

## Cerebral Microhemorrhage

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**Background and Purpose**—With the advent of modern MRI imaging techniques, cerebral microhemorrhages have been increasingly recognized on gradient-echo (GE) or T2\*-weighted MRI sequences in different populations. However, in clinical practice, their diagnostic value, associated risk, and prognostic significance are often unclear. This review summarizes the pathophysiology, differential diagnosis, epidemiology, and clinical significance of cerebral microhemorrhages.

**Summary of Review**—Focal areas of signal loss on GE MRI imaging pathologically represent focal hemosiderin deposition associated with previous hemorrhagic events. Cerebral microhemorrhages have been noted in healthy elderly, ischemic cerebrovascular disease, intracerebral hemorrhage (ICH), cerebral amyloid angiopathy (CAA), and in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Microhemorrhages have been associated with older age, hypertension, smoking, white matter disease, lacunar infarcts, previous ischemic stroke, or ICH. In CAA, microhemorrhages predict both the risk of recurrent lobar ICH and future clinical decline. In patients with ischemic cerebrovascular disease, microhemorrhage number and location may be associated with executive dysfunction and may predict the occurrence of ICH and lacunar infarction.

**Conclusions**—When cerebral microhemorrhages are diagnosed on MRI, conclusions regarding their significance and associated risks should be made based on the population examined. Further studies to characterize the associated risks of cerebral microhemorrhages in different stroke populations are needed to use this new imaging marker in therapeutic decisions. (*Stroke*. 2006;37:550-555.)

**Key Word:** CADASIL ■ cerebral hemorrhage ■ cerebral amyloid angiopathy ■ stroke

MRI techniques are not only crucial for the diagnosis and treatment of acute ischemic stroke<sup>1</sup> but are now providing new insights into the pathophysiology and diagnosis of intracerebral hemorrhage (ICH) and microangiopathic disease. In recent years, there has been a growing interest in gradient-echo (GE) or T2\*-weighted MRI, a technique highly sensitive in the detection of old and recent cerebral hemorrhage.<sup>2,3</sup> GE MRI is capable of detecting millimeter-sized paramagnetic blood products (including hemosiderin) in brain parenchyma.<sup>4</sup> With this technique, the number of visible hemorrhagic brain lesions has been considerably increased. In addition, because hemosiderin remains stored at sites of previous bleeding,<sup>5</sup> hemorrhagic burden can be assessed over time. This potentially has important implications for the diagnosis and treatment of patients with ICH or ischemic stroke. Herein we discuss the presumed pathophysiology, prevalence, and clinical implications of cerebral microhemorrhage (or microbleed).

### Definition

Spontaneous ICH usually results in a focal neurologic deficit and is easily diagnosed by computed tomography (CT) scan. It is caused by arterial rupture, leads to hematoma formation in the lobar hemispheres or deep gray structures, and is

associated with high mortality.<sup>6</sup> Cerebral microhemorrhages, best visualized by MRI, result from rupture of small blood vessels in basal ganglia or subcortical white matter and are most often clinically asymptomatic.<sup>2</sup>

Microhemorrhages were first described after the clinical use of GE MRI<sup>2,3,7</sup> and are usually defined as rounded foci of <5 mm in size that appear hypointense and distinct from vascular flow voids, leptomeningeal hemosiderosis, or non-hemorrhagic subcortical mineralization<sup>2,8</sup> (Figure). The reduction of the GE magnetic resonance (MR) signal is caused by hemosiderin, a blood breakdown product that causes magnetic susceptibility-induced relaxation leading to T2\* signal loss. GE MR has a greater sensitivity for detection of hemosiderin deposits compared with conventional spin-echo MR sequences.<sup>4</sup> Microhemorrhages appear larger on GE sequences compared with the actual tissue lesions because of the so-called “blooming effect” of the MR signal at the border of these lesions.<sup>9,10</sup> Because hemosiderin remains in macrophages for many years after hemorrhage,<sup>11,12</sup> GE sequences allow for reliable assessment of an individual’s recent and past hemorrhages.

