MRI Brain Findings in Adults with Lesional Refractory Epilepsy and Correlation to Surgical Outcome

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Abstract

Introduction: Refractory epilepsy which is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom is common in patients with structural brain lesions including acquired disorders and genetic abnormalities. High resolution Magnetic Resonance Imaging MRI of the brain has proven its precision as a diagnostic tool for recognition of different structural lesions underlying medically intractable seizures.

Objective: To recognize common MRI lesions in a series of adult patients with refractory epilepsy admitted to the epilepsy monitoring unit at Prince Sultan Military Medical City PSMMC for pre surgical evaluation for epilepsy surgery with correlation to surgical outcome and to compare our local data with the international literature.

Material and methods: 245 patients (100 Males and 145 Females; 14-53 years) with refractory epilepsy were included in this retrospective analysis. They presented with partial or without complex partial seizures 112 (46.0%), partial with secondary generalized tonic clonic seizures 76 (31.0%) or generalized seizures in 57 (23.0%) of patients. Clinical diagnosis of epilepsy and seizure classification were based on the revised criteria of the International League Against Epilepsy ILAE. Structural neuroimaging MRI brain, functional neuroimaging which include Interictal Fluorodeoxyglucose Positron Emission Computed Tomography FDG-PET, Ictal Technetium-99m hexamethyl-propylene amine oxime Single Photon Emission Computed Tomography 99m HMPAO SPECT, Electroencephalography EEG recording, epilepsy history and neurological examination were performed. MRI brain imaging epilepsy protocol used a 1.5 or 3 Tesla MRI scanner. All patients included in this study received appropriate epilepsy surgery and post-operative seizure control was followed in the epilepsy clinic with six-month post-operative inter ictal EEG, follow up MRI brain after epilepsy surgery were performed in all patients and 50 patients had additional video-EEG recording post-operative during the follow up period. Epilepsy surgery seizure control outcome was classified according to Engel Classification system. All patients were followed for at least two years post-operatively to assess seizure control. Pre-operative MRI diagnosis was correlated with the epilepsy surgery seizure control outcome.

Results: MRI detected different structural brain abnormalities in 245 (100%) patients, including temporal lobe location in 142 (58%) patients, frontal lobe location in 74 (30%) patients and parieto-occipital lobes location in 29 (12%) patients. On MRI hippocampal sclerosis HS is diagnosed in 86 (35%) patients, cerebral tumors in 74 (30%) patients and among the cerebral tumors MRI suggested the diagnosis of developmental tumors that is; glio-neutral tumors in 45 out of 74 (61%) of tumor patients, malformations of cortical development MCD in 42 (17%) patients, vascular malformations in 15 (6%) patients, dual pathologies in 12 (5%) patients and remote gliotic lesions in 16 (7%) patients. The histopathological diagnosis confirmed the MRI brain diagnosis in all included patients. At 2 years of post-operative follow-up 196 (80%) patients were classified as Engel Class I, 37 (15%) patients Engel Class II, 6 (3%) patients Engel Class III and 6 (3%) patients as Class IV seizure freedom. In the class IV group two patients failed epilepsy surgery because they had high grade astrocytoma with post-operative tumor recurrence and four patients failed epilepsy surgery due to incomplete resection of epileptogenic lesions. Patients with MRI diagnosis of HS 82 out of 86 (95%) patients, low grade tumor 59 out of 74 (80%) patients and vascular malformation 12 out of 15 (80%) had best epilepsy surgery outcome. Patients with high grade tumors 2 out 3 (67%) patients and incomplete surgical resection of epileptogenic lesions 4 out of 5 (80%) patients had the worst epilepsy surgery outcome.

Conclusion: This study revealed that MRI brain structural lesions were commonly associated with refractory
epilepsy. Temporal lobe structural brain lesions were most common lesions in adult epilepsy patients with refractory epilepsy referred for epilepsy surgery. The presence of HS, low grade tumors and vascular malformations correlated with best surgical outcome while high grade tumors and incomplete surgical resection of the lesions correlated with worst surgical outcome. Our results were consistent with the international reported literature.

