Leukoaraiosis, Ischemic Stroke, and Normal White Matter on Diffusion-Weighted MRI

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Background and Purpose—Leukoaraiosis is a radiological finding of uncertain pathogenesis with bilateral patchy or diffuse areas of hyperintensity of the cerebral white matter (WM) on T2-weighted MRI. Using diffusion-weighted MRI (DWI), we aimed to test (1) whether the average apparent diffusion coefficient (ADC<sub>av</sub>) values of the regions of leukoaraiosis vary according to the degree of the severity of leukoaraiosis and whether the regions of leukoaraiosis could be distinguished (2) from normal WM or (3) from ischemic strokes of various ages.

Methods—We compared 85 patients with leukoaraiosis, 22 healthy subjects with no leukoaraiosis on the conventional MR images, and 10 patients with ischemic strokes serially imaged <6 hours, 24 hours, 1 week, 1 month, and 3 months after stroke onset. All subjects were studied with DWI in 3 orthogonal directions with 2 b values (<i>b</i>=0 and <i>b</i>=1000 s/mm²) at 1.5 T. ADC<sub>av</sub> values were determined for the regions of leukoaraiosis, ischemic lesions, and normal WM.

Results—The more severe the leukoaraiosis was, the higher the ADC<sub>av</sub> values of the leukoaraiotic regions became. The ADC<sub>av</sub> values (in 10⁻³ mm²/s) of the regions of leukoaraiosis (0.92 to 1.27) were significantly higher than that of the normal WM (0.69±0.04) and that of the ischemic strokes at 6 hours (0.38±0.07), 24 hours (0.36±0.10), and 1 week (0.51±0.09). One-month-old ischemic strokes (1.08±0.33) had ADC<sub>av</sub> values similar to those of leukoaraiotic regions, whereas 3-month-old infarcts (1.59±0.32) showed significantly higher ADC<sub>av</sub> values than the leukoaraiotic regions.

Conclusions—The regions of leukoaraiosis show characteristic changes in ADC<sub>av</sub> values, and DWI can be used to differentiate acute and chronic ischemic stroke lesions from leukoaraiosis. (Stroke. 2002;33:45-50.)

Key Words: leukoaraiosis ■ magnetic resonance imaging, diffusion-weighted ■ stroke ■ white matter

Leukoaraiosis refers to bilateral and either patchy or diffuse areas of hypodensity of the cerebral white matter (WM) on CT or hyperintensity on T2-weighted MRI. It is a radiological finding that probably is caused by chronic cerebral ischemia, but the pathogenesis and its clinical significance are incompletely understood. Some individuals remain asymptomatic for prolonged periods, whereas others develop gait disturbance, cognitive impairment, mood disorders, disability, and even dementia. Leukoaraiosis increases overall morbidity and mortality and enhances the risk for stroke. Leukoaraiosis is common, and epidemiological studies demonstrate a high prevalence in subjects >65 years old evaluated by CT or MRI.

Diffusion-weighted MRI (DWI) is useful in detecting focal brain ischemia even in the hyperacute (<6 hours) stage. Acute brain ischemia causes a rapid decrease in water diffusion, and ischemic regions appear hyperintense on DW images. The lesions disappear over 5 to 10 days (pseudonormalization) and reappear as hypointense lesions thereafter. In addition to acute stroke, DWI may also provide information on the extent and elucidate the mechanism of leukoaraiosis.

The net diffusion of the water molecules measured from a tissue is referred to as the apparent diffusion coefficient (ADC). On DW images, tissues with faster diffusion appear dark and tissues with slower diffusion appear bright, whereas on ADC maps, the reverse is true. The purposes of this study were to test (1) whether the average ADC (ADC<sub>av</sub>) values of the regions of leukoaraiosis vary according to the degree of the severity of leukoaraiosis and whether the regions of leukoaraiosis could be identified by the use of DWI and distinguished (2) from the normal WM and (3) from the ischemic strokes of various ages.

