Early New Diffusion-Weighted Imaging Lesions Appear More Often in Stroke Patients With a Multiple Territory Lesion Pattern

Tim Bastian Braemswig*; Tatiana Usnich, MD*; Fredrik N. Albach, MD; Peter Brunecker, Dr rer medic; Ulrike Grittner, PhD; Jan F. Scheitz, MD; Jochen B. Fiebach, MD; Christian H. Nolte, MD

Background and Purpose—New diffusion-weighted imaging (DWI) lesions are common in patients with acute ischemic stroke. They are associated with an initial nonsingle lesion pattern. Previous studies have not analyzed this association in detail. We differentiated nonsingle lesions in 1 vascular supply territory only (scattered lesion pattern) from nonsingle lesions in ≥2 vascular supply territory (multiple territory lesion -pattern).

Methods—Patients with an acute ischemic stroke underwent 3 MRI (3T) examinations: on admission, on the following day, and 4 to 7 days after symptom onset. First, DWI lesions were delineated manually by raters blinded to clinical details. Second, DWI images were coregistered and analyzed visually for new hyperintensities. The initial lesion pattern was categorized as single, scattered, or multiple territory.

Results—Of 340 patients enrolled, 43% had a single lesion pattern, 40% had a scattered lesion pattern, and 17% had a multiple territory lesion pattern. In multivariable analysis, the categorical variable lesion pattern was independently associated with new DWI lesions (odds ratio$_{\text{multiple territory lesion pattern}}$, 3.64 [95% confidence interval, 1.75–7.58]; odds ratio$_{\text{scattered lesion pattern}}$, 1.96 [95% confidence interval, 1.09–3.56]). Patients with multiple territory lesion pattern had significantly more often diabetes mellitus, and their new lesions were more often located remotely from the initial area of hypoperfusion compared with patients with scattered lesion pattern.

Conclusion—Lesion pattern on initial image is an independent risk factor for new DWI lesions. The risk for new DWI lesions is highest in patients with multiple territory lesion pattern.   (***Stroke***. 2013;44:2200-2204.)

Key Words: stroke ■ diffusion-weighted imaging ■ magnetic resonance imaging ■ new DWI lesions ■ silent brain infarction

New diffusion-weighted imaging (DWI) lesions are common in patients with acute ischemic stroke, especially within the first week after the index event. Most of the patients with new DWI lesions do not exhibit obvious new neurological symptoms (appear clinically silent).[1,2] But new DWI lesions are associated with higher risk of future strokes.[3] Moreover, in the general population, silent strokes are associated with future strokes, cognitive decline, and depression.[4,5]

In previous studies, the development of new DWI lesions was found to be associated with characteristics of the initial lesion pattern as shown by cerebral imaging. An initial nonsingle lesion pattern predicted subsequent new lesions.[2,6,7] However, nonsingle lesions are heterogeneous and comprise lesions in 1 vascular supply territory only (scattered lesion pattern) and lesions in ≥2 vascular supply territories (multiple territory lesion pattern). Differentiation between these 2 types might reveal a difference in the risk for new DWI lesions and

thereby help to understand the underlying mechanisms of the new DWI lesions. More precisely, new DWI lesions may represent the natural progression of the disease (eg, new lesions caused by vessel recanalization), or they may represent de novo lesions (eg, new lesions located remotely from the area of initial hypoperfusion).[8,9]

Studies that differentiate between initially scattered and initially multiple territory lesion patterns are lacking. We hypothesized that patients with scattered and multiple territory lesion patterns differ in their risk of developing new DWI lesions and also differ in clinical characteristics.

Methods

Patients

Patients were included in this study as part of an ongoing prospective observational study conducted by the Center for Stroke Research Berlin (CSB) at the Benjamin Franklin Campus of the

Charité–Universitätsmedizin Berlin. The study enrolled all patients that were able to undergo MRI within 24 hours after symptom onset of a clinically diagnosed ischemic stroke. Details of this study have been published previously.[2,9,10] Patients included in this analysis were recruited between March 2008 and December 2010. Patients who underwent endovascular interventions and patients without evidence of infarction on MRI were excluded. All patients received standard stroke unit care. The study was approved by the local Ethics Committee (EA4/026/08). All patients gave written informed consent.

