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Whole-Brain Susceptibility-Weighted Thrombus Imaging in Stroke: Fragmented Thrombi Predict Worse Outcome

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ABSTRACT

BACKGROUND AND PURPOSE: The prevalence and clinical importance of primarily fragmented thrombi in patients with acute ischemic stroke remains elusive. Whole-brain SWI was used to detect multiple thrombus fragments, and their clinical significance was analyzed.

MATERIALS AND METHODS: Pretreatment SWI was analyzed for the presence of a single intracranial thrombus or multiple intracranial thrombi. Associations with baseline clinical characteristics, complications, and clinical outcome were studied.

RESULTS: Single intracranial thrombi were detected in 300 (92.6%), and multiple thrombi, in 24 of 324 patients (7.4%). In 23 patients with multiple thrombi, all thrombus fragments were located in the vascular territory distal to the primary occluding thrombus; in 1 patient, thrombi were found both in the anterior and posterior circulation. Only a minority of thrombus fragments were detected on TOF-MRA, first-pass gadolinium-enhanced MRA, or DSA. Patients with multiple intracranial thrombi presented with more severe symptoms (median NIHSS scores, 15 versus 11; $P = .014$) and larger ischemic areas (median DWI ASPECTS, 5 versus 7; $P = .006$); good collaterals, rated on DSA, were fewer than those in patients with a single thrombus (21.1% versus 44.2%, $P = .051$). The presence of multiple thrombi was a predictor of unfavorable outcome at 3 months ($P = .040$; OR, 0.251; 95% CI, 0.067–0.939).

CONCLUSIONS: Patients with multiple intracranial thrombus fragments constitute a small subgroup of patients with stroke with a worse outcome than patients with single thrombi.

ABBREVIATION: SVS = susceptibility vessel sign

Little is known about the proportion of acute ischemic strokes caused by multiple intracranial thrombi. Rarely, distal thrombus fragments that are separate from the primary occluding thrombus can be detected on DSA. Incomplete vessel occlusion by the primary thrombus with distal passage of contrast is required for this observation. Therefore, the true prevalence of multiple intracranial thrombi in the stroke population and the implications for clinical outcome remain unknown.

Advanced gradient-echo-based MR imaging sequences, such as SWI, are highly sensitive in distinguishing structures that have different susceptibility values than their surroundings (eg, deoxygenated blood, hemosiderin, ferritin, or calcium).[1] SWI offers the possibility to directly visualize thrombotic material, commonly referred to as the susceptibility vessel sign (SVS), independent of the presence of blood flow or contrast media.[2-4] Recent studies confirmed that 1.5T and 3T SWI is a fast, robust, and highly sensitive imaging technique in acute stroke without relevant image interference following gadolinium application.[5,6] We performed SWI, covering the whole brain in patients with acute ischemic stroke of the anterior or posterior circulation to determine the prevalence of multiple intracranial thrombi before thrombolytic treatment and to study the associations between the presence of fragmented thrombi and baseline clinical and imaging characteristics, stroke etiology, and clinical outcome.

MATERIALS AND METHODS

Patients and Clinical Data

Five hundred fifty-seven patients with acute ischemic stroke treated at our stroke unit from January 2010 to August 2013 underwent MR imaging after admission. Of these, 442 patients had MR imaging including SWI before initiation of thrombolytic therapy. Patients with anterior or posterior circulation stroke due to tandem occlusions (ICA and MCA), carotid-T occlusions, iso-

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From the Departments of Diagnostic and Interventional Neuroradiology (P.P.G., G.S., J.G., S.J., P.M., K.H., R.K.V., C.W., M.E.-K.) and Neurology (H.P.M., U.F., S.J.), Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland.

