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AJNR Am J Neuroradiol 1993, 14 (3) 753-762
http://www.ajnr.org/content/14/3/753

This information is current as of July 22, 2023.
Optimizing the Diagnosis of Hippocampal Sclerosis Using MR Imaging

Graeme D. Jackson,1,3,4 Samuel F. Berkovic,2 John S. Duncan,1 and Alan Connelly3

PURPOSE: To establish the optimal imaging parameters and MR features of hippocampal sclerosis.

METHODS. Twenty-five outpatients with intractable temporal lobe epilepsy and 10 control subjects were studied at 1.5T. Four features of hippocampal abnormality were specifically evaluated: increased hippocampal signal on T2-weighted images, decreased signal on T1-weighted images, hippocampal atrophy, and disruption of the internal hippocampal structure. RESULTS. Hippocampal sclerosis was diagnosed alone in 64% of patients and with ipsilateral pathology in a further 8%. In these 18 cases, increased hippocampal signal on T2-weighted images was seen in 77%, hippocampal atrophy in 83%, decreases signal on T1-weighted images in 83%, and disruption of the internal hippocampal structure in 89%. No abnormality was reported in any of the 10 control cases. CONCLUSIONS. Four MR features diagnostic of hippocampal sclerosis are reported. Inversion recovery images are very useful for identifying decreased signal in the hippocampus and loss of internal structure within the hippocampus. Based on an appreciation of these four features in optimized images, hippocampal sclerosis can be diagnosed with a high degree of accuracy and sensitivity.

Index terms: Sclerosis, hippocampal; Degenerative brain disease; Brain, magnetic resonance; Brain, temporal lobe; Seizures

AJNR 14:753–762, May/Jun 1993

Pathologic examination shows hippocampal sclerosis in approximately 65% of epilepsy patients who undergo temporal lobectomy (1–3). Until recently, many magnetic resonance (MR) studies have failed to detect hippocampal sclerosis reliably (4–8). Most reports have relied solely on the detection of an increased signal on T2-weighted images in the mesial temporal region. Although this increase is an important feature of hippocampal sclerosis, it can also be caused by small mesial temporal tumors, increased cerebrospinal fluid (CSF) space, and posttraumatic damage. It may also arise from flow artifacts due to the proximity of blood vessels. Its diagnostic relevance has thus been questioned (9).

In our experience, increased signal on T2-weighted images is present in most cases of hippocampal sclerosis. However, it may be subtle and restricted to the hippocampal gray matter, and can even be obscured by the windowing process when hard copy film is made for clinical reporting. The degree of abnormality needed to diagnose pathology, and the criteria used for this diagnosis, also varies among the imaging specialists reporting (10, 11). As a result, increased signal on T2-weighted images in the mesial temporal region has been reported with variable frequency in cases of hippocampal sclerosis. While most studies have reported increased signal on T2-weighted images in 30% of cases or less (4, 5, 7, 8), a few reports have put this figure as high as 70% (10, 11).

The importance of hippocampal atrophy as a sign of hippocampal sclerosis has been less emphasized. Using a retrospective blinded reporting method in a series of 81 temporal lobectomy cases, hippocampal sclerosis was reliably diag-
nosed by MR imaging performed at 0.3T. Of 51 pathologically proved cases of hippocampal sclerosis, 93% were detected using the criteria of visually graded hippocampal atrophy and/or increased hippocampal signal on T2-weighted images (11). To achieve these results, understanding the imaging anatomy of the hippocampus and the pathologic anatomy of hippocampal sclerosis is essential. Images in the appropriate planes with both T1- and T2-weighted sequences enable accurate assessment of hippocampal morphology and the location of any signal abnormality. Volumetric analysis of coronal hippocampal images has provided quantitative confirmation of the observation that reduced hippocampal size, when present, does reliably predict the side of the epileptogenic temporal lobe (12, 13).

In this paper, we present findings in 25 consecutive outpatients with intractable temporal lobe epilepsy and 10 healthy control subjects studied at 1.5T. We have confirmed the previous findings, in an outpatient population, and have allowed the identification of further radiologic signs of hippocampal sclerosis.

Materials and Methods

We evaluated 25 consecutive adult patients referred from the National Hospital for Neurology and Neurosurgery with the problem of intractable temporal lobe epilepsy. Mean age was 28 years (range, 15 to 48 years) and the mean age of seizure onset was 10 years (range, 3 months to 24 years). Patients had an average of eight seizures per month (range, three to 48), including simple partial, complex partial, and secondarily generalized seizures. Eleven (43%) of these had febrile convulsions in childhood lasting more than 30 minutes.