Imaging Protocol

The examinations were performed on a 3-Tesla MRI scanner (Tim Trio, Siemens Medical, Erlangen, Germany). DWI was acquired with 230 mm field-of-view, fifty 2.5 mm axial slices without extra gap, with 1 B0 and along 6 directions of B=1000 s/mm², repetition time/echo time=7600/93 ms, and an acquisition matrix of 192×192. Other sequences included axial fluid-attenuated inversion recovery, T2*-weighted imaging, perfusion imaging, and 3-dimensional time-of-flight MR angiography of the intracranial circulation. We conducted 3 MR studies: on admission, on the following day, and 4 to 7 days after onset of symptoms.

Image Analysis

DWI images were pseudonymized and afterward reviewed in random order. Raters (F.N.A., T.U., T.B.B., J.B.F., and C.H.N.) were blinded to clinical information. Hyperintensities on initial DWI were delineated manually by 3 raters (F.N.A., T.U., and T.B.B.) and then coregistered and resliced to 1 mm isotropic voxel size. Coregistered DWIs were analyzed visually for new hyperintensities through slice-by-slice comparison of the first and second, as well as the second and third DWI. New hyperintensities had to be clearly separate from the index lesion. In this study, all new diffusion hyperintensities regardless of size and apparent diffusion coefficient value were considered.[2,9]

The initial lesion pattern was assessed on the first DWI and categorized as single, scattered, or multiple territory. Several lesions in only 1 vascular supply territory were defined as scattered lesion pattern. Several lesions in ≥2 vascular supply territory were defined as multiple territory lesion pattern. The classification was based on the following 3 vascular supply areas: territory of the left internal carotid artery, territory of the right internal carotid artery, and the vertebrobasilar territory (Figure). Vascular territories were defined according to established patterns.[11] Fetal configuration of posterior cerebral artery was taken into account. In addition, perfusion images from the first examination were reviewed. New DWI lesions were classified as being remote lesions if they were either outside or both outside and inside the area of initial perfusion deficit.[9] Interrater agreement was assessed by comparing delineated regions of interest. To estimate interrater agreement, the raters (F.N.A., T.U., and T.B.B.) delineated hyperintensities on 10 DWI images and the overlap ratio was determined. Interrater agreement as determined by the median overlap ratio was 0.69.[12]

Clinical Data

Sociodemographic and laboratory data, as well as time period between symptom onset and first MRI (time-to-first-image), were collected from the medical records. Symptomatic carotid stenosis was defined as stenosis >50% on color-coded duplex sonography or magnetic resonance angiography ipsilateral to the initial infarct (according to the European Carotid Surgery Trial [ECST] definition).[13] Recanalization was defined as a Thrombolysis in Myocardial Infarction (TIMI) Score of 2 or 3 on follow-up magnetic resonance angiography in patients with an initial TIMI Score of 0 or 1.[14] All patients were assessed for stroke severity directly before the first MRI examination and on the day of discharge by physicians certified to assess the National Institutes of Health Stroke Scale (NIHSS).[15] A clinical stroke recurrence was defined as a functional deterioration in the neurological status clearly distinct from that of the index stroke, attributable to a different vascular territory or the new event was of a different stroke subtype.[1,2,16] All patients were assessed 4 times daily for worsening or new neurological symptoms by a stroke physician dedicated to stroke care and patients' complaints were taken into account. At the time of follow-up clinical examination, physicians were blinded to MRI results. Stroke subtype was classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria after a review of the clinical and imaging information.[17] This was an observational study. Secondary prevention measures were implemented according to current practice guidelines.[18]

Statistics

X^2 test was used for comparisons of nominal and categorical variables. The Mann–Whitney U test was used for comparisons of continuous variables. Multivariable logistic regression analysis using a backward stepwise variable selection method was performed to calculate odds ratios and corresponding 95% confidence intervals for the risk of new DWI lesions. Variables were included in the multivariable logistic regression model if univariate analysis suggested an association with P<0.1. The variable lesion pattern was entered as categorical variable (single, scattered, multiple territory). Finally, characteristics of patients with scattered and with multiple territory lesion pattern were compared.