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Please address correspondence to Gerhard Schroth, MD, Department of Diagnostic and Interventional Neuroradiology, University of Bern, Inselspital, Freiburgstr 10, 3010 Bern, Switzerland; e-mail: gerhard.schroth@insel.ch

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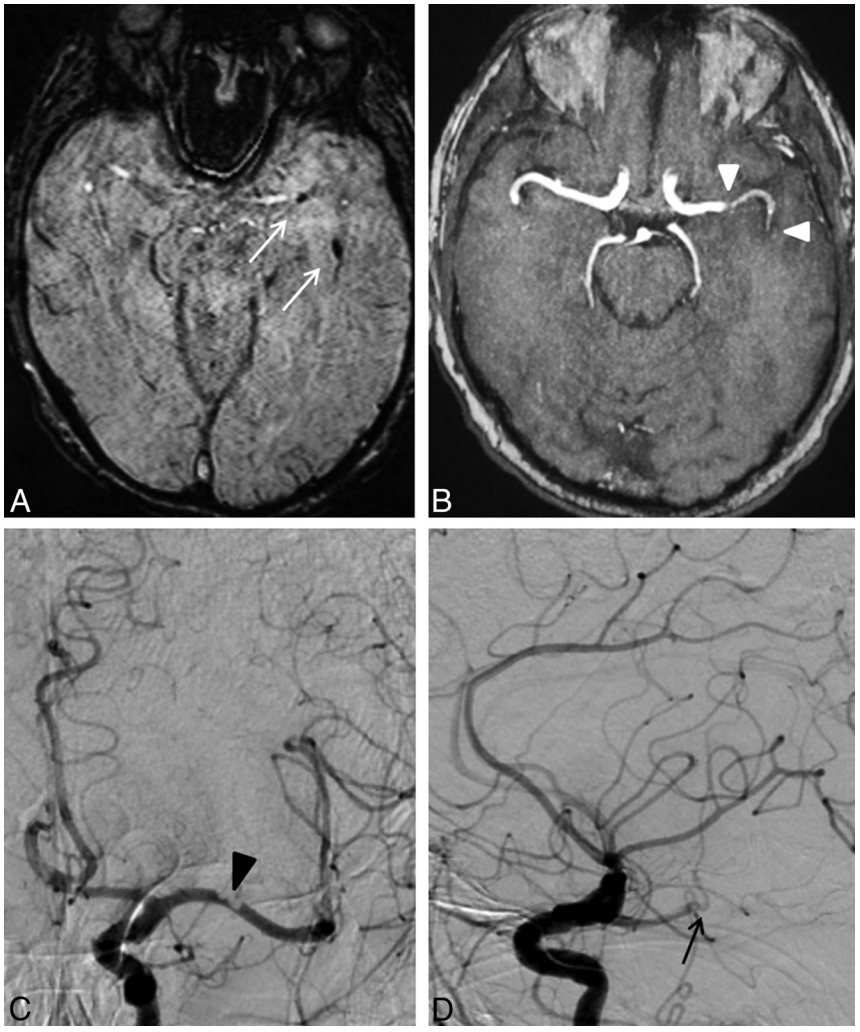

FIG 1. An 85-year-old man with right-sided hemiparesis and aphasia (NIHSS 13). Pretreatment SWI shows susceptibility vessel signs in the left M1 and M2 segments (*A*, *white arrows*). On TOF-MRA (MIP), diminished flow signal is seen distal to the thrombus fragment in the M1 segment with complete loss of flow signal at the site of the distal thrombus fragment (*B*, *white arrowheads*). DSA demonstrates incomplete occlusion of the vessel lumen by a thrombus in the M1 segment (*C*, anteroposterior projection, *black arrowhead*). On the lateral projection, occlusion of the temporo-occipital M2 branch by a more distal thrombus fragment is visible (*D*, *black arrow*). Although both TOF-MRA and DSA can show the distal vessel occlusion, only SWI allows estimation of the length of the distal fragment and exclusion of additional distal thrombi.

lated occlusions of the MCA (M1, M2, or M3/4 segments), occlusions of the anterior cerebral artery, occlusions of the basilar artery either isolated or in combination with the vertebral artery, and occlusions of the posterior cerebral artery were considered for the final analysis. Three hundred forty-seven patients fulfilled all inclusion criteria. Following the imaging, all patients underwent recanalization therapy with IV rtPA, endovascular techniques, or a combination of both.

Clinical data were continuously recorded in the data base of our stroke center. The Trial of Org 10172 in Acute Stroke Treatment criteria were used for the categorization of stroke etiology.[7] The occurrence of symptomatic and asymptomatic intracranial hemorrhage, within 72 hours from stroke onset, was recorded according to the Prolyse in Acute Cerebral Thromboembolism II criteria.[8] Clinical outcome was assessed 3 months after stroke by using the modified Rankin Scale. The study was approved by our institutional review board.

