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Thalamic Lesions in Vascular Dementia

Low Sensitivity of Fluid-Attenuated Inversion Recovery (FLAIR) Imaging

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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, Papez¹ 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

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TABLE 1. Lesions on T2-WI and FLAIR

Signal on FLAIR	Signal on T2-WI			Total
	Not Detected	Hyperintense	Hypointense	
Not detected	0	77	20	97
Hyperintense	3	49	0	52
Hypointense	3	14	30	47
Predominantly hypointense	0	5	0	5
Hypointense with hyperintense rim	0	13	0	13
Total	6	158	50	214

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.¹⁴ 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.¹⁹ 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 hyperintensity.

Statistical Evaluation

Statistical analysis was performed with the use of SPSS 11.0. We used χ^2 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).

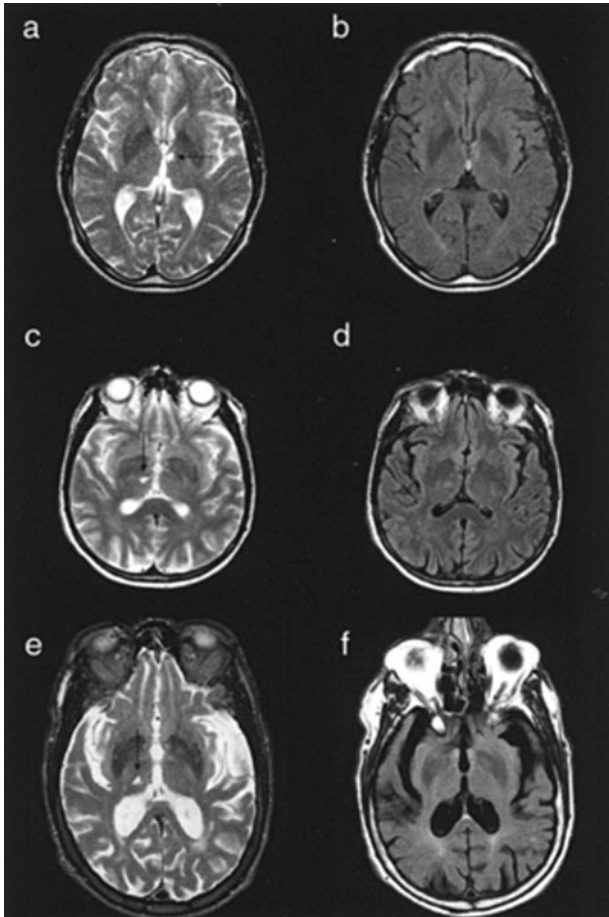
The vast majority (79%) of the 97 lesions not detected on FLAIR were hyperintense on T2-WI (Table 3).

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 2. Detection on FLAIR and Distribution by Size of Focal Lesions on T2-WI

Size on T2-WI	Detection on FLAIR		
	Not Detected	Detected	Total
1–5 mm	66	53	119
5–10 mm	26	34	60
>10 mm	5	24	29



a, c, and e, T2-weighted images showing a left tuberothalamic artery infarction and 2 right-sided paramedian thalamic infarctions in 3 different patients (aged 68, 52, and 79 years). b, d, and f, Correspondent fluid-attenuated inversion recovery images do not reveal thalamic abnormalities.

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.^{20,21} Most studies advocate superiority of FLAIR over conventional spin-echo imaging in a wide range of pathologies.^{22–32} FLAIR images also have the advantage of easily identifying CSF-like lesions.³³

Some studies showed that FLAIR was more often associated with image artifacts^{22,34} or could not corroborate the

aforementioned superiority of FLAIR.^{34,35} Disadvantages of FLAIR include a reduced sensitivity to detect infratentorial or spinal cord lesions.^{34,36–38} 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.³⁹ Age-related increases in T1 relaxation times of human brain also have been shown, particularly in the thalami,⁴⁰ 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 infarctions⁴¹ 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.⁴² MRI-pathological correlation studies performed to determine the background of age-related subcortical gray and white matter hyperintensities on T2-WI found different types of pathology: infarctions, gliosis, myelin and axonal loss, breakdown of the ependymal lining, and enlarged perivascular spaces.^{17,43–47} Areas of myelin pallor can be hyperintense on T2-WI but isointense on T1-WI,^{17,45} 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),⁴¹ 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^{19,48–52} and are much less frequently located in the thalami.⁵² 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 3. Detection on FLAIR and Signal on T2 and T1-WI

	Detected on FLAIR		Not Detected on FLAIR		
	Hyperintense on T2-WI	Hypointense on T2-WI	Hyperintense on T2-WI	Hypointense on T2-WI	
Isointense on T1-WI	20	10	30	13	$\chi^2=0.079$ $P=0.779$
Hypointense on T1-WI	61	20	47	7	$\chi^2=2.785$ $P=0.095$
Total	81	30	77	20	$\chi^2=1.164$ $P=0.281$

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 diencephalon seems to represent another region not suitable for evaluation by FLAIR MRI.

