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MR of Mesial Temporal Sclerosis: How Much Is Enough?

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In this issue of the *AJNR*, Mamourian et al (1) assess the relationship between fornix asymmetry and mesial temporal sclerosis. While the authors have justifiably kept their focus narrow, their study raises several broader more important questions: What is mesial temporal sclerosis and why is it important to diagnosis? What imaging findings and techniques are necessary for diagnosing mesial temporal sclerosis and which combination of techniques is the most cost-effective? What is the significance of the secondary MR findings associated with mesial temporal sclerosis? Although there is insufficient information available to answer all aspects of these questions, there are enough data to review the importance of mesial temporal sclerosis, the types of imaging techniques used to diagnosis this entity, and the possible significance of secondary MR findings.

Mesial Temporal Sclerosis

Mesial temporal sclerosis, also known as hippocampal sclerosis, is the most common cause of temporal lobe epilepsy found at surgery. Histologically, it is characterized by a pattern of neuronal loss within the hippocampus affecting principally the pyramidal cell layers of the cornu ammonis and the granule layer of the dentate gyrus. A number of morphologic and cytochemical findings are associated with mesial temporal sclerosis, especially within the dentate gyrus. These changes include selective loss of inhibitory interneurons, abnormal spouting of axons, reorganization of neural transmitter receptors, alterations in second messenger systems, and hyperexcitability of the granule cells. The pathophysiology of these changes is not completely understood. It is postulated that an insult to the developing brain during childhood, such as a complicated febrile seizure or encephalitis, damages the dentate interneuron system. The damaged dentate gyrus becomes reorganized, leading to an aberrant hyperexcitable synaptic system. This is clinically manifested as recurrent seizures, or epilepsy (2–4).

Patients with medically refractory epilepsy due to mesial temporal sclerosis have only one reliable method for treatment: surgical resection of the hippocampus. Surgical resection of the hippocampus and anterior temporal lobe can cure epilepsy in as many

as 90% of these patients, making it imperative that imaging techniques accurately show this disorder. Imaging has dramatically changed our ability to identify mesial temporal sclerosis before surgery (5–7).

Imaging Techniques

There is a wide range of imaging techniques available for diagnosing and locating mesial temporal sclerosis. These include MR imaging using simple visual inspection, MR hippocampal volumetrics, MR hippocampal T2 relaxometry, MR spectroscopy, single-photon emission computed tomography (SPECT), ictal SPECT, and positron emission tomography (PET). These methods all have high sensitivities. MR is the most extensively used imaging technique; it is widely available, and a trained observer readily detects mesial temporal sclerosis or other causes of epilepsy on MR (5–10). Quantitative techniques using either volume or T2 measurements of the hippocampus involve more sophistication and are labor intensive (11–13). MR spectroscopy is still in the early stages of evaluation, especially single-voxel studies of the hippocampus and temporal lobe (14). Interictal SPECT imaging is easily available but lacks the sensitivity and specificity of ictal SPECT imaging. The yield from ictal SPECT imaging can be very high but depends on the temporal relationship between seizure occurrence and injection of radiopharmaceutical, and ideally requires computer-assisted techniques that compare ictal with interictal SPECT imaging. PET is very sensitive but is not universally available (15). There is no consensus on the most cost-effective combination of techniques for diagnosing mesial temporal sclerosis and predicting postoperative outcome. The paradigm for assessing patients before epilepsy surgery varies widely and depends on institution philosophy (16).