Imaging

Standard stroke MR imaging protocol was performed, which included diffusion-weighted imaging, T2-weighted imaging, TOF-MRA, SWI, first-pass gadolinium-enhanced MRA of the cervical and intracranial arteries, and perfusion imaging. The scans were acquired on 1.5T and 3T MR imaging systems (Magnetom Avanto and Magnetom Verio; Siemens, Erlangen, Germany).

For the 1.5T scanner, the SWI parameters were the following: TR, 49 ms; TE, 40 ms; number of averages, 1; FOV read, 230 mm; FOV phase, 75.0%; voxel size, 0.9 × 0.7 × 1.8 mm; flip angle, 15°; acquisition time, 2 minutes 59 seconds. For the 3T scanner, the parameters were as follows: TR, 28 ms; TE, 20 ms; number of averages, 1; FOV read, 230 mm; FOV phase, 75.0%; voxel size, 0.9 × 0.9 × 2.0 mm; flip angle, 15°; acquisition time, 2 minutes 59 seconds. The SWI and minimum-intensity-projection images were generated automatically by the scanner software.

DSA was performed via a transfemoral approach by using a biplane, high-resolution angiographic system (Axiom Artis zee; Siemens).

Image Analysis

MR images were interpreted in consensus by a neuroradiologist and a radiologist in training. SWI was analyzed for the presence of the SVS in the supraclinoid segment of the ICA, the MCA, the anterior cerebral artery, the intradural segment of the vertebral artery, the basilar artery, and the posterior cerebral artery. The SVS was defined as an area of signal drop within the course of an artery that either exceeded the diameter of the contralateral nonoccluded vessel or that of the adjacent vessel segment on both the SWI and minimum-intensity-projection series.[3] The length of the main thrombus and distal thrombus fragments, if applicable, was measured on SWI. In case of carotid-T, tandem, and combined basilar artery and vertebral artery occlusions, total clot length could not be determined because of either susceptibility artifacts in the proximity of the skull base or thrombi located partially outside the FOV.

A distal thrombus fragment was defined as an SVS being separated from the more proximal SVS by >2 mm—that is, the largest dimension of a voxel in SWI (Figs 1 and 2). The distance between the primary occluding thrombus and distal thrombus