Subjects and Methods

Subject Characteristics

The study comprised 3 groups of subjects: group 1, 85 subjects with leukoaraiosis (22 healthy subjects [9 men, 13 women] with leukoaraiosis, 53 carotid stenosis patients [33 men, 20 women] with leukoaraiosis, and 10 ischemic stroke patients [5 men, 5 women] with leukoaraiosis); group 2, 22 healthy subjects (12 men, 10 women) with no leukoaraiosis; and group 3, 10 patients (5 men, 5 women) with ischemic strokes serially imaged <6 hours (mean 4.4±1.0 hours, range 2.7 to 5.9 hours, n=10), 24 hours (mean 28±2.7 hours, range 23.8 to 31 hours, n=10), 1 week (mean 6.6±0.6 days, range 5.8 to 7.3 days, n=10), 1 month (mean 33±2.9 days, range 30 to 36 days, n=4), and 3 months (mean 90±5.8 days, range 80 to 95 days, n=6) after the insult.

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The 10 ischemic stroke patients in group 3 were the same 10 patients with ischemic stroke and coexisting leukoaraiosis as in group 1. The leukoaraiotic changes in these 10 patients were evaluated on their 24-hour ADC<sub>av</sub> maps. The infarct volumes measured on 1-week images were 0.016±0.02 L. The infarct characteristics were as follows: Four were cortical, and 6 were subcortical. Four were due to atherosclerosis, 3 were cardioembolic, 2 were caused by small-vessel disease, and in 1 patient the cause could not be determined. Five were left-sided, and 5 were right-sided.

The healthy subjects (22 individuals with leukoaraiosis, 42 to 85 years old [68±9.6 years] and 22 individuals without leukoaraiosis, 52 to 73 years old [60±6.4 years]) were chosen from a strictly healthy population and had no symptoms, signs, or histories of any neurological or systemic disease that might have affected the brain (eg, diabetes, chronic obstructive pulmonary disease, hypertension, or metabolic disorders), nor did they have a family history of dementia or multiple sclerosis. None were taking medication regularly, except for female hormone replacement therapy or topical drug treatment. The healthy subjects with and without leukoaraiosis were not entirely age- and sex-matched, because it was difficult to find absolutely healthy individuals with no leukoaraiosis in the same age group. We have shown, however, that the ADC<sub>av</sub> values in the cerebral WM do not change with aging and between sexes (0.70±0.03x10<sup>-3</sup> mm<sup>2</sup>/s in 50- to 64-year-old and 0.71±0.04×10<sup>-3</sup> mm<sup>2</sup>/s in 65- to 85-year-old healthy subjects; 0.70±0.03×10<sup>-3</sup> mm<sup>2</sup>/s in men and 0.71±0.03×10<sup>-3</sup> mm<sup>2</sup>/s in women; unpublished data, Helenius et al).

In patients with carotid stenosis (group 1), 11 were neurologically healthy, and 42 were symptomatic with transient ischemic attacks (n=35) and/or stroke (lacunar stroke, n=27; cortical infarcts, n=12).

All subjects were white and all except 2 were Finnish in origin. This study was approved by the Ethics Committees of the Departments of Neurology and Radiology, Helsinki University Central Hospital, and was carried out according to the institutional guidelines and the Declaration of Helsinki. All subjects gave written informed consent before enrollment into the study.

**Imaging Techniques**

The study was performed with a Siemens Magnetom Vision imager (Siemens Medical Systems) operating at 1.5 T. A standard head coil with standard restraints was used to fix the subject’s head. In addition to axial DW images, conventional fluid-attenuated inversion recovery (FLAIR), T1-, T2-, and proton density-weighted images were obtained. All imaging studies were completed without any adverse effect or complication.