The hallmark of mesial temporal sclerosis on MR imaging is an atrophic hippocampus associated with hyperintense signal on long-repetition-time sequences confined to the hippocampus (5–10). These findings, atrophy and hyperintensity, are often referred to as the two primary MR findings of mesial temporal sclerosis. Patients with these primary MR findings have a 70% to 90% probability of being free of seizures after temporal lobectomy (5, 17). On the

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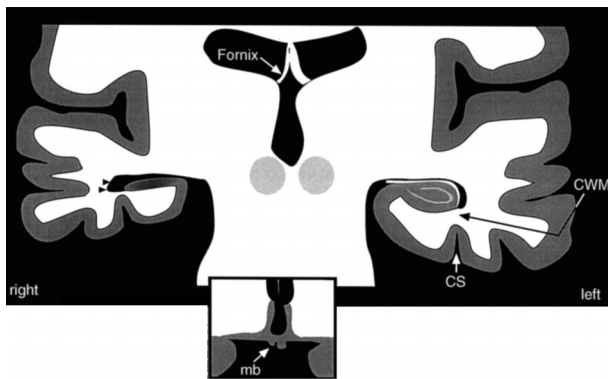


FIG 1. Diagram of a coronal T1-weighted MR image showing classic findings associated with mesial temporal sclerosis. In this case of right mesial temporal sclerosis, note the primary finding of right hippocampal atrophy. The other primary MR sign is hippocampal hyperintensity on long-TR sequences (not shown). Secondary findings include ipsilateral atrophy of the temporal lobe, collateral white matter (CWM, the white matter between the hippocampus and gray matter overlying the collateral sulcus), and fornix. Other secondary findings are temporal horn dilatation (arrowheads) and loss of the normal internal architecture of the hippocampus. Compare the left hippocampus, which demonstrates the normal hippocampal architecture due to alternating U-shaped gray and white matter internally, to the right hippocampus with loss of this internal pattern. The insert shows atrophy of the ipsilateral mamillary body (mb) on a more anterior image. CS indicates collateral sulcus.

other hand, if there are no primary MR findings, the patient has less than a 50% likelihood of becoming seizure free after surgery. Although these yields are impressive, they are selective. Some patients *with* mesial temporal sclerosis have either absent or equivocal primary MR findings of mesial temporal sclerosis. The use of secondary MR features can help improve the sensitivity and positive predictive value in this group of patients, especially when used in conjunction with other localizing techniques described above.

Secondary Findings of Mesial Temporal Sclerosis

What are the secondary MR findings of mesial temporal sclerosis? Figure 1 provides an overview of secondary findings, which include the following, all ipsilateral to the side of mesial temporal sclerosis: loss of the normal internal architecture of the hippocampus (best seen on inversion-recovery, thin-section fast spin-echo, or thin-section spoiled gradient-echo sequences); temporal lobe volume loss; dilatation of the temporal horn; narrowed collateral white matter; smaller fornix; and an atrophic mamillary body (7, 18–21). One reason that these findings are relegated to the category of secondary findings is because mild asymmetries of these structures occur in healthy subjects (22, 23). Mamourian and colleagues question whether fornix asymmetry is linked more to lateral

ventricular size asymmetry than to temporal lobe epilepsy (1). The authors show a statistically significant relation between lateral ventricular size and mesial temporal sclerosis, implying that an asymmetric smaller fornix is due to the enlargement of the ventricle rather than to the sclerosis. However, if enlargement of the ipsilateral ventricle and decreased size of the ipsilateral fornix are both the result of mesial temporal sclerosis, it would follow that there would be an association between ventricular size and fornix size. Unfortunately, the sample size of this study may be too small to assess such relationships; thus we are left with more questions than answers.

Most studies assessing secondary MR findings have involved fewer than 50 subjects. The frequency of secondary MR findings ipsilateral to temporal lobe epilepsy has been reported as 3% of 33 patients for a smaller mamillary body (19), 22% to 33% of nine for temporal horn dilatation (24), 22% to 37% of 41 patients for temporal lobe atrophy (11), 67% of nine patients for collateral white matter atrophy (24), 89% of 25 patients for disruption of the internal architecture of the hippocampus (8), and 92% of 13 patients (18) and 39% of 33 patients (19) for a smaller fornix. At our institution, we have noted secondary MR findings in about 40% to 60% of 65 patients with histologically proved mesial temporal sclerosis.

