Evaluation of Hyperintense Vessels on FLAIR MRI for the Diagnosis of Multiple Intracerebral Arterial Stenoses

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Background and Purpose—Hyperintense vessel sign (HVS) on fluid-attenuated inversion recovery (FLAIR) has been described in hyperacute stroke patients with arterial occlusion. We sought to determine whether HVS was more frequent in patients with intracerebral arterial stenoses than in those without stenosis regardless of the presence of a brain infarct.

Methods—In this case-control study (19 symptomatic patients with multiple intracerebral arterial stenoses compared with 19 age-matched asymptomatic patients without stenosis), we looked for HVS (ie, focal or tubular hyperintensities in the subarachnoid space) on FLAIR images. We compared the proportion of HVS-positive patients in the 2 groups and evaluated the concordance between the arterial distribution of stenoses on angiogram and that of HVS on FLAIR.

Results—HVS was found in 13 of 19 patients (68%) in the study group and 1 of 19 control patients (5.2%) (P<0.0001). The concordance between the territorial distribution of stenoses on angiogram and HVS on FLAIR was higher for the right and left middle cerebral artery (κ=0.6 and 0.63, respectively) compared with the right and left anterior cerebral artery (κ=0.35 and 0.2, respectively). HVSs were observed in 1 of 7 patients with posterior cerebral artery stenoses on angiogram. HVSs were seen equally in patients with acute focal (7 of 10) or diffuse (6 of 9) cerebral involvement. In the 6 HVS-positive patients with acute stroke confirmed by MRI, additional HVSs were observed in a different arterial territory than that of the stroke lesion.

Conclusions—Although their significance remains unclear, multiple HVSs are more frequently observed in symptomatic patients with multiple intracerebral stenoses than in asymptomatic patients without stenosis. (Stroke. 2003;34:1886-1891.)

Key Words: arteries ■ brain ■ magnetic resonance imaging ■ stenosis

Cerebral arterial stenoses can be caused by a wide range of diseases such as central nervous system infectious or inflammatory vasculitis,1-3 intracranial atherosclerosis,4 or vasospasm.5,6 The diagnosis of intracerebral arterial stenosis can be clinically challenging because the initial presentation is highly variable, with focal to diffuse neurological manifestations and acute to chronic evolution.5-7 Digital subtraction angiography (DSA) remains the keystone diagnostic technique for delineating proximal or distal segmental stenoses of intracranial arteries. Yet, in practice, MRI precedes angiographic studies in the evaluation of these patients. Fluid-attenuated inversion recovery (FLAIR) is now part of many routine clinical MR protocols for brain imaging because of its excellent capacity to depict parenchymal signal changes. There is increasing evidence that FLAIR sequence could also be useful for detecting abnormal arterial blood flow kinetics. Indeed, several groups have reported an increased intensity in cerebral blood vessels on FLAIR in the setting of acute ischemia in patients with major vessel occlusion or severe stenosis.8,9 This so-called hyperintense vessel sign (HVS) on FLAIR MRI is thought to indicate the presence of slow flow or stasis in small arteries, veins, and collateral vessels.10 We hypothesized that HVSs could be associated with the presence of multiple intracerebral arterial stenoses regardless of the presence of a brain infarct. To test this hypothesis, we conducted a case-control study to compare the FLAIR images of 19 patients with intracerebral arterial stenoses and 19 control subjects without intracerebral stenoses.

Subjects and Methods

Patients and Control Subjects

Study Group
From our database of patients admitted between August 1999 and December 2002, we retrospectively selected those who fulfilled the following criteria: (1) presence of acute or subacute neurological signs or symptoms at admission; (2) multiple cerebral arterial stenoses demonstrated by DSA or MR angiography; (3) MRI with an axial FLAIR sequence obtained <1 week before angiogram; (4) no
Evidence of subarachnoid hemorrhage on CT and/or lumbar puncture; (5) a lumbar puncture excluding meningitis when clinically suspected; and (6) no evidence of stenosis of extracranial arteries on DSA, MR angiography, or ultrasonographic examination. Nineteen patients (8 men, 11 women) between 22 and 67 years of age (mean age, 43 years) fulfilled these criteria and constituted the study group. At the time of MR, all patients presented signs of neurological impairment, suggesting focal cerebral involvement in 10 and diffuse encephalopathy in the remaining 9. Of the latter 9 patients, 1 was referred for subacute psychiatric disorders, 6 were admitted because of prominent intense headaches of sudden onset, and the remaining 2 presented with diffuse neurological symptoms (tremor, altered mental state, and sleepiness). Intracerebral arterial stenoses were attributed to a reversible angiopathy in 8 cases (associative conditions included blood transfusion (n = 1), eclampsia (n = 2), undetermined (n = 5)). All of them had MR angiographic follow-ups showing regression or disappearance of arterial stenoses and a benign clinical course that did not require corticosteroid or other immunosuppressive therapy. For the other 11 patients, infectious angiitis was diagnosed in 2 patients, and intracranial atherosclerosis, dysplasia, and Sjögren angiitis were found in 1 patient each. The cause remained unknown in 6 patients despite a complete workup, including a leptomeningeal biopsy in 2 cases.

