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Review

Unexpected brain imaging findings in patients with seizures

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ABSTRACT

New imaging technologies have advanced our ability to localize the epileptogenic zone in patients with epilepsy. As a result of the constant improvement of the image quality, magnetic resonance imaging (MRI) has become the most important ancillary tool in the management of patients with epilepsy. Magnetic resonance imaging for the evaluation of patients with epilepsy should be done using a special temporal lobe protocol and read by physicians experienced with the findings in patients with epilepsy. On the other hand, in the healthy populations, incidental structural brain abnormalities have been reported in 18% of people. Incidental, subtle, or unexpected structural brain abnormalities have also been reported in many patients who were investigated because of having seizures. In the current narrative review, we will discuss some of these instances, where structural brain abnormalities are discovered unexpectedly, are subtle (but important) and/or may be considered as incidental.

1. Introduction

New imaging technologies have advanced our ability to localize the epileptogenic zone in patients with epilepsy. As a result of the constant improvement of the image quality, magnetic resonance (MR) imaging (MRI) has become the most important ancillary tool in the management of patients with epilepsy. In more than 80% of patients with drug-resistant focal epilepsy and 20% of patients with a single unprovoked seizure, brain MRI identifies relevant abnormalities [1–4].

Magnetic resonance imaging for the evaluation of patients with epilepsy should be done using a special temporal lobe protocol and read by physicians experienced with the findings in patients with epilepsy. In one study, sensitivity of "nonexpert" reports of standard MRI for focal lesions was 39%, of "expert" reports of standard MRI was 50%, and of epilepsy dedicated MRI reported by experts was 91%. Dedicated MRI showed focal lesions in 85% of patients with "nonlesional" standard MRI. In particular, hippocampal sclerosis was missed in 86% of cases with standard MRI. Neuropathological findings were predicted correctly in only 22% of "nonexpert" standard MRI reports, but by 89% of dedicated MRI reports [5,6]. Therefore, it is important to have a dedicated epilepsy protocol for brain MRI and similarly, it is important that the MRI is read and interpreted by physicians who are experienced in reviewing MRIs from patients with epilepsy.

On the other hand, in the healthy populations, incidental structural brain abnormalities have been reported in 18% of people [7]. Incidental, subtle or unexpected structural brain abnormalities have also been reported in many patients who were investigated because of having seizures. In the current narrative review, we will discuss some of these instances, where structural brain abnormalities are discovered unexpectedly, are subtle (but important) and/or may be considered as incidental. Table 1 summarizes the unexpected brain imaging findings in patients with various types of seizures.

2. Psychogenic nonepileptic seizures (functional seizures)

Psychogenic nonepileptic seizures (PNES) or functional seizures are relatively common occurrences in epilepsy clinics [8]. This condition is considered to be the most common differential diagnoses of epilepsy; misdiagnosis of these patients is common in daily practice. As a result, patients with PNES are at risk of receiving unnecessary diagnostic procedures and treatments [8]. Pathophysiology of this condition is still

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Table 1
Unexpected brain imaging findings in patients with seizures.

Seizure	Structural abnormalities	Functional abnormalities	EEG-fMRI abnormalities
Psychogenic Nonepileptic Seizures (PNES)	Patients with PNES may have abnormal, but often nonspecific brain MRI findings [10–14].	Patients with PNES may show subtle structural and functional connectivity brain abnormalities [9].	
			Hemodynamic changes
			associated with GSWDs
Idiopathic generalized epilepsies (IGEs)	Structural brain MRI abnormalities are not rare in patients with IGE [15,29,30].	Patients with IGE show changes in functional and structural connectivity between various regions of the brain [21,23,25,26,28,31]	consistently observed in
			the thalamus, as well as
			DMN areas in patients with
			IGE [19,20]
Dual pathology	Dual pathology occurs in 10–30% of adults and in about 50% of children and adolescents with TLE [38]		

DMN: default mode network; EEG–fMRI: electroencephalography–functional magnetic resonance imaging; GSWDs: generalized spike–wave discharges; IGE: idiopathic generalized epilepsy; TLE: temporal lobe epilepsy.

poorly understood, but is seems unlikely that gross structural brain abnormalities can explain the seizures in PNES [9]. However, prior to a definite diagnosis, patients with PNES are often investigated with neuroimaging. In one study, 40% of patients in a large cohort of PNES had a brain MRI, and this was associated with a higher seizure frequency and comorbid epilepsy [10]. In practice, it makes sense and is justifiable to perform a brain MRI in patients with suspected epilepsy, irrespective of whether they turn out to have PNES. In another study of 224 patients with PNES-only, 60% of the patients had brain imaging studies [11].

