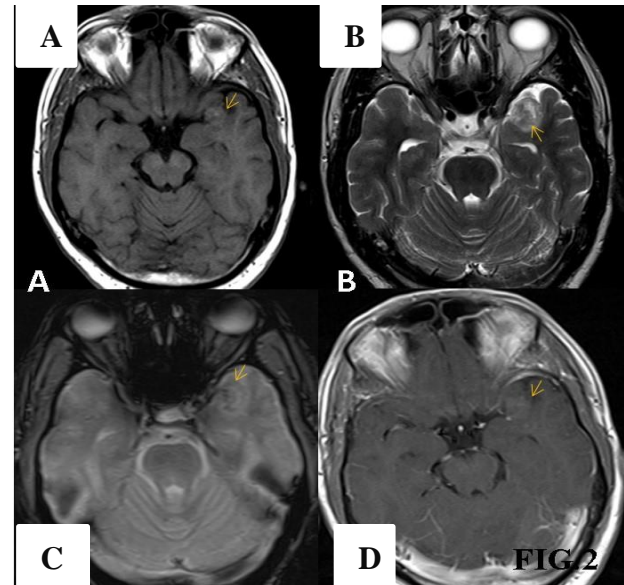
MTS was the most common condition which was diagnosed by visual assessment in 9 (64.2%) cases, with 5 (35.7%) additional cases diagnosed by MHV. MTS was found more often on the left than the right side, and MHV revealed bilateral MTS in 4 (28.5%) cases which were not seen visually (Figure 1A and 1B).



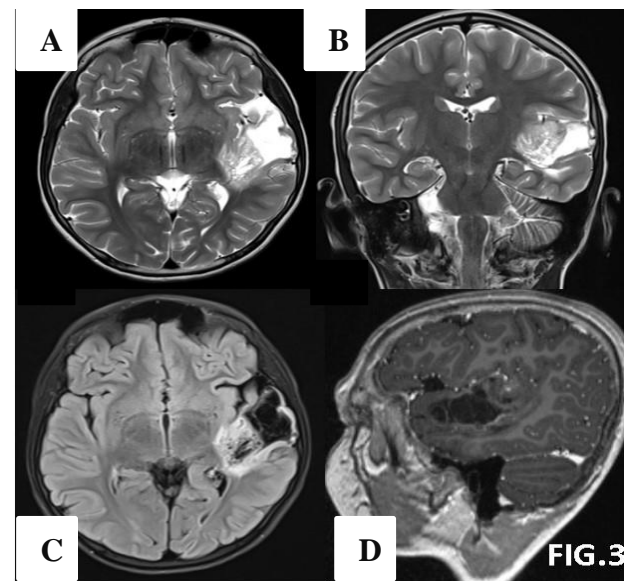
**Figure 1: A). T2W coronal MR image with right sided mts(arrow). B) T2W coronal MR image with bilateral MTS.**

Of the diagnosed neoplasms, there were equal number of gangliogliomas, dysembryoplastic neuroepithelial tumors (DNET) and low grade astrocytomas. Temporal lobe was the commonest site (4, 66.6%) and all three neoplasm types of our study were seen in this location. One (16.7%) ganglioglioma was found in parietal lobe and one (16.7%) DNET was found in frontal lobe. No neoplasm was seen in occipital lobe. There were more

number of lesions left sided (5, 83.3%) as compared to right. Four cases (66.7%) had cortical based lesions (Figure 2, Figure 3 and Figure 4).



