The Microbleed Anatomical Rating Scale (MARS)

Reliability of a tool to map brain microbleeds

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ABSTRACT

Objective: Brain microbleeds on gradient-recalled echo (GRE) T2*-weighted MRI may be a useful biomarker for bleeding-prone small vessel diseases, with potential relevance for diagnosis, prognosis (especially for antithrombotic-related bleeding risk), and understanding mechanisms of symptoms, including cognitive impairment. To address these questions, it is necessary to reliably measure their presence and distribution in the brain. We designed and systematically validated the Microbleed Anatomical Rating Scale (MARS). We measured intrarater and interrater agreement for presence, number, and anatomical distribution of microbleeds using MARS across different MRI sequences and levels of observer experience.

Methods: We studied a population of 301 unselected consecutive patients admitted to our stroke unit using 2 GRE T2*-weighted MRI sequences (echo time [TE] 40 and 26 ms). Two independent raters with different MRI rating expertise identified, counted, and anatomically categorized microbleeds.

Results: At TE = 40 ms, agreement for microbleed presence in any brain location was good to very good (intrarater κ = 0.85 [95% confidence interval (CI) 0.77–0.93]; interrater κ = 0.68 [95% CI 0.58–0.78]). Good to very good agreement was reached for the presence of microbleeds in each anatomical region and in individual cerebral lobes. Intrarater and interrater reliability for the number of microbleeds was excellent (intraclass correlation coefficient [ICC] = 0.98 [95% CI 0.97–0.99] and ICC = 0.93 [0.91–0.94]). Very good interrater reliability was obtained at TE = 26 ms (κ = 0.87 [95% CI 0.61–1]) for definite microbleeds in any location.

Conclusion: The Microbleed Anatomical Rating Scale has good intrarater and interrater reliability for the presence of definite microbleeds in all brain locations when applied to different MRI sequences and levels of observer experience. *Neurology*® 2009;73:1759–1766

GLOSSARY

BOMBS = Brain Observer Microbleed Scale; **CAA** = cerebral amyloid angiopathy; **CI** = confidence interval; **DPWM** = deep and periventricular white matter; **FA** = flip angle; **FLAIR** = fluid-attenuated inversion recovery; **FOV** = field of view; **GRE** = gradient-recalled echo; **ICC** = intraclass correlation coefficient; **MARS** = Microbleed Anatomical Rating Scale; **NEX** = number of excitations; **NHNN** = National Hospital for Neurology and Neurosurgery; **TE** = echo time; **TR** = repetition time.

Microbleeds—small, rounded hypointensities visualized on gradient-recalled echo (GRE) T2*-weighted MRI brain scans—are commonly detected in healthy individuals (especially with advancing age)[1] and patients with cerebrovascular disease.[2] It has been suggested that microbleeds are a useful biomarker for pathologic damage to small vessels from hypertension or cerebral amyloid angiopathy (CAA).[1] However, many important areas of clinical uncertainty regarding microbleeds remain, including their potential role in predicting the risk of intracranial hemorrhage (especially in patients treated with thrombolytics or antithrombotics); their value for diagnosing small vessel diseases, including CAA; and their contribution to cognitive impairment.[3,4]

Supplemental data at www.neurology.org

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To study the important clinical questions regarding microbleeds, a measurement instrument that reliably rates their presence, number, and anatomical distribution in the brain is required. The measurement instrument used must have adequate intrarater and interrater reliability, but few studies have systematically investigated these aspects.[5] The wide variations in observer agreement in previous studies (table e-1 on the *Neurology*® Web site at www.neurology.org) may be related to the following factors: properties of the rating scales (which only 1 study has reported in detail),[5] levels of observer experience in MRI interpretation and training background (e.g., neurology, radiology),[4,6] MRI sequence characteristics, and microbleed defining criteria (table e-2). We developed the Microbleed Anatomical Rating Scale (MARS), an anatomically detailed scale designed to be reliable, easy to use, and generalizable across MRI sequences and observers with various imaging experience. We specifically included a categorization of microbleeds into individual brain lobes, because this anatomical information may be important to assess their contribution to vascular cognitive impairment or diagnosing CAA.[3,7-9] We systematically measured the intrarater and interrater reliabilities of the scale for microbleed presence and number in lobar, deep, and infratentorial regions in a representative stroke population.