MR imaging was performed at the Hospitals for Sick Children. Two neurologists independently assessed each patient and reached a consensus diagnosis including lateralization and localization of the epileptic focus, if possible, after review of all available data apart from the MR. These included clinical interview, multiple surface interictal electroencephalograms (EEGs), detailed neuropsychologic evaluation, and when necessary, ictal video EEG. Depth electrode studies were performed in three cases. Both left- and right-handed patients were included. Pathology was obtained in all 10 patients who subsequently underwent temporal lobe resection and the diagnosis of hippocampal sclerosis was based on visually graded neuronal loss of greater than 50% in Sommer's sector supported by gliosis in the cornu ammonis and end folium.

Ten control subjects of similar age who had no medical problems underwent identical MR imaging. All images were obtained from a Siemens 1.5-T whole-body system, using a circularly polarized head coil as both transmitter and receiver.

Imaging Planes

The hippocampus is most completely assessed by images in two orthogonal planes. The optimal planes for diagnosis of hippocampal sclerosis are along the long axis of the body of the hippocampus and at right angles to this (11, 14–16). This orientation avoids oblique images of the hippocampus that can be difficult to interpret because of partial volume effects. The anterior border of the brain stem, extending across the pons as seen in the sagittal view, was the radiographic landmark for orientation of the central section of the coronal sequence (Fig. 1, line A). The central section of the axial images lies along the line drawn from the lowest point of the splenium of the corpus callosum to the inferior frontal lobe margin (Fig. 1, line B). This imaging axis is at approximately 35° to standard axial and coronal images.

Imaging Protocol

Visualization of the hippocampal gray matter is important for the diagnosis of hippocampal sclerosis, so accurate distinction of gray matter from white matter, and of gray matter from CSF, is essential. Inversion-recovery images (3500/26 (TR/TE); inversion time, 300 ms; section thickness, 5 mm) in the tilted axial and coronal planes give optimal anatomical definition of the hippocampal gray matter. The inversion-recovery sequence was chosen because it provides details of the internal structure of the hippocampus and demonstrates decreased signal on T1-weighted images in gliotic areas. We used an asymmetrical field of view with a 256 × 128 matrix to reduce scanning time to 7.5 minutes per sequence. With the acquisition of both axial and coronal images, the whole hippocampus can

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Fig. 1. Landmarks for orientation of the central section of the modified imaging axis in the coronal (A) and axial (B) planes are shown in the sagittal scout view. The latter plane is tilted approximately 35° from the standard CT imaging axis. Generally these axes are approximately at right angles to each other.
Fig. 2. The normal anatomy of the hippocampus is shown in these tilted coronal and axial T1-weighted inversion-recovery images (3500/26; inversion time, 300 ms). In all figures, the patient’s left is on the right side of the image.

A. The hippocampus has an oval cross section, as shown in this coronal section angled parallel to the long axis of the brain stem. The hippocami are symmetrical, and the signal in the hippocampal gray matter on T1-weighted images appears similar in intensity to normal cortical gray matter. Internal structure can be seen within the hippocampi (see Fig. 6).

B. In this angled axial section through the long axis of the hippocampus, the entire hippocampal head and body can be seen. The hippocampus appears as a curved sausage-shaped structure with the head forming the most anterior portion and the curved body of the hippocampus extending posteriorly with constant thickness (as labeled in Fig. 3). The head of the hippocampus lies directly below the amygdala and in this section none of the amygdala is seen.

TABLE 1: MR imaging diagnosis (outpatient population, n = 25)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Percentage</th>
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<tr>
<td>Hippocampal sclerosis alone</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Foreign-tissue lesions</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Other significant*</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>No abnormality</td>
<td>2 (8%)</td>
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</table>

*One FTL and one dysplasia also showed HS.

be assessed despite a section gap of 2.5 mm. Increased hippocampal signal on T2-weighted images was assessed on the second echo of a coronal double echo short tau inversion-recovery sequence (4000/23 and 85; inversion time, 145 ms) that covered the entire brain (17).

Image Evaluation

The diagnosis of hippocampal sclerosis was based both on the previously pathologically validated criteria of a visually graded unilaterally small hippocampus and/or increased signal on T2-weighted images localized to the gray matter of the hippocampus (11), and on the additional criteria of disruption of the internal morphology of the hippocampus and the presence of decreased signal in the gray matter of the hippocampus seen in inversion recovery images.