Some investigations have studied structural brain imaging abnormalities in patients with PNES in an endeavor to better understand the pathophysiology of this condition [12–14]. Compared with the healthy population, no consistent structural brain imaging abnormalities have been identified in previous studies [9,12]. Consistent with many other studies, 36% of the whole cohort of patients with PNES in one study, and 27% of those with PNES-only had abnormal brain MRI findings [10–14]. This may suggest that structural brain abnormalities play a role in the development of PNES. However, these studies had several limitations, including their retrospective design and not including control groups. In addition, common epileptogenic structural brain abnormalities (e.g., tumors, mesial temporal sclerosis, etc.) may frequently be observed in patients with comorbid PNES and epilepsy (19 out of 46 patients; 41%), but these structural brain abnormalities were rarely observed in those with PNES-only (4 out of 86 patients; 5%) [10]. Most of the brain imaging abnormalities in patients with PNES included nonspecific findings (e.g., white matter nonspecific changes or cysts) (Fig. 1).

While there is evidence for a relatively high prevalence of structural brain abnormalities in patients with PNES, multicenter studies are required, which include larger number of patients with a unified methodology of imaging. When designing such studies confounding factors including comorbid psychopathologies have to be considered.

In addition, an association of PNES with organic brain dysfunction appears to be very likely based on the recent evidence of functional and structural brain connectivity abnormalities in these patients [9]. Multiple small studies investigated and showed subtle structural and connectivity brain abnormalities (e.g., voxel-based morphometry, cortical thickness analysis, cortical surface area, connectivity characteristics, white matter diffusion abnormalities, etc.) in patients with PNES. Similarly, multiple functional imaging studies investigated and showed brain connectivity abnormalities in these patients. It is likely that abnormal brain connectivity in these patients provides a neurobiological correlate for the underlying mechanisms, where emotions can influence executive control, resulting in altered motor function and seizures [9].

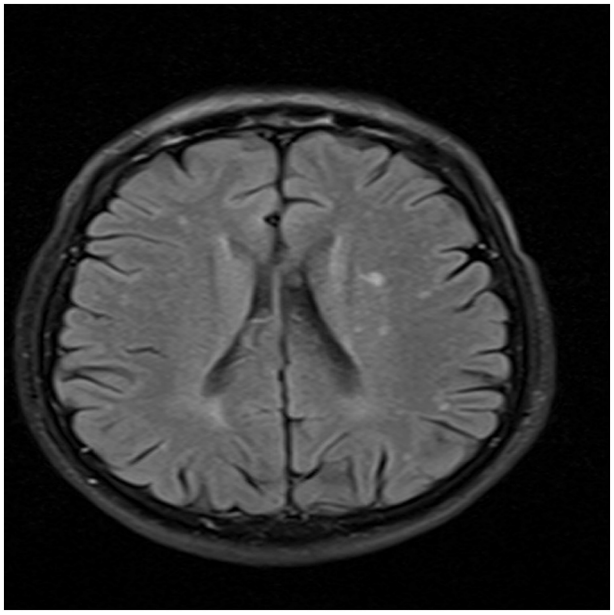

Fig. 1. White matter nonspecific changes in a patient with psychogenic nonepileptic seizures (PNES).

3. Idiopathic generalized epilepsies (IGEs)

Idiopathic (genetic) generalized epilepsies (IGEs) are epilepsy syndromes diagnosed by strict clinical and electroencephalographic (EEG) features that are proposed by the International League Against Epilepsy (ILAE) [15]. Idiopathic (genetic) generalized epilepsies are considered to be genetic in nature and are deemed not to be associated with gross structural brain abnormalities. However, brain MRI abnormalities are not rare in patients with IGE [15]. On the other hand, epilepsy can be conceptualized as a disorder involving brain networks, rather than

single sources of pathology in the human brain. Findings from several imaging modality studies indicate that IGEs affect widespread areas of the brain through specific subcortical and cortical networks [16–18]. Here, we summarize the subcortical and cortical imaging abnormalities which have been reported in IGE.