METHODS

Study population. We considered unselected, consecutive patients (n = 426) admitted to the Stroke Service at the National Hospital for Neurology and Neurosurgery (NHNN) from July2004 to October 2007. The Stroke Service takes all suspected stroke patients admitted from the surrounding district and has a policy of performing MRI with GRE T2* sequence in all of them unless there is a contraindication (e.g., too medically unstable, severe claustrophobia, metallic implants). Patients who did not have an MRI were excluded. We excluded patients without GRE T2*-weighted MRI of sufficient quality for analysis (e.g., due to motion artifact) (figure e-1).

Standard protocol approvals, registrations, and patient consents. This study on human subjects received approval from the NHNN and Institute of Neurology Joint Research Ethics Committee.

Imaging protocols. All MRIs were carried out at 1.5-T field strength using 2 MRI systems.

The majority of patients (n = 271) were imaged on GE Medical Genesis Signa system (GE HealthCare, Waukesha, WI) using an echo time (TE) of 40 ms for the T2*-weighted sequence. The parameters of the sequences were as follows: axial T2-weighted fast spin echo (repetition time [TR] 6,000, TE 105, flip angle [FA] 90, matrix 256 × 224, field of view [FOV] 24 × 18, slice thickness 5 mm, slice gap 1.5 mm, number of excitations [NEX] 2); axial GRE T2* (TR 300, TE 40, FA 20, FOV 24 × 18, matrix 256 × 160, slice thickness 5 mm, slice gap 1.5 mm, NEX 1). A smaller number of patients (n = 30) were imaged on a Siemens (Berlin and Munich, Germany) Avanto system using TE = 26 ms for the T2*-weighted sequence. The parameters of the sequences were as follows: axial T2-weighted fast spin echo (TR 4320, TE 106, FA 150, matrix 448 × 392, FOV 24 × 18, slice thickness 5 mm, slice gap 1.5 mm, NEX 2); axial GRE T2* (TR 800, TE 26, FA 20, FOV 24 × 18, matrix 512 × 448, slice thickness 5 mm, slice gap 1.5 mm, NEX 1).

Brain microbleed rating. We tested the reliability of the scale for microbleeds presence and number in all individual cerebral regions in the patients scanned at TE = 40 ms. The images of the patients scanned at TE = 26 ms were studied in a secondary analysis for presence of microbleeds only. Images were displayed using the Agfa IMPAX PACS system (Agfa, Mortsel, Belgium) on 3-megapixel premium diagnostic grayscale displays (Barco [Kortrijk, Belgium] Coronis 3MP MDCG-3120-CB) and assessed by a clinical neurologist (S.M.G.) and trainee neurologist (U.J.C.) in semidark conditions. Rater 1 (S.M.G.) had 5 years' experience in neuroimaging; rater 2 (U.J.C.) had 1 year's experience. Rater 2 rated the MRIs twice at a 4-week interval, chosen as the minimum time likely to be used in prospective studies. Rater 1 rated the MRIs twice at a 1-year interval on a subsample of the first 100 consecutive patients. Both raters had received training sessions in microbleed detection from a senior neuroradiologist (H.R.J.). Each rater was blinded to clinical data and the other rater's ratings. Cases of disagreement were reviewed by a consultant vascular neurologist (D.J.W.) and consultant neuroradiologist (H.R.J.), both with extensive experience in microbleed rating. Appropriate guidance was incorporated into instructions for future users of the scale.

The MARS. We classified microbleeds into "definite" and "possible" categories because a previous study suggested that such classification improves reliability.[5] Definite microbleeds were defined as small, rounded or circular, well-defined hypointense lesions within brain parenchyma with clear margins ranging from 2 to 10 mm in size on GRE T2*-weighted images; possible microbleeds were less well defined, less hypointense, or not strictly rounded or circular. The 2- to 10-mm size range includes the highest upper limit defined in previous studies (table e-2).[4] We included a lower size limit in accordance with consensus guidelines on standards for neuroimaging in vascular cognitive impairment.[9] Microbleed mimics were carefully excluded using all available imaging (figure e-2 and figure). In the basal ganglia, we considered strictly unilateral lesions without evidence of corresponding infarction (on T2-weighted and fluid-attenuated inversion recovery [FLAIR] images) or calcification (on CT scans) to be definite.

