■ ILAE Neuroimaging Task Force Highlight

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Epileptic Disorders

Imaging characteristics of temporopolar blurring in the context of hippocampal sclerosis

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ABSTRACT

We present an illustrative case to address anterior temporal lobe atrophy with poor delineation of the temporopolar gray-white matter interface based on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in patients with temporal lobe epilepsy associated with hippocampal sclerosis (TLE-HS). A 52-year-old woman with pharmacoresistant seizures since the age of six months underwent a previous MRI scan using a suboptimal protocol which was reported as unremarkable. MRI performed according to an epilepsy protocol showed classic signs of left HS and ipsilateral temporal polar atrophy with blurring of the gray-white matter boundary on FLAIR images. She underwent a left amygdalohippocampectomy and anterior temporal resection and remains seizure-free after 24 months. Histopathological analyses showed HS and no signs of focal cortical dysplasia (FCD). Blurring and atrophy of the ipsilateral temporal pole are common in TLE-HS and often misinterpreted as FCD. This relates to delayed myelination in patients with seizures before the age of two, is more pronounced on FLAIR sequences, and gives a false impression of cortical thickening. However, the T1-weighted images show a relatively well-demarcated cortical-subcortical transition and normal cortical thickness. By contrast, the cortical thickening in FCD is observed on both T1-weighted and FLAIR images. Since FCD also occurs in temporal lobe regions, it is important to differentiate the extra-hippocampal MRI abnormalities in TLE-HS from those likely to be FCD. This case highlights the importance of evaluation based on detailed imaging, which should always be conducted considering the EEG, seizure semiology, and other clinical information.

Key words: hippocampal sclerosis, temporal pole blurring, temporal lobe epilepsy, MRI

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Case study

A 52-year-old woman with a history of pharmacoresistant seizures since the age of six months was admitted for presurgical evaluation. Her seizures were stereotypical and characterized by a subjective sensation of "difficult to describe" non-specific aura. She also reported episodes of ascending epigastric sensation, followed by impaired awareness, oro-alimentary ictal automatism, and head deviation to the left side. She had bilateral hand automatism and postictal nose-wiping with the left hand. Occasionally, she would collapse, with semiology evolving to asymmetric clonic jerking, then to a bilateral tonic-clonic seizure. Following the seizures, she was confused and tired. The focal seizures with impaired awareness occurred daily or several times per week.

Her antiseizure medications included levetiracetam at 1,000 mg bid, oxcarbazepine at 600 mg bid, and clobazam at 10 mg QD. She previously tried phenobarbital, phenytoin, carbamazepine, lacosamide, valproic acid, clonazepam, and topiramate without success. Her birth and development were normal, and she had remarkable personal history for prolonged febrile seizure in early childhood.

Preadmission investigation from another center included three routine EEGs with frequent interictal spikes and sharp waves over the left anterior temporal region were reported. One MRI scan performed six years earlier in another department, with suboptimal quality and without thin coronal cuts, was reported as unremarkable. Based on a second MRI scan, abnormal T2-weighted and fluid-attenuated inversion recovery (FLAIR) signal in the left temporal pole was reported.

Course in hospital

A focused review of MRI, performed using the harmonized neuroimaging of epilepsy structural sequences (HARNESS-MRI) protocol [1], guided by the patient's semiology, revealed signs of left hippocampal sclerosis (HS) [2], atrophy of the anterior temporal lobe, and an increased FLAIR signal in the temporal pole white matter associated with blurring of the gray-white matter interface and apparent increased cortical thickness (*figure 1*). The T1-weighted images, however, showed only a mild signal change in the temporal pole white matter, a clear demarcation between the gray and white matter, and normal cortical thickness (*figure 1*).

Interictal EEG showed intermittent slowing predominantly in the medial-anterior left temporal lobe, sometimes temporal intermittent rhythmic delta activity (TIRDA), and sharp waves typically maximum in anterior temporal electrodes (*figure 2*). In three of her habitual focal impaired awareness seizures, lateralizing signs (early head and eye left deviation and postictal nose-wiping performed with the left hand) were evident during scalp video-EEG monitoring. The EEG seizure onset was in the left medial temporal region, maximum at F7-T3 (*figure 2*).