**Keywords:** MRI brain; Lesional refractory epilepsy; Surgical outcome; Correlation

### Introduction

About 30% to 40% of patients with epilepsy are diagnosed with refractory epilepsy which is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [1]. After failing the trial of two to three AEDs in monotherapy or poly therapy regimens or when the MRI brain shows a structural lesion and no response to adequate dose of one AED it is recommended to refer those patients for evaluation for epilepsy surgery [2]. Often refractory epilepsy is associated with a structural brain lesion which could be of various etiologies [1,2]. Most common acquired disorders include HS, stroke, trauma, tumor or infection and genetic abnormalities include tuberous-sclerosis, malformations of cortical development MSD, or vascular malformations such as cavernoma or arteriovenous malformation [1,2]. Usually the patient is admitted to an epilepsy monitoring unit EMU to record the electroclinical seizures and perform high resolution MRI brain and additional functional neuroimaging such as FDG-PET, 99 m HMPAO SPECT scans of the brain or Magnetic Resonance Spectroscopy MRS as needed. Appropriate diagnosis is based on the epilepsy history, clinical characteristic of seizures which are classified according to the revised criteria of ILAE [3] and ictal or interictal encephalography EEG recordings [4]. MRI brain is considered a precise non-invasive technique for recognition of different structural causes underlying intractable seizures [1,2,5]. Several studies revealed the high diagnostic sensitivity and specificity of MRI brain in refractory epilepsy [1-5]. Evidence exists that MRI successfully visualizes morphological changes in about 80% of patients with epilepsy [6]. High-resolution MRI is a highly sensitive and specific noninvasive method to diagnose HS in vivo [5]. Qualitative MRI interpretation, and quantitation of hippocampal volume (volumetry) and T2 signal (T2 relaxometry), are very sensitive and specific in detecting lesions that cause other temporal lobe lesions that may have similar clinical manifestations of HS, such as tumors, dysplasia, vascular malformations and other lesions, such as temporal-lobe encephaloceles [5,7]. MRI brain can detect most common lesions causing neocortical epilepsy, which are: low-grade tumors, malformations of cortical development, posttraumatic and post ischemic lesions, inflammatory infectious scars, cavernous malformations, and arteriovenous malformations. However, routine MRI brain may be unremarkable, particularly in some forms of malformations of cortical development MSD [4,5]. The presence of HS or another epileptogenic lesion on the MRI brain with concordance of the lesion and the EEG data has positive predictive value for successful epilepsy surgery while non lesional MRI brain or the presence of MRI brain lesions not concordant with the EEG data has negative predictive value of seizure control outcome after epilepsy surgery [8]. Therefore, we decided to revise the patterns of brain lesions in MRI brain of patients with medically refractory seizures admitted to the epilepsy monitoring unit at PSMMC for pre-surgical evaluation for epilepsy surgery with correlation of the lesion with the epilepsy surgery outcome to recognize common MRI lesions in our patients with refractory epilepsy and to compare our local data with the international literature.

### Materials and Methods

245 patients (100 Males and 145 Females; aged 14-53 years) with refractory epilepsy were included in this retrospective analysis. They presented with partial with or without complex partial seizures 112 (46.0%), partial with secondary generalized tonic clonic seizures 76 (31.0%) or generalized seizures in 57 (23.0%) of patients (Table 1). Clinical diagnosis of epilepsy and seizure classification were based on the revised criteria of the International League Against Epilepsy ILAE [2]. Neuroimaging of the brain that includes structural neuroimaging MRI brain in all patients and functional neuroimaging when indicated and includes Interictal Fluorodeoxyglucose Positron Emission Computed Tomography FDG-PET, Ictal and interictal Technetium-99 m hexamethyl-propylene amine oxime Single Photon Emission Computed Tomography 99 m HMPAO SPECT, EEG recording, epilepsy history and neurological examination were performed. MRI brain epilepsy protocol used a 1.5 or 3 Tesla MRI scanner. The MRI brain epilepsy protocol included the temporal lobes and the entire brain from nasion to inion, T1-weighted magnetization prepared rapid gradient echo MPRAGE or spoiled gradient recalled SPGR images 1.5-mm slice thickness with no intervening gap obtained in the coronal oblique plane to enhance gray/white matter differentiation, which was essential for analysis of cortical architecture. The images were acquired as a 3-dimensional 3D volume to allow appropriate postprocessing to correct any head misalignment and to reformat images into multiple planes to evaluate any subtle malformation of cortical development MCD. The MRI brain epilepsy protocol also included both coronal and axial fluid-attenuated inversion recovery FLAIR sequences with a 2- to 3-mm slice thickness and a 0- to 1-mm interslice gap. In addition conventional thin-slice 3-mm, T2-weighted, axial and coronal sequence was also obtained. Contrast imaging with Gadolinium was not standard in the MRI brain epilepsy protocol unless the MRI brain showed a mass, a vascular malformation or to visualize leptomeningeal angiomatosis. All patients included in this study received appropriate epilepsy surgery and post-operative seizure control was followed in the epilepsy clinic with six-month post-operative inter ictal EEG, follow up MRI brain after epilepsy surgery performed in all patients and 50 patients had additional video-EEG recording post operatively during the follow up period. Epilepsy surgery
seizure outcome was classified according to Engel Classification system that is; Class I: Seizure freedom with or without persisting seizure aura or non-disabling seizures, Class II rare disabling seizures, Class III worthwhile seizure improvement and Class IV no worthwhile seizure improvement [9]. All patients were followed for at least two years post-operatively to assess seizure control (Table 1). Pre-operative MRI brain diagnosis was correlated with the epilepsy surgery seizure outcome. Statistical analysis of the frequency (numbers and percentages) is used in this retrospective study.