Microbleeds were classified into deep, lobar, and infratentorial categories. Lobar MRI landmarks were defined according to Stark and Bradley[10] and included cortical and subcortical regions (including subcortical U fibers). Deep regions included the basal ganglia, thalamus, internal capsule, external capsule, corpus callosum, and deep and periventricular white matter (DPWM); infratentorial regions included the brainstem and cerebellum. All regions were presented for easy reference in an anatomical diagram (drawn by S.M.G. using representative axial magnetic res-

Figure Microbleed Anatomical Rating Scale

Patient ID: Date of Birth _ _/_ _/_ _ _ _ Date of MRI _ _/_ _/_ _ _ _

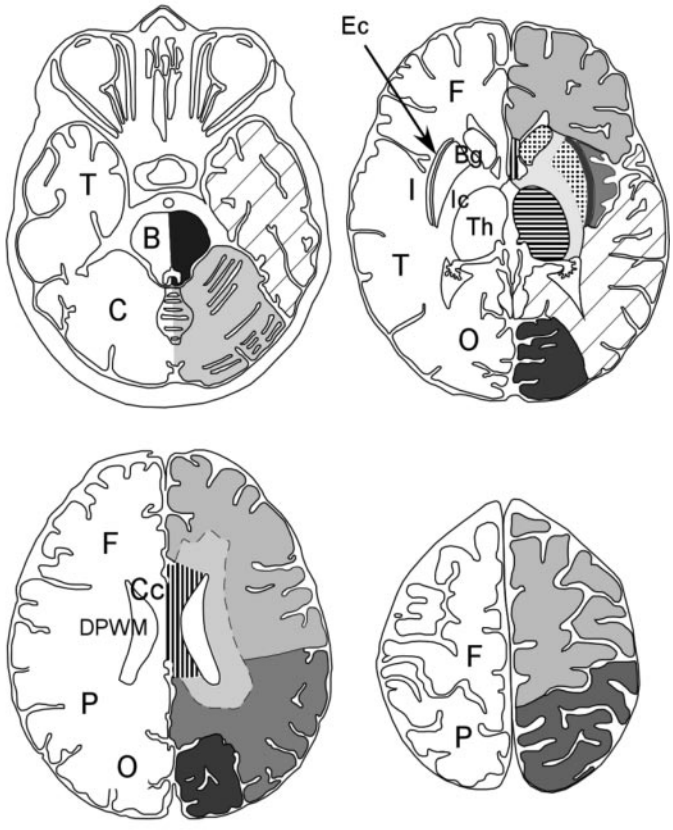
DEFINITE MICROBLEEDS: Small, round, well-defined, hypointense on GRE T2*; 2-10 mm; not well seen on T2

MICROBLEED MIMICS

- Vessels: linear / curvilinear lesions in subarachnoid space, usually cortical or juxta-cortical (visible on T2)
- Mineralization in globi pallidi or dentate nuclei: symmetrical hypointensities (may be bright flecks on CT)
- Haemorrhages within area of infarction (look at the T2, FLAIR or DWI sequences to identify infarction)
- Air-bone interfaces: frontal / temporal lobes (check adjacent GRE T2* slices to clarify)
- Partial volume artifact at the edges of the cerebellum (check adjacent GRE T2* to clarify)
- Small haemorrhages close to a large ICH (visible on GRE T2*) or to an infarct (visible on T2, FLAIR or DWI)

Right Left

		DEFINITE		POSSIBLE	
		R	L	R	L
Infratentorial TOTAL	Brainstem (B)				
	Cerebellum (C)				
Deep TOTAL	Basal Ganglia (Bg)*				
	Thalamus (Th)				
	Internal Capsule (Ic)				
	External Capsule (Ec)				
	Corpus Callosum (Cc)				
	Deep and periventricular WM (DPWM)				
Lobar** TOTAL	Frontal (F)				
	Parietal (P)				
	Temporal (T)				
	Occipital (O)				
	Insula (I)				
	TOTALS				



* (Caudate, Lentiform), **Lobar regions include cortex and subcortical white matter

The rating form is available on the *Neurology*® Web site at www.neurology.org. GRE = gradient-recalled echo; FLAIR = fluid-attenuated inversion recovery; DWI = diffusion-weighted imaging; ICH = intracerebral hemorrhage.

onance images) adjacent to the scale. DPWM was defined as white matter adjacent to or within approximately 10 mm of the lateral ventricular margin. Definite and possible microbleeds were reported at each location on the MARS rating form (figure). The sum of definite and possible microbleeds was recorded as total microbleeds.