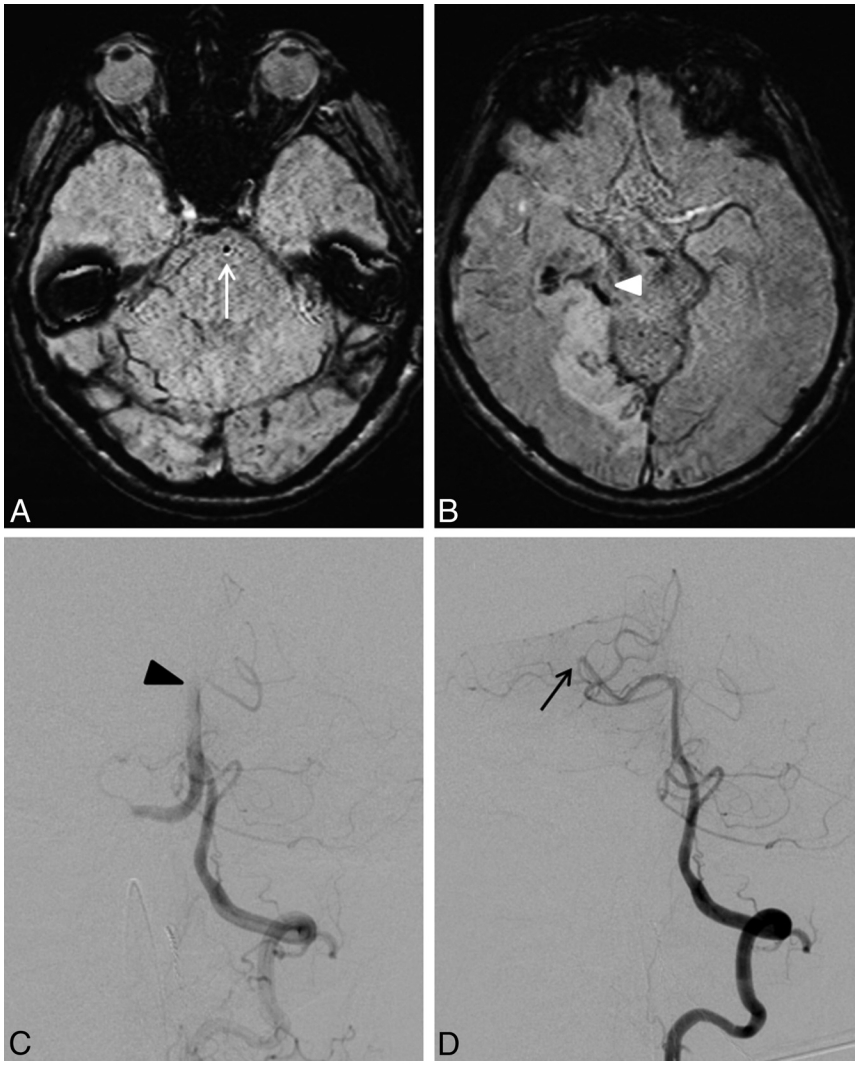

FIG 2. A 69-year-old male patient with a sudden decrease in consciousness. SWI shows susceptibility artifacts from thrombotic material in the basilar artery (*A*, *white arrow*) and the right posterior cerebral artery (*B*, *white arrowhead*). Hemorrhagic transformation of a subacute infarction in the vascular territory of the right posterior cerebral artery is seen. DSA confirms occlusion of the basilar artery (*C*, anteroposterior projection, *black arrowhead*). Following successful endovascular recanalization of the basilar artery, the occlusion in the perimesencephalic segment of the right posterior cerebral artery, already known from pretreatment SWI, becomes visible in DSA as well (*D*, anteroposterior projection, *black arrow*).

fragments was measured on a reconstructed plane, including both the distal part of the primary occluding thrombus and the proximal part of the thrombus fragment.

In patients with anterior circulation stroke, with the exception of the 4 patients with isolated anterior cerebral artery occlusion, the extent of ischemic lesions was assessed on pretreatment DWI by using the Alberta Stroke Program Early CT Score.[9]

Leptomeningeal collaterals were assessed on DSA as described previously.[10]

Statistical Analysis

Categoric variables were compared with the χ^2 test and the Fisher exact test as appropriate, and continuous variables, with the Mann-Whitney *U* test. To determine the predictors of clinical outcome, we performed a forward stepwise logistic regression, including all variables with a $P < .2$ in univariate analysis. These variables were age, sex, baseline NIHSS score, occlusion site, degree of collaterals, DWI ASPECTS, atrial fibrillation, diabetes mellitus, arterial hypertension, hypercholesterolemia, coronary artery disease, current smoking, and the presence of multiple intracranial thrombi on pretreatment imaging. Clinical outcome was dichotomized into favorable (mRS 0–2) and poor outcome (mRS 3–6). Collateral status was dichotomized into good and moderate/poor collaterals. A P value $< .05$ was considered significant. Statistics were performed with SPSS, Version 21 (IBM, Armonk, New York).

RESULTS

The SVS was detected in 324 of 347 patients (93.4%) on pretreatment SWI. Multiple intracranial thrombi were found in 24 patients (7.4% of all patients with visible SVSs). Fragmented thrombi occurred with a similar frequency in anterior and posterior circulation strokes (3/36 [8.3%] versus 21/288 [7.3%], $P = .739$). Nineteen patients had 1 distal fragment, 3 had 2 fragments, and 2 had 3 fragments. One of 31 fragments was located in the M1 segment of the MCA; 15, in the M2 segment; 11, in the M3 or M4 segment; 2, in the P2 segment of the posterior cerebral artery, and 2, in the P3 segment. Thirty thrombus fragments were found in the vascular territory distal to the primary occluding thrombus. One patient with a carotid-T occlusion was found to have a thrombus fragment in the P3 segment of the ipsilateral posterior cerebral artery, most likely by distal migration through a fetal variant of the posterior cerebral artery.

The mean distance of thrombus fragments from the primary occluding thrombus was 19.6 ± 15.6 mm. The mean length of thrombus fragments was 7.1 ± 4.0 mm.

TOF-MRA and first-pass gadolinium-enhanced MRA detected distal thrombus fragments in 8 and 11 of 24 patients (25.0% and 33.3%, respectively), with multiple intracranial thrombi on SWI. Nineteen of the 24 patients with multiple intracranial thrombi on SWI underwent DSA. In this group, thrombus fragments were confirmed in 8 patients (42.1%) on DSA.