Although only a few studies relating these MR findings to tissue pathology have been published<sup>2,10,13</sup>; all have demonstrated that these areas of GE hypointensity correlate well

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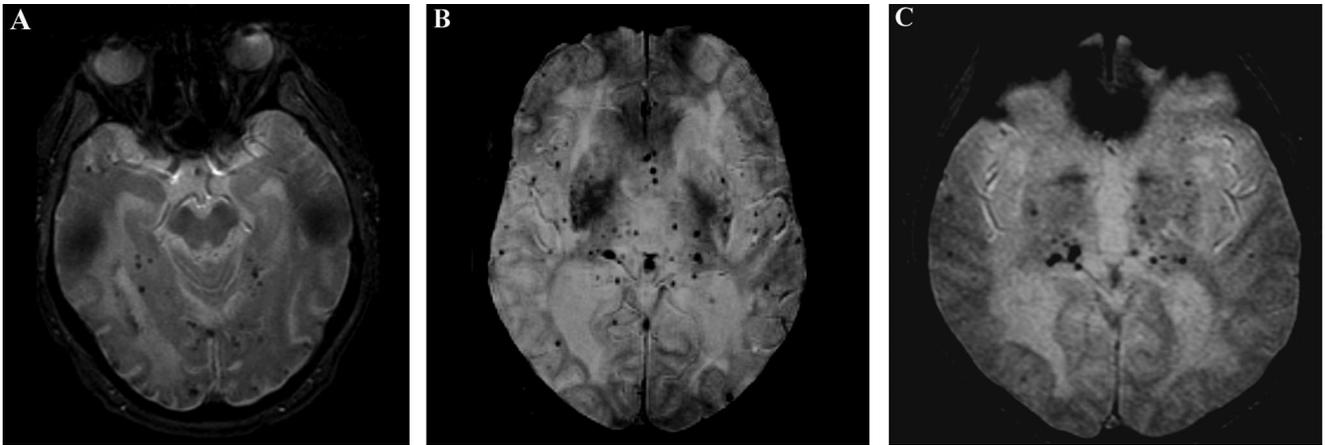
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Examples of cerebral microhemorrhages in various populations. GE MRI sequences (A) in a patient with probable CAA demonstrating numerous microhemorrhages in the temporal and occipital lobes (B) in a patient with CADASIL. Multiple microhemorrhages are seen in the thalamus and cortical–subcortical junction and (C) in a patient with long-standing history of hypertension with microhemorrhages in the deep structures and cortical–subcortical junction.

with brain parenchymal areas of hemosiderin-laden macrophages. Tanaka et al demonstrated that hypointense lesions seen on GE MRI were associated with rupture of vessels  $<200\ \mu\text{m}$  in diameter and perivascular hemosiderin deposition in 3 cases.<sup>13</sup> In 7 patients who died of ICH, histopathological examination revealed focal hemosiderin deposits in 21 of 34 hypointense areas seen on GE MRI.<sup>2</sup> In all brains, cerebral vessels showed evidence of moderate to severe fibrohyalinosis. Two patients showed evidence of cerebral amyloid angiopathy (CAA). These pathologic data suggest that cerebral microhemorrhage results from underlying small-vessel pathologies such as hypertensive vasculopathy<sup>14</sup> or CAA.<sup>15–17</sup>

### Differential Diagnosis

In the differential diagnosis of cerebral microhemorrhage, other causes of signal loss on GE sequences should be considered. Vascular flow voids of small cerebral vessels in cross-section may appear indistinguishable from areas of microhemorrhage. However, this is usually overcome by examining multiple slices showing a typical vessel course. Calcium or iron deposits in the basal ganglia may also have a similar appearance but are typically symmetrical in distribution and produce hyperdensity on CT images. Cerebral cavernous malformations (CCMs) can lead to accumulation of hemosiderin close to the vascular channels of the malformation and cause hypointense signal on GE images.<sup>18</sup> However, depending on the chronicity of hemorrhage, these lesions have well-defined appearances on T1- and T2-weighted images (although very small lesions may be overlooked on T1-weighted images).<sup>10,19,20</sup> In addition, CCM is rare in the general population (prevalence  $\approx 0.5\%$ )<sup>21–24</sup> and multiple lesions in CCM are most often seen in the hereditary form of the disorder.<sup>19,25</sup> In 2 cases, capillary telangiectasias have been reported to cause focal signal loss on T2\*-weighted images.<sup>26</sup> Finally, GE hypointensities resulting from shear injury have been reported in head trauma<sup>27</sup> but should be considered only in the appropriate circumstances.