Comparison between an existing scale (BOMBS) and MARS. Both raters evaluated the first 100 consecutive patients using the Brain Observer Microbleed Scale (BOMBS)[5] to calculate the interrater reliability. The second MARS ratings of both raters were then used to recalculate its interrater reliability for the same sample.

Table Reliability of MARS at TE = 40 ms for presence and number of microbleeds (κ agreements and correlation coefficients)

	Presence of microbleeds*				Number of microbleeds†			
Microbleeds	n (%), rater 1	n (%), rater 2	IA (95% CI)	IE (95% CI)	n (range), rater 1	n (range), rater 2	IA (95% CI)	IE (95% CI)
Any location								
Definite	67 (25)	87 (32)	0.85‡ (0.77-93)	0.68‡ (0.58-0.78)	266 (0-23)	360 (0-29)	0.98 (0.97-0.99)	0.93 (0.91-0.94)
Possible	52 (19)	63 (23)	0.72‡ (0.62-0.82)	0.31§ (0.17-0.45)	109 (0-14)	147 (0-22)	0.86 (0.83-0.89)	0.58 (0.49-0.65)
Total	84 (31)	105 (39)	0.84‡ (0.78-0.90)	0.61‡ (0.51-0.71)	375 (0-35)	507 (0-49)	0.98 (0.97-0.98)	0.91 (0.89-0.93)
Lobar, deep, and IT								
Definite								
Lobar	46 (17)	60 (22)	0.85‡ (0.77-0.93)	0.72‡ (0.62-0.82)	156 (0-14)	209 (0-22)	0.98 (0.97-0.98)	0.91 (0.89-0.93)
Deep	37 (14)	40 (15)	0.94‡ (0.88-1)	0.71‡ (0.59-0.83)	83 (0-8)	97 (0-9)	0.97 (0.96-0.98)	0.92 (0.90-0.94)
IT	16 (6)	32 (12)	0.85‡ (0.75-0.95)	0.64‡ (0.48-0.80)	27 (0-8)	54 (0-6)	0.91 (0.88-0.93)	0.73 (0.67-0.78)
Possible								
Lobar	32 (12)	40 (15)	0.76‡ (0.64-0.88)	0.39§ (0.23-0.55)	66 (0-14)	95 (0-20)	0.89 (0.86-0.91)	0.72 (0.66-0.78)
Deep	19 (7)	20 (7)	0.56§ (0.36-0.76)	0.20§ (0-0.40)	34 (0-12)	23 (0-2)	0.47 (0.37-0.56)	0.16 (0.05-0.28)
IT	9 (3)	22 (8)	0.54§ (0.34-0.74)	0.22§ (0.02-0.42)	9 (0-1)	29 (0-3)	0.97 (0.97-0.98)	0.145 (0.03-0.26)
Total								
Lobar	60 (22)	74 (27)	0.84‡ (0.76-0.92)	0.64‡ (0.54-0.74)	222 (0-28)	304 (0-42)	0.96 (0.94-0.96)	0.91 (0.89-0.93)
Deep	49 (18)	50 (18)	0.87‡ (0.79-0.95)	0.67‡ (0.55-0.79)	117 (0-17)	120 (0-10)	0.85 (0.81-0.88)	0.88 (0.85-0.91)
IT	23 (8)	46 (17)	0.80‡ (0.70-0.90)	0.56§ (0.42-0.70)	36 (0-8)	83 (0-6)	0.85 (0.81-0.88)	0.66 (0.58-0.72)
Individual lobes and regions (definite microbleeds)								
Frontal	24 (9)	24 (9)	0.89‡ (0.79-0.99)	0.77‡ (0.63-0.91)	41 (0-4)	53 (0-7)	0.95 (0.93-0.96)	0.84 (0.80-0.87)
Temporal	22 (8)	36 (13)	0.87‡ (0.77-0.97)	0.73‡ (0.59-0.87)	53 (0-5)	80 (0-9)	0.96 (0.95-0.97)	0.81 (0.77-0.85)
Parietal	21 (8)	26 (10)	0.98‡ (0.94-1)	0.74‡ (0.60-0.88)	35 (0-7)	49 (0-5)	0.93 (0.92-0.95)	0.75 (0.69-0.79)
Occipital	13 (5)	15 (6)	0.70‡ (0.50-0.90)	0.62‡ (0.40-0.84)	24 (0-4)	19 (0-3)	0.75 (0.69-0.79)	0.65 (0.58-0.72)
Insula	3 (1)	7 (3)	0.85‡ (0.65-1)	ND	3 (0-1)	8 (0-2)	0.89 (0.87-0.92)	ND
Thalamus	20 (7)	27 (10)	0.96‡ (0.90-1)	0.84‡ (0.72-0.96)	44 (0-6)	57 (0-8)	0.95 (0.94-0.96)	0.91 (0.88-0.93)
Basal ganglia	18 (7)	16 (6)	0.87‡ (0.75-0.99)	0.44§ (0.22-0.66)	23 (0-4)	26 (0-4)	0.88 (0.85-0.91)	0.59 (0.51-0.66)
Other deep locations‖	13 (5)	8 (3)	ND	ND	16 (0-2)	14 (0-3)	ND	ND
Brainstem	7 (3)	11 (4)	0.95‡ (0.85-1)	0.77‡ (0.55-0.99)	8 (0-2)	15 (0-4)	0.96 (0.95-0.97)	0.76 (0.71-0.81)
Cerebellum	11 (4)	27 (10)	0.81‡ (0.69-0.93)	0.55§ (0.43-0.67)	19 (0-7)	39 (0-5)	0.86 (0.83-0.89)	0.73 (0.66-0.78)