Results

We enrolled 340 patients with a complete set of 3 examinations (37% women; median age, 71 years [interquartile range {IQR}, 60–79]; median NIHSS, 4 [IQR, 2–6]). The median time from symptom onset to first, second, and third MRI was 10 hours (IQR, 2–17), 34 hours (IQR, 25–41), and 114 hours (IQR, 99–130), respectively. On the first image, 147 patients (43%) had a single lesion pattern, 136 patients (40%) had a scattered lesion pattern, and 57 patients (17%)
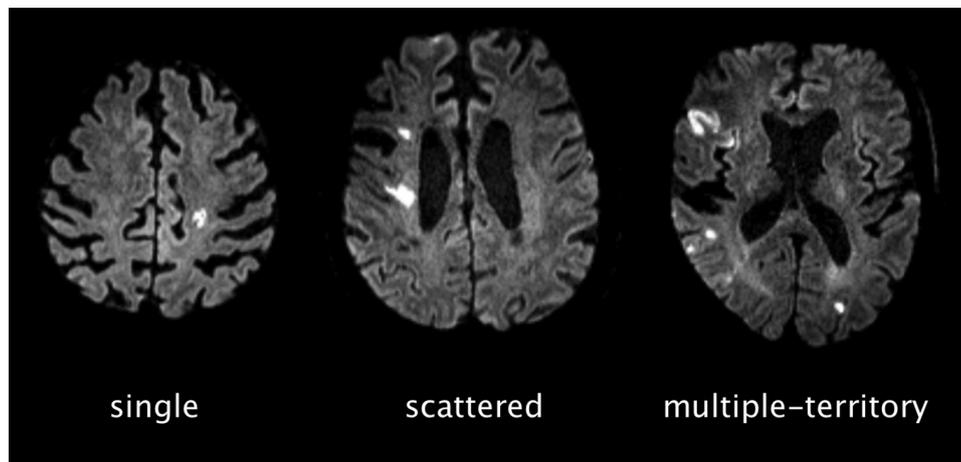

Figure. Single, scattered, and multiple territory lesion pattern.

had a multiple territory lesion pattern. New DWI lesions were detected in 130 patients (38%). Clinical stroke recurrence within the first week occurred in 6 patients (1.8%). All of these 6 patients were men with a median age of 63 years (IQR, 54–77) and a median stroke severity of 3 points on the NIHSS (IQR, 2–16). All 6 patients had a scattered lesion pattern (100% of these patients had symptomatic carotid stenosis, 17% thrombolysis, 17% recanalization, and 0% diabetes mellitus).

Patients with and without new DWI lesions differed significantly in the presence of atrial fibrillation, symptomatic carotid stenosis, use of thrombolysis, vessel recanalization (all more often in patients with new lesions) and on time-to-first image and TOAST. They also differed on lesion pattern category (Table 1).

In multivariable analysis, the categorical variable lesion pattern was independently associated with new DWI lesions. The adjusted odds ratio for new DWI lesions was ≈4× higher for multiple territory lesion pattern and twice as high for scattered lesion pattern (compared with the reference single lesion pattern). Vessel recanalization, symptomatic carotid stenosis, and time-to-first-image were also independently associated with new DWI lesions (Table 2).

Comparison between patients with scattered and multiple territory lesion pattern revealed differences on frequency of vessel recanalization, use of thrombolysis (both more often in patients with scattered lesion pattern), and presence of diabetes mellitus (more often in patients with multiple territory lesion pattern). New DWI lesions in patients with a multiple territory lesion pattern were more often located remotely from the area of initial hypoperfusion (Table 3).

Discussion

Previous studies[2,6,7] identified the initial lesion pattern as a factor strongly associated with subsequent DWI lesions. Nonsingle lesion pattern predicted subsequent new lesions. Differentiation of nonsingle lesion pattern was not considered so far. For the first time, our study found a difference in the risk of new DWI lesions between patients with scattered and patients with multiple territory lesion pattern. The odds ratio for new lesions was twice as high in patients with a multiple territory lesion pattern compared with those with a scattered lesion pattern. Category of initial lesion pattern independently influences risk for new DWI lesions and needs to be considered.

There are possible explanations for our observations of a higher risk of new lesions in patients with initial multiple territory lesion pattern, as patients with scattered or multiple territory lesion pattern differed on clinical characteristics. First, diabetes mellitus was more frequent in patients with multiple territory lesion pattern. Patients with diabetes mellitus have a higher risk of both incident[19] and recurrent stroke.[20] Diabetes mellitus causes atherosclerotic changes and is associated with several subtypes of ischemic stroke, including large artery occlusive, thromboembolic and lacunar strokes.[21] Moreover, diabetes mellitus promotes a hypercoagulatory state.[22,23] Therefore, the higher risk of new DWI lesions in patients with multiple territory lesion pattern may in part be explained by

Table 1. Sociodemographic and Clinical Parameters: Patients With and Without New Lesions