DWI was performed with a spin-echo echo-planar imaging sequence having a repetition time of 4000 ms, an echo time of 103 ms, and a gradient strength of 25 mT/m covering 19 slices 5 mm thick (interslice gap 1.5 mm, field of view 230×230 mm<sup>2</sup>, and matrix size 96×128 interpolated to 256×256). Diffusion was measured in 3 orthogonal directions (x, y, and z) with 2 b values (b=0 and b=1000 s/mm<sup>2</sup>). The total acquisition time of the DW images was 20 seconds.

**Data Analysis**

DW images were transferred to a separate workstation for data analysis. First, the images in the 3 orthogonal directions were coregistered. The natural logarithms of the images were averaged to form a rotationally invariant resultant image. With a linear least-squares regression on a pixel-by-pixel basis, the resultant image and the natural logarithm of the reference T2-weighted image (b=0) were fitted to the b values, where the slope of the fitted line was ADC<sub>av</sub>. The calculations were performed with a commercially available software program (MatLab, Mathsoft Inc).

**Rating Scale for Leukoaraiosis**

A neuroradiologist (O.S.) blinded to the clinical data of the subjects evaluated the conventional MR images according to a previously validated rating scale.<sup>14,15</sup> Periventricular hyperintensities (PVHs) were classified on the basis of size and shape into 5 groups: HI-1 (small focal, <5 mm, n=47), PVH-2 (large cap/smooth halo, 6 to 10 mm, n=22), and PVH-3 (extending cap/irregular halo, >10 mm, n=16). Hyperintensities (HIs) were classified, on the basis of size and shape, into 5 groups: HI-1 (small focal, <5 mm, n=41), HI-2 (large focal, 6 to 10 mm, n=25), HI-3 (focal confluent, 11 to 25 mm, n=13), HI-4 (diffusely confluent, >25 mm, n=6), and HI-5 (diffuse lesions affecting the majority of WM area, n=0).

**Region of Interest Analysis**

While drawing the regions of interest (ROIs) on the trace images or on the ADC<sub>av</sub> maps, we simultaneously located the lesions on the conventional images to avoid mistakes. The ischemic stroke ROIs (n=2 to 6 per subject) were drawn on the trace images, where the acute, 24-hour-old, and 1-week-old lesions could easily be identified, and were subsequently transferred to the equivalent ADC<sub>av</sub> maps. The 1- and 3-month-old lesions as well as the regions of leukoaraiosis (n=8 to 14 per subject) and the normal WM ROIs (n=4 per subject) were drawn directly to the ADC<sub>av</sub> maps (Figure 1). The normal WM ROIs were the frontal and occipital WM from both hemispheres. Contamination of the normal WM ROIs with the regions of leukoaraiosis was carefully avoided. In each ROI, the surface area was measured, and the mean, SD, and range of the ADC<sub>av</sub> values were obtained. The ROI analysis was performed with a commercially available image analysis software (Alice, Hayden Image Processing Group, Perceptive Systems Inc).

**Statistical Analysis**

The ADC<sub>av</sub> values of leukoaraiosis, ischemic stroke, and normal WM were compared by Kruskal-Wallis 1-way ANOVA, as well as the groups of varying degrees of leukoaraiosis and stroke. Groupwise comparison between any 2 groups was made by use of the Mann-Whitney U test. Comparison between hemispheres in carotid stenosis patients was made by paired t test. A 2-tailed value of P<0.05 was considered significant.
**Results**

All ADC$_{av}$ values are given as $\times 10^{-3}$ mm$^2$/s. The ADC$_{av}$ values of the leukoaraiotic regions and the normal WM of all subjects in group 1 are presented in the Table. The correlation of the ADC$_{av}$ values with the severity of leukoaraiosis is presented in Figure 2.

As the leukoaraiosis increased (PVH-1 to -3 and HI-1 to -4), the ADC$_{av}$ values showed a directly proportional increase ($P<0.01$ for both PVH and HI) (Figure 2, A and B).