*Unweighted κ statistic.
†Intraclass correlation coefficient.
‡Good/very good agreement.
§Moderate agreement.
‖Internal capsule, external capsule, corpus callosum, deep and periventricular white matter.
MARS = Microbleed Anatomical Rating Scale; TE = echo time; IA = intrarater; CI = confidence interval; IE = interrater; IT = infratentorial; ND = not done.

Statistics. Intrarater and interrater agreements for the presence or absence of microbleeds were calculated using the nonparametric unweighted κ measure of agreement. The κ results were interpreted as poor (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80), or very good (0.81–1) agreement as per Landis and Koch.[11] We used the intraclass correlation coefficient to assess the intrarater and interrater reliabilities for the number of microbleeds. The intrarater reliabilities of each rater were compared. All statistical tests were conducted using SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL).

RESULTS

Participants. MRI was performed in 355 consecutive patients (83%) admitted to the stroke unit. Fifty-four patients were excluded from the final analysis for insufficient quality MRI due to motion artifact (n = 43) or absence of GRE T2*-weighted MRI sequence (n = 11). The final cohort consisted of 301 patients, including 271 patients scanned at TE = 40 ms and 30 patients scanned at TE = 26 ms. This is summarized in the patient flow diagram (figure e-1). The radiologic findings of our patients included ischemic stroke (n = 109, 36%), small vessel disease with acute infarction (n = 106, 35%), small vessel disease without acute infarction (n = 28, 10%), intracerebral hemorrhage (n = 15, 5%), intracerebral hemorrhage with small vessel disease (n = 12, 4%), and subarachnoid hemorrhage (n = 9, 3%). Thirteen subjects (4%) had a normal intracranial MRI scan; 9 subjects (3%) had other pathology. One hundred seventy-two were male, 129 were female; the mean age was 65.2 years (range 18–97 years). CT was available in the majority of patients (94%, n = 283).

Microbleeds in any location of the brain. Results of intrarater and interrater reliabilities for the presence and number of definite, possible, and total microbleeds in the brain are shown in table. Raters disagreed on the presence or absence of 1 or more definite microbleeds in 69 cases (25%), of which 28 (41%) were thought to have a single definite microbleed by at least 1 of the raters. Because the clinical and pathophysiologic significance of a single microbleed is uncertain, we investigated the effect of excluding patients with 1 definite microbleed from the analysis. After excluding these patients, there was a substantial improvement of the interrater agreement for the presence of definite microbleeds in any location (κ = 0.91 [95% confidence interval (CI) 0.85–0.97]). The intrarater reliability of rater 1 for the presence of microbleeds in all locations at a 1-year interval was good (κ = 0.75 [95% CI 0.61–0.89], but lower than that of rater 2 at a 4-week interval (κ = 0.89 [95% CI 0.79–0.99]).

Microbleeds in lobar, deep, and infratentorial regions. Microbleeds were most prevalent in the lobar region (17%–22%), followed by deep (14%–15%) and infratentorial regions (6%–12%). Intrarater and interrater reliabilities for the presence and number of definite microbleeds in lobar, deep, and infratentorial regions were good to very good (table).