**Figure 2: Ganglioglioma. A) T1W Cortical based lesion (arrow) in left temporal lobe with hyperintense focus. B) T2W appears hyperintense. C) T2\* shows blooming focus. D) Postcontrast T1W shows minimal contrast enhancement.**

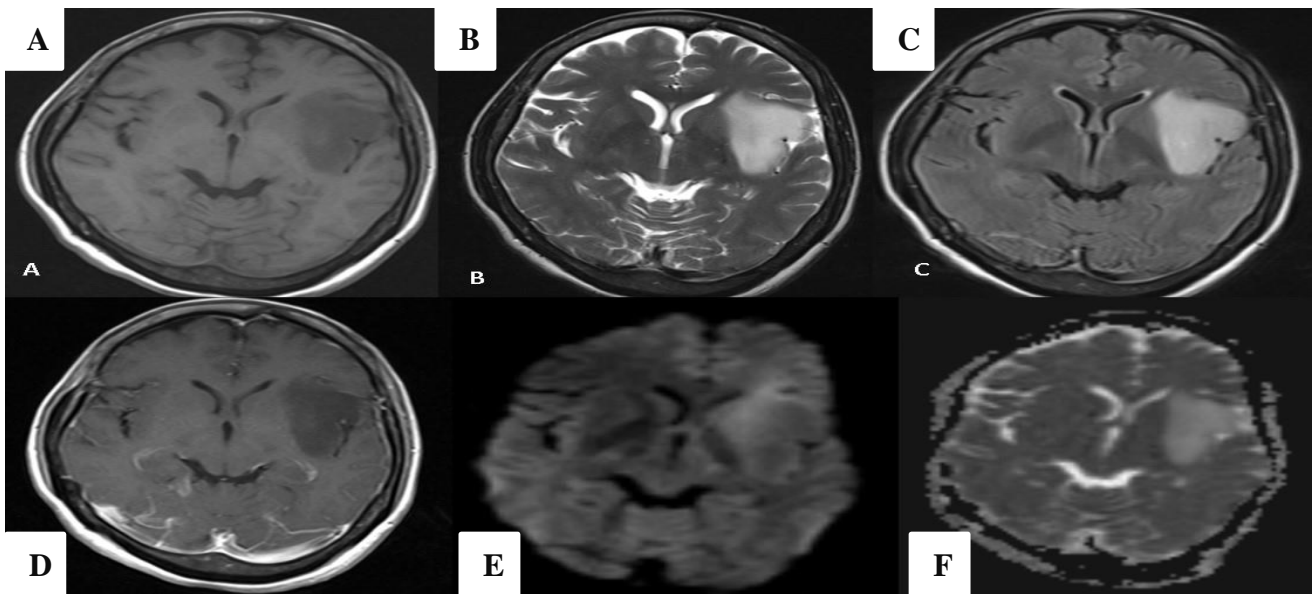


**Figure 3: DNET A, B) T2W Axial /Coronal shows a multiseptate cystic lesion in left temporal lobe. C) FLAIR shows a hyperintense rim around the lesion. D) Sagittal postcontrast T1W shows no enhancement.**

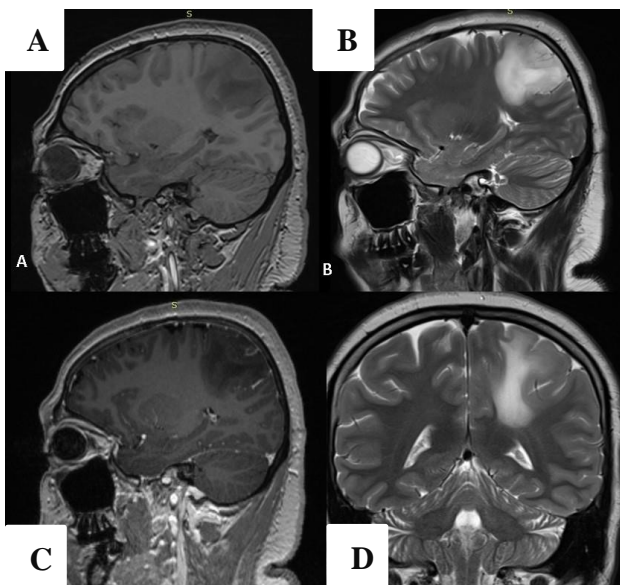
Out of 5 cases of MCD, there were 2 (40%) cases of focal cortical dysplasia (isolated) and 2 (40%) cases of pachygyria lined abnormal CSF cleft. There was 1 (20%) case of heterotopia with subtle focal cortical dysplasia. Most of our MCD cases had lesion in parietal lobe (3,

60%) followed by frontal lobe (1, 20%) and temporal lobe (1, 20%) cases. A total of 3 (60%) cases of MCD

were in right side and 2 (40%) cases of MCD in left side (Figure 5, Figure 6 and Figure 7).