Baseline clinical characteristics of patients with fragmented and single thrombi are shown in Table 1. Patients with multiple intracranial thrombi presented with a significantly higher median NIHSS score on admission (15 versus 11, $P = .014$). No significant difference in vascular risk factors or stroke etiology was found between the 2 groups. The prestroke use of antiplatelet

Table 1: Baseline clinical characteristics

	Fragmented Thrombus (*n* = 24) (7.4%)	Single Thrombus (*n* = 300) (92.6%)	*P*
Age (yr) (mean) (SD)	73.1 (11.3)	68.6 (14.0)	.109
Women (No.) (%)	9 (37.5)	139 (46.3)	.403
Baseline NIHSS score (median) (range)	15 (6–36)	11 (1–36)	.014
Vascular risk factors			
Hypertension (No.) (%)	15 (62.5)	192 (64.0)	.883
Diabetes mellitus (No.) (%)	5 (20.8)	45/298 (15.1)	.395
Atrial fibrillation (No.) (%)	13/23 (56.5)	123/263 (46.8)	.392
Current smoking (No.) (%)	2/22 (9.1)	57/286 (19.9)	.271
Hypercholesterolemia (No.) (%)	14/23 (60.9)	161/296 (54.4)	.548
Coronary artery disease (No.) (%)	5 (20.8)	58/298 (19.5)	.794
Previous stroke (No.) (%)	2 (8.3)	31/298 (10.4)	1.00
Stroke etiology			.558
Large artery disease (No.) (%)	3 (12.5)	31 (10.3)	
Cardioembolic stroke (No.) (%)	14 (58.3)	135 (45.0)	
Other determined etiology (No.) (%)	2 (8.3)	38 (12.7)	
Unknown etiology (No.) (%)	5 (20.8)	96 (32.0)	

Table 2: Imaging characteristics and treatment

	Fragmented Thrombus (*n* = 24) (7.4%)	Single Thrombus (*n* = 300) (92.6%)	*P*
Affected vascular territory			.739
Anterior circulation (No.) (%)	21 (87.5)	267 (89.0)	
Posterior circulation (No.) (%)	3 (12.5)	33 (11.0)	
Occlusion site			.372
Tandem occlusion (No.) (%)	3 (12.5)	29 (9.7)	
Carotid-T (No.) (%)	3 (12.5)	14 (4.7)	
MCA M1 (No.) (%)	8 (33.3)	123 (41.0)	
MCA M2 (No.) (%)	6 (25.0)	74 (24.7)	
MCA M3/4 (No.) (%)	1 (4.2)	23 (7.7)	
Anterior cerebral artery (No.) (%)	0 (0.0)	4 (1.3)	
Basilar artery (No.) (%)	3 (12.5)	16 (5.3)	
Posterior cerebral artery (No.) (%)	0 (0.0)	17 (5.7)	
Primary thrombus length on SWI (mm) (mean) (SD)	10.3 (6.4) (*n* = 18)	10.3 (5.6) (*n* = 248)	.699
Total clot length (mm) (mean) (SD)	20.1 (10.7) (*n* = 18)	10.3 (5.6) (*n* = 248)	<.001
DWI ASPECTS (media) (range)	5 (0–8) (*n* = 21)	7 (0–10) (*n* = 263)	.006
Leptomeningeal collaterals	*n* = 19	*n* = 199	.051
Good (No.) (%)	4 (21.1)	88 (44.2)	
Moderate/poor (No.) (%)	15 (78.9)	111 (55.8)	
Treatment			.625
Intravenous thrombolysis only (No.) (%)	6 (25.0)	102 (34.0)	
Bridging thrombolysis (No.) (%)	7 (29.2)	69 (23.0)	
Endovascular intervention only (No.) (%)	11 (45.8)	129 (43.0)	