Microbleeds in individual anatomical regions. For the presence of microbleeds, intrarater agreement was good to very good in all individual regions. Interrater agreement was good to very good for the presence of microbleeds in individual lobes, in the thalamus and brainstem; moderate interrater agreement was obtained in the cerebellum and basal ganglia. All interrater and intrarater reliabilities for microbleed presence and number are shown in the table. We could not calculate the reliability for microbleeds in the insula and in deep locations other than the thalamus and basal ganglia because of the small number of patients with microbleeds in these regions.

The reliability of the scale for possible and total microbleeds was lower than that for definite microbleeds in all regions of the brain (table).

Agreement for microbleed rating at TE = 26 ms. At TE = 26 ms (n = 30), we obtained very good intrarater and interrater agreements for the presence of definite microbleeds (intrarater κ = 1 and interrater κ = 0.87 [95% CI 0.61–1]) in any location of the brain.

Comparison between MARS and BOMBS. On the sample of the first consecutive 100 patients, the interrater reliability of BOMBS for the presence of definite microbleeds in all locations was κ = 0.64 (95% CI 0.48–0.80); the interrater reliability of MARS was κ = 0.75 (95% CI 0.61–0.89).

DISCUSSION

With the increasing interest in the clinical relevance of microbleeds in individuals with cerebrovascular disease or dementia and in normal aging, there is a need for a reliable instrument to rate their presence, number, and distribution throughout the brain. Although some previous studies have reported information on the reliability of microbleed rating,[12-20] only one[5] clearly described the characteristics of the instrument used, and most did not report the intrarater and interrater reliabilities for all relevant anatomical regions. Here, we have shown that MARS has good to very good intrarater and interrater reliability for microbleed presence and number in individual cerebral lobes, deep regions, and infratentorial regions.

The main difference between MARS and another recently described scale, BOMBS,[5] is that MARS is designed to assess microbleeds in individual cerebral lobes. Lobar anatomical information may be important for studies investigating the impact of microbleeds on cognitive functions in cerebrovascular and degenerative diseases[3,8,9,21,22] or for the diagnosis of CAA, in which a preferential parietooccipital distribution for microbleeds has been reported.[23] Indeed, our classification is based partly on the theoretical

potential for microbleed distribution to help distinguish CAA from hypertensive small vessel disease.[1] The deep category includes brain structures potentially affected by hypertensive disease of the small penetrating arteries; lobar regions include the corticosubcortical regions (cortex and subcortical white matter), more likely to be affected by CAA. The use in MARS of a lobar scheme similar to previously validated age-related white matter change scales[9,24] allows the investigation of regional correlations among white matter changes, microbleeds, and clinical factors. MARS has other features designed to maximize ease of use: the rating form includes a convenient summary of the total microbleed counts for the whole brain and each anatomical region, and a clear guide to anatomical boundaries of the cerebral lobes and regions (figure). MARS does not subclassify microbleeds according to their size, which in BOMBS may unnecessarily complicate the ratings without adding extra useful information. Although the 95% CIs overlapped, our raters had a higher interrater reliability in favor of MARS compared with BOMBS when tested in the same population.

The present study has strengths in comparison with some previous reports on microbleed rating. First, we systematically tested MARS in a representative stroke population; many previous studies have included healthy populations[13,25,26] or patients with a single cerebrovascular diagnosis (intracerebral hemorrhage,[27-29] CAA[16,30]). Second, intrarater reliability has not been addressed with an adequate interval in most previous studies[1,31] but is critically important for longitudinal cohort studies. MARS has shown high agreement with up to a 1-year intrarater interval, suggesting that it may be useful for such follow-up studies. The lower intrarater reliability for rater 1 is probably due to the longer interval between ratings compared with rater 2. Third, our study investigated the reliability of quantifying the number of microbleeds, which may be relevant in exploring their relationship with other quantitative imaging or clinical data; most previous studies tested the reliability of rating microbleed presence but not number.[1,8,14,25,32] Fourth, our results suggest that MARS may be reliable when applied to a range of MRI sequences, in particular across different TE values. The interrater reliability in our cohort studied at TE = 26 ms was better than at TE = 40 ms; this may be because some microbleeds or microbleed mimics are missed at TE = 26 ms, therefore paradoxically increasing the apparent reliability of the scale despite reduced sensitivity. However, we did not repeat MRI studies with different TE on the same patients to investigate this possibility. Previous studies on microbleeds reported TE values from 15 to 50 ms (table e-2),[5,25,26] which may substantially affect the reported prevalence of microbleeds.[6] Long TEs may increase the number and size of microbleeds detected[33] but could also reduce image quality and increase unwanted susceptibility artifacts.[6] Many other MRI acquisition characteristics influence microbleed detection, including magnetic field strength, slice thickness, FA, and postprocessing techniques (including susceptibility-weighted imaging), but the optimum MRI protocol for detecting microbleeds needs further study.[6,34-37] The use of a validated scale could help to identify the MRI acquisition strategy with highest reliability. Finally, our scale had good reliability for raters with different levels of experience in neuroimaging. Our less-experienced rater documented the highest number of microbleeds, suggesting that stringency in rating might increase with experience, even when both observers undergo similar training (as in our study). This suggests that to maximize the reliability of microbleed rating, the same observer should be used for all ratings if possible, even where training is standardized; for multicenter studies, a single rating center for analysis may also improve reliability. In future studies, automated methods of microbleed detection may help to further improve agreement for microbleed number.