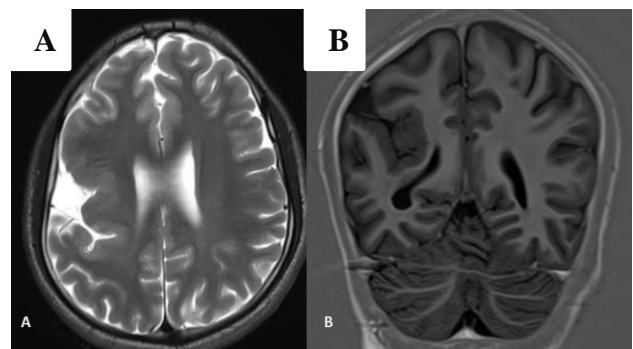


**Figure 4: Low grade astrocytoma. A) T1WI axial shows a hypointense left insular well defined temporal lobe mass. B, C) On T2W and FLAIR the mass is hyperintense. D) Postcontrast T1W shows no enhancement. E, F) DWI and ADC show no diffusion restriction.**



**Figure 5: Focal cortical dysplasia. A) T1W sagittal shows a broad thick cortex with indistinct grey white matter interface. B, D) T2W sagittal and coronal images show abnormal wedge shaped hyperintense lesion. C. Post-contrast T1W sagittal image shows no enhancement.**

We had two cases with vascular malformations which were Cerebral cavernous malformation (CCM) and Arteriovenous malformation (AVM) (Figure 8 and Figure 9).



**Figure 6: A) T2W axial shows a CSF cleft lined by parenchyma having broad gyri and shallow sulci, consistent with pachygyria. B) T1W coronal image of the same patient.**

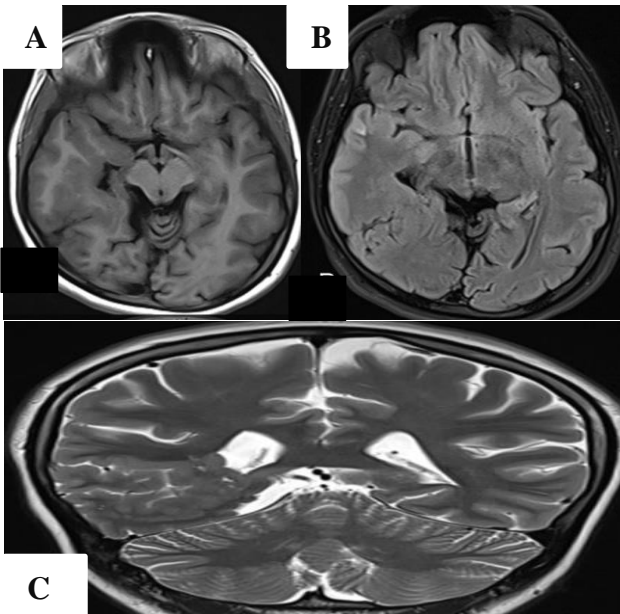
One case of neurocutaneous syndrome was a patient of tuberous sclerosis (Figure 10).

