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Thalamic Lesions in Vascular Dementia
Low Sensitivity of Fluid-Attenuated Inversion Recovery (FLAIR) Imaging
António J. Bastos Leite, MD; Elisabeth C.W. van Straaten, MD; Philip Scheltens, MD, PhD; Geert Lycklama, MD, PhD; Frederik Barkhof, MD, PhD

Background and Purpose—The criteria of the National Institute of Neurological Disorders and Stroke (NINDS)–Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) include thalamic lesions for the diagnosis of vascular dementia (VaD). Although studies concerning VaD and brain aging advocate the use of fluid-attenuated inversion recovery (FLAIR) or T2-weighted images (T2-WI) to detect ischemic lesions, none compared the sensitivity of these sequences to depict thalamic lesions.

Methods—We performed a blinded review of T2-WI and FLAIR images in 73 patients fulfilling the radiological part of the NINDS-AIREN criteria (mean age, 71 years; range, 49 to 83 years). This sample was drawn from a large multicenter trial on VaD and was expected to have a high prevalence of thalamic lesions. In a side-by-side review, including T1-weighted images as well, lesions were classified according to presumed underlying pathology.

Results—The total number of thalamic lesions was 214. Two hundred eight (97%) were detected on T2-WI, but only 117 (55%) were detected on FLAIR ($\chi^2=5.1; P<0.05$). Although the mean size of lesions detected on T2-WI and not on FLAIR (4.4 mm) was significantly lower than the mean size of lesions detected on both sequences (6.7 mm) ($P<0.001$), 5 of the 29 lesions >10 mm on T2-WI were not visible on FLAIR. FLAIR detected only 81 (51%) of the 158 probable ischemic lesions and 30 (60%) of the 50 probable microbleeds.

Conclusions—FLAIR should not be used as the only T2-weighted sequence to detect thalamic lesions in patients suspected of having VaD. (Stroke. 2004;35:415-419.)

Key Words: dementia, vascular ■ magnetic resonance imaging ■ thalamus

In 1937, Papez described an anatomic circuit beginning and ending in the hippocampal formation possibly related to emotional experience. The projections of the Papez circuit involve the fornix, mammillary bodies, mamillothalamic tracts, anterior thalami, cingulate cortex, and cingulate bundles. The early notion that the Papez circuit subserves emotion has been abandoned and replaced by the proposal it is primarily involved in mnemonic functions. Lesions of the major components of this circuit have been shown to disrupt memory in humans, particularly those localized in the anterior group of thalamic nuclei.2–6 However, lesions affecting other thalamic components or connections not considered in the circuit, such as the mediodorsal (dorsomedial), intralaminar, and pulvinar nuclei or the thalamofrontal networks, may also cause cognitive deficits and marked behavioral changes.2,7–11

MRI and CT are crucial for the diagnosis of cerebrovascular diseases. The first studies using CT for the evaluation of brain lesions in patients with ischemic stroke confirmed the importance of thalamic infarctions as a cause of dementia.12,13 Therefore, the criteria of the National Institute of Neurological Disorders and Stroke (NINDS)–Association Internationale pour la Recherche et l’Enseignement en Neurosciences (AIREN) include radiological evidence of thalamic lesions for the diagnosis of probable vascular dementia (VaD).14 Moreover, a single thalamic infarction may induce VaD.15

MRI studies concerning VaD and brain aging advocate the use of fluid-attenuated inversion recovery (FLAIR) or T2-weighted images (T2-WI) to detect and characterize brain abnormalities.16–18 However, to our knowledge no comparative study was performed to assess which MRI sequence yields the highest sensitivity for thalamic lesions. In this study we sought to compare the sensitivity of each of these sequences to depict thalamic lesions in patients with VaD.

Subjects and Methods

Patients
The subjects were derived from cases belonging to the VantagE study, a multicenter, phase III, prospective, randomized, double-blind clinical trial on the effects of rivastigmine in patients with...
VaD. For the present study we selected a sample of 73 patients (mean age, 71 years; range, 49 to 83 years) fulfilling the radiological part of the NINDS-AIREN criteria. On the basis of earlier central reading of the images for trial inclusion, we knew that approximately 75% of the current sample might be expected to have either unilateral or bilateral focal thalamic lesions. To avoid any clinical bias, we were blinded to all clinical and center data of the patients.