Table 3: Intracranial bleeding complications and clinical outcome

	Fragmented Thrombus (*n* = 24) (7.4%)	Single Thrombus (*n* = 300) (92.6%)	*P*
Symptomatic intracranial hemorrhage (No.) (%)	3 (12.5)	17 (5.7)	.176
Asymptomatic intracranial hemorrhage (No.) (%)	6 (25.0)	34 (11.3)	.097
Favorable outcome (mRS 0–2) at 3 months (No.) (%)	6/23 (26.1)	171/286 (59.8)	.002
Death at 3 months (No.) (%)	7/23 (30.4)	43/292 (14.7)	.069

drugs or anticoagulants did not differ between the groups. Imaging characteristics and treatment are compared in Table 2. In patients with isolated MCA, anterior cerebral artery, basilar artery, and posterior cerebral artery occlusions, total clot length was determined. Clot length in patients with fragmented thrombi was significantly higher than that in patients with a solitary thrombus (20.1 ± 10.7 versus 10.3 ± 5.6 mm, $P < .001$).

Patients with fragmented thrombi had significantly lower median DWI ASPECTS, meaning larger ischemic areas on DWI, than patients with a solitary thrombus (5 versus 7, $P = .006$). Good collaterals as assessed on DSA were found in fewer patients with fragmented thrombi than in those without, but the difference was not significant (4/19 [21.1%] versus 88/199 [44.2%], $P = .051$). One hundred eight patients (33.3%) were treated with IV rtPA alone, 140 (43.2%) underwent endovascular treatment, and 76 (23.5%) had a combination of both. Treatment was similar in both groups. Clinical outcome at 3 months was worse in patients with fragmented thrombi (mRS 0–2: 6/23 [26.1%] versus 171/286 [59.8%]; $P = .002$; Table 3).

The following variables showed $P < .2$ in univariate analysis and were included in the binary logistic regression analysis: NIHSS, age, DWI ASPECTS, multiple intracranial thrombi on pretreatment imaging, occlusion site, atrial fibrillation, diabetes mellitus, arterial hypertension, coronary artery disease, and current smoking. In our stepwise regression model, NIHSS was included as the first variable, followed by age, DWI ASPECTS, and finally the presence of multiple thrombi. The absence of multiple thrombus fragments ($P = .040$; OR, 0.251; 95% CI, 0.067–0.939), higher DWI ASPECTS ($P = .004$; OR, 1.328; 95% CI, 1.093–1.614), younger age ($P < .001$; OR, 0.919; 95% CI, 0.889–0.950), and lower NIHSS score ($P < .001$; OR, 0.832; 95% CI, 0.773–0.894) predicted good outcome.

DISCUSSION

Using whole-brain SWI, we found multiple intracranial thrombi in 24 of 324 patients with acute stroke with the SVS (7.4%) before initiation of any thrombolytic therapy. Most distal thrombus fragments (95.8%) affected the same vascular territory distal to the proximal occluding thrombus and were therefore a priori invisible with normal angiographic techniques. We found significant associations between the presence of multiple intracranial thrombi and a higher NIHSS score on admission as well as larger ischemic areas on pretreatment DWI. The presence of fragmented thrombi was a predictor of unfavorable clinical outcome at 3 months.

A study that analyzed the histologic structure of clots extracted by endovascular means by using the Merci retriever (Concentric Medical, Mountain View, California) reported that in 64% of cases, thrombi were retrieved in multiple fragments.[11] It is likely that the prevalence of fragmented thrombi had been lower before mechanical disruption of the clot during deployment and retraction of the thrombectomy device. This supposition is supported by our in vivo studies demonstrating thrombus fragmentation and distal embolization during retrieval of the initially single thrombus with distal thrombectomy devices.[12]

Although our results are based purely on thrombus fragmentation before thrombolytic treatment, it could be speculated that iatrogenic thrombus fragmentation might have a similarly negative impact on outcome. This may, among other contributing factors, explain the disappointing clinical outcome in studies that used thrombus fragmentation techniques exclusively (Multi Mechanical Embolus Removal in Cerebral Ischemia**,** Penumbra Pivotal Stroke Trial, Mechanical Retrieval and REcanalization of Stroke Clots Using Embolectomy trials)[13-15] or in part (Interventional Management of Stroke III, SYNTHESIS Expansion [A randomized controlled trial between loco-regional intra-arterial and systemic intravenous thrombolysis with Alteplase in acute ischemic stroke]).[16,17] The SYNTHESIS Expansion study reported that thrombus fragmentation with a microguidewire was performed in approximately two-thirds of patients.[17] In contrast, the goal of current mechanical thrombectomy in acute stroke is removal of the thrombus en bloc with the lowest possible rate of thrombus fragmentation, as applied and improved in experienced stroke centers.[10,18,19]