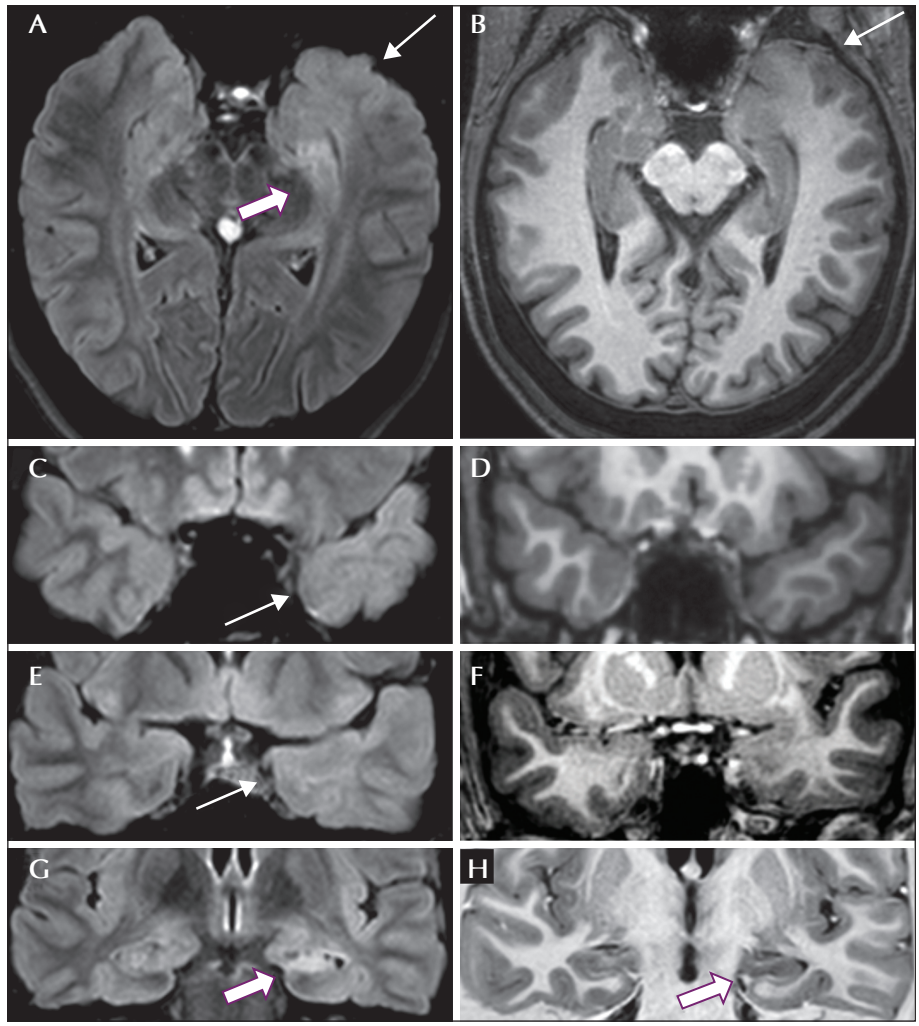
Ictal single-photon emission computed tomography (SPECT), performed during video-EEG monitoring, showed marked hyperperfusion in the temporal lobe, insula, and basal ganglia in the left hemisphere (*supplementary figure 1*).

She underwent a left amygdalohippocampectomy and anterior temporal lobe resection. The histopathology showed HS ILAE type 1 [3]. The anterior temporal lobe had a preserved cortical architecture and no histopathological changes of focal cortical dysplasia (FCD) (*figure 3*). She remains seizure-free 24 months after surgery (Engel Class IA).

Discussion

This case highlights the importance of acquiring high-resolution thin coronal MRI perpendicular to the long axis of the hippocampi, along with 3D T1-weighted and FLAIR images in patients with focal epilepsies, mainly in those with semiology consistent with temporal lobe seizures [1].