References

- Papez JW. A proposed mechanism of emotion. *Arch Neurol Psychiatry*. 1937;38:725-734.
- Bogousslavsky J, Regli F, Uske A. Thalamic infarcts: clinical syndromes, etiology, and prognosis. *Neurology*. 1988;38:837-848.
- Gaffan EA, Gaffan D, Hodges JR. Amnesia following damage to the left fornix and to other sites: a comparative study. *Brain*. 1991;114:1297-1313.
- Clarke S, Assal G, Bogousslavsky J, Regli F, Townsend DW, Leenders KL, Blecic S. Pure amnesia after unilateral left polar thalamic infarct: topographic and sequential neuropsychological and metabolic (PET) correlations. *J Neurol Neurosurg Psychiatry*. 1994;57:27-34.
- Saito K, Kimura K, Minematsu K, Shiraiishi A, Nakajima M. Transient global amnesia associated with an acute infarction in the retrosplenium of the corpus callosum. *J Neurol Sci*. 2003;210:95-97.
- Schott JM, Crutch SJ, Fox NC, Warrington EK. Development of selective verbal memory impairment secondary to a left thalamic infarct: a longitudinal case study. *J Neurol Neurosurg Psychiatry*. 2003;74:255-257.
- Guard O, Bellis F, Mabilhe JP, Dumas R, Boisson D, Devic M. Thalamic dementia after a unilateral hemorrhagic lesion of the right pulvinar. *Rev Neurol (Paris)*. 1986;142:759-765.
- Bogousslavsky J, Regli F, Delaloye B, Delaloye-Bischof A, Assal G, Uske A. Loss of psychic self-activation with bilateral infarction: neurobehavioural, CT, MRI and SPECT correlates. *Acta Neurol Scand*. 1991;83:309-316.
- Sandson TA, Daffner KR, Carvalho PA, Mesulam MM. Frontal lobe dysfunction following infarction of the left-sided medial thalamus. *Arch Neurol*. 1991;48:1300-1303.
- Tatemichi TK, Desmond DW, Prohovnik I, Cross DT, Gropen TI, Mohr JP, Stern Y. Confusion and memory loss from capsular genu infarction: a thalamocortical disconnection syndrome? *Neurology*. 1992;42:1966-1979.
- Van der Werf YD, Weerts JG, Jolles J, Witter MP, Lindeboom J, Scheltens P. Neuropsychological correlates of a right unilateral lacunar thalamic infarction. *J Neurol Neurosurg Psychiatry*. 1999;66:36-42.
- Ladurner G, Liff LD, Sager WD, Lechner H. A clinical approach to vascular (multiinfarct) dementia. *Exp Brain Res*. 1982;suppl 5:243-250.
- Ladurner G, Sager WD, Flooh E. Computer tomography and vascular (multiinfarct) dementia: a qualitative and quantitative investigation. *Exp Brain Res*. 1982;suppl 5:264-271.
- Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology*. 1993;43:250-260.
- Leys D, Scheltens P, Vermersch P, Pruvo JP. Morphological imaging in the diagnosis of dementia, II: vascular dementia. *Rev Med Interne*. 1995;16:195-200.
- O'Brien JT, Wiseman R, Burton EJ, Barber B, Wesnes K, Saxby B, Ford GA. Cognitive associations of subcortical white matter lesions in older people. *Ann N Y Acad Sci*. 2002;977:436-444.
- Udaka F, Sawada H, Kameyama M. White matter lesions and dementia: MRI-pathological correlation. *Ann N Y Acad Sci*. 2002;977:411-415.
- Schmidt R, Enzinger C, Ropele S, Schmidt H, Fazekas F. Progression of cerebral white matter lesions: 6-year results of the Austrian Stroke Prevention Study. *Lancet*. 2003;361:2046-2048.
- Jungreis CA, Kanal E, Hirsch WL, Martinez AJ, Moosy J. Normal perivascular spaces mimicking lacunar infarction: MR imaging. *Radiology*. 1988;169:101-104.
- De Coene B, Hajnal JV, Gatehouse P, Longmore DB, White SJ, Oatridge A, Pennock JM, Young IR, Bydder GM. MR of the brain using fluid-attenuated inversion recovery (FLAIR) pulse sequences. *AJNR Am J Neuroradiol*. 1992;13:1555-1564.
- Hajnal JV, Bryant DJ, Kasuboski L, Pattany PM, De Coene B, Lewis PD, Pennock JM, Oatridge A, Young IR, Bydder GM. Use of fluid attenuated inversion recovery (FLAIR) pulse sequences in MRI of the brain. *J Comput Assist Tomogr*. 1992;16:841-844.
