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Hospital-Based Study**

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ORIGINAL
RESEARCH

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Incidental Acute Infarcts Identified on Diffusion-Weighted Images: A University Hospital-Based Study

BACKGROUND AND PURPOSE: Pathogenesis of leukoaraiosis is incompletely understood and accumulation of small infarctions may be one of the possible sources of such white matter lesions. Thus, the purpose of this study was to identify the rate of incident infarction as depicted on diffusion-weighted images (DWIs) obtained from a general patient population.

MATERIALS AND METHODS: During the 4-year study period, a total of 60 patients (36 men and 24 women) had an incidental DWI-defined infarction without overt clinical symptoms suggestive of a stroke or a transient ischemic attack. All of the MR images were obtained by using a similar protocol on 2 identical 1.5T whole-body scanners. The patient's vascular risk factors, as well as the presence of white matter lesions (WMLs) on MR imaging and atheromatous changes on MR angiography, were assessed retrospectively. The incidental DWI-defined infarcts were also characterized in terms of their lateralization, lobe, and specific location.

RESULTS: A total of 16,206 consecutive brain MR images were done during the study period; the overall incidence of incidental infarcts was 0.37%. Most of these patients with an incidental infarct had vascular risk factors and WMLs on MR images. Most of these patients (80%) had a single lesion on DWI. A total of 88 lesions were identified; most were located in the white matter of the supratentorial brain, primarily in the frontoparietal lobes. There were also lesions involving the brain stem ($n = 2$). The lesions involving cerebrum were more commonly located in the right side (right to left = 52:34).

CONCLUSION: Small, DWI-defined acute brain infarctions can be found incidentally in an asymptomatic population; this finding may account, at least in part, for the pathogenesis of WMLs identified on MR imaging.

White matter lesions depicted on MR imaging have been a center of debate for many years. These white matter rarefactions were originally described on CT and termed "leukoaraiosis" by Hachinski et al.¹ Epidemiologic studies have shown that leukoaraiosis is correlated with age, hypertension (HT), and arteriosclerosis.²⁻⁶ Other reported causative factors include cigarette smoking⁶ and glucose intolerance.⁵ These predisposing factors are also found in patients with lacunar infarcts; thus, it has been proposed that leukoaraiosis and symptomatic lacunar infarcts share a similar underlying vasculopathy, namely, subcortical occlusive small-vessel disease secondary to arteriolosclerosis.⁷⁻⁹

Population studies have noted that leukoaraiosis progresses over a period of years.^{6,10} The mechanism by which these lesions increase over time remains unknown. It has also not been determined whether a new white matter lesion (WML) focus grows slowly over a period of months or whether it suddenly appears and evolves rapidly as an acute infarct. Previously proposed mechanisms include both insidious and acute processes.¹¹⁻¹⁷ For instance, one of the proposed insidious mechanisms is apoptosis induced by chronic ischemia.¹⁴ Microembolic events have been proposed as an

acute pathogenetic process.^{15,16} Other proposed etiologies, which could be either insidious or acute, include intermittent changes in cerebral perfusion pressure resulting in incomplete infarction¹⁷ and white matter damage by altered blood-brain barrier permeability.¹¹⁻¹³

Whatever the mechanism, these lesions will be seen on diffusion-weighted imaging (DWI), if at least some of them occur due to an acute process. Given that DWI has a unique contrast property and a relatively short acquisition time, this imaging technique has been incorporated into many routine brain MR protocols, including, among others, protocols for strokes,¹⁸⁻²¹ headaches, seizures, and tumors.²²⁻²⁴

Over the past few years, we have used DWI for our routine brain protocol assuming that incidental infarcts would be identified on DWI performed in a general patient population. Although relatively uncommon given the total number of MR examinations that were done, a number of patients with incidental acute or subacute infarcts were identified. These patients' clinical and imaging data were retrospectively analyzed to elucidate the significance of our observations.

Materials and Methods

This study was approved by our institutional review board.


Patient Population

The study was carried out in our university hospital-based MR center from August 2002 to November 2006 (52 months). During the study period, we prospectively recorded patients who had an incidental hyperintensity on DWI. When a radiologist found an incident infarct during the MR reading, he or she recorded the name, identification number, and date of the scan in an on-line database. Medical records of each patient were reviewed to include only those who were asymp-

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omatic at the time of MR. Apparent diffusion coefficient (ADC) maps were calculated for all of these cases. Patients were included in this study when they had a lesion with a low ADC or in whom, on follow-up, the lesion disappeared. ADC was defined as being low when it was lower by at least 15% than that of the surrounding brain tissue on the same section. Patients who had specific neurologic symptoms or a transient ischemic attack were excluded. In addition, patients who had undergone recent cardiovascular surgery or conventional angiography within 1 month prior were excluded, because these patients may have had procedure-related infarcts.