Although there is a paucity of data on the significance of the secondary MR findings, these might yield important information in terms of the pathophysiology, diagnosis, and prognosis of mesial temporal sclerosis. From a pathophysiologic perspective, MR findings may further our understanding of mesial temporal sclerosis. With MR imaging, we can assess the entire brain and may be able to discover findings and associations that can not be recognized at surgery and pathologic examination because of limited brain resection. Autopsy series of the brains of patients with mesial temporal sclerosis are rare. Many of the secondary signs appear to be related to the afferent and efferent pathways of the hippocampus (Fig 2). The fornix and mamillary bodies are part of the major efferent system of the hippocampus, while the entorhinal cortex, temporal lobe, and collateral white contribute to the afferent pathway. The presence of secondary MR findings indicates that one should think about mesial temporal sclerosis as a process involving diffuse regions of the brain rather than as one limited to the hippocampus.

Secondary MR findings can help in the diagnosis and lateralization of mesial temporal sclerosis. In patients with subtle primary findings of unilateral mesial temporal sclerosis, these secondary imaging features help improve diagnostic confidence as demonstrated in a recent abstract (25). In this study of 50 patients and 16 control subjects, the authors found that while hippocampal volume alone was very sensitive (94%), the combination of fornix volume plus

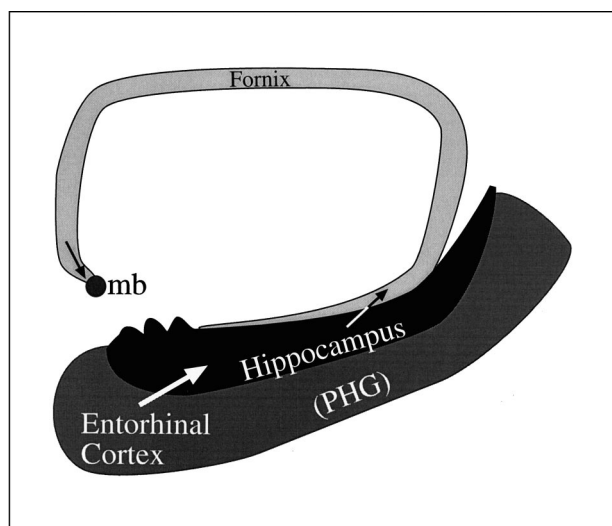


FIG 2. Lateral diagram of the circuitry associated with the hippocampus. In this simple model, note that the main afferent fibers to the hippocampus come from the entorhinal cortex, which is part of the parahippocampal gyrus (PHG). The main efferent pathway from the hippocampus is the fornix, which connects to the mammillary body (mb).

mamillary volume plus hippocampal volume was more sensitive (98%). Interestingly, the use of the fornix plus mamillary body volume *without* hippocampal volume proved to lateralize temporal lobe epilepsy correctly in 82% of patients.

In cases of bilateral hippocampal abnormalities, secondary findings can determine the more important side to resect. They might also provide clues for distinguishing those patients *thought* to have mesial temporal sclerosis before surgery, but who will be found to have hippocampal gliosis at surgery; as a group, these patients have poor postoperative seizure control.

Since mesial temporal sclerosis appears to be the end-stage process associated with a number of initiating insults (eg, childhood febrile seizures, encephalitis) it is possible that secondary MR signs could offer a way to categorize patients further according to cause and outcome. An important question is whether one or more of these signs can be linked to postoperative outcome. For example, do we know whether patients with mesial temporal sclerosis and ipsilateral temporal lobe atrophy more than two standard deviations below the norm have better outcomes than those patients with mesial temporal sclerosis but without temporal lobe atrophy?

Conclusions

Although the secondary MR findings associated with mesial temporal sclerosis are not sensitive predictors of this entity by themselves, they may offer

clues in subtle cases, improve sensitivity in patients with bilateral findings, and further our knowledge of this entity. While Mamourian and colleagues (1) are to be commended for thinking about these issues, they have not gone far enough. Much more research is needed to define the exact role of secondary MR findings associated with mesial temporal sclerosis.

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