3.1. Thalamus

The thalamus and a complex, reciprocal thalamocortical network are critically important in certain generalized seizures. Simultaneous EEG–fMRI studies found that hemodynamic changes associated with generalized spike–wave discharges (GSWDs) have been consistently observed in the thalamus, as well as default mode network (DMN) areas [19,20]. There is compelling evidence that dysfunction in the corticothalamic circuitry contributes to the pathogenesis of generalized seizures [16–18,21]. A recent resting-state functional MRI study examined 97 IGE patients and found increased functional connectivity in 4 corticothalamic networks compared with controls: 1) prefrontalthalamic network; 2) motor/premotor-thalamic networks; 3) parietal/ occipital-thalamic networks; 4) temporal-thalamic network.

Decreased control over the highly excitable motor network may also underlie the behavioral symptoms of seizures such as myoclonic jerks.

3.2. Default mode network

The default mode network composes of precuneus/posterior cingulate cortex, medial prefrontal cortex, lateral parietal cortex and inferior temporal cortex, and plays an important role in self-referential activities, including evaluating salience of internal and external cues, remembering the past, and planning the future. DMN regions in cortex are functionally and structurally connected to thalamus and it is believed that the DMN is involved in the generation of the GSWDs since deactivation in the default mode areas along with a thalamic activation was consistently found in EEG-fMRI studies [19,20].

3.3. Basal ganglia

The basal ganglia, a set of brain structures related to motor control, is proposed to be implicated in the modulation of epileptic discharges generalization in patients with IGE. Modulation enhanced the integration in basal ganglia networks of patients, and modulation was stronger in patients with than without GSWDs, suggesting that basal ganglia is implicated in the modulation of epileptic discharges generalization in IGE [22]. Of particular relevance to juvenile myoclonic epilepsy (JME) is the role of basal ganglia in executive and attentional function. The disruption of functional and structural connectivity in the basal ganglia to the superior frontal and supplementary motor area (SMA) regions was found in patients with JME, which are associated with changes in executive behavior and implicated as anatomical correlates of myoclonus in patients with JME [23]. These alterations of basal ganglia–thalamo–cortical loop implicate specific basal ganglia networks dysfunction in patients with IGE.

3.4. Frontal lobe

Idiopathic generalized epilepsy is typically associated with normal intelligence, but many patients exhibit specific, frontal-lobe cognitive deficits [24]. The presence of specific hypo- and hyper-connectivity in frontal areas indicated that IGE does not homogeneously affect the entire brain, and the frontal lobe might be the epicenter of the effects of IGEs [25–27]. Vollmar et al. demonstrated changes in functional and structural connectivity between the SMA and motor cortex during a working memory task [25,26]. Precipitation of myoclonic jerks by cognitive tasks is a known clinical feature in some patients with JME; the increased functional connectivity (FC) between the SMA and prefrontal cognitive areas and the motor system was interpreted as possible mechanism for seizures triggered by cognitive effort. Regions of cortical hyper-excitability may overlap with areas physiologically activated during cognitive or motor activities. Hence, a complex task involving several functional cortical systems may summon a "critical mass of cortex activated", which leads to seizure precipitation. The abnormal motor cortex coactivation during a working memory task may represent the functional correlate of this mechanism [25–27]. Szaflarski et al. found greater spike-related activation of paracingulate cortex in an EEG–fMRI study in patients with valproate-unresponsive IGE versus patients with valproate-responsive IGE [27]. A further study found a positive correlation between paracingulate FC and GSWD frequency in frontal regions related to attention and execution functions as well as precentral gyrus. This might indicate an increased crosstalk between motor, default mode, and executive networks in patients with frequent GSWDs, suggesting differences in paracingulate connectivity are associated with frequent GSWDs and uncontrolled seizures in IGE [28].