Imaging Methods

All of the images were obtained by using 1 of 2 identical, 1.5T whole body scanners (Gyrosan Intera; Philips Medical Systems, Best, Netherlands). The routine brain imaging protocol at our institute requires 14 minutes and consists of T1-weighted images (TR = 611 ms; TE = 13 ms), T2-weighted images (TR = 4754 ms; TE = 100 ms), fluid level-attenuated inversion recovery (FLAIR) images (delay time = 2200 ms; TR = 8000 ms; TE = 100 ms), T2*-weighted images (TR = 666 ms; TE = 23 ms), and DWI. Time-of-flight MR angiography (TR = 30 ms; TE = 2.3 ms) was optional depending on the reason for the imaging request.

DWI scanning was performed with an image acquisition time of approximately 4 minutes. A single-shot echo-planar imaging technique was used for DWI (TR/excitation time = 6000/88 ms) with a b-value of 1000 s/mm² and image averaging of 2 times. Motion sensitizing gradients were applied to 15 different directions. A parallel imaging technique was used to record the 128 × 53 data points, which were reconstructed to a 128 × 128 resolution. A total of 42 sections were obtained with a thickness of 3 mm without intersection gaps.

Patient Data Analysis

Stroke risk factors, including diabetes mellitus, HT, hyperlipidemia (HL), past history of coronary disease, carotid disease, and smoking, were recorded. In addition, the patients' electrocardiography (ECG) results were reviewed to determine the presence of atrial fibrillation (AF) or left ventricular hypertrophy (LVH).

A history of HT was defined as a systolic blood pressure >160 mm Hg or a diastolic blood pressure >95 mm Hg. Diabetes was defined as a previously documented diagnosis, current use of insulin or oral hypoglycemic medication, or a fasting blood glucose above 126 mg/dL. The total cholesterol was considered to be high in patients with a level at or more than 250 mg/dL. The triglyceride level was considered to be high in patients with a level at or more than 400 mg/dL. The hematocrit value was considered to be high when it was at or more than 47%. Atherosclerosis was considered to be present if there was an occlusion, clear stenosis, or other atherosclerotic plaque, including ulceration of a major artery, on carotid sonography examination or MR angiography.

Imaging Data Analysis

Degrees of WMLs and periventricular hyperintensity (PVH) were rated according to the definition of Fazekas et al.²⁵ The WMLs were rated on a scale of 0–3 with 0 indicating absent; 1 indicating punctuate; 2 indicating early confluent; or 3 indicating confluent. The PVHs at the frontal and peritrigonal white matter were also rated on a scale of 0–3, with 0 indicating caps; 1 indicating pencil-thin linings; 2 indicating smooth halos; or 3 indicating irregular. The degree of atheromatous changes on MR angiography was graded on a scale of 0–3, with 0 indicating none; 1 indicating mild; 2 indicating moderate; or 3

indicating severe. Severe stenosis was defined as a lesion that affects the distal flow in at least 1 of the major vessels. Mild and moderate stenoses were those without distal flow compromise. These gradings were done by a single operator for consistency.

Each lesion identified on DWI was classified in terms of side (right or left), lobe (frontal, parietal, occipital, or temporal), and location (cortex, central gray matter, subcortical white matter, or deep white matter). In addition, lesion size, lesion ADC, and percentage of ADC (ratio of the lesion ADC compared with that of surrounding brain tissue) were recorded.

Results

There were 60 patients (36 men and 24 women) with incidental infarcts on DWI during the 52-month study period. Given that there was a total of 16,206 consecutive brain MR images performed during this study period, the overall incidence of incidental infarcts was 0.37%. Therefore, there was an average of at least 1 incidental infarct case in our institute per month.