Regions of the brain that caused discrepancies among our raters and with reduced reliability included the basal ganglia, cerebellum, and occipital lobes. In the basal ganglia, susceptibility effects from calcification or iron deposits can mimic microbleeds; CT may be helpful to distinguish calcification. In the posterior fossa, causes of disagreement include physiologic iron deposits in the dentate nuclei and partial volume artifact from adjacent bony structures. Airbone interfaces can cause susceptibility artifacts elsewhere, e.g., in the inferior frontal or temporal lobes. Problems from misclassifying microbleed mimics can be minimized by careful inspection of adjacent slices and reference to T2, FLAIR, and diffusion-weighted images (figure e-2). Because of the lower agreement for possible microbleeds, including only definite microbleeds may improve the reliability of microbleed rating for research studies. Patients with only 1 potential microbleed accounted for most cases of disagreement, and interrater reliability substantially improved when these patients were excluded. We therefore suggest caution in rating a single microbleed as a definite lesion. More work is required to establish whether only patients with multiple microbleeds should be included in research studies, and how this affects microbleed prevalence in different diseases. This issue is further complicated because the classification of patients into those having single vs multiple microbleeds may vary with the

MRI technique used; e.g., higher field strengths, thinner slices, or susceptibility-weighted imaging seem to increase the conspicuity and number of microbleeds detected.[6]

Our study has some limitations. First, the number of scans at TE = 26 ms was small (n = 30), which may increase the CIs for our reliability measures. Second, we chose to investigate the effect of TE on reliability (because TE is likely to have a marked effect on microbleed detection) but did not investigate the effect of changing other relevant MRI sequence characteristics.[6] Finally, both of our observers were neurologists, and it would be of interest to test the reliability of the scale in other types of rater (e.g., radiologists).

There is increasing interest in the use of biomarkers to detect and measure the risk of developing diseases and to measure disease progression and responses to treatment. Because microbleeds can be readily quantified, they may be a valuable imaging biomarker in the field of cerebrovascular disease. We have shown that the MARS has generally good intrarater and interrater reliability, and we hope that it will prove to be a useful contribution to efforts to reliably map brain microbleeds. Further studies are needed to establish optimal and standardized MRI protocols for microbleed identification, investigate the clinical and diagnostic significance of single (or few) vs multiple microbleeds, and develop clear standards for microbleed rating. This should allow the combination of reliable data from different centers for effective investigation of the many remaining important clinical questions.

AUTHOR CONTRIBUTIONS

The project was supervised by D.J.W., who contributed to study design, data collection, arbitration, and analysis and writing of the manuscript, and approved the final version. S.M.G. was responsible for data collection, analysis, interpretation, and writing of the manuscript. U.J.C. contributed to the analysis and interpretation of the data and to the writing of the manuscript. H.R.J. contributed to the study design, provided training in microbleed rating, was an arbitrator, and helped with the review of the manuscript. T.A.Y. and M.M.B. provided important feedback on the manuscript. C.K. provided statistical input. The imaging was conducted at the Lysholm Department of Neuroradiology of the National Hospital for Neurology and Neurosurgery and Department of Imaging at University College Hospitals.

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DISCLOSURE

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The Microbleed Anatomical Rating Scale (MARS): Reliability of a tool to map brain microbleeds

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