3.5. Temporal lobe

Temporal lobe functions are less well characterized in JME. Abnormal cortical thickness measures as well as disrupted maturation patterns have been reported in patients with new-onset JME for temporal lobe areas [29]. Caciagli and colleagues [30] detect increased motor system activation not only during increasing cognitive load, but also during a less demanding memory encoding task, which involved simple hand movements. Unilateral or bilateral hippocampal malrotation was identified in 51% of patients and 50% of siblings, against 15% of controls ($p < .05$) (Fig. 2). Subgroup analyses indicated distinct profiles of

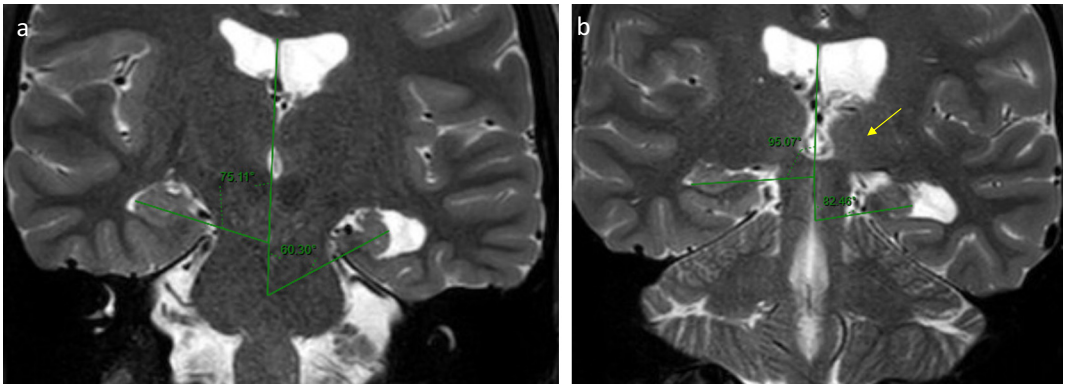

Fig. 2. a,b: 20- year-old male with nocturnal complex-partial seizures: hippocampal malrotation and mild left hippocampal hypoplasia. Hippocampal infolding angle (HIA) – defined as a line connecting the medial superior margin of the subiculum with the lateral margin of the cornu ammonis and the vertical midline of the cerebral hemisphere measured at the level of the cerebral peduncle (a) is 75° (normal) on the right and indicates marked malrotation by a HIA of 60° on the left; at the level of the superior cerebellar peduncle (b) normal value of the HIA on the right with 95° and marked malrotation (HIA 82°) on the left. Note enlarged lateral ventricle and smaller left thalamic volume (arrow).

hypoactivation along the hippocampal long axis in patients with JME with and without malrotation, and a more prominent role of the left posterior hippocampus for visual memory in patients with malrotation [30].

3.6. Cerebellum

The cerebellum shares reciprocal connections with thalamus, cortex, and basal ganglia through which it could, theoretically, modulate ictogenic activity throughout the brain [22]. Although, the cerebellum is not thought to be a primary cause of ictogenesis in IGE, both structural and functional neuroimaging studies showed loss of cerebellar connectivity with thalamus, basal ganglia, and cortex [28,31], and reduced cerebellar FC is associated with frequent discharges and often related to resistance to treatment [28]. These findings suggest that cerebellum could be a modulator of ictogenic circuits.

In conclusion, while patients with IGE are considered to have normal brain imaging studies, precise and detailed imaging techniques may provide sensitive methods of elucidating the underlying pathological mechanisms involved in IGEs.

4. Dual pathology in patients with temporal lobe epilepsy (TLE)

Temporal lobe epilepsy (TLE) is the most common type of focal epilepsy (40–60%) and hippocampal sclerosis (HS) accounts for the principle underlying pathology in TLE [32]. However, if HS is identified in a patient with TLE, this does not mean that HS is necessarily the only epileptogenic structural brain abnormality (Figs. 3 and 4). Dual pathology is defined as coexistence of HS and an extrahippocampal neocortical lesion with histopathological confirmation of an additional significant pathology [32]. Recognition of HS by brain MRI and identification of an extrahippocampal lesion has contributed to increased notification of dual pathology in patients with TLE [33]. Magnetic resonance imaging enables detection of HS as the hallmark of dual pathology in vivo by a dedicated protocol [34]. The degree of T2 and fluid-attenuated inversion