Characteristics	No New Lesions (n=210)	New Lesions (n=130)	P Value
Sex (women)	75 (35.7%)	52 (40.0%)	0.427
Age (>70), y	109 (51.9%)	79 (60.8%)	0.110
NIHSS (>3)	102 (48.6%)	69 (53.1%)	0.419
Hyperlipoproteinemia	99 (47.1%)	62 (47.7%)	0.921
Diabetes mellitus	48 (22.9%)	34 (26.2%)	0.490
Arterial hypertension	160 (76.2%)	105 (80.8%)	0.322
Atrial fibrillation	40 (19.0%)	43 (33.1%)	0.003
TOAST			<0.001
Large artery	36 (17.1%)	35 (26.9%)	
Cardioembolic	54 (25.7%)	46 (35.4%)	
Small vessel stroke	50 (23.8%)	0 (0%)	
Other determined	8 (3.8%)	5 (3.8%)	
Undetermined	62 (29.5%)	44 (33.8%)	
Antiplatelet therapy	59 (28.1%)	39 (30.0%)	0.706
Double antiplatelet	11 (5.2%)	3 (2.3%)	0.186
Anticoagulation	11 (5.2%)	9 (6.9%)	0.521
Statins*	47 (22.8%)	25 (19.5)	0.478
CHD	28 (13.3%)	19 (14.6%)	0.739
PAOD†	10 (4.9%)	11 (8.7%)	0.166
Previous stroke	50 (23.8%)	34 (26.2%)	0.626
Symptomatic carotid stenosis‡	8 (3.8%)	13 (10.1%)	0.020
Thrombolysis	32 (15.2%)	45 (34.6%)	<0.001
Vessel recanalization§	18 (8.6%)	42 (32.6%)	<0.001
Lesion pattern			<0.001
Single	117 (55.7%)	30 (23.1%)	
Scattered	68 (32.4%)	68 (52.3%)	
Multiple territory	25 (11.9%)	32 (24.6%)	
Glucose‖, mg/dL			
>180	23 (11.8%)	15 (12.5%)	0.852
>126	72 (36.9%)	55 (45.8%)	0.117
LDL¶ (>130 mg/dL)	72 (36.0%)	40 (33.3%)	0.628
INR#			
>2	5 (2.4%)	6 (4.7%)	0.258
>1.7	7 (3.4%)	6 (4.7%)	0.550
CRP** (>1 mg/dL)	37 (18.3%)	23 (18.3%)	0.989
Time-to-first-image, h; median (IQR)	12 (3–19)	5 (2–13)	<0.001

CHD indicates coronary heart disease; CRP, c-reactive protein; INR, international normalized ratio; IQR, interquartile range; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; PAOD, peripheral artery occlusive disease; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*The variable statins was known in 206/128 patients, respectively.

†The variable PAOD was known in 204/126 patients, respectively.

‡The variable symptomatic carotid stenosis was known in 210/129 patients, respectively.

§The variable vessel recanalization was known in 210/129 patients, respectively.

‖The variable glucose was known in 195/120 patients, respectively.

¶The variable LDL was known in 200/120 patients, respectively.

#The variable INR was known in 205/127 patients, respectively.

**The variable CRP was known in 202/126 patients, respectively.

Table 2.   Risk of Developing New DWI Lesions Based on Multiple Logistic Regression Analysis

Characteristics	OR (95% CI)	P Value
Symptomatic carotid stenosis	2.98 (1.11–7.96)	0.030
Vessel recanalization	4.56 (2.27–9.17)	<0.001
Time-to-first-image, h	0.96 (0.93–0.99)	0.015
Initial lesion pattern (single=ref)		
Scattered	1.96 (1.09–3.56)	0.026
Multiple territory	3.64 (1.75–7.58)	0.001

CI indicates confidence interval; DWI, diffusion-weighted imaging; OR, odds ratio; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Adjusted for atrial fibrillation, thrombolysis, and TOAST.

more severe atherosclerosis and a hypercoagulatory state promoted by diabetes mellitus.

Second, patients with multiple territory lesion pattern displayed a higher frequency of new DWI lesions located remotely from the area of initial hypoperfusion. These lesions located remotely from the area of initial hypoperfusion are a characteristic considered to argue in favor of true de novo lesions.[9] Hypercoagulatory state would enhance de novo lesions. In contrast, thrombolytic or spontaneous vessel recanalization would entail new lesions located only inside the area of initial hypoperfusion.[9] Thrombolysis and vessel recanalization were indeed associated with scattered lesion pattern.

Furthermore in our study, the risk of new DWI lesions in subsequent MR images was independently associated with the time-to-first-image. Time dependency has not drawn much attention in previous studies on new lesions to date. The later the first image was obtained, the less likely the manifestation of subsequent new lesions. Many new lesions may, therefore, evolve early in the course of the disease (eg, before the first image). This may be because of very early recanalization. Serial imaging with more imaging time points and shorter imaging intervals are needed to better understand this novel finding.