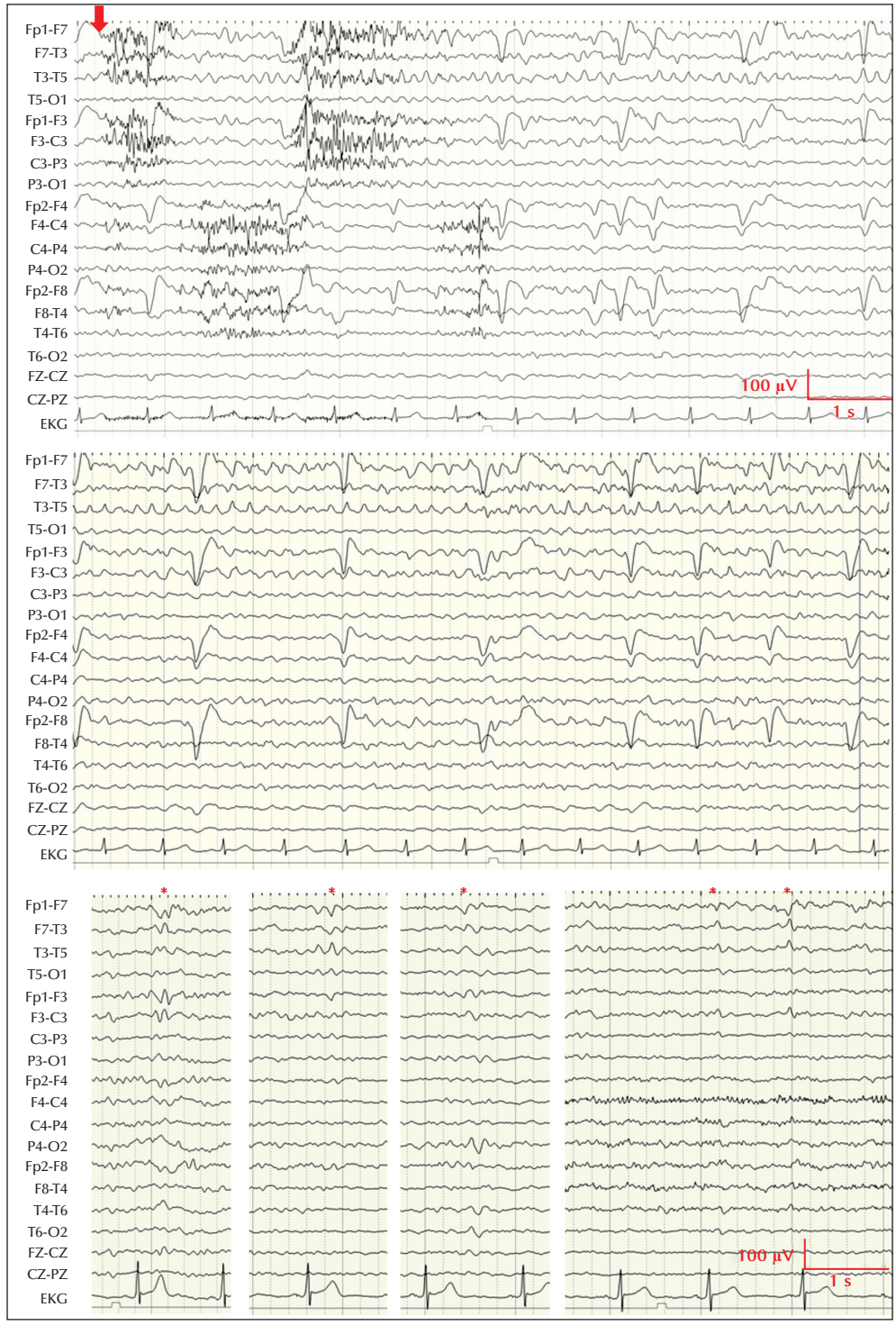
MRI should always be reviewed in light of the clinical and EEG findings [1, 4]. Although our patient had long-standing pharmacoresistant seizures, a suboptimal MRI in another service was reported as normal, and surgery was, unfortunately, not considered earlier. Despite