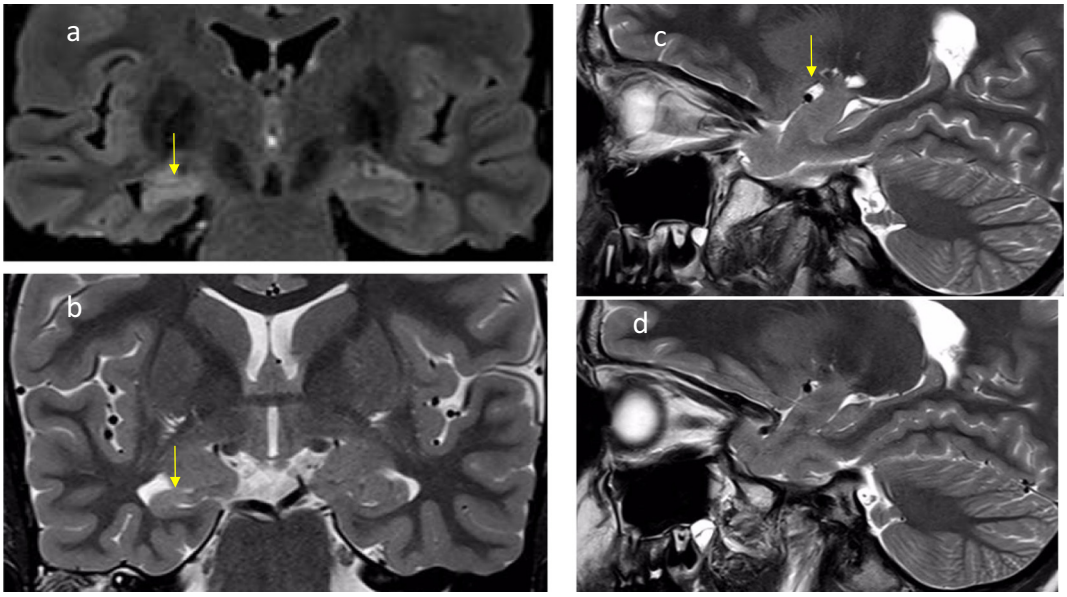

Fig. 3. a–d: Mesial temporal lobe Epilepsy with hippocampal sclerosis, amygdala and temporal lobe volume reduction in a 10-year-old boy. Coronal FLAIR (a), and T2 w (b) images through hippocampus (b), sagittal T2 w slice through right (c) and left (d) hippocampus and amygdala. Marked gliosis of cornu ammonis (a) with atrophy of pes hippocampi and loss of interdigitations (b). Generalized atrophy of temporal lobe volume as evidenced by position of sylvian fissure and amygdala volume loss indicated by width of choroid fissure are additional findings present in 50% and 20% of patients with mesial temporal lobe sclerosis respectively.