### Epidemiology

#### Healthy Populations With or Without Vascular Risk Factors

Areas of cerebral microhemorrhage have been noted in various healthy populations. The overall prevalence of microhemorrhages in healthy Japanese adults ( $n=450$ ; average age 52.9 years) was found to be 3.1% and correlated with the presence of hypertension and smoking.<sup>28</sup> Microhemorrhages occurred more frequently in the deep structures (thalamus, brain stem, basal ganglia, cerebellum) compared with the lobar hemispheres.

In the Austrian Stroke Prevention study,<sup>29</sup> small areas of previous asymptomatic hemorrhage were found in 18 (6.4%) subjects in the study ( $n=280$ ; average age 60 years). Individuals with microhemorrhages were older, more often carried the diagnosis of hypertension and, in particular, had higher systolic blood pressure. Subjects with microhemorrhage had more lacunar infarct burden and more extensive white matter hyperintensities, suggesting that microhemorrhages may be a marker of the severity of the underlying small-vessel pathology. Of note, in those subjects with hypertension, microhemorrhages more commonly occurred in the basal ganglia compared with the cortical–subcortical junction.

An analysis of 472 healthy subjects from the Framingham study (average age 64.4 years) demonstrated cerebral microhemorrhages to have an overall prevalence of 4.7%.<sup>30</sup> Only age and male sex were found to be independent predictors of microhemorrhage. In contrast with the other studies, lesions in the cerebral hemispheres were more common than lesions in the basal ganglia or deep structures.

Finally, a study of 129 hypertensive patients (average age 65.6 years) found the microhemorrhages in 56% of patients.<sup>31</sup> The number of microhemorrhages was correlated to the number of lacunes and to the extent of white matter hyperintensities. Microhemorrhages were more commonly found in the corticosubcortical regions compared with the deep gray structures.

### Ischemic Stroke

Microhemorrhages have been documented in patients with ischemic cerebrovascular disease with a highly variable reported prevalence (range 18% to 68%).<sup>32–38</sup> However, many of these studies have major limitations, including nonselective clinical criteria, inclusion of multiple stroke subtypes, and variable size-based definition of microhemorrhage.

An early study prospectively analyzed patients with ischemic stroke, myocardial infarction (MI), or peripheral arterial disease and found evidence of local hemosiderin deposition to be present in 31 of 221 patients (14%).<sup>34</sup> Hemosiderin deposition (which included hemorrhagic lacunes and microhemorrhages) was more predominant among ischemic stroke patients (26%) compared with patients with MI (4%) or peripheral arterial disease (13%). The frequency of microhemorrhages alone was not reported. There were no differences in the location of these lesions based on age or the presence of hypertension.

More recently, Lee et al evaluated 102 consecutive survivors of acute stroke (72 with ischemic stroke; 30 with ICH).<sup>38</sup> Microhemorrhage was detected in 64% of patients. To investigate the relationship between cerebral microhemorrhage and hypertension-induced cardiac damage, left ventricular mass index was measured by transthoracic echocardiography. In multivariable analysis, the number of microhemorrhages was associated with left ventricular hypertrophy and history of previous stroke. Left ventricular mass index grade was an independent risk factor for microhemorrhage severity in the central gray matter and infratentorial areas but not in the subcortical white matter.

Microhemorrhages have been reported in 27% patients with acute lacunar infarction.<sup>35</sup> Extent of white matter lesions was independently associated with microhemorrhage after adjustment for number of lacunar infarcts. Microhemorrhages were most commonly found at the cortical–subcortical junction, basal ganglia, or thalamus. These results further emphasize that cerebral microhemorrhages may be pathophysiologically linked to ischemic small-vessel disease (lacunar infarcts, white matter disease).