- Rydberg JN, Hammond CA, Grimm RC, Erickson BJ, Jack CR Jr, Huston J, Riederer SJ. Initial clinical experience in MR imaging of the brain with a fast fluid-attenuated inversion-recovery pulse sequence. *Radiology*. 1994;193:173-180.
- Hashemi RH, Bradley WG Jr, Chen DY, Jordan JE, Queralt JA, Cheng AE, Henrie JN. Suspected multiple sclerosis: MR imaging with a thin-section fast FLAIR pulse sequence. *Radiology*. 1995;196:505-510.
- Alexander JA, Sheppard S, Davis PC, Salverda P. Adult cerebrovascular disease: role of modified rapid fluid-attenuated inversion-recovery sequences. *AJNR Am J Neuroradiol*. 1996;17:1507-1513.
- Filippi M, Yousry T, Baratti C, Horsfield MA, Mammì S, Becker C, Voltz R, Spuler S, Campi A, Reiser MF, Comi G. Quantitative assessment of MRI lesion load in multiple sclerosis: a comparison of conventional spin-echo with fast fluid-attenuated inversion recovery. *Brain*. 1996;119:1349-1355.
- Thurnher MM, Thurnher SA, Fleischmann D, Steuer A, Rieger A, Helbich T, Trattng S, Schindler E, Hittmair K. Comparison of T2-weighted and fluid-attenuated inversion-recovery fast spin-echo MR sequences in intracerebral AIDS-associated disease. *AJNR Am J Neuroradiol*. 1997;18:1601-1609.
- Aprile I, Iaiza F, Lavaroni A, Budai R, Dolso P, Scott CA, Beltrami CA, Fabris G. Analysis of cystic intracranial lesions performed with fluid-attenuated inversion recovery MR imaging. *AJNR Am J Neuroradiol*. 1999;20:1259-1267.
- Arakia Y, Ashikaga R, Fujii K, Nishimura Y, Ueda J, Fujita N. MR fluid-attenuated inversion recovery imaging as routine brain T2-weighted imaging. *Eur J Radiol*. 1999;32:136-143.
- Jager HR, Albrecht T, Curati-Alasonatti WL, Williams EJ, Haskard DO. MRI in neuro-Behcet's syndrome: comparison of conventional spin-echo and FLAIR pulse sequences. *Neuroradiology*. 1999;41:750-758.
- Bynevelt M, Britton J, Seymour H, MacSweeney E, Thomas N, Sandhu K. FLAIR imaging in the follow-up of low-grade gliomas: time to dispense with the dual-echo? *Neuroradiology*. 2001;43:129-133.
- Essig M, Metzner R, Bonsanto M, Hawighorst H, Debus J, Tronnier V, Knopp MV, van Kaick G. Postoperative fluid-attenuated inversion recovery MR imaging of cerebral gliomas: initial results. *Eur Radiol*. 2001;11:2004-2010.
- Herskovits EH, Itoh R, Melhem ER. Accuracy for detection of simulated lesions: comparison of fluid-attenuated inversion-recovery, proton density-weighted, and T2-weighted synthetic brain MR imaging. *AJR Am J Roentgenol*. 2001;176:1313-1318.
- Barkhof F, Scheltens P. Imaging of white matter lesions. *Cerebrovasc Dis*. 2002;13:21-30.
- Okuda T, Korogi Y, Shigematsu Y, Sugahara T, Hirai T, Ikushima I, Liang L, Takahashi M. Brain lesions: when should fluid-attenuated inversion-recovery sequences be used in MR evaluation? *Radiology*. 1999;212:793-798.
- Baratti C, Barkhof F, Hoogenraad F, Valk J. Partially saturated fluid attenuated inversion recovery (FLAIR) sequences in multiple sclerosis: comparison with fully relaxed FLAIR and conventional spin-echo. *Magn Reson Imaging*. 1995;13:513-521.
- Keiper MD, Grossman RI, Brunson JC, Schnall MD. The low sensitivity of fluid-attenuated inversion-recovery MR in the detection of multiple sclerosis of the spinal cord. *AJNR Am J Neuroradiol*. 1997;18:1035-1039.
- Stevenson VL, Gawne-Cain ML, Barker GJ, Thompson AJ, Miller DH. Imaging of the spinal cord and brain in multiple sclerosis: a comparative study between fast FLAIR and fast spin echo. *J Neurol*. 1997;244:119-124.
- Tubridy N, Barker GJ, MacManus DG, Moseley IF, Miller DH. Optimization of unenhanced MRI for detection of lesions in multiple sclerosis:

- a comparison of five pulse sequences with variable slice thickness. *Neuroradiology*. 1998;40:293–297.
39. Stevenson VL, Parker GJ, Barker GJ, Birnie K, Tofts PS, Miller DH, Thompson AJ. Variations in T1 and T2 relaxation times of normal appearing white matter and lesions in multiple sclerosis. *J Neurol Sci*. 2000;178:81–87.
 40. Steen RG, Gronemeyer SA, Taylor JS. Age-related changes in proton T1 values of normal human brain. *J Magn Reson Imaging*. 1995;5:43–48.
 41. Poirier J, Derouesne C. Cerebral lacunae: a proposed new classification. *Clin Neuropathol*. 1984;3:266.
 42. van Waesberghe JH, Castelijns JA, Weerts JG, Nijeholt GJ, Hillegers JP, Polman CH, Barkhof F. Disappearance of multiple sclerosis lesions with severely prolonged T1 on images obtained by a FLAIR pulse sequence. *Magn Reson Imaging*. 1996;14:209–213.
 43. Awad IA, Johnson PC, Spetzler RF, Hodak JA. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly, II: postmortem pathological correlations. *Stroke*. 1986;17:1090–1097.
 44. Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer WW. Brain MR: pathologic correlation with gross and histopathology, II: hyperintense white-matter foci in the elderly. *AJR Am J Roentgenol*. 1988;151:559–566.
 45. Fazekas F, Kleinert R, Offenbacher H, Payer F, Schmidt R, Kleinert G, Radner H, Lechner H. The morphologic correlate of incidental punctate white matter hyperintensities on MR images. *AJNR Am J Neuroradiol*. 1991;12:915–921.
 46. Chimowitz MI, Estes ML, Furlan AJ, Awad IA. Further observations on the pathology of subcortical lesions identified on magnetic resonance imaging. *Arch Neurol*. 1992;49:747–752.
 47. Scheltens P, Barkhof F, Leys D, Wolters EC, Ravid R, Kamphorst W. Histopathologic correlates of white matter changes on MRI in Alzheimer's disease and normal aging. *Neurology*. 1995;45:883–888.
 48. Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer WW. Brain MR: pathologic correlation with gross and histopathology, I: lacunar infarction and Virchow-Robin spaces. *AJR Am J Roentgenol*. 1988;151:551–558.
 49. Pullicino PM, Miller LL, Alexandrov AV, Ostrow PT. Infraputamina 'lacunes': clinical and pathological correlations. *Stroke*. 1995;26:1598–1602.
 50. Adachi M, Hosoya T, Haku T, Yamaguchi K. Dilated Virchow-Robin spaces: MRI pathological study. *Neuroradiology*. 1998;40:27–31.
 51. Bokura H, Kobayashi S, Yamaguchi S. Distinguishing silent lacunar infarction from enlarged Virchow-Robin spaces: a magnetic resonance imaging and pathological study. *J Neurol*. 1998;245:116–122.
 52. Takao M, Koto A, Tanahashi N, Fukuuchi Y, Takagi M, Morinaga S. Pathologic findings of silent, small hyperintense foci in the basal ganglia and thalamus on MRI. *Neurology*. 1999;52:666–668.
 53. Challa VR, Moody DM. The value of magnetic resonance imaging in the detection of type II hemorrhagic lacunes. *Stroke*. 1989;20:822–825.
 54. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, Hartung HP. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. *AJNR Am J Neuroradiol*. 1999;20:637–642.
 55. Kim DE, Bae HJ, Lee SH, Kim H, Yoon BW, Roh JK. Gradient echo magnetic resonance imaging in the prediction of hemorrhagic vs ischemic stroke: a need for the consideration of the extent of leukoariosis. *Arch Neurol*. 2002;59:425–429.
 56. Ripoll MA, Siosteen B, Hartman M, Raininko R. MR detectability and appearance of small experimental intracranial hematomas at 1.5 T and 0.5 T. *Acta Radiol*. 2003;44:199–205.