Control Group
The control group consisted of 19 asymptomatic age-matched patients (9 men, 10 women; mean age, 42.2 years). They were selected from a population of patients who had been treated with endovascular coiling for an intracranial aneurysm and were undergoing a 1-year intracranial DSA and FLAIR MR follow-up study. Patients with extracranial or intracranial arterial stenoses on DSA were not included in the control group.

Imaging Techniques and Analysis
HVS on FLAIR
All MR examinations were performed with a 1.5-T MR unit (GE Signa Horizon Echospeed) including a fast FLAIR sequence with 20 interleaved slices, 256×192 matrix, 10,002-ms repetition time, 148-ms effective echo time, 2200-ms inversion time, and 32-kHz bandwidth. The field of view was 28×28 cm, with 6-mm slice thickness, no gap, and an inversion pulse applied over twice the slice thickness for the 10 patients admitted for sudden neurological deficit, in accordance with our routine emergency MR procedure for acute stroke. All other patients were imaged with a slightly different FLAIR sequence using a field of view of 24×24 cm, 5-mm slice thickness, 1.5-mm gap, and inversion pulse applied over 3 times the slice thickness. Overall, 38 sets of FLAIR images were available for analysis.

FLAIR was considered positive (HVS+) when focal or tubular hyperintensities relative to gray matter were seen in the subarachnoid space on >1 axial slice. Each hyperintense vessel was assigned to a portion of the Willis circle (ie, proximal when they were located in the area of the A1, M1, and P1 or P2 segments; distal when located elsewhere) and a vascular distribution (anterior [ACA], middle [MCA], or posterior [PCA] cerebral artery). For hyperintensities that were distally located, reviewers were instructed not to take into account paramedian tubular or bridge-shaped hyperintensities seen at the vertex and localized slightly away from the cortical surface because these were considered to correspond to venous structures. Two neuroradiologists, blinded to the clinical and angiographic data, independently reviewed the randomly presented FLAIR images after they were removed from other sequences. In the event of discrepancy, the final result was reached by consensus. In addition, to check for intraobserver reproducibility, 1 reviewer examined the FLAIR images again 1 week later, with the images presented in a different order than that of the first session.

On FLAIR, the reviewers looked for parenchymal signal changes in the cortical and subcortical areas in the vicinity of each HVS. On diffusion-weighted imaging (DWI), available in 15 patients of the study group, reviewers looked for signs of acute stroke, ie, hyperintensities on DWI (b=1000 s/mm²) with a corresponding decrease in the apparent diffusion coefficient.

Stenoses on Angiograms
DSA was performed by femoral approach with contrast injection in at least 3 vessels (both internal carotid arteries and 1 or 2 vertebral arteries). Biplane, frontal, and lateral DSA images were obtained serially with an exposure rate of 2 images per second during the first 6 seconds followed by 1 image per second during the next 13 to 16 seconds. Intracranial 3-dimensional time-of-flight MR angiography, obtained during the same imaging session as the FLAIR sequence, was performed with a repetition time of 33 ms, an echo time of 3.3 ms, a flip angle of 20°, an acquisition bandwidth of 12.5 kHz, a scanning time 6 minutes 56 seconds, and 2 axial slabs centered on the circle of Willis. Angiograms were retrospectively evaluated on film screen by a neuroradiologist blinded to the clinical and MRI data. He searched for focal arterial stenoses on DSA when available (n = 16) or otherwise on MR angiogram (n = 3). Stenoses were classified as proximal when they involved the A1, M1, P1, or P2 segments; otherwise, they were classified as distal. Each stenosis was assigned a vascular distribution (ACA, MCA, or PCA).