The patients' ages ranged from 39 to 90 years (mean ± SD: 70 ± 10 years). Most of these patients (72%) were more than 65 years of age. Incidental infarcts were noted most frequently in patients in their 60s and 70s, whereas they were less common in patients younger than their 50s (<50, *n* = 1; 50s, *n* = 8; 60s, *n* = 21; 70s, *n* = 21; >80, *n* = 9). The specific reasons that a brain MR examination was requested are listed in On-line Table 1. Follow-up of a previous cerebrovascular accident (*n* = 19) was the most common reason for an MR examination; the next most common reason was memory disturbances (*n* = 13). Approximately two thirds (65%) of these examinations were referred from either the neurology (*n* = 23) or neurosurgery (*n* = 16) departments.

Vascular Risk Factors

At least 1 vascular risk factor was found in most of the patients (92%). More than half (*n* = 32) of these patients had >2 vascular risk factors. The incidence of vascular risk factors is summarized in On-line Table 2. More than half of the patients had HT (58%). HL was found in 30% of the patients. AF was found on ECG in 12% of patients. LVH was suspected on ECG in 22% of patients. A clinical history suggestive of coronary disease was present in 28%.

WMLs and Atherosclerosis on MR

Most of these patients (97%) had WMLs of various degrees (On-line Table 2). The degree of WMLs ranged from 0 to 3, and the average score ± SD was 2.2 ± 0.7. The degree of PVH ranged from 0 to 3, and the average was 1.7 ± 0.9. Atheromatous changes on MR angiography were also noted in most patients (*n* = 37 [80%] of 46). The degree of atheromatous changes ranged from 0 to 3, and the average was 1.5 ± 1.0.

Lesion Characteristics on DWI

Of the 60 patients with incidental infarct(s), 48 (80%) had a single lesion, and 12 (20%) had multiple lesions. Patients with multiple lesions had an average of 3.3 lesions per case.

A total of 88 lesions were identified on DWI. The size of the lesions (in the longest dimension) ranged from 3 to 21 mm (mean ± SD = 6.0 ± 3.7 mm). The incidental infarcts were most frequently located in the subcortical and deep white matter, though there were also lesions involving the brain stem

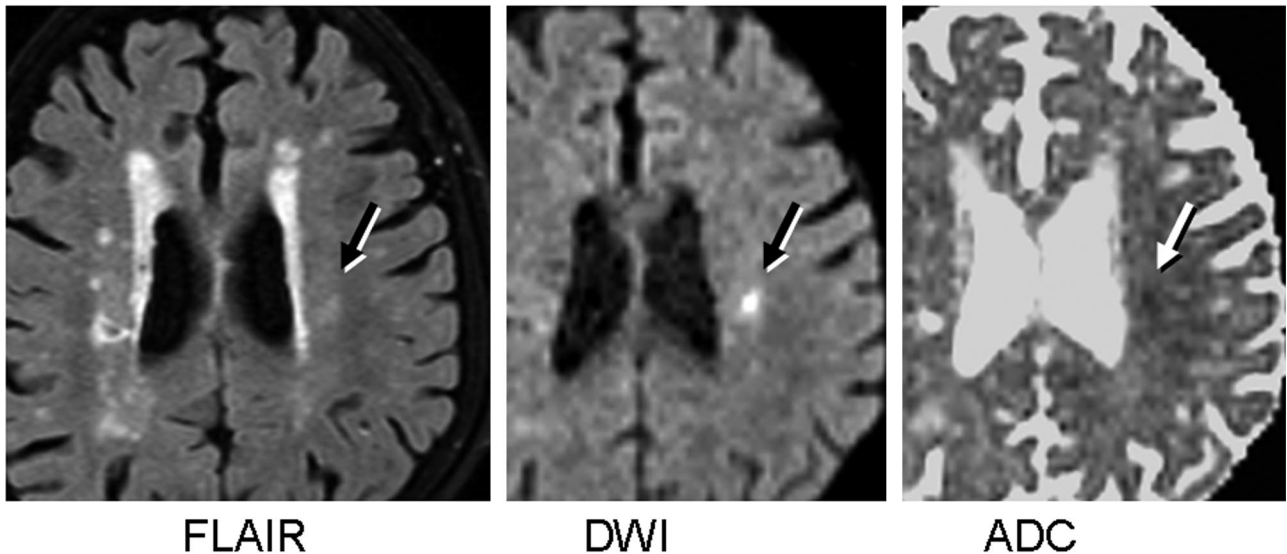


Fig 1. A 75-year-old woman, who was being regularly seen by her neurologist for a gradual decline in cognitive function over a few years, was referred to the department of radiology for MR examination to rule out temporal lobe atrophy, which could indicate Alzheimer disease. On FLAIR, multiple WMLs are seen, and on DWIs, there is a single focus of hyperintensity among these multiple WMLs at the left centrum semiovale (black arrows). The lesion also has a reduced ADC (white arrows), which suggests that this is a relatively acute lesion. The presence of minimal temporal lobe atrophy (not shown) does not support a diagnosis of Alzheimer disease.