### Intracerebral Hemorrhage

Cerebral microhemorrhages have been well described in patients with both deep hemispheric and lobar ICH.<sup>3,8,11,13,39,40</sup> The presence of microhemorrhage has been shown to be nearly 10-fold more common in this population than in healthy elderly.<sup>39</sup> A recent study that examined a cohort of 109 consecutive patients presenting with primary ICH (deep and lobar) found microhemorrhages to be present in 54% with the majority of these subjects having multiple lesions (median 6).<sup>39</sup> Individuals with microhemorrhage were more likely to be hypertensive, have a previous history of stroke, have more lacunar infarcts, more extensive white matter lesions, and evidence of old hemorrhage. There was a correlation between microhemorrhage distribution and the location of primary ICH. That is to say, individuals with deep ICH tended to have microhemorrhage in the basal ganglia and thalamus compared with individuals with lobar ICH.

Jeong et al evaluated 107 patients with deep and lobar ICH (27% lobar; 73% deep) and found that 70% had microhemorrhages and they were frequently multiple (range 1 to 96; median 3).<sup>41</sup> Age, extensive white matter hyperintensity, and number of lacunes were independently associated with the presence of microhemorrhage. Potential triggering events (defined as events or activities that may significantly increase blood pressure) were independently associated with the absence of microhemorrhage.

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### Cerebral Amyloid Angiopathy

Microhemorrhages have also been studied in specific small-vessel vasculopathies, most notably CAA,<sup>8,11</sup> which accounts for the majority of primary lobar ICH in the elderly.<sup>42</sup> A set of validated criteria (termed the Boston criteria) have been established to identify those lobar ICHs caused by CAA during life.<sup>43</sup> The presence of multiple, strictly lobar hemorrhages (including microhemorrhages) detected by GE MRI sequences has been shown to be highly specific for severe CAA in elderly patients with no other definite cause of ICH, such as trauma, ischemic stroke, tumor, coagulopathy, or excessive anticoagulation (termed probable CAA-related ICH).<sup>5,43</sup> The Boston criteria have been compared against the established gold standard of histologic examination of specimens from autopsy, hematoma evacuation, or cortical biopsy.<sup>43</sup> Thirty-nine primary lobar ICH patients  $\geq 55$  years of age with available pathologic tissue were diagnosed on clinical and radiologic grounds with possible or probable CAA. All 13 patients diagnosed with probable CAA demonstrated pathological evidence of CAA in cerebral blood vessels. Eleven of these 13 patients underwent GE imaging, and 73% showed evidence of multiple hemorrhagic lesions, including microhemorrhages. Sixteen of 26 patients (63%) with the diagnosis of possible CAA (single lobar macrohemorrhage or microhemorrhage) demonstrated pathologic evidence of CAA. Interestingly, in patients with probable or possible CAA, no association was found between number of microhemorrhages and age, sex, apolipoprotein E (APOE) genotype, or other vascular risk factors, including hypertension, coronary artery disease, diabetes, or previous stroke.<sup>8</sup>

As has been reported previously in lobar macrohemorrhages,<sup>44,45</sup> the distribution of microhemorrhages in CAA seems to show a posterior cortical predominance.<sup>46</sup> In 59 patients with probable CAA, microhemorrhages occurred more frequently in the temporal and occipital lobes compared with other hemispheric regions.<sup>46</sup> Additionally, lesions tended to cluster in the same lobe in subjects with multiple lesions.

### Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Microhemorrhages have been reported to occur in  $\approx 25\%$  to 69% of patients affected with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).<sup>47–49</sup> The main clinical manifestations of the disease include attacks of migraine with aura, mood disturbances, recurrent ischemic strokes, and progressive cognitive decline.<sup>50</sup> A study of 15 Dutch CADASIL families showed that microhemorrhages occurred in 10 of 40 *Notch3* mutation carriers.<sup>47</sup> In a small cohort of German CADASIL patients,