The ADC$_{av}$ values of the normal WM of the subjects with leukoaraiosis (group 1 as a whole) did not differ from those of the healthy subjects with no leukoaraiosis (mean 0.69±0.04, range 0.63 to 0.75) (group 2). With more detailed analysis within group 1, however, the ADC$_{av}$ values of the normal WM varied according to the degree of the severity of leukoaraiosis, being highest in the most severely leukoaraiotic groups (Figure 2, D and E; $P<0.01$ for all). In patients with carotid stenosis, the ADC$_{av}$ values of the normal WM between the stenotic and the nonstenotic sides were slightly but significantly different from each other (mean 0.70±0.04, range 0.61 to 0.81, versus mean 0.69±0.05, range 0.55 to 0.78, $P<0.05$, respectively). Instead, the ADC$_{av}$ values of the leukoaraiotic regions were not different between brain hemispheres in these patients (mean 0.95±0.12, range 0.81 to 1.31, versus mean 0.95±0.11, range 0.81 to 1.31, $P=1.0$).

The regions of leukoaraiosis showed significantly higher ADC$_{av}$ values than the normal WM of the same group (group 1, n=85, $P<0.01$) or than the normal WM of group 2 (n=22, healthy subjects with no leukoaraiosis, mean 0.69±0.04, range 0.63 to 0.75, $P<0.01$) (Table).

The ADC$_{av}$ values of the ischemic strokes at the hyperacute stage (mean 0.38±0.07, range 0.25 to 0.49, n=10), the 24-hour stage (mean 0.36±0.10, range 0.21 to 0.55, n=10), and the 1-week stage (mean 0.51±0.09, range 0.35 to 0.62, n=10) were significantly lower than the ADC$_{av}$ values of the regions of leukoaraiosis ($P<0.01$ for all) (Figure 2, A, B, and C). At 1 month, the ischemic lesions showed ADC$_{av}$ values (mean 1.08±0.33, range 0.61 to 1.32, n=4) similar to those of the regions of leukoaraiosis. Instead, at the chronic stage (3 months), the ischemic lesions had significantly higher ADC$_{av}$ values (mean 1.59±0.32, range 1.27 to 1.97, n=6) than the regions of leukoaraiosis ($P<0.01$).

**Discussion**

Bilateral, patchy, and diffuse areas of hyperintensity of the cerebral WM on T2-weighted MRI, referred to as leukoaraiosis, were found to be hyperintense on the ADC$_{av}$ maps in this study and in a previous report. Leukoaraiosis is characterized with axonal loss and proliferation of glial cells. Especially axonal loss may contribute to ADC increase, because axons produce significant hindrance to water diffusion. Axonal loss, furthermore, leads to an increase in water content of the tissue. A previous study with a small number of patients has shown a decrease in fractional anisotropy in the regions of leukoaraiosis and an increase in ADC values similar to our results.

The more severe the leukoaraiosis was, the higher the ADC$_{av}$ values of the leukoaraiotic regions became. This finding was surprising and novel. Presumably, the cause and pathogenesis of leukoaraiosis may contribute to this finding. Numerous potential factors have been suggested to contribute to the pathogenesis, chronic hypoperfusion being the most popular hypothesis. Leukoaraiosis is known to increase with age even in neurologically healthy subjects. Failure of blood supply, ischemia, and blood pressure dysregulation also induce leukoaraiosis. Disturbed flow of cerebrospinal fluid is known to increase periventricular WM changes, and leukoaraiosis is found in Alzheimer’s disease,
Figure 2. Evaluation of ADC\textsubscript{av} values. A, ADC\textsubscript{av} values of the regions of leukoaraisis in PVH groups; B, ADC\textsubscript{av} values of the regions of leukoaraisis in HI groups; C, ADC\textsubscript{av} values of ischemic strokes of different stages; D, normal WM ADC\textsubscript{av} values in PVH groups; and E, normal WM ADC\textsubscript{av} values in HI groups.
in vascular dementia,26 and in many hereditary diseases, including CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).6 In autopsy studies, periventricular venous collagenosis, perivascular degeneration,27 lacunar infarcts, incomplete infarctions, and gliosis have been found to be associated with leukoaraiosis.2,28,29 Despite the large number of studies, the cause and pathogenesis of leukoaraiosis remain controversial. As discussed above, however, axonal loss is likely to contribute to ADC increase, and in severe leukoaraiosis, axonal loss replaced by interstitial water may be remarkably high, which may explain our finding.