In our series, good collaterals as assessed on DSA were found in fewer patients with multiple intracranial thrombi, though the difference was not significant. No additional differences in other well-known predictors of outcome were found between patients with and without multiple thrombi. There is evidence from multiple studies that good leptomeningeal collaterals reduce and slow penumbral tissue loss, resulting in better clinical outcome.[20,21] When one considers the differences in collateral status between patients with and without multiple fragments, the probable role of autolysis should be discussed. Zanette et al[22] reported that spontaneous lysis occurs in a high percentage of patients with distal MCA occlusions, similar to the sites where most of the distal thrombus fragments were found in our cohort. Because good collaterals were seen less often in patients with multiple thrombus fragments than in those with a single thrombus, one could hypothesize that fewer endogenous thrombolytic factors may have reached the distal thrombus fragments in patients with poor collateralization, resulting in the persistence of these fragments.

Thrombus burden must be taken into account when looking for factors that could explain the differences in outcome. Total clot length, defined as the combined length of the primary occluding thrombus and the distal thrombus fragments, was significantly higher in patients with fragmented thrombi compared with those with a solitary thrombus. It remains unclear whether longer thrombi are more likely to fragment or distal fragments lead to secondary clot formation due to stagnation of blood flow, thus increasing total clot length. A recent study assessed clot burden in patients with anterior circulation stroke on T2*-weighted imaging by using a scoring system based on the vessel segments that were affected by thrombotic material. Patients with fewer and more distal vessel segments involved had a higher revascularization rate and were more likely to have favorable clinical outcome.[23] Because absolute thrombus length was not part of the scoring system, the comparability with our results is limited. One has to consider that assessment of thrombus burden by measuring the total length of thrombus fragments could result in overestimation in patients with multiple thrombi. Migration of distal thrombus fragments to smaller-sized vessels may result in reorientation and elongation of distal thrombi, resulting in a total clot length disproportionate to total clot volume.

TOF-MRA, first-pass gadolinium-enhanced MRA, and DSA detected only a minority of distal thrombus fragments seen on SWI. The lower yield of these imaging techniques in the detection of distal thrombus fragments most likely results from their dependence on the presence of blood flow or contrast media, both of which are usually reduced or absent distal to the primary vessel occlusion. Besides DWI and imaging of the whole angioarchitecture from the aortic arch up to distal branches of the cerebral arteries, imaging of the thrombus and its fragments with SWI has become a standard sequence of our stroke protocol due to its high therapeutic relevance.[5]

Our study has some limitations. Image analysis was only performed in consensus. In our experience, the SVS and distal thrombus fragments are easily detectable and we did not deem it necessary to additionally assess interobserver variability. Furthermore, each MR imaging study was routinely evaluated by a neuroradiologist and radiologist in training, and the findings were documented in our PACS. In 16 of the 24 patients (66.7%) with multiple thrombi on SWI, a distal vessel occlusion or thrombus fragment or both separate from the primary occlusion had already been described in the radiology report. Most interesting, in the 8 patients in whom distal thrombus fragments were not described initially, the fragments were located in closer proximity to the primary thrombus than in those in whom the distal occlusion was mentioned (7.0 ± 4.0 versus 24.2 ± 15.9 mm). One could speculate that these fragments were either harder to detect or had not been considered important enough to be described in the radiology report. In this single-center study, data from imaging were partly analyzed retrospectively. The small size of the patient group with fragmented thrombi limits the generalizability of the results. Evaluation of ICA and basilar artery thrombi on SWI was greatly limited by the extensive susceptibility artifacts in the proximity of the skull base.

CONCLUSIONS

Multiple intracranial thrombi were detected on pretreatment SWI in 7.4% of patients with acute ischemic stroke of the anterior or posterior circulation. The presence of fragmented thrombi was a predictor of worse outcome. Patients with multiple thrombus fragments presented with more severe symptoms on admission, had more extensive ischemic areas on pretreatment DWI, and demonstrated worse collaterals as seen on biplane angiography. To know that multiple thrombi are present not only helps in planning the endovascular treatment, especially mechanical thrombectomy because distal fragments render the intervention more

difficult, but may also be of use in prognostication of functional outcome.

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