MRI Technique
The patients were scanned on different scanners operating from 0.5 to 1.5 T. Axial T2 spin-echo weighted images (echo time [TE] 80 to 120 ms, repetition time [TR] 3000 to 4000 ms, slice thickness 5 mm); axial FLAIR (TE 110 to 150 ms, TR 9000 to 10000 ms, inversion time 2000 to 2200 ms, slice thickness 5 mm); and axial, sagittal, and coronal T1 spin-echo weighted images (TE 11 to 20 ms, TR 500 to 700 ms, slice thickness 5 mm) were acquired. To maintain blinding, we were restricted from access to information about the type of the scanner used for each particular patient as well as the location of the imaging center.

Image Assessment
The initial assessment was performed in a blinded way, in which the T2-WI and FLAIR images were evaluated in pseudorandom order, with the use of 16-bit digital imaging files. All lesions were marked and numbered with digital overlays. We included only focal thalamic abnormalities >1 mm and excluded those suggestive of perivascular spaces. Perivascular spaces were defined as sharply demarcated areas with a signal isointensity relative to cerebrospinal fluid (CSF), following the course of a perforating vessel on sagittal or coronal images. Care was also taken to avoid the inclusion of pulsation artifacts, recognizable by linear patterns of signal banding due to phase misregistration.

For further subtyping and analysis, T2-WI, FLAIR, and T1-weighted images (T1-WI) were evaluated side by side. The greatest dimension of each focal abnormality was measured, and all were classified on each of the 3 imaging sequences in the following categories: hyperintense, hypointense, predominantly hypointense (hypointense with a small hyperintense component), and hypointense with a peripheral rim of hypointensity.

Statistical Evaluation
Statistical analysis was performed with the use of SPSS 11.0. We used χ² statistics to compare categorical data, such as proportions of lesions detected by each sequence. For comparisons of continuous variables, Student’s t test was applied because the data were normally distributed.

Results
The total number of focal thalamic lesions detected was 214. One hundred twenty-four (58%) of the 214 measured <5 mm, 61 (29%) between 5 and 10 mm, and 29 (14%) >10 mm. One hundred nine (51%) were localized in the right thalamus and 105 (49%) on the left.

Two hundred eight (97%) of the 214 lesions were identified on T2-WI, but only 117 (55%) were detected on FLAIR ($\chi^2 = 5.1; P < 0.05$). Almost half (47%) of the lesions found on T2-WI were not detected on FLAIR (Table 1). Although the mean size of lesions detected on T2-WI and not on FLAIR (4.4 mm) was significantly lower than the mean size of lesions detected on both sequences (6.7 mm) ($P < 0.001$), 5 of the 29 lesions >10 mm on T2-WI were not visible on FLAIR (Table 2) (Figure).

One hundred eight (50%) of the lesions were hyperintense on T2-WI and hypointense on T1-WI and probably correspond to infarctions. Fifty lesions (23%) were hyperintense on T2-WI and isointense on T1-WI and may correspond to areas of myelin pallor. Fifty lesions (23%) were hypointense on T2-WI and T1-WI and probably represent microbleeds (hemorrhagic lacunae).

FLAIR detected 61 (56%) of the 108 probable infarctions, 30 (60%) of the 50 probable microbleeds, and 20 (40%) of the 50 probable areas of myelin pallor. Thirty-two of the probable infarctions were hyperintense on FLAIR (incomplete or noncystic infarctions), and 29 were totally or partially hypointense (cystic and partially cystic infarctions).

The vast majority (79%) of the 97 lesions not detected on FLAIR were hyperintense on T2-WI (Table 3).

Discussion
Our study shows that FLAIR imaging is not very sensitive in detecting focal thalamic lesions and is therefore not well suited as a stand-alone sequence in the evaluation of patients suspected of VaD.