**Inclusion criteria**
- Patients above the age of twelve years with intractable epilepsy.

**Table 1** Demographic features and follow up of patients.

| Gender | Age | Pre-operative epilepsy duration | Seizures per month | Pre-operative AEDs trials | Seizure type N (%) | Post-operative Follow up |
|--------|-----|---------------------------------|-------------------|--------------------------|-------------------|-------------------------|
| Males 100 | 14 -53 years | 1-10 years | 5-20 seizures/month | 3-7 AEDs | P. ± CPS, 112 (46%) P. with GTCS 76 (31%) GTCS 57 (23%) | 2-7 years |
| Females 145 | | | | | |

P.: Partial Seizure; CPS: Complex Partial Seizure; GTCS: Generalized Tonic Clonic Seizure

**Results**

The MRI brain detected different structural brain abnormalities in 245 (100%) patients. Temporal lobe lesions occurred in 142 (58%) patients, frontal lobe lesions in 74 (30%) patients and parieto-occipital lobes lesions in 29 (12%) patients (Figure 1). A variety of etiologies were identified. HS in 86 (35%) patients, cerebral tumors in 74 (30%) patients, malformations of cortical development MCD in 42 (17%) patients, vascular malformations in 15 (6%) patients, dual pathologies that is the coexistence HS with another lesion type in 12 (5%) patients and remote gliotic lesions in 16 (7%) patients (Figure 2).

![Figure 1](image1.png)

Figure 1 Temporal lobe in 142 (58%) patients, frontal lobe in 74 (30%) patients and parieto-occipital lobes in 29 (12%) patients.

MRI brain examples from our cases are illustrated in Figure 3. HS was diagnosed on MRI brain with reduced hippocampal volume: hippocampal atrophy, increased T2 and FLAIR signal and disrupted anatomical morphology of the hippocampal structures with loss of internal architecture that is; the normal interdigitations of hippocampus, dentate gyrus and stratum radiata a thin layer of white matter that separates the dentate nucleus from the Ammon horn (Figure 3a), cerebral tumors commonly located in the cerebral cortex and most common tumor was ganglioglioma a glio-neural tumor that appeared on MRI brain as a cystic mass with enhancing mural nodule (Figure 3b) or an entirely solid enhancing mass, malformations of cortical development MCD that appeared on MRI brain as a mass or as cortical or subcortical hyperintensities seen on T2 and FLAIR-images with blurred interface between grey and white matter (Figure 3c), vascular malformations with cavernoma as the most common vascular malformation seen in our patients. The cavernoma appeared best on brain MRI T2 weighted image T2WI and T2* gradient echo sequences. The T2WI showed the cavernoma as a popcorn ball with locules of variable size that contain blood products in different stages of evolution which produced the popcorn appearance with a hemosiderin rim surrounding the lesion. The cavernoma appeared almost completely black on the gradient echo due to blooming artefacts (Figure 3d), dual pathologies that is; HS with other lesions such as a cavernoma, small tumor, gliosis or MCD (Figure 3e) and remote gliotic lesions (Figure 3f). The histopathological diagnosis confirmed the MRI brain diagnosis in all included patients. After appropriate epilepsy surgery with adequate brain resection Engel Class I outcome is achieved in 196 (80%) patients, Engel Class II in 37 (15%) patients, Engel Class III in 6 (3%) patients and Class IV in 6(3%) patients (Figure 4). In class IV group one patient failed epilepsy surgery because he had high grade astrocytoma with post-operative
tumor recurrence and one patient failed epilepsy surgery due to incomplete resection of gliotic lesion in the primary hand area. The MRI diagnosis was correlated with epilepsy surgery seizure control outcome with Engel Class I outcome achieved predominantly in patients with HS in 82 out of 86 (95%) patients, low grade tumor in 59 out of 74 (80%) patients and vascular malformations in 12 out of 15 (80%) patients. Patients with high grade tumors 2 of 3 (67%) patients and patients with incomplete surgical resection of epileptogenic lesions 4 out of 5 (80%) patients had the worst epilepsy surgery outcome that is; Engel Class IV (Figure 5).

