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BACKGROUND AND PURPOSE: MR diffusion-weighted (DW) imaging with apparent diffusion coefficient (ADC) has had widespread use clinically in a variety of intracranial diseases; however, only a few studies report ADC changes in patients with hippocampal sclerosis. We sought to determine the ability of ADC to lateralize the epileptogenic lesion in patients with hippocampal sclerosis.

METHODS: Nineteen healthy volunteers and 18 patients with intractable temporal lobe epilepsy whose MR imaging diagnosis was unilateral hippocampal sclerosis were examined prospectively with DW imaging and ADC mapping. DW images were obtained at 1.5 T with a spin-echo echo-planar sequence (6500/103 [TR/TE]) with variable diffusion gradients. ADCs were calculated from bilateral hippocampi. The ability of DW imaging and ADC to lateralize the lesion was evaluated visually and by comparing ADC values between healthy volunteers and patients with hippocampal sclerosis.

RESULTS: In all patients, visual assessment of DW images failed to lateralize the lesion. However, the mean ADC value measured at the hippocampal area was significantly higher on the lesion side than on the contralateral side ($P < .001$). The overall correct lateralization rate of ADC was 100% (18 of 18 patients). Mean ADC in sclerotic hippocampi was also significantly higher than that in healthy volunteers. The normal-appearing hippocampus of the contralateral side in the patients had higher ADC values compared with those of healthy volunteers ($P = .045$).

CONCLUSION: ADC can be used as a complementary tool in lateralizing the epileptogenic lesion in patients with hippocampal sclerosis, although the practical role of ADC value is yet to be determined in patients with inconclusive MR imaging findings.

Hippocampal sclerosis is a common structural abnormality in patients with refractory temporal lobe epilepsy and is potentially curable by surgical resection. Conventional MR imaging has been the imaging method of choice for localizing hippocampal sclerosis. In some cases, however, accurate localization of the epileptogenic focus is difficult even with combined use of electroencephalography, MR imaging, single photon emission computed tomography (SPECT), positron emission photograph (PET), and/or MR spectroscopy.

Recently, MR diffusion-weighted (DW) imaging with apparent diffusion coefficient (ADC), which allows the quantitative measurement of diffusion of water molecules, has had widespread use clinically in a variety of intracranial diseases such as ischemia and tumors (1–5). A few recent studies have shown that ADC is significantly increased in the sclerotic hippocampi of patients with refractory temporal lobe epilepsy (6, 7).

The purpose of this study was to evaluate the lateralizing ability of DW imaging and the ADC value of the hippocampus by comparing the ipsilateral diseased hippocampus and contralateral hippocampus of patients with hippocampal sclerosis and normal hippocampi in healthy volunteers.

Methods

Subjects

This study was approved by our institutional review board, and all participants provided written informed consent before entering the study. Nineteen healthy volunteers without a history of neurologic diseases (four women, 15 men; mean age, 28 years; range, 19–39 years) and 18 patients with intractable temporal lobe epilepsy whose MR imaging diagnosis was unilateral hippocampal sclerosis (six female, 12 male patients; mean age, 30 years; range, 16–42 years) were examined prospectively with DW imaging and ADC. The interval between the time of the last seizure and the examination ranged from 2 days to 2 months. No patient was in ictus or within 24 hours after ictus. MR imaging diagnosis of hippocampal sclerosis was based on the presence of atrophy and/or high signal intensity of the hippocampus on T2-weighted images as determined by consensus of two experienced neuroradiologists (K.H.C., M.H.H.). Surgical excision of the anterior temporal lobe had been performed in 16 of the 18 patients, and hippocampal sclerosis was proved by histopathologic examination in these 16 patients. In the remaining two patients, the diagnosis was supported by other examinations such as PET and/or ictal SPECT.