($n = 2$) (On-line Table 3). The lesions of cerebrum were most frequently located in the frontal and parietal lobes, which is congruent with the typical distribution of leukoaraiosis described in the literature.^{26,27} These supratentorial lesions were more frequent on the right side (right-to-left ratio = 52:34).

The mean ADC \pm SD of these incidental lesions was 0.71 ± 0.14 mm²/s, whereas the mean ADC of surrounding brain tissue was 0.83 ± 0.12 mm²/s. The mean percentage of ADC of the lesions was $77\% \pm 12\%$; this indicates an approximately 23% decrease in the ADC of the lesions compared with the surrounding brain tissue. A representative case is illustrated in Fig 1.

Discussion

This study showed that incidental acute and subacute infarcts can be found on DWI in an unselected patient population. Most of these patients had leukoaraiosis located in the cerebral hemispheres on T2-weighted images or FLAIR. Thus, it is suggested that at least some of the WMLs consist of small acute infarctions identified on DWI. It has been proposed that leukoaraiosis and symptomatic lacunar infarcts share a similar underlying vasculopathy,^{28,29} because they are both epidemiologically correlated with vascular risk factors.²⁻⁶ Our data further support this hypothesis.

If indeed these incident infarcts were acute in nature, the patients' lack of symptoms must be explained. Lesion location and lesion size are undoubtedly the most important factors determining whether the patient becomes symptomatic.^{3,5,30} In previous studies, it has been pointed out that subcortical infarcts that are not associated with obvious symptoms and are silent simply because they occur in clinically ineloquent regions of the brain. The right hemispheric preponderance found in the present study may also support this hypothesis. Using MR tractography, an MR data postprocessing technique that allows direct clinicoradiologic correlation, one may be able to determine whether the white matter infarct involves an eloquent area. We are currently studying this issue.

The pathogenesis of leukoaraiosis is incompletely understood. Studies have linked leukoaraiosis with demyelination, gliosis, necrosis, cavitation, and vacuolization, conditions commonly associated with cerebrovascular disease.⁵ Our observation using DWI may support these previous works that have indicated vascular etiology for leukoaraiosis. What remains unclear is whether such DWI-defined acute lesions are one of the most dominant causes of leukoaraiosis or whether they constitute only small fraction of the entire WMLs. In view of multifactorial etiology of leukoaraiosis, we believe that these DWI-defined infarcts are only responsible for part of the leukoaraiosis. Further study will be necessary to elucidate this point.

Prevention and treatment of these WMLs are now regarded as important issues. Especially important will be the management of vascular risk factors.³¹ Our data showing tiny acute DWI-defined infarcts being at least part of the problem may further support the relevance of such movement.

Because the present study was a hospital-based study, it is obvious that there was a selection bias. A more ideal study would be community based and would involve asymptomatic volunteers. However, such a study could be extremely expensive, depending heavily on the frequency of MR examination. However, given our results, such a project may be justified.

The present study has several other limitations. First, no MR-pathologic correlation could be done; such a correlation is unlikely to be obtained, given the low rate of autopsies in patients with small infarcts identified on DWI. Animal models of HT, vascular dementia, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy may clarify the nature of these incidental infarcts, though the need for frequent MR scanning of the animals may hamper the implementation of such a study. Furthermore, the selection of a particular animal model will probably bias the study toward a single etiology of ischemia. Second, we used 3-mm-section DWI for our study, which has higher spatial resolution than conventional DWI that typically uses more than 5-mm-

section thickness. Thus, our detection rate of incidental infarcts may have been higher than the detection rate in other institutes. Finally, the overall incidence of 0.37% in our study is probably an underestimation of what is actually occurring in brains of the elderly population, considering the fact that the MR images were single time spot evaluations and the lesions will stay hyperintense on DWI for only a limited amount of time. The true incidence of incident infarcts may become apparent when a population-based study is conducted with sufficiently short scan intervals.

Conclusion

Small acute brain infarctions can be found incidentally on DWI in an asymptomatic patient population. It is conceivable that these silent DWI-defined infarcts account for at least some of the leukoaraiosis, and, thus, further study may be necessary to investigate the clinical relevance of these lesions.

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