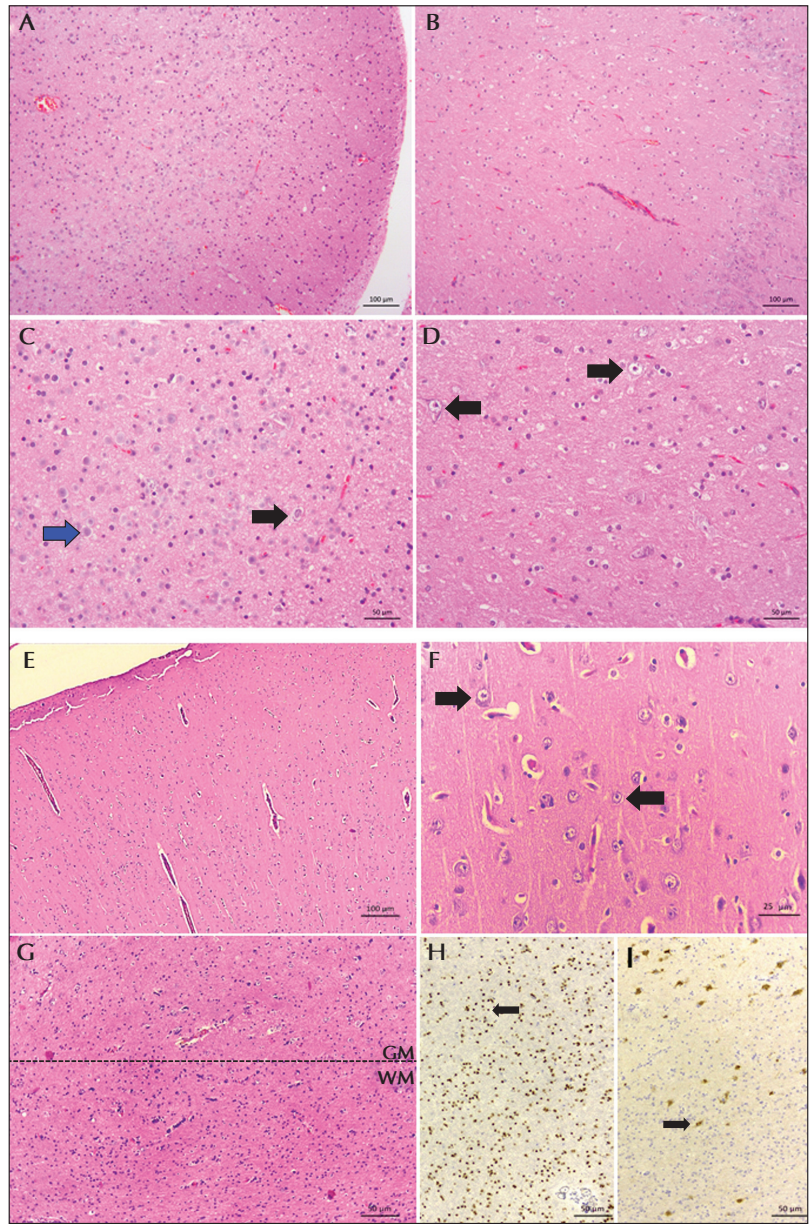
■ **Figure 1.** Left hippocampal sclerosis and ipsilateral temporopolar blurring. (A) Axial FLAIR showing hyperintense signal in the hippocampal head (arrow) and ipsilateral temporal pole atrophy with blurring of the transition between gray matter and white matter and hyperintense signal in the white matter (white arrow), also seen on coronal FLAIR images in (C) and (E). (B) Axial T1-weighted image shows discreet changes in the white matter signal with preserved cortical thickness in the temporal pole, also demonstrated on coronal T1-weighted images in (D) and (F). (G) Coronal FLAIR showing left hippocampal atrophy, flattening, and hyperintense signal (arrow). (H) Coronal T1-weighted inversion recovery showing hypointense signal and loss of normal internal hippocampal structure (arrow).

its demonstrated benefits in reducing seizures and improving quality of life, epilepsy surgery remains critically underutilized in patients with pharmacoresistant epilepsy [5, 6]. Potentially eligible patients often have to wait for decades until they receive presurgical investigations at tertiary centers and are eventually offered surgery [7]. Our patient had TLE with seizure onset early in life, with a clear semiology, EEG, and ictal SPECT indicating a left anterior-mesial temporal seizure onset. MRI performed with an optimized protocol showed left hippocampal atrophy associated with hyperintense T2-weighted and FLAIR signal and loss of the internal structure, indicating HS that was confirmed by post-operative histopathological assessment (*figures 1, 3*).