Three independent observers blinded to other information evaluated the images and reached a consensus diagnosis in cases of disagreement. Control and patient scans were mixed during the assessment procedure. Each observer was asked to make an overall diagnosis and to note the lateralization of the pathology. Each of the four features of hippocampal pathology, namely, decreased signal on T1-weighted images, increased signal on T2-weighted images, atrophy, and loss of internal morphologic structure, was assessed individually in all cases. The morphology of the hippocampus was assessed by grading the presence of normal hippocampal internal structure, and the side-to-side symmetry of the hippocampal gray matter.

Results

We (11, 14) and others (15, 18) have previously emphasized the importance of knowing the details of normal and pathologic hippocampal anatomy for accurate interpretation of MR imaging (Figs. 2 and 3). We assessed hippocampal morphology and hippocampal T1 and T2 signal intensity in 10 healthy volunteers. In no control case was abnormal internal structure or significant side-to-side asymmetry reported; this finding is consistent with the findings in controls using hippocampal volume measurements (18). The signal on T1- and T2-weighted images within the hippocampus was evaluated in tilted axial and coronal sections by each of the three observers. No abnormality of these features was reported in any control case by any of the three observers.

Hippocampal sclerosis was the sole MR imaging diagnosis in 16 of these 25 outpatients (64%). Two further cases of hippocampal sclerosis were found on the same side as other pathology (a glioma and cortical dysplasia). Foreign-tissue lesions such as a hamartoma or glioma were found in 20%, and significant other pathology in 8% (cortical dysplasia and temporal cyst). No detectable MR imaging pathology was reported in 8% (Table 1). The frequency with which each MR imaging feature of hippocampal sclerosis was reported in the 18 patients diagnosed by all three
observers as hippocampal sclerosis is shown in Table 2.

Decreased signal on T1-weighted images (Figs. 3B, 3C, and 4A) was found in 15 (83%) cases with the MR diagnosis of hippocampal sclerosis, and increased signal on T2-weighted images (Fig. 4B) was reported in 14 (77%). Signal abnormality on both T1- and T2-weighted images was present in 11 cases. There was variability among the latter cases in the relative degree of signal abnormality on T1- and T2-weighted images. In some, the T1-weighted imaging change was more obvious than the signal abnormality on T2-weighted images, and in others, the reverse was true.

These diagnostic features can also be seen in axial images (Fig. 3). In some cases, decreased T1-weighted signal is seen most clearly in this image orientation. The axial plane has the advantage that seeing the entire length of the abnormal hippocampal segment in a single image allows determination of the posterior extent of the signal abnormality (eg, Fig. 3C).

Hippocampal atrophy was found in 83% of the cases diagnosed as hippocampal sclerosis (Figs. 3B, 4A, and 5A). Although, in our experience, the oblique coronal plane is the more sensitive for assessing atrophy in the majority of cases, oblique axial images enable assessment of the length of hippocampal atrophy in a single section (Fig. 3B). In three cases, the hippocampus diagnosed as showing sclerosis was not assessed as atrophic in the midhippocampal body. Signal abnormalities in T1- and T2-weighted images, and loss of internal morphology, easily enabled the correct lateralization and diagnosis of hippocampal pathology even without visible hippocampal atrophy. In one of these cases, pathology confirmed the presence of hippocampal sclerosis following temporal lobe resection. However, other findings were difficult to interpret, and surgery is not contemplated at present.

All four diagnostic features were found together in only 39% of cases (Table 3). If any one feature was taken on its own, the sensitivity of the diagnosis of hippocampal sclerosis would have been only 89% at best (Table 2). This reflects the fact that different features are more prominent in some cases than others, and may be due to heterogeneity within the pathologies that are interpreted as hippocampal sclerosis.

Temporal lobe resection with removal of medial structures or selective amygdalo hippocampectomy was performed in 10 of the 25 patients in this series. Sufficient hippocampal material for diagnosis was available in six cases, and in all of those, the MR imaging diagnosis of hippocampal sclerosis was confirmed pathologically.

Discussion

The structural anatomy of the normal hippocampus is shown by these imaging techniques (Fig. 2). This degree of detail allows the identification of subtle degrees of pathology, and detailed noninvasive assessment of the normal hippocampus.