The findings that the ADCav values of the normal WM increased from the mildest to the most severe degrees of leukoaraiosis and that the ADCav values of the normal WM in carotid stenosis patients between the stenotic and nonstenotic sides were different may indicate that the WM is already undergoing changes toward leukoaraiosis before it can be detected on the conventional MR images. Because we delineated the normal WM ROIs with great care, it is most unlikely that there was contamination from tissues with leukoaraiosis. Therefore, a partial-volume effect was excluded. DWI may provide information on the extent and severity of leukoaraiosis, and it may detect areas of WM that, even though they appear normal on conventional MRI, are prone to undergo leukoaraiotic change over time. A follow-up study in the future may confirm this finding.

Because a rapid decrease of 30% to 40% in ADC values occurs in acute brain ischemia,11,30 hyperacute and acute ischemic lesions of the brain appear hypointense on ADCav maps.11–33 As expected, we could easily distinguish ischemic strokes during the first week from the regions of leukoaraiosis on the ADCav maps. The ADC values of chronic (≥3-month-old) brain infarcts are higher than those of the normal brain tissue, because diffusion in necrotic regions approaches that of free water (a mean ADCav value for the lateral ventricles is 2.9±0.22, ranging from 1.7×10–3 to 3.2×10–3 mm2/s; unpublished data, Helenius et al). Not surprisingly, the ADCav values in the regions of leukoaraiosis were lower than those of chronic infarction. It seems that DWI is useful in distinguishing ischemic stroke lesions of the acute and of the chronic stage from the regions of leukoaraiosis. Because the ADCav values of 1-month-old infarcts and leukoaraiotic regions were similar, DWI appeared not to be useful in distinguishing leukoaraiosis from brain infarction at that time point. Even though the patient numbers in the 1- (n=4) and 3-month-old (n=6) infarcts were small, the results of 3 previous studies agree well with our findings of the ADC values in chronic ischemia31,34,35 and further support our findings.

Classification of leukoaraiosis is a challenge. Several rating scales with various approaches have been designed. Some make a distinction between different regions, whereas others use an overall estimate of leukoaraiosis. The scales often refer to definite pulse sequences. We preferred to use a previously validated rating scale developed at our hospital14,15,36 and evaluated leukoaraiosis on T2-weighted, proton density–weighted, and FLAIR images separately in all WM areas and periventricular and other regions.14,36 Our scale has the advantage of taking into account the number, size, and shape of the leukoaraiotic lesions.

In this study, to characterize the ADCav values of leukoaraiosis, we compared spin-echo echo-planar DWI findings of 85 subjects with leukoaraiosis, 22 healthy control subjects without leukoaraiosis, and 10 patients with ischemic strokes serially imaged from the hyperacute to the chronic stage. Apart from being different from the normal WM, the ADCav values of the leukoaraiotic regions showed a consistent trend of an increase in proportion to the severity of the leukoaraiotic change. In the course of ischemic stroke, the evolution of the ADCav values remained below that of the leukoaraiotic regions at the hyperacute and subacute stages up to 1 week, equaled them at 1 month, and significantly exceeded them at 3 months. In conclusion, the regions of leukoaraiosis show characteristic changes in ADCav values, and DWI can be used to differentiate acute and chronic ischemic stroke lesions from leukoaraiosis.

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