Despite the largest number of patients included in an analysis of new DWI lesions to date, limitations have to be considered. First, patients were included only in this study after giving written informed consent. Therefore, severely affected patients are under-represented. Second, this is a single-center study. Thus, the results of this study cannot be generalized easily. Third, the interrater agreement as determined by the median overlap ratio[12] was moderate. Fourth, category of lesion pattern relies on published boundaries of vascular territories and cannot account for interindividual variations. Finally, the number of clinically overt stroke recurrence was too small for detailed analysis.

In summary, the lesion pattern on first image is independently associated with development of new DWI lesions. Compared with single lesion pattern, the risk is higher in patients with scattered lesion pattern and highest in patients with multiple territory lesion pattern. The higher prevalence of diabetes mellitus in patients with multiple territory lesion pattern may point to a hypercoagulatory state. In addition, new DWI lesions in these patients were more often located remotely from the area of initial hypoperfusion. Therefore, patients with a multiple territory lesion pattern may have an increased risk for de novo lesions.

Table 3.   Sociodemographic and Clinical Parameters: Patients With Initial Scattered and Multiple Territory Lesion Pattern

Characteristics	Scattered (n=136)	Multiple Territory (n=57)	P Value
Sex (women)	53 (39.0%)	26 (45.6%)	0.392
Age (>70), y	86 (63.2%)	35 (61.4%)	0.810
NIHSS (>3)	73 (53.7%)	36 (63.2%)	0.226
Hyperlipoproteinemia	66 (48.5%)	25 (43.9%)	0.553
Diabetes mellitus	27 (19.9%)	19 (33.3%)	0.045
Arterial hypertension	110 (80.9%)	47 (82.5%)	0.798
Atrial fibrillation	46 (33.8%)	16 (28.1%)	0.435
TOAST			0.189
Large artery	40 (29.4%)	10 (17.5%)	
Cardioembolic	50 (36.8%)	19 (33.3%)	
Small vessel stroke	0 (0%)	0 (0%)	
Other determined	3 (2.2%)	2 (3.5%)	
Undetermined	43 (31.6%)	26 (45.6%)	
Antiplatelet therapy	42 (30.9%)	14 (24.6%)	0.377
Double antiplatelet	5 (3.7%)	3 (5.3%)	0.614
Anticoagulation	9 (6.6%)	7 (12.3%)	0.193
Statins*	35 (26.3%)	8 (14.0%)	0.064
CHD	23 (16.9%)	5 (8.8%)	0.143
PAOD†	12 (9.0%)	2 (3.7%)	0.215
Previous stroke	34 (25.0%)	17 (29.8%)	0.488
Symptomatic carotid stenosis‡	8 (5.9%)	6 (10.7%)	0.242
Thrombolysis	40 (29.4%)	8 (14.0%)	0.024
Vessel recanalization§	39 (28.9%)	4 (7.0%)	0.001
New lesion (first or second interval)	68 (50.0%)	32 (56.1%)	0.436
New remote lesions‖	27 (47.4%)	24 (88.9%)	<0.001
Glucose¶, mg/dL			
>180	15 (11.8%)	10 (19.2%)	0.194
>126	49 (38.6%)	28 (53.8%)	0.061
LDL# (>130 mg/dL)	42 (33.3%)	16 (28.6%)	0.525
INR**			
>2	5 (3.8%)	3 (5.4%)	0.626
>1.7	5 (3.8%)	5 (8.9%)	0.151
CRP†† (>1 mg/dL)	24 (18.5%)	17 (30.4%)	0.073
Time-to-first-image, h; median (IQR)	6 (2–14)	12 (3–19)	0.053

New remote lesions are new lesions located remotely from the area of initial hypoperfusion.

CHD indicates coronary heart disease; CRP, c-reactive protein; INR, international normalized ratio; IQR, interquartile range; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; PAOD, peripheral artery occlusive disease; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*The variable statins was known in 133/57 patients, respectively.

†The variable PAOD was known in 134/54 patients, respectively.

‡The variable symptomatic carotid stenosis was known in 136/56 patients, respectively.

§The variable vessel recanalization was known in 135/57 patients, respectively.

‖The variable new outside lesions was known in 57/27 patients, respectively.

¶The variable glucose was known in 127/52 patients, respectively.

#The variable LDL was known in 126/56 patients, respectively.

**The variable INR was known in 132/56 patients, respectively.

††The variable CRP was known in 130/56 patients, respectively.

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