Statistical Analysis
The proportions of HVS+ patients in the study group and control group were compared by use of Fisher’s exact test. Intraobserver and interobserver agreement for the diagnosis of HVS was assessed by calculating the κ statistical analysis and their 95% confidence interval (CIs). We also evaluated the concordance between the topography of stenoses on angiogram and the topography of HVS on FLAIR by calculating the κ statistics and their 95% CIs. To do so, each cerebral arterial territory (ACA, MCA, PCA) was considered abnormal on FLAIR when it contained at least 1 HVS. Similarly, each arterial territory was considered abnormal on angiogram when it contained at least 1 arterial stenosis. A Wilcoxon signed-rank test was used to compare the presence of each HVS with the presence of underlying parenchymal lesion on FLAIR. Fisher’s exact test was used to analyze the occurrence of HVS according to initial clinical presentation. The level of statistical significance was P<0.05.

Results
HVS on FLAIR
HVS was identified by consensus in 13 patients (68%) in the study group and 1 patient (5.2%) in the control group (P = 0.0001) (Figures 1 and 2). During the first reading, observer 1 identified HVS in 12 of the 19 patients in the study group and 2 of the 19 patients in the control group, whereas observer 2 identified HVS in 14 of the 19 patients in the study group and 2 of the 19 patients in the control group. The intraobserver agreement for the identification of HVS was κ=0.89 (95% CI, 0.68 to 1) for the study group and κ=0.82 (95% CI, 0.63 to 1) for the whole population. The interobserver agreement was substantial between the first reading of observer 1 and observer 2 (study group: κ=0.76; 95% CI, 0.45 to 1.0; whole population: κ=0.83; 95% CI, 0.66 to 1) and substantial between the second reading of observer 1 and observer 2 (study group: κ=0.66; 95% CI, 0.33 to 0.99; whole population: κ=0.67; 95% CI, 0.45 to 0.90). The distribution of HVS on FLAIR is presented in the Table.

HVS and Angiogram
The Table shows the distribution of stenoses on angiogram in the 13 HVS+ and 6 HVS− patients of the study group. Of the 13 HVS+ patients, arterial stenoses were seen on angiogram in the corresponding territories in all but 2 patients. Yet, stenoses were more widespread on angiogram than were
HVSs on FLAIR because additional arterial stenoses were observed in arterial territories with no HVS on FLAIR in 9 of 13 HVS patients. The concordance between the territorial distribution of stenoses on angiogram and HVS on FLAIR was higher for the right and left MCA (κ=0.6; 95% CI, 0.3 to 0.9; and κ=0.63; 95% CI, 0.3 to 1.0, respectively) compared with the right and left ACA (κ=0.35; 95% CI, 0.0 to 0.7; and κ=0.2; 95% CI, 0.0 to 0.4). For the PCA territories, concordance was not calculated because HVSs on FLAIR were observed in only 1 of the 7 patients with stenoses of the PCA on angiogram. These concordances remained unchanged after exclusion of the 3 patients for whom only an MR angiography was available.

Figure 1. Reversible cerebral angiitis in a 48-year-old woman presenting with seizures and headaches of sudden onset and right hemiparesis. A, Initial axial FLAIR sequence shows multiple bilateral focal and tubular hyperintensities within the subarachnoid space (arrows), likely adjacent to the cortical surface, and subcortical bilateral parenchymal signal changes. HVSs are bilaterally distributed in the ACA and right MCA territories. B, DWI shows the absence of parenchymal hyperintensities. Right (C) and left (D) internal carotid DSAs demonstrate multiple stenoses of proximal and distal segments of the ACA and MCA. Arrows on DSA point to stenoses that could be responsible for the HVSs seen on FLAIR. Spontaneously, the focal deficit resolved within a week. E, Five weeks later, the stenoses almost completely regressed on MR angiogram, and tubular hyperintensities were no longer visible on FLAIR.

HVSs on FLAIR because additional arterial stenoses were observed in arterial territories with no HVS on FLAIR in 9 of 13 HVS+ patients. The concordance between the territorial distribution of stenoses on angiogram and HVS on FLAIR was higher for the right and left MCA (κ=0.6; 95% CI, 0.3 to 0.9; and κ=0.63; 95% CI, 0.3 to 1.0, respectively) compared with the right and left ACA (κ=0.35; 95% CI, 0.0 to 0.7; and κ=0.2; 95% CI, 0.0 to 0.4). For the PCA territories, concordance was not calculated because HVSs on FLAIR were observed in only 1 of the 7 patients with stenoses of the PCA on angiogram. These concordances remained unchanged after exclusion of the 3 patients for whom only an MR angiography was available.