MR Imaging, DW Imaging, and ADC Measurement

All MR imaging examinations were performed with a 1.5-T unit (EchoSpeed; GE Medical Systems, Milwaukee, WI). Conventional routine MR imaging in the 18 patients with temporal lobe epilepsy included 2D T1-weighted sagittal spin-echo (14.4, 5.5, 2 [TR/TE/NEX]) and T2-weighted axial fast spin-echo (4500/104/2) sequences with 5-mm thickness, 2D T2-weighted fast spin-echo (5500/114/2) and fluid-attenuated inversion recovery (FLAIR) (10,002, 133, 2) sequences with 3-mm thickness, and a 3D T1-weighted gradient-echo sequence (spoiled gradient recalled acquisition in the steady state [SPGR]) (14.4, 5.5, 2) with 1.5-mm thickness in oblique coronal plane perpendicular to the long axis of the hippocampus. After the routine MR images were obtained, DW imaging was performed with a spin-echo echo-planar imaging sequence with the following parameters: 6500/103 (TR/TE), matrix size of 128 × 128, 210-mm field of view, 5-mm section thickness with no gap. For each subject, three sets of axial DW images were obtained with application of three different diffusion gradients (b = 0, 500, 1000 s/mm^2) along the three axes simultaneously. Iterative nonlinear least squares fit of a monoexponential decay was used to produce an trace ADC map. ADC values were measured in the hippocampal region, being approximately 1.5–2.5 cm^3 and containing 150–250 voxels, bilaterally in the healthy volunteers and in the patients with hippocampal sclerosis (Fig 1).

Analysis

Both qualitative and quantitative assessments were performed. For qualitative assessment, all the DW images and ADC maps were visually evaluated whether or not there was an abnormality to lateralize the epileptogenic focus. Presence or absence of the abnormality was determined by the consensus of the two experienced neuroradiologists (K.H.C., M.H.H.) without knowledge of any clinical and conventional MR imaging information.

For quantitative assessment, ADC values were calculated by a rater (I.C.S.) who had detailed knowledge of the hippocampal anatomy. In each patient with hippocampal sclerosis, the ADC value of the ipsilateral hippocampal region was compared with that of the contralateral hippocampus. Mean ADC values of the hippocampus were calculated in the following three groups: group 1, the ipsilateral diseased hippocampus (n = 18) in the patients with hippocampal sclerosis; group 2, the contralateral normal hippocampus (n = 18) in the patients with hippocampal sclerosis; and group 3, bilateral hippocampi (n =
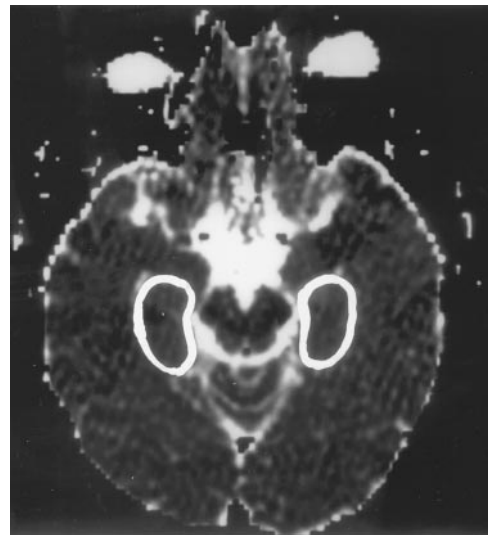

Fig 1. 17-year-old male patient with left hippocampal sclerosis. ADC map shows regions of interest approximately 1.5 x 2.5 cm placed in both hippocampal areas for measurement of ADC values. ADC was higher in the lesion side (113 × 10^{-5} mm^2/s) than in the contralateral side (88 × 10^{-5} mm^2/s).

38) in the healthy volunteers. The mean ADC values of the three groups were compared with one another to determine if there were any significant differences among the three groups. We compared both sides in the healthy volunteers to determine if there was any difference between the right and left hippocampi. Asymmetry indices, [(right - left)/(right + left)]/2, were calculated for the healthy volunteers and the patient groups and compared with each other. Significant lateralizing asymmetry was assumed when values outside 2 standard deviations (SDs) from the normal mean were found. SPSS 9.0 software (SPSS, Inc., Chicago, IL) was used for statistical analysis, where $P < .05$ was considered to indicate a statistically significant difference.

Results

In the qualitative study, visual assessment of the DW images failed to lateralize the lesion. DW images and ADC maps appeared normal without signal intensity asymmetry in all patients.

