

PAPER

Pathogenesis of deep white matter medullary infarcts: a diffusion weighted magnetic resonance imaging study

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Background and Purpose: The pathogenesis of deep white matter medullary (WMM) artery infarcts remains controversial. To address this question, we analysed the stroke patterns of WMM infarcts using diffusion weighted magnetic resonance imaging (DWI) to detect embolic signals and investigate stroke subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classifications.

Methods: We identified WMM infarcts on DWI using templates to determine the subcortical vascular territories. We classified WMM infarcts into those with small artery disease (SAD), large artery disease (LAD), cardioembolism (CE), two or more aetiologies, or undetermined aetiology. Clinical course, risk factors, and cortical spotty lesions were compared.

Results: Of the 1420 consecutive patients, 103 (7.3%) met the criteria for WMM infarcts. The stroke subtypes were as follows: 65 (63.1%) patients with LAD, 18 (17.5%) with SAD, 12 (11.7%) with CE, four (3.9%) with two or more aetiologies, three (2.1%) with undetermined aetiology, and one (1.0%) with other determined aetiology. LAD (87.7%) or CE (83.3%) was significantly accompanied by cortical embolic signals as compared to SAD (0%, $p < 0.001$). The LAD infarcts were larger and tended to be chain-like in shape. Ischaemic stroke recurrence was more common in strokes with cortical embolic signals than in those without embolic signals (18.9% v 0%, $p = 0.009$).

Conclusions: In present study, the most common pathogenesis of WMM infarcts was LAD. Our study indicates that WMM infarcts accompanying cortical embolic signals warrant evaluation of the underlying embolic sources in the large artery or the heart.

The deep white matter medullary (WMM) arteries, namely the superficial penetrating arteries, arise from the cortical branches of the middle cerebral artery (MCA) and descend towards the upper part of the lateral ventricle, supplying blood to the centrum ovale.^{1,2} The WMM arteries usually have a single territory and do not interdigitate.³ Together with the deep perforating arteries, the WMM arteries are the main arteries responsible for white matter infarcts.

Despite several studies using different imaging techniques, the pathogenesis of WMM infarcts remains controversial. In the era of brain CT and T2 weighted magnetic resonance imaging (MRI), the most common cause of WMM infarcts was thought to be small vessel disease.^{1,4,5} With the development of diffusion weighted MRI (DWI) and transcranial Doppler sonography (TCD), which can detect embolic signals, the importance of embolic mechanisms in either the large arteries or the heart has recently been suggested.⁶ In addition, potential sources of emboli have been demonstrated in a pathology study of WMM infarcts.⁷

Various lesion patterns identified on DWI suggest underlying stroke mechanisms,^{8–10} which might be of help clinically for directing further diagnostic tests and allocating specific treatment for secondary stroke prevention. There have been only a few DWI studies of patients with WMM infarcts. As those studies were restricted to small WMM infarcts or were comparative analyses with other infarcts,^{6,11} understanding of WMM infarcts is limited. We showed previously that approximately 72% of WMM infarcts were associated with large artery disease (LAD).¹¹ To address the pathogenesis of WMM infarcts, we extended our previous collection of patients with WMM¹¹ infarcts and analysed the stroke patterns and subtypes of WMM infarcts using DWI.

METHODS

From September 2000 to October 2004, we retrospectively studied consecutive patients with acute ischaemic stroke or transient ischaemic attacks (TIA) who were admitted to Ajou University Hospital within 7 days of symptom onset.

A WMM infarct was defined as an isolated infarct on DWI located in the territory of the white matter medullary artery, according to the templates of Bogousslavsky and Regli (fig 1A).¹ Radiologically, the outermost limit of WMM infarcts was taken to be the cortical ribbon, while the innermost limit was the corona radiata at the level of the deep perforating artery. All WMM infarcts were detected by DWI. To avoid including infarcts that extended beyond the boundary of the WMM arteries, we excluded infarcts located within the border zone area between the MCA and the anterior or posterior cerebral arteries. We carefully excluded infarcts located within the internal border zone between the WMM arteries and the deep perforating arteries.^{11,12} Other subcortical lesions with no signal changes on DWI, such as leukoaraiosis in T2 weighted MRI, were also excluded. Each DWI was assessed by two authors (LPH and OSH), and interobserver agreement was found to be very good ($\kappa = 0.925$).