## Cerebral Microhemorrhage in Various Populations

Population	Prevalence	Predominant Location	Associated Factors	Risk
Healthy elderly <sup>28–31</sup>	3%–6%	Basal ganglia, deep structures, cortical–subcortical	Age, HTN, smoking, WMD, lacunar burden, male sex	Unknown
Ischemic disorders				
Ischemic stroke <sup>32–35, 37,51,52</sup>	18%–68%	Basal ganglia, deep structures, cortical–subcortical	WMD, HTN, low total serum cholesterol, <sup>36</sup> high HDL, <sup>36</sup> LVH, <sup>38</sup> Executive dysfunction <sup>51</sup>	ICH, <sup>*52,53</sup> lacunar infarction <sup>*53</sup>
CADASIL <sup>47–49</sup>	25%–69%	Basal ganglia, deep structures, cortical–subcortical	Age	Unknown
Hemorrhagic disorders				
ICH (deep or lobar) <sup>32,33,37,39,41</sup>	54%–74%	Basal ganglia, deep structures > cortical–subcortical	HTN, left ventricular hypertrophy, <sup>38</sup> previous ischemic/hemorrhagic stroke, lacunar infarction, WMD	ICH <sup>*53</sup>
CAA <sup>5,8,11,46</sup>	≈63%–73% <sup>43</sup>	Cortical–subcortical (with posterior predominance)	Cognitive impairment (trend)	Recurrent lobar ICH (3-year risk 14%–51%), cognitive/functional impairment or death (HR, 1.9; 95% CI, 1.2–2.8)

\*Insufficient data to for estimation of the risk. HTN indicates hypertension; WMD, white matter disease; LVH, left ventricular hypertrophy; HDL, high-density lipoprotein.

11 of 16 subjects harbored microhemorrhages, and each individual commonly had multiple lesions.<sup>48</sup> Frequency of microhemorrhage is associated with age in CADASIL and does not appear related to vascular risk factors.<sup>47,48</sup> Microhemorrhages were most commonly found in the thalamus (61%), followed by the subcortical white matter (26%) in the Dutch series. In the German cohort, they most commonly occurred at the cortical–subcortical junction (38%), cerebral white matter (20%), thalamus and basal ganglia (20%), or brain stem (14%).

Dichgans et al examined 7 autopsy CADASIL cases and found evidence of hemosiderin-laden macrophages in 6 of 7 cases.<sup>48</sup> In all cases, these macrophages were found in the vicinity of 100 to 300  $\mu$ m blood vessels, the vessel walls of which showed characteristic degenerative changes. There was no evidence of amyloid deposition or vascular malformations, which strongly supports the involvement of CADASIL-related ultrastructural modifications of the vessel wall in the occurrence of these lesions.

The principle studies discussed above are summarized in the Table.

### Clinical Significance

The importance of cerebral microhemorrhages in the diagnosis, clinical aspects, and prognosis in cerebrovascular disease has been best described in CAA.<sup>5,8,11,46</sup> Since being shown to be an accurate marker of the disease,<sup>11</sup> their presence has also become an important prerequisite to establish the diagnosis of CAA in life.<sup>43</sup>

The high frequency of microhemorrhages in CAA<sup>11</sup> has been shown to be related to disease progression, recurrent ICH, and CAA-related impairment.<sup>5,8</sup> Greenberg et al<sup>8</sup> evaluated 94 elderly patients ( $\geq 55$  years of age) presenting with lobar ICH for number of baseline hemorrhages. Microhemorrhages were 2.5 $\times$  more common than macrohemorrhages. Among patients who underwent an MRI 16 months later, 50% experienced new, frequently multiple microhemor-

rhages. A large number of hemorrhages at baseline and APOE  $\epsilon 2$  or  $\epsilon 4$  genotype were the only predictors of new microhemorrhages. Both the number of hemorrhages at baseline and the number of new microhemorrhages at follow-up increased the risk of recurrent hemorrhage (3-year cumulative risk 14%, 17%, 38%, and 51% in subjects with 1, 2, 3 to 5, or  $\geq 6$  baseline hemorrhages, respectively). The distribution of new microhemorrhages at follow-up has been correlated with the distribution of baseline microhemorrhages.<sup>46</sup> In those who experienced recurrent lobar ICH, the location of hematoma was positively associated with the distribution of baseline hemorrhages (including microhemorrhages). Individuals with cognitive impairment showed a trend toward increased number of baseline hemorrhages. Finally, the number of baseline hemorrhages increased the incidence of cognitive impairment, functional dependence or death at follow-up (mean 27.9 months; hazard ratio [HR], 1.9).

Impairment of cognitive function associated with microhemorrhage has also been reported in ischemic disease. In a small case-control study of patients with ischemic stroke or transient ischemic attack, individuals with microhemorrhages performed significantly worse on standard tests of executive function compared with those without microhemorrhages.<sup>51</sup> The number of microhemorrhages was the only independent predictor of executive dysfunction in these patients. Subjects with executive dysfunction had more microhemorrhages in the frontal lobes and basal ganglia compared with those subjects without executive dysfunction. However, the investigators did not evaluate all potential confounders, particularly the number or location of associated lacunar infarctions.