<table>
<thead>
<tr>
<th>TABLE 1. Lesions on T2-WI and FLAIR</th>
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<tbody>
<tr>
<td><strong>Signal on T2-WI</strong></td>
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<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Signal on FLAIR</strong></td>
</tr>
<tr>
<td>Not detected</td>
</tr>
<tr>
<td>Hyperintense</td>
</tr>
<tr>
<td>Hypointense</td>
</tr>
<tr>
<td>Predominantly hypointense</td>
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<tr>
<td>Hypointense with hyperintense rim</td>
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<tr>
<td><strong>Total</strong></td>
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| TABLE 2. Detection on FLAIR and Distribution by Size of Focal Lesions on T2-WI |
|-------------------------------|-----------------|-----------------|-----------------|
| **Size on T2-WI**             | Not Detected    | Detected        | Total           |
| 1–5 mm                        | 66              | 53              | 119             |
| 5–10 mm                       | 26              | 34              | 60              |
| >10 mm                        | 5               | 24              | 29              |
FLAIR sequences employ a long inversion time that suppresses the signal from CSF and a long TE that provides heavy T2 weighting. Therefore, the major interest of FLAIR is to detect and characterize brain lesions around CSF spaces. Most studies advocate superiority of FLAIR over conventional spin-echo imaging in a wide range of pathologies. FLAIR images also have the advantage of easily identifying CSF-like lesions. Some studies showed that FLAIR was more often associated with image artifacts or could not corroborate the aforementioned superiority of FLAIR. Disadvantages of FLAIR include a reduced sensitivity to detect infratentorial or spinal cord lesions. The reason for this is unknown but most likely reflects different relaxation characteristics in those regions, both in normal-appearing tissue and in lesions. For example, T1 and T2 relaxation times of infratentorial lesions in patients with multiple sclerosis are closer to the relaxation times of local normal-appearing white matter than those of supratentorial lesions, resulting in reduced contrast between posterior fossa lesions and the background. Age-related increases in T1 relaxation times of human brain also have been shown, particularly in the thalami, and may serve to explain the lack of sensitivity of FLAIR for thalamic lesions in elderly patients with VaD.

Alternatively, the occurrence of cystic changes in lacunar infarctions will lead to a prolongation of T1 relaxation time, and the signal from these lesions may be suppressed, as in CSF spaces. The same may occur with multiple sclerosis lesions severely hypointense on T1-WI. MRI-pathological correlation studies performed to determine the background of age-related subcortical gray and white matter hypointensities on T2-WI found different types of pathologies: infarctions, gliosis, myelin and axonal loss, breakdown of the ependymal lining, and enlarged perivascular spaces. Areas of myelin pallor can be hypointense on T2-WI but isointense on T1-WI, and it seems possible that differences in type of pathology can also influence detection on FLAIR.

Although the proposed neuropathological classification of lacunae includes both ischemic (type I) and hemorrhagic (type II) vascular abnormalities and enlarged perivascular spaces (type III), in VaD it is important to differentiate the vascular lesions. MRI-pathological correlation studies found that the great majority of enlarged perivascular (Virchow-Robin) spaces normally surround perforating arteries that enter the striatum in the anterior perforated substance, just above the internal carotid artery bifurcation and lateral to the anterior commissure. They are responsible for the so-called état criblé of the basal ganglia and are much less frequently located in the thalami. Therefore, it is unlikely that those lesions classified as cystic infarctions on the basis of MRI are in fact Virchow-Robin spaces or could account for the greater number of lesions detected on T2-WI. Actually, FLAIR performed more poorly for all types of presumed pathology.

A limitation of our study is that we used images acquired on a wide range of scanners and sequences, not all of which

<table>
<thead>
<tr>
<th>TABLE 3. Detection on FLAIR and Signal on T2 and T1-WI</th>
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<tr>
<td>Detected on FLAIR</td>
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<tr>
<td>Hyperintense on T2-WI</td>
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<tr>
<td>Hypointense on T2-WI</td>
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<td>Hyperintense on T2-WI</td>
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<td>Hypointense on T2-WI</td>
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<tr>
<td>Isointense on T1-WI</td>
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<tr>
<td>20</td>
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<tr>
<td>$P=0.779$</td>
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<tr>
<td>Hypointense on T1-WI</td>
</tr>
<tr>
<td>61</td>
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<tr>
<td>$P=0.095$</td>
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<tr>
<td>Total</td>
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<td>81</td>
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<td>$P=0.281$</td>
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may be optimally tuned. On the other hand, this reflects the normal variability of vendor-supported sequences, and given the more complex contrast mechanisms in FLAIR, these may be less stable than for T2-WI. For the detection of type II hemorrhagic lacunae,53,54 both spin-echo and FLAIR are insensitive compared with T2*-WI gradient-echo sequences.55,56 but these were not available in the context of this trial. Nevertheless, we detected a fair amount of probable microbleeds.

In conclusion, the accuracy of T2-WI for the detection of thalamic lesions in patients with probable VaD is far superior to FLAIR. Given the great clinical importance of these lesions, FLAIR should not be used as the only T2-weighted sequence in patients suspected of having VaD.

In addition to the posterior fossa and spinal cord, the diencéphalon seems to represent another region not suitable for evaluation by FLAIR MRI.

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