In the quantitative study, ADC values were higher in the ipsilateral hippocampus than in the contralateral hippocampus in 100% of the 18 patients with hippocampal sclerosis. The mean ADC value in group 1 (diseased hippocampi) was significantly higher than that in group 2 (contralateral hippocampi): 105 ± 11 × 10^{-5} mm^2/s versus 93 ± 8 × 10^{-5} mm^2/s ($P = .001$). In group 3 (hippocampi of volunteers), the mean ADC was 88 × 10^{-5}/s (SD 9 × 10^{-5} mm^2/s), and no significant difference was noted between right and left (right, 89 ± 9 × 10^{-5} mm^2/s; left, 87 ± 8 × 10^{-5} mm^2/s). The mean ADC of group 1 was significantly higher than that of group 3 ($P < .001$). The mean ADC of group 2 was also significantly higher than that of group 3 ($P = .045$). The ADC values of the hippocampi in the three groups are illustrated in Fig 2 and the Table. Mean asymmetry index in the control group was 2.83% (SD 8.99%) and in the patient group was −4.43% (SD 21.7%).
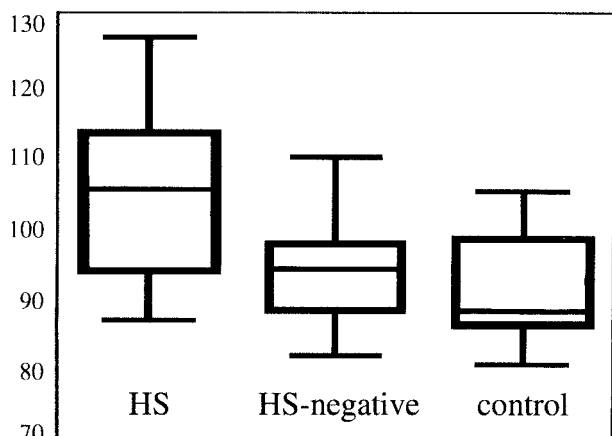
FIG 2. Boxplot shows ADC ranges in the three groups: *HS* indicates the sclerotic hippocampi in patients with hippocampal sclerosis; *HS-negative*, the contalateral hippocampi in patients; and *control,* hippocampi of healthy volunteers. Each box contains the 50% of ADC values falling between the 25th and 75th percentiles, and the "whisker" lines indicate the ranges from highest to lowest ADC values. The line crossing the box is the median. The differences in ADC values between any two of the three groups were significant ($P < .05$).

Mean (± SD) ADC values in the three groups

Group	ADC Value (mm^2/s)	Range (mm^2/s)
1 (n = 18)	$105 \pm 11 \times 10^{-5}$	$94–116 \times 10^{-5}$
2 (n = 18)	$93 \pm 8 \times 10^{-5}$	$85–102 \times 10^{-5}$
3 (n = 38)	$88 \pm 9 \times 10^{-5}$	$79–97 \times 10^{-5}$
Right (n = 19)	$89 \pm 9 \times 10^{-5}$	$80–98 \times 10^{-5}$
Left (n = 19)	$87 \pm 8 \times 10^{-5}$	$79–95 \times 10^{-5}$

Note.—Group 1 indicates diseased hippocampi; group 2, contralateral hippocampi; group 3, control hippocampi.

Five patients had an asymmetry index outside 2 SDs from the normal mean.

Discussion

In our study, the sclerotic hippocampi revealed significantly higher ADC values than that of the contralateral side in 100% of patients with hippocampal sclerosis and than that of the hippocampi in healthy volunteers. Our results are similar to those of published reports (6, 7). Hugg et al (6) studied eight patients with unilateral mesial temporal lobe epilesy and five control subjects. In all patients of their study, ADC was significantly elevated in the sclerotic hippocampi (mean ADC ± SD, $96 \pm 4 \times 10^{-5}$ mm^2/s) by a mean of 10% compared with that of the contralateral nonsclerotic hippocampi (mean ADC ± SD, $88 \pm 4 \times 10^{-5}$ mm^2/s). Mean ADC was significantly elevated in the sclerotic hippocampi compared with controls ($87 \pm 5 \times 10^{-5}$ mm^2/s), but there was no difference in mean ADC between the contralateral hippocampus in the group without hippocampal sclerosis and the control group. In another study by Wieshmann et al (7), which included 11 patients with hippocampal sclerosis (unilateral in eight and bilateral in three) and six control subjects, mean ADC was significantly increased in the group with hippocampal

sclerosis ($113 \pm 17 \times 10^{-5}$ mm^2/s) compared with the contralateral hippocampi ($94 \pm 13 \times 10^{-5}$ mm^2/s) and the control group ($91 \pm 3 \times 10^{-5}$ mm^2/s).