A vascular study was undertaken using either MR or CT angiography. MCA stenosis was evaluated according to the residual luminal diameter measured at the site of maximal narrowing and the diameter of the adjacent normal vessel.

Abbreviations: CE, cardioembolism; CI, confidence interval; DWI, diffusion weighted MRI; ICA, internal carotid artery; LAD, large artery disease; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SAD, small artery disease; TCD, transcranial Doppler; TIA, transient ischaemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment; WMM, deep white matter medullary

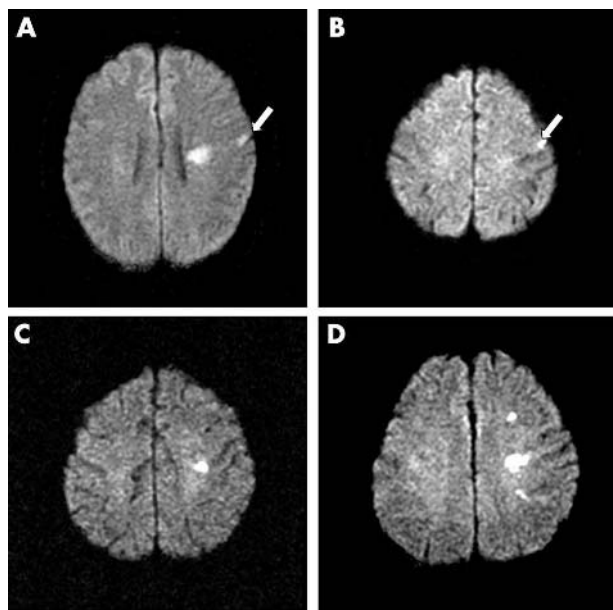


Figure 1 Diffusion weighted MRI images of WMM infarcts. Concomitant cortical embolic signals are shown (arrow in A and B). WMM infarcts can be oval in shape (C) or have a multiple chain-like appearance (D) in the superficial white matter.

from which the percentage of stenosis was calculated.¹³ Internal carotid artery (ICA) stenosis was evaluated using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.¹⁴ An echocardiogram and electrocardiogram were carried out in all cases. Based on the clinical, radiological, and cardiac test results, each case was assessed according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria¹⁵ to determine stroke subtype. LAD was defined as >50% stenosis or occlusion of ICA or MCA in the absence of sources of cardiac embolism. Small artery disease (SAD) was defined as a clinical lacunar syndrome with a relevant infarct of <1.5 cm in the absence of a cardioembolic source or large artery stenosis >50%. Cardioembolic (CE) stroke was defined as the presence of atrial fibrillation, myocardial infarction in the previous 6 months, or a high risk source of embolism identified on echocardiogram according to the TOAST criteria.¹⁵ Stroke of undetermined aetiology was used when no aetiological source could be identified. Stroke of other determined aetiology included carotid dissection, vasculopathies, and haematological disorders.

The National Institutes of Health Stroke Scale (NIHSS) score¹⁶ was determined at admission, as well as on days 1, 3, and 7 after admission. The clinical course was determined after a 1 week follow up period and defined as follows: improving, when the NIHSS score decreased by more than two points; stable, when the score decreased by less than two points; and worsening, when the score increased. We also evaluated the clinical outcome of stroke recurrence during a follow up of at least 3 months. Vascular risk factors were identified as follows: (a) hypertension: the use of antihypertensive agents, or a systolic blood pressure ≥ 160 mm Hg or a diastolic blood pressure ≥ 95 mm Hg on admission; (b) diabetes: the use of hypoglycaemic agents, or glycosylated haemoglobin >6.4%; (c) hypercholesterolemia: the use of antihyperlipidaemic agents or a serum cholesterol >220 mg/dl; and (d) smoking: any cigarette use within the 28 days preceding the index stroke.

To evaluate the frequency of concomitant embolic signals in infarcts, we examined spotty cortical lesions. Spotty

cortical lesions were defined as small hyperintense signals less than 10 mm in size detected by DWI that were smaller than the lesions of WMM infarcts (fig 1B).