## DISCUSSION

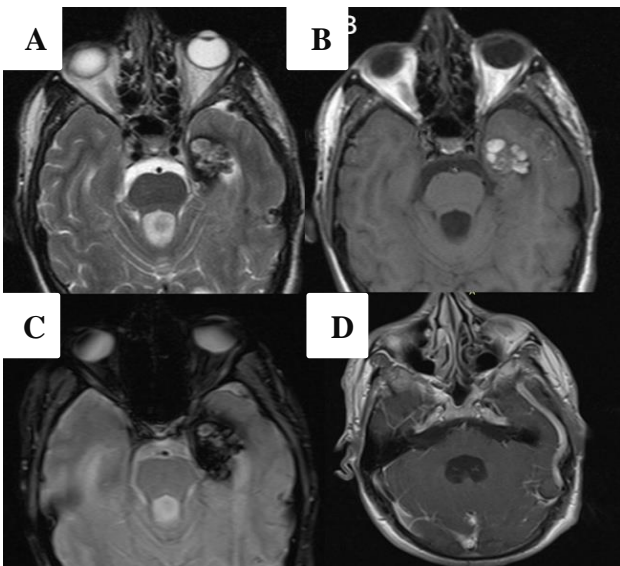
### *Mesial temporal sclerosis*

Mesial temporal sclerosis is the most common form of epilepsy with hippocampal sclerosis being the main pathologic substrate in such patients. Hippocampal sclerosis is seen in the presence of neuronal loss greater than 30-50%.<sup>10</sup> The etiology of the lesion has been postulated as a combination of acquired or developmental. Imaging findings that suggest MTS

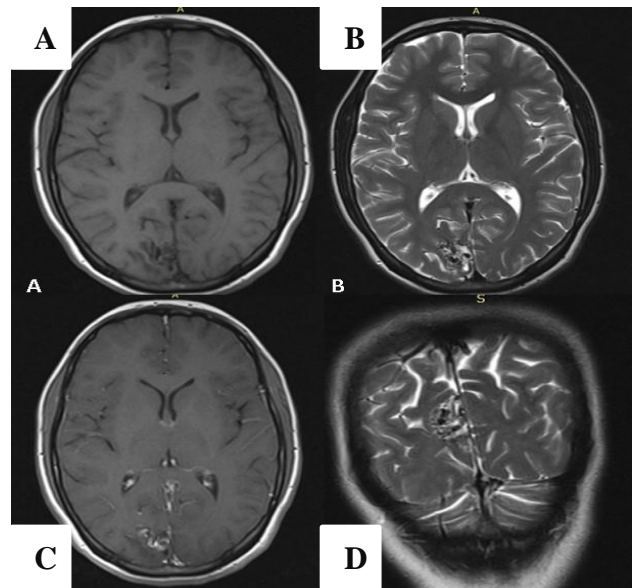
include: Primary signs- hippocampal T2 hyperintensity, reduced hippocampal size, loss of hippocampal interdigitations; secondary signs-atrophy of the collateral white matter, reduced gray and white matter differentiation in the anterior temporal lobe, decreased temporal lobe size, ipsilateral temporal horn enlargement, unilateral atrophy of the mamillary body, fornix columns, and the amygdale.<sup>11</sup>



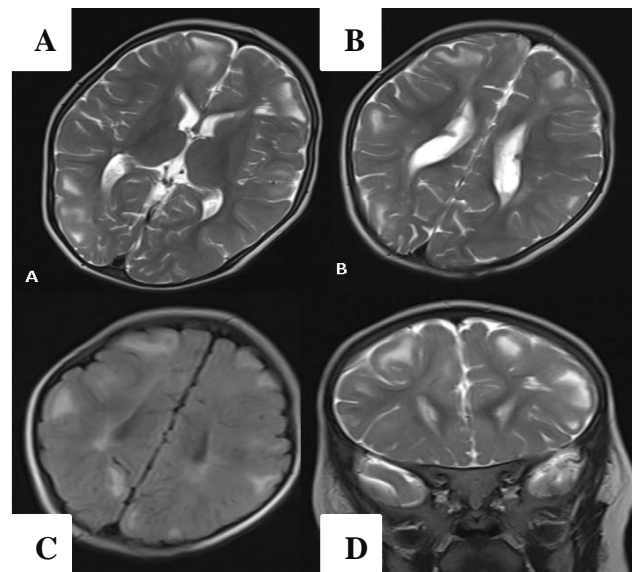
**Figure 7:** A) T1W axial image shows a focal mass of gray matter in the right temporal lobe. B) Flair axial. C) T2W coronal image of same patient shows heterotopic gray matter bulging into ipsilateral ventricle.