Figure 2 Hippocampal sclerosis HS in 86 (35%) patients, cerebral tumors in 74 (30%) patients, malformations of cortical development MCD in 42 (17%) patients, vascular malformations in 15 (6%) patients, dual pathologies in 12 (5%) patients and remote gliotic lesions in 16 (7%) patients.

Figure 3a Preoperative coronal FLAIR image with right Hippocampal Sclerosis HS: hippocampal atrophy, increased signal and disrupted anatomical morphology of the hippocampal structures with loss of internal architecture that is; the normal interdigitations of hippocampus, dentate gyrus and stratum radiata a thin layer of white matter that separates the dentate nucleus from the Ammon horn and post-operative coronal T2WI shows right temporal lobectomy with extensive mesial and lateral resection (white arrows).

Figure 3b Preoperative axial FLAIR image showing right parasagittal Ganglioglioma: Swelling in the right mesial frontal cortex with bright signal and small cystic component and faint enhancing nodule on axial T1 weighted image with Contrast +C. The post-operative axial FLAIR shows complete resection of the ganglioglioma (white arrows).

Figure 3c Preoperative axial FLAIR image shows right frontal para sagittal swelling with bright signal and coronal 3D SPGR shows right frontal para sagittal blurred grey white matter interface consistent with FCD. Post-operative axial T2WI shows complete resection of the FCD (white arrows).

Figure 3d Preoperative axial T2* gradient echo image shows left temporal cavernoma as a popcorn ball with locules of variable size that contain blood products in different stages of evolution. The cavernoma appeared almost completely black on the T2* gradient echo due to blooming artefacts. Post-operative axial FLAIR image shows complete resection of the cavernoma and the surrounding brain tissue (white arrows).
Discussion

MRI brain is considered as an integral diagnostic tool in the evaluation of individuals with medically refractory focal seizures being considered for surgical treatment [1-3]. Often refractory epilepsy is associated with a structural brain lesion which could be of various etiologies [1]. Most common acquired epileptogenic lesions include HS, stroke, trauma, tumor or infection and genetic disorders include tuberous-sclerosis, malformations of cortical development MSD, and vascular malformations such as cavernoma or arteriovenous malformations [1]. There is a strong evidence that preoperative MRI identified HS concordant with the seizure origin in the temporal lobe is a significant factor associated with a favorable epilepsy surgery outcome [8,10]. In consistence with the international MRI literature of HS the basic MRI features seen in our patients include reduced volume of hippocampus, alteration of inner architectural structure, as well as increased signal intensity of hippocampus on T2 weighted and FLAIR images [1,10].

Studies have shown that in HS amygdala atrophy can also be present and volumetric imaging is a useful additional MRI tool in refractory epilepsy with HS because it allows a quantitative analysis of the degree of damage to the hippocampi, as well as the lateralization of the affected lobe in MRI brain with subtle changes [11]. Other common pathological findings in individuals with intractable epilepsy include, vascular malformations, low-grade glial tumors and malformations of cortical development MCD [12]. The high diagnostic yield of MRI brain epilepsy protocol to identify those epileptogenic pathologies has been demonstrated [12]. In general, focal epilepsies can be practically divided into mesial temporal lobe epilepsies and neocortical epilepsies [12]. In the neocortical epilepsies neocortical lesions such as vascular malformations, low-grade glial neoplasms and malformations of cortical development MCD, post-traumatic and post ischemic lesions and inflammatory infectious scars, are more common and MCD such as focal cortical dysplasia FCD deserves especial attention because those lesions can be missed on routine MRI brain [13]. The MCD on MRI brain can appear as a mass or as a cortical or subcortical hyperintensities especially seen on T2 and FLAIR-images with blurred interface between grey and white matter [13]. The MRI changes can be subtle and at times the MRI brain fails to show the FCD [12,13].