In survivors of ischemic stroke, microhemorrhage may be associated with recurrent cerebrovascular events. Of 121 patients with acute ischemic stroke followed longitudinally, those with microhemorrhages more frequently developed subsequent ICH (9.3% versus 1.3%).<sup>52</sup> However, the significance of this result is unclear because of the possible confounding effect of anticoagulation and antiplatelet therapy

in these patients. In another prospective study of 337 survivors of ICH or lacunar infarction (59% ICH survivors; average age 66 years; mean follow-up 22.5 months), 20 patients experienced recurrent stroke (13 lacunar infarctions; 7 deep ICHs). Recurrence was found to be associated with previous history of ICH and  $\geq 5$  microhemorrhages.<sup>53</sup>

The risk of antiplatelet therapy in the presence of microhemorrhage has been examined in 2 studies. Microhemorrhages were noted to be more frequent in ICH patients taking aspirin compared with aspirin users without ICH.<sup>54</sup> Although this suggested that microhemorrhage could be a risk factor for ICH in those taking antiplatelet therapy, a recent study demonstrated that microhemorrhage did not modify the risk of recurrence in survivors of lobar and deep ICH taking antiplatelet therapy (HR=0.8,  $P=0.73$ ; and HR=1.2,  $P=0.88$ , respectively).<sup>55</sup> There are no prospective studies examining the risk of anticoagulation in the presence of microhemorrhage.

The risk of thrombolysis-related hemorrhage in patients with microhemorrhages has been examined in only 1 study.<sup>56</sup> One of 5 patients with microhemorrhage (versus 4 of 36 patients without microhemorrhage) undergoing thrombolytic therapy experienced a major symptomatic hemorrhage (statistically nonsignificant). This patient was a 96-year-old woman who developed a hematoma at the site of a previous microhemorrhage after receiving intra-arterial thrombolysis for an acute ischemic stroke in the contralateral hemisphere. The small sample size is the major limitation to reach any practical conclusion.

### Conclusion and Perspective

The frequency of cerebral microhemorrhage varies by population, its prevalence being lowest in healthy individuals, intermediate in ischemic stroke, and highest in hemorrhagic conditions. No longer considered an incidental finding on MRI, cerebral microhemorrhage is a sign of underlying small vessel pathology. Evidence of associated modifiable risk factors (most notably, uncontrolled hypertension) should be sought in all patients with microhemorrhage.

In lobar ICH patients with evidence of microhemorrhage restricted to the lobar regions, the diagnosis of probable CAA can be reliably made.<sup>5,43</sup> In these patients, the most important predictor of recurrent ICH and functional impairment is number of microhemorrhages.<sup>8</sup> Decision analysis models based on retrospective data suggest that anticoagulation considerably increases the risk of recurrent ICH in these patients and thus should probably be avoided.<sup>57</sup> In contrast, the risk of hemorrhage with antiplatelet therapy in this setting is likely nonsignificant or very low and the decision to treat should be balanced with ischemic risk in patients with thrombotic disease.<sup>55</sup>

However, in other populations, further studies are needed to determine the risk of cerebral microhemorrhage, particularly in healthy elderly, in survivors of deep ICH, and in patients with ischemic stroke. In addition, the risk related to the use of antithrombotic agents in the setting of microhemorrhages should be evaluated prospectively. The exact risk of thrombolysis-related ICH in patients with microhemorrhage<sup>56</sup> also needs to be ascertained in larger studies. Treatment with perindopril and indapamide has been shown to reduce white

matter lesion progression in ischemic stroke patients.<sup>58</sup> Whether antihypertensive therapy has any effect on the progression of microhemorrhage is unknown.

The true sensitivity of current GE techniques to detect microhemorrhages has not been investigated. Detailed radiopathologic correlation studies could address this question. In the near future, new imaging tools based on high-field MRI will become more clinically available, and the sensitivity to detect cerebral microhemorrhages may increase even further. This may allow the study of new populations of patients and refine the clinical value of this new MRI marker.

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