In addition to the signs of HS, the MRI showed atrophy of the anterior temporal lobe with mild hyperintense FLAIR signal and blurring of the gray-white matter boundary in the left temporal pole (*figure 1*). The most likely mechanism for this temporopolar blurring is delayed myelination and arrest of white matter



■ **Figure 2.** EEG findings. The top panel shows the onset of one of the patient's habitual seizures recorded during video-EEG monitoring (red arrow) on longitudinal bipolar montage. Note the muscle artifacts followed by a rhythmic theta-like activity in the left anterior temporal lobe, maximal at F7-T3 (equipotential) which becomes more evident towards the end of the seizure (middle panel). The lower panel shows samples of interictal slow sharp waves with phase reversals at F7 or equipotential between F7-T3. Different montages also showed maximal involvement at the T1 electrode (not shown here). LFF: 0.3 Hz and HFF: 70 Hz.



■ **Figure 3.** Microscopic features of the hippocampal sectors and the anterior temporal lobe. (A-D) Hippocampal sectors CA1 (A, C) and CA4 (B, D) showing neuronal loss and gliosis. C) Higher magnification of the region shown in (A); the black arrow indicates a remaining pyramidal neuron, and the blue arrow indicates one of the corpora amylacea in the gliotic background. (D) Higher magnification of the region shown in (B) (dentate gyrus on the right); the black arrows indicate remaining neurons. (E-I) Microscopic features of the temporal pole; no histopathological changes compatible with focal cortical dysplasia were evident. (E) Low-power magnification highlighting the preserved architecture of the cortex. (F) Higher magnification of the region shown in (E); the neurons (black arrows) show normal cytologic findings (size, shape, and orientation). (G) Blurring of the gray (GM) and white matter (WM) boundary; the dotted line shows the approximate cortical-subcortical transition. Histopathological analyses showed only an increase in oligodendrocytes (mainly in the WM) and a few heterotopic neurons. (H, I) Immunohistochemical markers for the population of cells in the white matter in (G). (H) Olig-2-positive oligodendrocytes (arrow). I) NeuN-positive neurons (arrow). (A-G) H&E stain; (H, I) peroxidase. Scale bars = 100 mm (A, B and E); 50 mm (C, D, G, H and I); 25 mm (F).

development as a consequence of seizures before or near the age of two [8-11]. This imaging feature, frequently seen in TLE-HS, is often interpreted as a focal cortical dysplasia (FCD). Since FCD also occurs in the temporal lobe regions, it is important to differentiate the extra-hippocampal MRI abnormalities in TLE-HS from those likely to be FCD.

In patients with FCD type I, MRI is frequently normal or shows diffuse or localized cerebral atrophy, while the main MRI features of FCD type II are focal cortical thickening and a mild degree of increased cortical signal intensity on T2-weighted and FLAIR sequences, blurring of the gray-white matter junction, focal abnormal cortical gyration, and cerebrospinal fluid cleft-cortical dimple [12]. The presence of hyperintense T2-FLAIR signal in the subcortical white matter with a wedge shape that extends to the ipsilateral ventricle ependymal surface (transmantle sign) indicates FCD type IIb, although not all patients with FCD IIb have a transmantle sign [12]. The cortical thickening in FCD type II, in general, is seen both on T1-weighted and T2-weighted FLAIR images (*see supplementary figure 2*). A closer inspection of our patient's MRI revealed that the blurring of the left temporal pole is pronounced on the FLAIR sequence but not on the T1-weighted images; although there is a subtle signal change in the white matter, the cortical-subcortical transition is relatively well-demarcated (*figure 1*). More importantly, the cortical thickness in the left temporal pole is similar to that of the contralateral hemisphere, which contrasts with an FCD lesion (*compare figure 1 with the lesion shown in supplementary figure 2*). As confirmed by postoperative histopathology, our patient did not have FCD, but anterior temporal lobe abnormalities associated with TLE-HS [8].