The hippocampus can be divided into three main parts (19); a head, a body, and a tail (Fig. 3). The hippocampal head (also known as the pes hippocampi indentatus) is the most anterior portion, and lies directly beneath the amygdala that caps in anteriorly and superiorly. The hippocampal head has characteristic indentations that can be seen in the appropriate axial and coronal T1-weighted images. The hippocampal body is a small curved sausage-shaped structure, which forms an incomplete ring of gray matter around the brain stem in the most medial portion of the temporal lobe. The body can be defined as the portion of the hippocampus that begins anteriorly

<table>
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<th>TABLE 2: Diagnostic features of hippocampal sclerosis (n = 18)</th>
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<tr>
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<tr>
<td>Hippocampal atrophy</td>
</tr>
<tr>
<td>Disrupted internal structure</td>
</tr>
<tr>
<td>Increased T2-weighted signal</td>
</tr>
<tr>
<td>Decreased T1-weighted signal</td>
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* Same cases in only 11 of the 15.
in the section in which the amygdala is no longer its immediate superior relation and it extends posteriorly to the hippocampal tail. The hippocampal tail curves upward out of this plane to merge with the fornix in the midline posteriorly and superiorly (Fig. 3).

Hippocampal sclerosis, in keeping with the pathology literature, was the sole MR diagnosis in 64% of this outpatient series of 25 cases (2). Overall it was found in 72% of cases, which included two in which it was present on the side of significant other ipsilateral pathology (foreign-tissue lesions, and cortical dysplasia). The diagnosis of hippocampal sclerosis in two difficult cases, confirmed pathologically, relied on the additional criteria of loss of internal hippocampal morphologic structure and hypointensity on inversion-recovery images.

The MR diagnostic criteria of decreased signal on T1-weighted images and disruption of internal morphologic structure correspond to features that have long been known to be the diagnostic histopathologic features of hippocampal sclerosis (1–3, 20, 21) (Table 4). The features that are used
Fig. 4. A, T1-weighted inversion-recovery images in the tilted coronal plane (3500/26; inversion time, 300 ms). Hippocampal sclerosis in a 24-year-old woman with a history of severe febrile convulsion at the age of 18 months, and intractable complex partial seizures of left temporal lobe origin. Tilted coronal section through the hippocampal body shows severe left hippocampal atrophy, signal hypointensity, and loss of the features of internal hippocampal structure (arrowhead).

B, In the same patient as in A, a similarly oriented T2-weighted image (4000/85; inversion time, 145 ms) shows increased signal intensity (arrowhead) in the same region as the signal hypointensity. Assessment of hippocampal atrophy and internal structure is difficult in this image.

Fig. 5. A, Severe atrophy and marked signal hypointensity (arrowhead) is seen on a T1-weighted image (3500/26; inversion time, 300 ms; section thickness, 5 mm) in the right hippocampal body of an 18-year-old man with a history of febrile convulsions complicated by left hemiparesis.

B, Signal abnormality on a T1-weighted image (3500/26; inversion time, 300 ms; section thickness, 5 mm) and loss of the normal internal structure of the hippocampus is seen in the left hippocampus of a 26-year-old patient with temporal lobe epilepsy (arrowhead). Atrophy of this hippocampus was not reported.

C, An abnormal hippocampus on the left (arrowhead) showing loss of definition of internal structure without definite hippocampal atrophy or signal change (3500/26; inversion time, 300 ms; section thickness, 5 mm). This was not diagnosed as hippocampal sclerosis, but we interpret this as pathologic. Note that the temporal lobe on that side is also atrophic, as is the entire hemisphere (enlarged lateral ventricle). Surface EEGs suggested a left temporal focus (see text).

to make the pathologic diagnosis of hippocampal sclerosis can now be assessed by MR images optimized to display hippocampal morphology and tissue abnormalities.

There is a large gradation of pathologic abnormality that falls within the diagnostic category of hippocampal sclerosis, from minor end-folium gliosis to extensive gliosis and cell loss (20). The more subtle degrees of hippocampal pathology depend on the assessment of hippocampal atrophy, gliosis, and neuronal cell loss in making a final pathologic diagnosis. Similarly, the use of all four MR imaging criteria applied to different sequences and optimally oriented axes enables hippocampal pathology to be diagnosed with maximal sensitivity using MR imaging.

**Altered Hippocampal Morphology**

The microscopic neuronal loss and gliosis that characterizes hippocampal sclerosis is associated with macroscopic atrophy of the hippocampus.
Normal hippocampal structure

Features of hippocampal sclerosis (changes in internal morphological structure)

AS-reported by nineteenth century pathologists in autopsies of patients with epilepsy (2). Normal internal morphologic structure of the hippocampus is produced by the alveus, the molecular cell layer of the dentate gyrus, and the pyramidal cell layer of the cornu ammonis, and can be seen on optimized coronal MR images (Figs. 6A and 6B).
In hippocampal sclerosis, the loss of this normal internal structure is a consequence of neuronal cell loss and replacement of normal anatomical layers with gliotic tissue (Figs. 6C and 6D).