The reason for higher ADC values in the sclerotic hippocampus is unknown. It might result from the relative increase of interstitial water proton secondary to the neuronal cell loss and/or gliosis. The ADC changes were discussed in the light of histopathologic changes in several reports (6–13). The initial ADC decrease is considered to be associated with neuronal swelling and the subsequent increase in ADC results from the microstructural damage that includes neuronal necrosis, gliosis, and expanded extracellular space. In the animal models for early detection of ischemic lesions (8,9), ADC was depressed rapidly with the onset of ischemia and rebounded to exceed baseline values chronically in the completed infarction coincident with an increase in the number of eosinophilic neurons and neuronal cell lysis and necrosis (10).

Another possible reason for the increased ADC in sclerotic hippocampi, we suggest, is partial volume averaging artifact because more CSF space is included in the region of interest in sclerotic hippocampi. This has been suggested by Pierpaoli et al (14) who reported that ADC measurements of the cortical gray matter were not reliable owing to the close proximity of the CSF in the cortical sulci. Furthermore, because we performed ADC measurements of the hippocampus in the axial plane, there might be an increased partial volume averaging artifact compared with measurement in the coronal plane, which is ideal for evaluation of the hippocampus. In fact, we encountered some difficulties in placing the region-of-interest cursor on the hippocampal region in the axial plane.

Review of recently published articles with animal seizure models revealed a pattern of evolution of ADC from the ictus; that is, acute postictal depression of ADC, interictal normalization, and then chronic elevation in the epileptogenic seizure focus (8–10). Righini et al (8) reported ADC alterations associated with prolonged complex partial seizures in experimental models. They observed time evolution of signal intensity on T2-weighted images and ADC from 3 hours to 9 days in the brain of rats, in which complex partial seizure was induced by intraperitoneal injection of kainic acid. In their experiment, the ADC decreased and subsequently increased from 24 to 72 hours, while the T2 signal intensity remained uniformly increased and returned to normal by 9 days. The ADC changes closely correlated with the presumed area of seizure onset and the resultant histopathologic changes. The authors concluded that the ADC measurement provides more specific information about the evolution of the lesions than does the T2-weighted image, and DW imaging enables detection of recent gray matter cellular damage through an ADC decrease. Nakasu et al (9) also described increases in signal intensity on DW images 1 hour after seizures induced by kainic acid in rats

before the development of changes on T2-weighted images.

In humans, to the best of our knowledge, there are two case reports of periictal DW imaging signal intensity changes in patient with status epilepticus (11, 15). Diehl et al (11) observed a single area of increased diffusion signal intensity on DW images (decrease in ADC) in the region of focal electrocorticographic seizures in a patient with focal status epilepticus. Wieshmann et al (15) reported focal DW imaging abnormalities in a patient with focal motor status epilepticus. They suggest that ictal and early postictal DW imaging techniques may be a useful noninvasive tool for the identification and delineation of epileptogenic foci in some patients with lesional focal epilepsy.

Another important finding observed in our study, which was not reported in the previous studies, is that the mean ADC value of the contralateral normal-appearing hippocampus in the patients with hippocampal sclerosis was also significantly higher than that of the hippocampus in the healthy volunteers. This finding suggests that microscopic pathologic change is present in the normal-appearing contralateral hippocampus of patients with unilateral hippocampal sclerosis, which is supported by the fact that bilateral hippocampal damage occurred in up to one-third of patients with hippocampal sclerosis, as described in previous MR spectroscopy (16) and postmortem (17) studies.

The major limitation of our study is that we performed the study only in patients whose MR imaging findings were positive. To elucidate the real ADC value of the hippocampus in patients whose conventional MR imaging was interpreted as inconclusive or normal, further study is needed to determine whether the ADC value would be positive in pathologically proved cases in which anatomic MR imaging is inconclusive.

Conclusion

Visual assessment of DW images and ADC maps failed to lateralize the lesion side in all patients with hippocampal sclerosis. However, quantitative measurement of ADC values enabled correct lateralization of the affected lesion side in 100% of the 18 patients. Therefore, ADC value can be used as a complementary tool in lateralizing the epileptogenic lesion in patients with hippocampal sclerosis. The normal-appearing hippocampus of the contralateral side in the patients had a higher mean ADC value compared with that of healthy volunteers. Further study is needed to evaluate the practical role of ADC values of the hippocampus in patients with medial temporal lobe epilepsy with inconclusive MR imaging findings of hippocampal sclerosis.

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