Statistical analyses were performed with a commercial software package (SPSS, version 10.0). The χ^2 and *t* tests were used to compare demographic characteristics with respect to stroke subtype when the variables were categorical and continuous, respectively. The Mann-Whitney and Fisher's exact test were used to compare radiological characteristics with respect to stroke subtype. The variables were considered for multivariate analysis if they had a $p \leq 0.1$ in the univariate analysis. A logistic regression analysis using the forward stepwise method was applied to identify independent predictors of WMM infarct accompanying cortical embolic signals. The independent variables were: sex, age, vascular risk factors, infarct diameter ≥ 15 mm or <15 mm, infarct shape, evidence of CE, the occurrence of two or more lesions in the WMM arterial territory, and the existence of large artery stenosis. The results are given as the odds ratio (OR) as estimates of relative risk with 95% confidence intervals (CI). Cumulative event-free rates for the time to an ischaemic event were estimated by the Kaplan-Meier product limit method. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Of the 1420 consecutive patients with acute ischaemic stroke or TIA, 103 (7.3%) met the criteria for WMM infarcts. The mean age of the patients was 64 (SD 10.9) years, and 42 (40.4%) were female.

The distribution of stroke subtypes according to the TOAST classification was as follows: 65 (63.1%) patients with LAD, 18 (17.5%) patients with SAD, 12 (11.7%) patients with CE, four (3.9%) patients with two or more aetiologies, three (2.1%) patients with undetermined aetiology, and one (1.0%) with other determined aetiology. Eight patients with WMM infarcts presented with a clinical diagnosis of TIA: six patients with LAD, one with SAD, and one with CE.

Details of the clinical and demographic features of the patients with LAD, SAD, and CE are listed in table 1. Clinically, the baseline NIHSS score was lower in the SAD group as compared to the LAD group (2.5 ± 1.5 v 1.4 ± 0.5 , $p = 0.001$). Hypertension was frequently associated with SAD, while LAD was significantly associated with a higher LDL level. There were no significant differences associated with age, sex, laboratory data, clinical outcome, TIA presentation, or vascular risk factors between the subgroups of WMM infarcts. The pattern of the clinical course during a 1 week follow up period was favourable; clinical improvement was observed in 100% of SAD, 82% of LAD, 92% of CE, and 50% of the two or more aetiologies and undetermined aetiology subgroups. Deterioration in clinical course was very infrequent.

On DWI, 94% of the SAD subgroup infarcts tended to be circular or oval in shape (fig 1C), whereas 46.2% of LAD infarcts presented as chain- or sausage-like lesions compared with 5.6% of the SAD subgroup lesions ($p = 0.001$; fig 1D). The SAD infarcts were smaller than the LAD infarcts (50 ± 26 v 97 ± 84 mm², $p < 0.001$). The occurrence of two or more lesions in the WMM arterial territory was more common in the LAD (63%) and CE (50%) subgroups than in the SAD subgroup (10.5%, $p < 0.001$ and $p = 0.014$, respectively). The presence of cortical embolic signals on DWI was significant for LAD (87.7%) and CE (83.3%) compared to SAD (0%, each $p < 0.001$). In LAD, larger artery stenosis consisted of MCA stenosis in 39 patients (59.4%) and ICA stenosis in 26 patients (40.6%). The analysis did not reveal any clinical or radiological differences between MCA and ICA disease. The

Table 1 Demographic features of subtypes of WMM artery infarcts

Value	LAD (n = 65)	SAD (n = 18)	CE (n = 12)	p value
Male	42 (64.6%)	9 (50.0%)	7 (58.3%)	NS
Age	63±10	66±8	67±12	NS
Risk factors				
Hypertension	35 (53.8%)	14 (82.4%)*	7 (58.3%)	0.05
Diabetes	24 (36.9%)	6 (35.3%)	4 (33.3%)	NS
Smoking	6 (35.3%)	33 (50.8%)	2 (16.7%)	NS
Glucose (mg/dl)	163.2±83.9	160.6±62.7	149.6±62.0	NS
Total cholesterol (mg/dl)	188.6±36.3	179.2±35.9	171.4±34.1	NS
LDL (mg/dl)	111.6±27.1	91.3±28.2	92.7±30.4	0.009
HDL (mg/dl)	43.1±13.6	47.5±17.3	53.8±18.5	NS
TG (mg/dl)	167.2±107.0	177.1±102.2	122.8±77.2	NS
Haematocrit	39.9±4.6	37.9±2.9	40.7±4.2	NS
ESR	16.9±18.6	13.3±10.9	12.1±11.1	
Clinical course				
Improving	52 (82%)	18 (100%)	11 (91.7%)	NS
Stable	9 (13.8%)	0 (0%)	0 (0%)	NS
Worsening	4 (6.4%)	0 (0%)	1 (8.3%)	NS
Initial NIHSS score	2.5±1.5*	1.4±0.5	2.2±1.3	0.001†

* χ^2 analysis; †t test.

frequency of concomitant embolic signals also did not differ between MCA and ICA stenosis (table 2).