Because of the large variation in normal size (13, 15), atrophy may be accurately detected only using the criterion of hippocampal asymmetry. Normal hippocampi were symmetrical as assessed subjectively in the current study, and by volumetric analysis in previous studies (15, 19). We found hippocampal atrophy in 83% of patients with hippocampal sclerosis by careful visual analysis of optimized images (Table 2). This frequency is comparable to that reported using volumetric techniques (12, 13). Accuracy of quantitative volume measurements require analysis of contiguous thin sections oriented at right angles to the long axis of the hippocampus which were not acquired in the current study.

Bilateral hippocampal abnormalities are also difficult to detect using atrophy as a sole criterion because of the variation of normal size. Like our qualitative visual method, reliable quantitative volumetric techniques rely on the comparison of the patient's two hippocampi (12). The use of absolute volumetric criteria may lead to errors of lateralization (12, 13).

Atrophy was not diagnosed in three cases in which signal change was present in the hippocampal gray matter. In two of these cases, subsequent review showed areas of focal atrophy in the hippocampal head that had not been detected with certainty in the reporting process. This emphasizes that the use of multiple criteria increases the sensitivity of the diagnosis of hippocampal sclerosis.

Loss of internal morphologic structure of the hippocampus has been identified in this study as an MR imaging feature of hippocampal pathology. It is a sensitive sign of hippocampal sclerosis, usually seen when atrophy is present, but we are uncertain whether it is sufficient for the diagnosis in the absence of other features. However, we suggest that a clearly visualized intact hippocampal internal structure is inconsistent with the diagnosis of hippocampal sclerosis.

Altered Hippocampal Signal Intensity

For reliable diagnosis of hippocampal sclerosis, a heavily T2-weighted image in the oblique coronal imaging plane is helpful. Our experience suggests that an abnormal signal on T1- or T2-weighted images arising from an atrophic hippocampus always represents hippocampal sclerosis. An abnormal signal arising from an apparently enlarged hippocampus may represent a hamartoma or glioma (11).

Increased T2-weighted signal when localized imprecisely to the "mesial temporal region" may be caused by foreign tissue such as a glioma or hamartoma, by gliotic tissue in the hippocampus, by increased CSF in the atrophied region, by flow artifacts, and occasionally by a developmental cyst in the hippocampal head stemming from failure of closure of the lateral aspect of the hippocampal fissure (22). Careful determination of the exact location of this signal change using T1-weighted images to give clear anatomical detail enables the correct diagnosis to be made. The MR imaging diagnosis that is based on all four diagnostic features of hippocampal sclerosis in optimized images is more sensitive than any single feature, such as atrophy or T2-weighted signal hyperintensity, taken on its own (Table 2).

For reasons discussed earlier, the frequency with which increased signal on T2-weighted images is found in cases of hippocampal sclerosis has varied markedly between different series (4, 5, 7, 8, 10, 11). We have found hyperintensity on T2-weighted images by visual grading in 77% of cases. We are currently investigating the prev-
Hippocampal sclerosis may be diagnosed with MR, but the sensitivity of this diagnosis, the MR criteria by which this diagnosis is made, and the necessity for volumetric techniques is still controversial. We report a qualitative technique and diagnostic features that enable hippocampal pathology to be diagnosed in virtually all cases.

The technique reported in this paper relies partly on inversion-recovery images. Although it takes 7.5 minutes, this sequence provides important diagnostic information that is not easily seen using fast gradient-echo techniques or T1 weighted spin-echo sequences. Intractable temporal lobe epilepsy is a common problem, and hippocampal pathology is the most frequent underlying abnormality. Images that can be provided by standard MR imaging systems enable accurate qualitative assessment of hippocampal pathology.

We propose that altered hippocampal signal intensity (on T1 and/or T2 weighted images) and altered hippocampal morphology (atrophy and/or loss of internal structure) constitute the MR diagnostic features of hippocampal sclerosis. We have focused this study on outpatients, and report MR techniques and diagnostic criteria that any center with an MR facility can adopt without needing to develop new quantitative methods of analysis.

The diagnosis of hippocampal sclerosis is important to a patient with intractable epilepsy who is being considered for epilepsy surgery. The most sensitive and specific technique should be used (26), as the reliable noninvasive diagnosis of hippocampal sclerosis may speed up the assessment process for patients undergoing epilepsy surgery, and provide evidence of pathology to support the decision to offer surgery.

Acknowledgments

We are grateful to the Department of Pathology (National Hospital for Neurology and Neurosurgery), Professor D. Gadian (Institute of Child Health, London, UK), and Julie Shepherd and Sandra Powell (Neuroradiography).
References