The frequency of temporal pole signal abnormalities in TLE varies from 28% up to 66% in retrospective series [9-11, 13]. These abnormalities were always ipsilateral to the atrophic hippocampus and defined as loss of gray-white matter differentiation, associated with abnormal signal on T2, FLAIR, and proton density sequences. The variable frequency of temporal pole abnormalities in TLE among different studies is probably due to different MRI techniques.

Garbelli *et al*. [8] performed postoperative high-field 7T MRI ultrastructural morphological studies. They showed that the temporopolar blurring in TLE-HS patients was associated with degeneration of white matter fibers and correlated with earlier seizure onset, but not with seizure frequency. In their study, postoperative 7T MRI showed a clear border between gray and white matter in patients with temporal blurring on preoperative 1.5T and 3T T2-weighted images, but the signal intensity in the white matter was heterogeneous. The presence of FCD, heterotopic neurons in the white matter, or widespread gliosis were equally distributed in TLE-HS patients with and without temporopolar blurring, which indicates that these histopathological abnormalities do not explain the temporopolar blurring [8]. Furthermore, the presence of temporopolar blurring, as shown in our patient, was not found to correlate with postoperative seizure outcome in patients with TLE-HS [8, 10, 14].

There has been an increasing number of MRI postprocessing methods for aiding diagnosis of epileptogenic lesions, mostly aimed at FCDs. However, it is still unclear which method and MRI sequence are better, given the lack of studies directly comparing the different approaches [15]. In addition, it is still undetermined whether these postprocessing methods will detect temporopolar blurring, but it is reasonable to assume that methods based on T2 relaxometry and diffusion tensor imaging would do better than morphometric approaches using T1-weighted images.

The surgical approach for TLE-HS varies among centers. Some perform selective amygdalohippocampectomy (SAH) routinely, and others an anterior temporal lobe resection (ATL) with varying degrees of cortical resection [7]. Seizure outcome was similar with either SAH or ATL for TLE-HS with temporopolar blurring since the temporal pole is not epileptogenic in these patients [14]. Nowadays, some centers are using laser ablation. If one suspects an FCD in the temporal pole, the surgical approach will perhaps change for those performing selective approaches, but not for those performing anterior temporal resection plus amygdalohippocampectomy.

Altogether, these findings indicate apparent temporal pole cortical thickening in patients with HS, which is due to delayed myelination and arrest of white matter development as a consequence of seizures before or near the age of two, and, at least in part, related to imaging resolution and a partial volume effect of FLAIR images on 1.5 or 3T scans. Higher-resolution T1-weighted images are helpful to differentiate blurring caused by white matter developmental changes from true increased cortical thickness, as demonstrated in the present case report. ■

Supplementary material.
Supplementary figures and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
The authors have nothing to disclose.

References

1. Bernasconi A, Cendes F, Theodore W, Gill RS, Koepp MJ, Hogan RE, *et al*. Recommendations for the use of structural MRI in the care of patients with epilepsy: a consensus report from the ILAE Neuroimaging Task Force. *Epilepsia* 2019; 60: 1054-68.

2. Cendes F, Sakamoto AC, Spreafico R, Bingaman W, Becker AJ. Epilepsies associated with hippocampal sclerosis. *Acta Neuropathol* 2014; 128: 21-37.

3. Blümcke I, Thom M, Aronica E, Armstrong DD, Bartolomei F, Bernasconi A, *et al*. International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. *Epilepsia* 2013; 54: 1315-29.

4. Wang I, Bernasconi A, Bernhardt B, Blumenfeld H, Cendes F, Chinvarun Y, *et al*. MRI essentials in epileptology: a review from the ILAE Imaging Taskforce. *Epileptic Disord* 2020; 22(4): 421-37.

5. Engel Jr J, Wiebe S, French J, Sperling M, Williamson P, Spencer D, *et al*. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology* 2003; 60(4): 538-47.