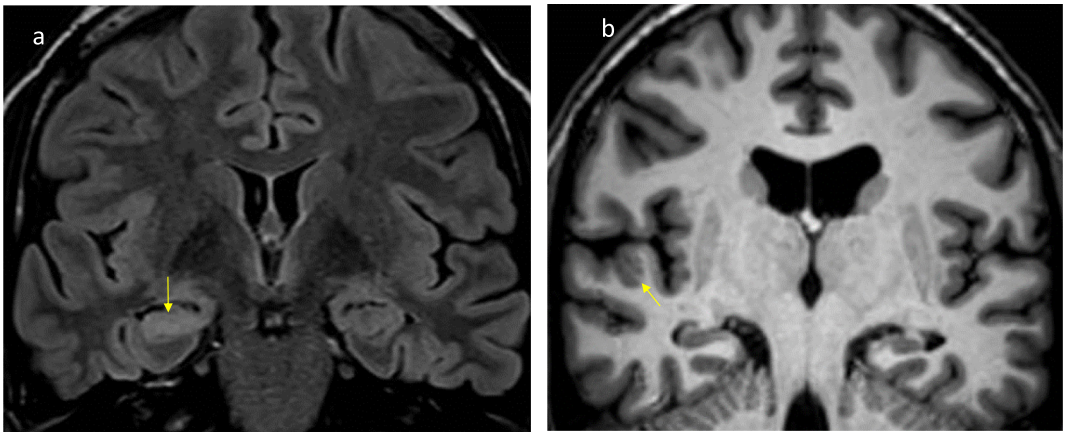

Fig. 4. a,b. Dual pathology with mesial temporal sclerosis and localized perisylvian polymicrigyria in a 32 year old female. Coronal FLAIR (a), and T1 Inversion recovery image (b) through hippocampus. Marked signal increase in right hippocampus indicating gliosis with only subtle atrophy (a). Dual pathology is visualized by a localized area of undulated polymicrogyric thinned cortex with white matter digitations and fused surface layer representing localized polymicrogyria (b).

recovery (FLAIR) signal change and atrophy serve as surrogate markers of pyramidal cell loss and gliosis in the hippocampus and dentate gyrus. In comparison to histology, HS is identified by MRI based on visual identification of atrophy in 76% of patients [35] and increased hippocampal signal in 82% [36]. Quantitative MRI increases the accuracy for seizure lateralization to 88% by applying intracranial volume adjusted hippocampal measurements. The rate was found to rise to 94% when asymmetry of hippocampal volume is used as a classifier for seizure lateralization [35]. In another study based on retrospective analysis of 125 patients with HS, hippocampal volumetry provided an accuracy of 95% compared to a normative control series. Specificity increased to 99% when volumetry and T2 signal analysis (relaxometry) were combined [36].

Identification of the neocortical component of a dual pathology by imaging is often a challenge. Refinements in structural MRI by 3-T high field MR, voxel-based morphometry and new sequences such as SWI (susceptibility weighted imaging), MP2RAGE (magnetization-prepared two rapid acquisition gradient echoes), and DIR (double inversion recovery) have aided to increasingly identify extrahippocampal components of dual pathology. An alternative MR approach to voxel based morphometry is quantitative measurement of longitudinal relaxation (qT1). Longitudinal relaxation provides an in "vivo proxy" for altered cortical microstructure rather than cortical geometry. This quantitative technique correctly lateralized the seizure focus in 92% of 24 patients, displayed a gradient from upper cortical levels that tapered off toward the gray/white matter interface and identified subfield hippocampal abnormalities [37].

Dual pathology is expected to occur in 10–30% of adult patients with TLE. In the pediatric and adolescent age group dual pathology accounts for about 50% of TLE and due to preferential selection for resection has a significantly higher incidence of 58–76% in surgical series [38]. The most common extrahippocampal components in dual pathology detected by neuroimaging and neuropathology consist of malformations of cortical development- focal cortical dysplasia in particular, followed by tumors (e.g., ganglioglioma), vascular malformations (e.g., cavernoma), and gliotic scars as sequelae of trauma, infarct, or infection [32]. While the temporal lobe is the prevailing site of the additional lesion in patients with dual pathology extratemporal locations may rarely be causative as well [32]. Key points in the presurgical MRI evaluation of patients with drug-resistant TLE therefore are recognition of the hippocampal lesion plus identification of the presence and the extent of an additional cortical pathology.

In temporal lobe dual pathology, epileptic activity may be generated by the neocortical lesion, mesial temporal lesion, or both [39]. To elucidate the causal relationship between the lesions defined by MRI and the source of epilepsy careful electroclinical evaluation and even sometimes intracranial EEG recordings may be required. In particular, extratemporal lesions identified by MRI in patients with TLE require very careful electroclinical correlation in order not to mislead the indication for surgery and/or the extent of resective intervention [40].

In conclusion, MRI by structural and quantitative assessment techniques contributes to increasingly turning "cryptogenic focal" epilepsies into lesional epilepsies; MRI identification of dual pathology has significant electroclinical diagnostic implications and therapeutic consequences with respect to the type and extent of resective epilepsy surgery. These implications reinforce the necessity for application of the most advanced MRI techniques and also a close interdisciplinary collaboration by neuroradiologists, epileptologists, neurosurgeons, and neuropathologists in order to achieve good results in patients with drug-resistant epilepsy, who are undergoing presurgical evaluation and epilepsy surgery.

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Author contributions

All authors were involved in the conception, design, review process and preparing the manuscript. All have approved this final version and all authors agree to be accountable for all aspects of the work.

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