Figure 2. Reversible angiitis in a 50-year-old woman who presented with photophobia, nausea, and vomiting with severe headaches of sudden onset. CT scan and lumbar puncture were normal. MRI was obtained 2 days after symptom onset. A, Axial FLAIR sequence shows bilateral focal and tubular hyperintensities within the subarachnoid space, deep in the sulci, distributed in the right ACA and MCA territories bilaterally (arrows). Additional parenchymal signal changes are also visible in the cortical and subcortical areas posteriorly. B, DWI shows the absence of parenchymal hyperintensities. Right (C) and left (D) internal carotid DSAs demonstrate multiple proximal and distal stenoses of the MCA (arrows) that could be responsible for the HVSs seen on FLAIR and reveals additional stenoses of the left ACA territory (arrowheads). D, Four weeks later, tubular hyperintensities are no longer visible on FLAIR.

HVS, Parenchyma, and Clinical Presentation
Of the 13 HVS+ patients, HVSs were more frequently observed without underlying parenchymal signal changes in the adjacent cortex or subcortical area than with underlying signal changes (P<0.05). The Table shows that all patients with stenoses attributed to a reversible angiopathy were HVS+ and that HVSs were observed equally in patients who initially presented with focal (7 of 10) or diffuse (6 of 9) cerebral involvement. Interestingly, in 6 of the 7 HVS+ patients with acute stroke confirmed by MRI, HVS was not confined to the limits of the acute stroke lesion but was also observed in a different arterial territory than that of the stroke lesion (Figure 3).

Discussion
The FLAIR sequence is now part of many routine clinical imaging protocols. An inversion pulse is used with long repetition and echo times to create heavy T2-weighted images with cerebrospinal fluid (CSF) nulling, thereby providing excellent contrast between the CSF and the brain surface. Because of the so-called “flow-void” phenomenon, normal arteries are not usually visible against the dark CSF background on FLAIR sequences.13 Recently, hyperintense vessels have been described on FLAIR images in hyperacute stroke patients with an arterial occlusion8,9,14 and are considered to be an indicator of slow flow and inadequate collateral
Circulation. The results of this case-control study suggest that (1) the assessment of HVS on FLAIR is reproducible, (2) multiple HVS on FLAIR is significantly more frequent in patients with multiple intracerebral stenoses (68%) than in asymptomatic patients without intracerebral stenoses (5.2%) regardless of the presence of a brain infarct, and (3) HVSs on FLAIR underestimate the extent of intracerebral stenoses as demonstrated by angiogram.

The study group consisted of patients with a heterogeneous group of disorders that had in common the presence of multiple intracerebral stenoses. HVSs were observed regardless of the underlying cause of the multiple intracerebral stenoses. Interestingly, HVSs seemed to be more frequent in patients with reversible angiopathy (8 of 8) than in the other patients. In reversible angiopathy, the presumably spastic mechanism of the widespread stenoses could produce more abrupt hemodynamic changes than those occurring in other vasculopathies, with a more chronic and progressive course. However, the small sample size of the studied population makes it difficult to draw any definitive conclusion from the observed associations.

For the purposes of our study, the control group should have consisted only of patients with no intracranial arterial stenoses. These can be ruled out only on DSA, which is no longer part of the routine diagnostic workup in our institution. We chose to select patients who had been treated for an intracranial aneurysm and were undergoing intracranial DSA and FLAIR MR follow-up. They fulfilled the main criteria for a control group because none had intracranial arterial stenoses. We assumed that after 1 year of treatment the aneurysm would not cause any hemodynamic impairment of the downstream arterial circulation and that CSF changes resulting from the initial subarachnoid hemorrhage would have completely resolved. This was further confirmed by the fact that none of the control patients had diffuse CSF hyperintensities.
The physiopathology of HVS is still unclear. The mechanisms of HVS in patients with intracerebral stenoses and those with arterial occlusion may be similar. In hyperacute stroke patients with occlusion of a major intracerebral artery, sufficient data are available to suggest that HVS on FLAIR represent altered hemodynamics. Indeed, HVS in acute stroke has been shown to correlate not only with slow anterograde and leptomeningeal collateral arterial flow on DSA but also with intravascular enhancement on T1-weighted pulse sequence, regional hyperperfusion, and larger infarct volume. These data support the hypothesis that HVS is the result of an arterial slow-flow phenomenon. In patients with multiple arterial stenoses, HVS could correspond to hemodynamic changes distally to arterial stenoses. Alternatively, it could be a direct picture of the stenosis itself. Indeed, arterial wall thickening, a known pathological feature of some forms of vasculitis, could also produce vascular hyperintensities on FLAIR. Yet, this alternate hypothesis is unlikely to explain the presence of HVS in spastic stenoses such as those observed in reversible angiopathy.