Ideal MRI brain epilepsy protocol should result in excellent spatial resolution and contrast of the MRI images in a short time however this is a difficult goal due to limitations of the physical principles of MRI. The images must include T1- and T2-weighted sequences covering the entire brain in at least two orthogonal planes, with minimum thickness allowed on the 1.5 or the 3 Tesla MRI machines [2]. Contrast injection with Gadolinium is not routinely necessary except if a tumor or inflammatory lesion is suspected [2]. The optimum MRI brain in patients with focal epilepsy should include a volumetric acquisition 3D with thin sections of less than 2 mm thickness to enable reformatting of images when necessary for better evaluation of patients with subtle structural lesions, such as FCD [11]. The sensitivity of MRI brain epilepsy protocol in

**Figure 3e** Preoperative coronal FLAIR image shows right temporal dual pathologies with right HS and right smaller temporal pole in comparison to the left with right temporal pole bright signal and blurred grey white matter interface consistent with FCD. The post-operative axial CT scan brain image shows extensive right temporal resection (white arrows).

**Figure 3f** Preoperative axial FLAIR image shows right frontal lateral atrophy with bright signals consistent with remote gliosis. Post-operative axial CT scan brain image shows extensive right frontal resection (white arrows).

**Figure 4** Post epilepsy surgery seizure control outcome at 2 years of follow up.

**Figure 5** MRI diagnosis correlation with epilepsy surgery seizure control outcome.
identifying epileptogenic lesions in medically refractory epilepsies has been reported to be more than 80% [5]. The MRI sensitivity depends on the pathologic substrate, applied techniques, and the experience of the radiologist [5]. MRI-negative epileptic patients have less chance of epilepsy surgery than those with MRI-demonstrated lesions and when epilepsy surgery is performed seizure freedom is two to three times lower than in the presence of a lesion on histopathology or MRI brain [14]. Recently many of MRI-negative cases have been shown to demonstrate subtle changes using high resolution MRI brain [15]. In MRI negative epilepsy, multimodal imaging techniques should be considered to localize epileptogenic lesions adequately. Among the multimodal imaging, interictal fluorodeoxyglucose positron emission tomography FDG-PET, ictal single-photon emission computed tomography SPECT, ictal/interictal subtraction of SPECT scans, PET/MRI co-registration, multiplanar reconstruction, and curvilinear reformatting [16]. These modalities represent noninvasive methodology to evaluate patients with focal epilepsy however intracranial EEG remains the gold standard for ictal data in guiding resection in patients with MRI negative epilepsy or with bitemporal or multi lobar pathology [16,17].

The pattern of MRI brain lesions seen in our reported patients is limited as it includes only adult patients with lesional epilepsy therefore congenital lesions such as tuberous sclerosis, Sturge Weber syndrome and neuro-cutaneous lesions which are more common in pediatric epilepsy not seen and patients with MRI brain negative epilepsy not included. Outcome of epilepsy surgery is influenced by several factors [18]. Uni-temporal MR brain abnormalities, early onset of epilepsy, and seizure-type predominance are factors associated with good postoperative outcome [18]. Although there is variation in the methodology of estimating long term epilepsy surgery outcome among published reports, consistent patterns of results show that the long-term epilepsy surgery outcome of five or more years seizure freedom rate following temporal lobe epilepsy surgery was as good as the established excellent short-term results of epilepsy surgery and outcome at one year after surgery can predict the long-term outcome after temporal lobe epilepsy surgery [19,20]. On the other hand, long-term seizure freedom was consistently lower after extratemporal surgery and palliative procedures [20].

Available data suggest that long-term seizure control can be achieved in over 80% of patients with mesial temporal lobe epilepsy and neocortical epilepsy associated with type 2 FCD and in up to two-thirds of patients with extratemporal lobe epilepsy [21]. Consistent published data on the positive and strong predictors of seizure remission after epilepsy surgery outcome include history of febrile seizures, HS, tumors and abnormal MRI with EEG/MRI concordance and extensive surgical resection [21]. On the other hand, post-operative discharges negative MRI brain and the need for intracranial EEG monitoring predicted an unfavorable prognosis of epilepsy surgery [8,22]. Our results are consistent with the international reported literature.

**Conclusion**

This study revealed that refractory epilepsy is commonly associated with structural lesions on MRI brain and confirmed the role of high resolution MRI brain epilepsy protocol in detection of subtle lesions. Temporal lobe structural brain lesions were the most common lesions in adult epilepsy patients with refractory epilepsy referred for epilepsy surgery. The presence of HS, low grade tumors and vascular malformations was correlated with best surgical outcome. High grade tumors and incomplete surgical resection of the lesions were associated with worst surgical outcome. Our results are consistent with the international reported literature.

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