In the multivariate logistic regression analysis, the occurrence of two or more lesions (OR, 5.6; 95% CI, 1.4 to 22.8, $p=0.017$) in the WMM arterial territory was the only significant predictor of WMM infarcts accompanied by cortical embolic signals.

During a mean follow up period of 17±9 months, recurrent ischaemic strokes were more common in strokes with cortical embolic signals than in strokes without embolic signals (18.9% v 0%, $p=0.009$). Figure 2 presents the Kaplan-Meier estimates of recurrent stroke in WMM infarcts accompanying cortical embolic signals and WMM infarcts without embolic signals. Two patients with WMM infarcts presented with TIA and in 12 patients WMM infarcts recurred in the same territory as previous strokes (eight patients with MCA territory infarcts, three with WMM infarcts, one with a subcortical infarct, and one with an external border zone infarct).

DISCUSSION

The pathogenesis of WMM infarcts remains controversial. The differences in pathogenesis suggested in studies of WMM infarcts may result from differences in imaging sensitivity. As WMM infarcts are small and the superficial white matter is frequently affected by leukoaraiosis, it is difficult to detect acute ischaemic lesions using CT or conventional MRI. In a study of WMM infarcts using DWI, Yonemura *et al*⁶ reported that conventional MRI studies could identify only 47% of symptomatic WMM infarcts. In the present study, we used DWI, the most sensitive imaging method for detecting the lesions of acute ischaemic WMM infarcts and cortical

embolic signals, and analysed the aetiological subtypes of the WMM infarcts.

Our study demonstrated that LAD was the most common subtype of WMM infarct according to the TOAST classification. The next most common subtypes were SAD and CE. The incidence of LAD in our series was much higher than in previous studies.¹⁻⁵ However, Yonemura *et al*⁶ reported that 53% of small WMM infarcts were associated with MCA or ICA stenosis, which was similar to the proportion in our series.

Each subtype of WMM infarct has different clinical and radiological characteristics. The initial neurological deficit was greater in LAD than in SAD, and this corresponded to the difference in infarct size between the two groups. As SAD in the basal ganglia or deep white matter, SAD infarcts appeared round or oval, whereas LAD infarcts tended to have a chain-like shape. Multiple lesions in the WMM arterial territory were significantly associated with LAD or CE as compared to SAD. Regardless of the stroke subtype, the short term clinical course of WMM infarcts in our series was excellent; only a very small portion of WMM infarcts (~4%) showed deterioration in clinical course.

A recent study suggested the important role of emboli in the pathogenesis of WMM infarcts. In a pathology study of superficial perforator infarcts, Lammie and Wardlaw⁷ demonstrated that 10 of 12 cases had potential sources of emboli originating from either the heart or large artery. In a substudy of the European Carotid Surgery Trial, Boiten *et al*¹⁷ suggested that the majority of small WMM infarcts were associated with carotid large artery disease leading to disturbed haemodynamics or artery-to-artery embolism. A recent study analysing the clinical characteristics of small

Table 2 Neuroradiological characteristics of subtypes of WMM artery infarcts

	LAD	SAD	CE	p value
Shape				0.001*‡
Circular or oval	35 (53.8%)	17 (94.4%)	8 (66.7%)	
Sausage or chain	30 (46.2%)	1 (5.6%)	4 (33.3%)	
Infarct size (mm ²)	97±84	50±26	112±103	<0.001†
Cortical spotty lesion	57 (87.7%)	0 (0%)	10 (83.3%)	<0.001*
Two or more lesions	41 (63.1%)	2 (11.1%)	6 (50%)	<0.001*‡, 0.034*s
Site of stenosis				0.012*
MCA	39 (59.4%)	–	–	
ICA	26 (40.6%)	–	–	

CE, cardioembolism; ICA, internal carotid artery; LAD, larger artery disease; MCA, middle cerebral artery; SAD, small artery disease.