**Figure 8:** Cavernous cerebral malformation. A) T2W axial image shows classic “popcorn ball” in left temporal lobe replacing the hippocampus. B) T1W axial image shows hyperintense signal within. C) T2\* shows blooming. D) Post contrast T1W axial shows developmental venous anomaly in left occipital region.



**Figure 9:** A) Arteriovenous malformation. B) T1W and T2W axial images show right occipital (AVM) with tightly packed multiple serpentine flow voids (arrow). C) Postcontrast T1W axial image shows enhancement. D) T2W coronal image in the same patient.



**Figure 10:** Tuberous Sclerosis A) T2W axial MR shows expanded gyri of cortical tubers. B) Cephalad image shows subependymal nodules isointense with gray matter. C) FLAIR axial image shows multiple cortical tubers. D) T2W coronal image demonstrates cortical tubers and hyperintense radial band extending outward.

This abnormality can be bilateral symmetrical or asymmetrical or unilaterally localized, depending on the type and time of injury with bilateral lesions being more common with early perinatal disturbances, whereas unilateral lesions being more common with late injuries. There is less than 10% detection of HS with Standard MRI imaging. In contrast, epilepsy-dedicated MRI has 100% detection of histologically proven HS in patients

undergoing epilepsy surgery.<sup>6</sup> Hippocampal volumetry improves the sensitivity by detecting subtle and bilateral hippocampal abnormalities as well as consistently lateralizes the seizure focus making it a strong surrogate marker for the presence and severity of hippocampal atrophy.<sup>12</sup> When HS is associated with an extrahippocampal epileptogenic lesion i.e. dual pathology resection of both is required for maximum chance of seizure freedom.<sup>13</sup>

### ***Long-term epilepsy-associated tumors (LEATs)***

Long-term epilepsy-associated tumors are identified in about 20-30% of patients operated on for refractory epilepsy.<sup>10</sup> These types of tumor include gangliogliomas, dysembryoplastic neuroepithelial tumors, pleomorphic xanthoastrocytomas, diffuse astrocytomas, oligodendrogliomas, and a few anaplastic tumors. They can occur in any part of the brain, but preferentially affect the temporal-lobe region.<sup>14</sup> They are generally slowly growing, low grade, cortically based tumors, more often arising in younger age groups and in many cases exhibit neuronal and glial differentiation.

Gangliogliomas and dysembryoplastic neuroepithelial tumors (WHO grade I tumors) predominate in this group. Gangliogliomas are mixed solid-cystic or solid cortical based lesions seen commonly in temporal lobe with no to minimal mass effect, frequent calcification (30-50%) and variable contrast enhancement in 50% cases with patterns varying from solid, rim, or nodular to cystic with an enhancing nodule.<sup>15</sup>

Dysembryoplastic neuroepithelial tumor (DNET) is focal circumscribed “bubbly” cortical mass indenting the overlying skull and extending subcortically. DNETs are strikingly hyperintense on T2WI with a multicystic or septated appearance. A characteristic hyperintense rim along the tumor periphery is present in 75% cases.

Pleomorphic xanthoastrocytomas are located adjacent to leptomeninges with an enhancing mural nodule. Moderate postcontrast enhancement of tumor nodule is typical. Over 90% PXAs abut the pia and may incite reactive thickening of adjacent dura with a “dural tail sign”. Oligodendrogliomas are WHO grade II tumors, seen as poorly circumscribed, grey-white matter junction masses, diffusely infiltrating the cortex which commonly show calcification and post-contrast enhancement. Low grade astrocytomas are also WHO grade II tumors but with inherent tendency to undergo malignant degeneration. These are infiltrating, ill defined tumors appear hypointense on T1, hyperintense on T2WI/FLAIR with no enhancement or hemorrhage.