6. Wiebe S, Blume WT, Girvin JP, Eliasziw M, Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001; 345(5): 311-8.

7. Jobst BC, Cascino GD. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. *JAMA* 2015; 313(3): 285-93.

8. Garbelli R, Milesi G, Medici V, Villani F, Didato G, Deleo F, *et al*. Blurring in patients with temporal lobe epilepsy: clinical, high-field imaging and ultrastructural study. *Brain* 2012; 135: 2337-49.

9. Meiners LC, Witkamp TD, De Kort GAP, Van Huffelen AC, Van Der Graaf Y, Jansen GH, *et al*. Relevance of temporal lobe white matter changes in hippocampal sclerosis: magnetic resonance imaging and histology. *Invest Radiol* 1999; 34: 38-45.

10. Mitchell LA, Jackson GD, Kalnins RM, Saling MM, Fitt GJ, Ashpole RD, *et al*. Anterior temporal abnormality in temporal lobe epilepsy: a quantitative MRI and histopathologic study. *Neurology* 1999; 52: 327-36.

11. Coste S, Ryvlin P, Hermier M, Ostrowsky K, Adeleine P, Froment JC, Mauguière F. Temporopolar changes in temporal lobe epilepsy: a quantitative MRI-based study. *Neurology* 2002; 59: 855-61.

12. Blümcke I, Cendes F, Miyata H, Thom M, Aronica E, Najm I. Towards a refined genotype-phenotype classification scheme for the international consensus classification of Focal Cortical Dysplasia. *Brain Pathol* 2021; 31: e12956.

13. Townsend TN, Bernasconi N, Pike GB, Bernasconi A. Quantitative analysis of temporal lobe white matter T2 relaxation time in temporal lobe epilepsy. *Neuroimage* 2004; 23(1): 318-24.

14. Schijns OE, Bien CG, Majores M, von Lehe M, Urbach H, Becker A, *et al*. Presence of temporal gray-white matter abnormalities does not influence epilepsy surgery outcome in temporal lobe epilepsy with hippocampal sclerosis. *Neurosurgery* 2011; 68: 98-106.

15. Martin P, Bender B, Focke NK. Post-processing of structural MRI for individualized diagnostics. *Quant Imaging Med Surg* 2015; 5: 188-203.

TEST YOURSELF

(1) A 28-year-old woman has pharmaco-resistant seizures characterized by a subjective sensation of non-specific aura which is "difficult to describe", an ascending epigastric sensation followed by impaired awareness and head deviation to the left side, and oroalimentary and bilateral hand ictal automatism followed by postictal nose-wiping with the left hand. Interictal EEG shows left temporal intermittent rhythmic delta activity (TIRDA).
What is the minimum information that should be included in the MRI requisition form?

A. Seizures not yet diagnosed
B. 28-year-old woman with pharmaco-resistant epilepsy.
C. 28-year-old woman with focal impaired awareness seizures, possible temporal lobe onset, side unknown.
D. 28-year-old woman with recurrent seizures, possible left temporal onset.
E. 28-year-old woman with recurrent seizures, possible right temporal onset.

(2) MRI scan performed using the HARNESS protocol, guided by the patient's semiology, revealed signs of left hippocampal sclerosis (HS), atrophy of the anterior temporal lobe and an increased FLAIR signal in the temporal pole white matter associated with blurring of the gray-white matter interface and apparent increased cortical thickness. How can you differentiate whether these findings in the temporal pole are related to a focal cortical dysplasia (FCD) or whether one of the MRI changes is associated with HS?

A. By comparing the cortical-subcortical transition and cortical thickness on 3D T1-weighted and FLAIR images with multiplanar reformatting.
B. By performing hippocampal volumetry.
C. By performing T2 relaxometry
D. By performing another MRI scan, adding MR spectroscopy.
E. By performing FDG-PET.

(3) Typical MRI features of focal cortical dysplasia (FCD) include:

A. MRI of FCD type I is frequently normal or shows diffuse or localized cerebral atrophy.
B. FCD type IIa presents with focal cortical thickening and a mild degree of increased cortical signal intensity on T2-weighted and FLAIR sequences.
C. The transmantle sign, best seen on a T2-FLAIR sequence, indicates FCD type IIb.
D. Cortical thickening in FCD type II is seen both on T1-weighted and T2-weighted/FLAIR sequences.
E. All of the above.

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.