We cannot be certain that the bright vessels we observed on FLAIR in patients with intracerebral arterial stenoses corresponded to arteries or to small superficial cortical veins. Distal arteries can potentially be distinguished from cortical veins on anatomic grounds. Although arteries usually follow the invaginated deep cortical surfaces, veins tend to move away from the cortical surface to reach for sinuses. Accordingly, to minimize the likelihood of analyzing veins, only distal hyperintensities that remained deep in the cortical sulcus on at least 2 adjacent slices were quoted as HVS +, and we excluded distal hyperintensities that were localized away from the cortical surface.

One can argue that the bright signal observed on FLAIR did not correspond to vessels. Indeed, several situations could mimic HVS on FLAIR. CSF pulsation artifacts can produce a high CSF signal. This effect, usually more prominent in the basal cisterns, is uncommon over the convexities of the brain where CSF motion is diminished and was not considered a confounding factor by the observers. In addition, applying the inversion pulse over 2 or 3 times the slice thickness further minimized the CSF flow-entering phenomenon. Sulcal hyperintensities on FLAIR can also be observed in other pathological conditions such as subarachnoid hemorrhage and meningitis. These last 2 conditions were initially excluded from our study population to avoid difficulties in interpreting FLAIR hyperintensities within the subarachnoid space. Yet, we hypothesize that it should be possible to distinguish between HVS and subarachnoid hemorrhage on FLAIR. Indeed, HVS usually consists of well-circumscribed bright foci or tubular hyperintensities running through normally dark CSF signal; subarachnoid hemorrhage hyperintensities are frequently diffuse and fill up the whole sulcus. Finally, cortical infarction resulting from multiple distal emboli could also produce punctuate or gyriform hyperintensities on FLAIR and thus be erroneously considered an HVS. This last hypothesis seems unlikely because none of the patients studied had multiple cortical infarcts on DWI, which has been shown to be highly sensitive for the detection of acute stroke, especially in the anterior circulation.

Of the 19 patients in the study group, 6 with arterial stenoses on angiogram had no HVS on FLAIR. In addition, the concordance between the territorial distribution of stenoses on angiogram and HVS on FLAIR was far from perfect. Although the concordance analysis between FLAIR and angiographic data was not conducted on each individual stenosis because of the difficulty in precisely comparing cross-sectional MR images with projected frontal or lateral views obtained from DSA, these data suggest that FLAIR alone is unable to detect each individual stenosis. This could be due to the lack of in-plane spatial resolution of the FLAIR sequence or to the partial volume effects that can occur when a 5- to 6-mm slice thickness is used. It could also be due to differences in hemodynamic features between arterial territories in a given patient or between HVS + and HVS − patients.

Several additional points need to be raised. The specificity of HVS for the diagnosis of intracerebral arterial stenoses remains to be elucidated because we did not study the prevalence of HVS in various cerebrovascular disorders and more generally in patients with acute neurological signs without intracerebral stenosis. Indeed, cerebral hemodynamic status could be modified under different circumstances such as extracranial stenosis, thrombophlebitis, or even severe metabolic disorders. Because the reliability of a retrospective analysis of subtle flow changes on DSA is questionable, we did not correlate the presence of HVS with a possible slow flow in the corresponding arterial territory on DSA. A careful analysis of subtle flow changes on DSA, quantitative perfusion measurements, and postcontrast MR angiograms, which have been shown to improve the assessment of intracranial vessel patency, could provide additional in vivo data on the pathogenesis of HVS in patients with cerebral arterial stenoses.

Despite the lack of clear-cut concordance between the distribution of stenoses on angiogram and HVS on FLAIR, our data show that HVSs are more frequently observed in asymptomatic patients with multiple intracerebral stenoses than in asymptomatic patients without stenoses. This could be a clinically relevant finding, especially when the presence of intracerebral arterial stenoses is unsuspected. By showing multiple HVS in patients with diffuse encephalopathy or acute stroke, the FLAIR sequence could help in selecting those patients likely to benefit from other imaging techniques focusing on the intracranial vasculature.

References


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Stroke. 2003;34:1886-1891; originally published online June 26, 2003; doi: 10.1161/01.STR.0000080382.61984.FE
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/34/8/1886

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