### ***Malformations of cortical development***

Approximately 40% of children with drug resistant epilepsy have malformations of cortical development. These include Focal Cortical Dysplasia and heterotopias.

Focal Cortical Dysplasia (FCD) are localised regions of non neoplastic malformed gray matter which are the single most common cause of severe epilepsy. The ILAE task force has proposed a three tier classification based on clinical imaging and neuropathologic findings. FCD type 1 is an isolated malformation with abnormal cortical layering that demonstrates either vertical persistence of developmental microcolumns or loss of horizontal structure or both. FCD type 2 is the most common type of FCD characterised histologically with altered cortical layering with dysmorphic neurons with or without balloon cells.

On imaging FCD appears as a wedge shaped area of T2/FLAIR hyperintensity extending from bottom of sulcus into subcortical deep white matter. FCD type 3 is a post migrational disorder secondary to ischaemia, infection, trauma, etc.

Heterotopias result due to arrest of normal neuronal migration along radial glial cells and can be found virtually anywhere between the ventricles and pia. They can be solitary or multifocal and often exist in association with other malformations.<sup>16</sup> Periventricular nodular heterotopia is the most common cause of cortical malformations in adults. In this condition, one or more subependymal nodules of gray matter line the lateral walls of ventricles giving a distinctive “lumpy bumpy” appearance. These nodules do not enhance or calcify.

Schizencephaly is a gray matter lined cleft that extends from the ventricular ependyma to the pial surface of the cortex. The lips of the cleft can be fused or closely apposed (closed lip schizencephaly) or appear widely separated (open lip schizencephaly). Vascular lesions like MCA occlusion and infections like TORCH are considered likely etiologies.<sup>16</sup>

### ***Vascular malformations***

Arterio-venous malformations (AVM) and cavernous cerebral malformations are the commonest seizure causing vascular malformations.<sup>16</sup>

AVMs are seen as tangled blood vessels with no intervening capillary network appearing as serpiginous flow voids on T1/T2WI with areas of T2 prolongation in adjacent brain.

Cavernous cerebral malformations show well circumscribed vascular spaces with blood in varying stages of evolution and characteristically no intervening brain tissue. Central part of these lesions contains areas of high signal on T1 and T2 weighted images, reflecting oxidised haemoglobin, with darker areas on T1 weighted images caused by deoxyhaemoglobin. The ring of surrounding haemosiderin appears dark on a T2 weighted image. Up to 50% of cavernous malformations are multiple and may occur on a familial basis.

### Neurocutaneous syndromes

The commonest neurocutaneous syndromes manifesting epilepsy are Tuberous sclerosis and Sturge-Weber syndrome.<sup>17</sup> Tuberous sclerosis complex is characterized by the presence of hamartomas that behave as slow-growing masses. Tubers are seen as cortical and subcortical lesions commonly in the frontal lobe appearing as high signal intensity on FLAIR which rarely enhance. Subependymal nodules are small lesions protruding into the lateral ventricles which are usually calcified.

Sturge-Weber syndrome (SWS) is characterised by DRE, progressive mental retardation and facial telangiectatic nevi, often in the trigeminal nerve distribution. The main imaging findings of SWS are cerebral atrophy, white matter abnormalities in the region of the leptomeningeal angiomas, hypertrophy of the overlying calvarium and congested deep cerebral veins. Post contrast shows typical leptomeningeal enhancement.

### CONCLUSION

Most lesions causing drug resistant epilepsy can be detected by 3T MR imaging using dedicated epilepsy protocol which is crucial for diagnostic and therapeutic planning. Thin slice coronal MRI sequences acquired in coronal orientation are particularly useful to assess temporal and calculate hippocampal volume. Manual hippocampal volumetry should be used in cases with negative visual assessment with high clinical suspicion of temporal lobe epilepsy.

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