*Fisher's exact test; †Mann-Whitney test; ‡indicates comparison between LAD and SAD; §indicates comparison between CE and SAD.

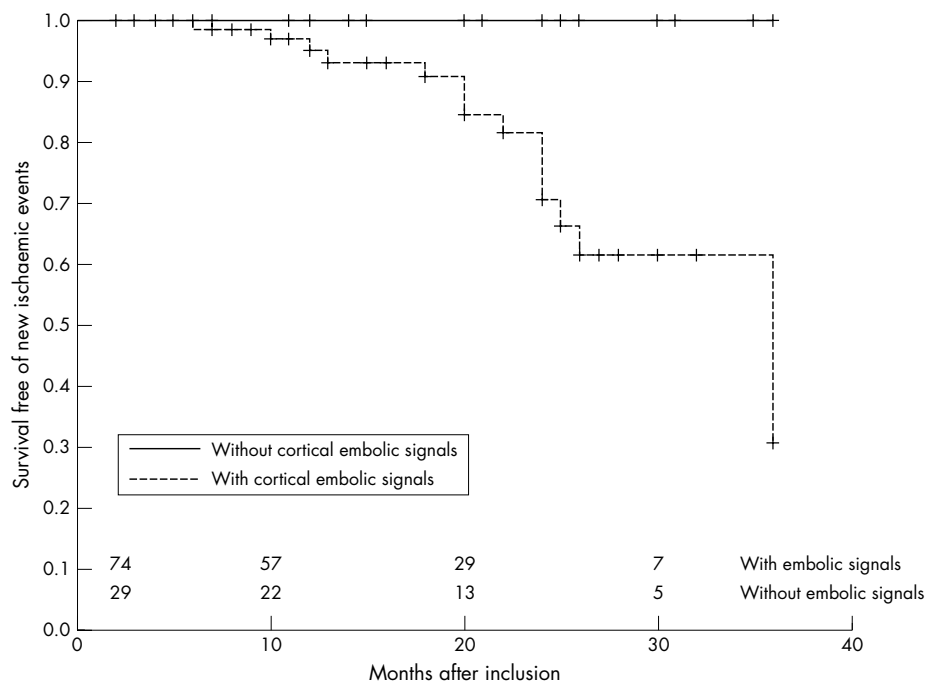


Figure 2 Kaplan-Meier estimates of the proportion of patients remaining free of any ischaemic event. Upper solid line indicates WMM infarcts without cortical embolic signals. Lower dotted line indicates WMM infarcts accompanying cortical embolic signals. The number of patients who remained event free and available for follow up is shown at the bottom.

WMM infarcts reported that they were significantly associated with emboligenic heart and LAD.⁶ Until now, however, few studies have used a tool, such as DWI, capable of providing direct evidence of underlying embolic events in WMM infarcts.

In our study using DWI, we detected small spotty cortical signals. A study of microembolic signals detectable on TCD and DWI indicated that the spotty cortical lesions detected on DWI are related to small emboli originating from either the heart or large artery.^{18,19} As expected, most LAD and CE infarcts were accompanied by cortical embolic signals. By contrast, no embolic signals accompanied SAD. Our data suggest that most LAD lesions in WMM infarcts have an embolic origin in either the MCA or the ICA. Therefore, the main cause of WMM infarcts in our series was an embolic mechanism, mainly from the large artery or partly from the heart. In our series, MCA disease responsible for LAD was 1.5 times more common than ICA disease. However, no clinical or radiological differences between MCA and ICA disease causing WMM infarcts were found. The proportion of MCA disease is striking in comparison to Western studies in which ICA stenosis predominates, and the proportion of MCA disease is even higher than in a Japanese study.⁶ This difference may be explained by the more frequent intrinsic pathology of the intracranial artery in Asians than in Westerners, while sample size and study design in the present study are comparable with the Japanese study.

In long term follow up, there was a higher recurrence rate of ischaemic stroke in patients with WMM infarcts accompanying cortical embolic signals than with WMM infarcts with no embolic signals. Interestingly, most recurrent ischaemic strokes showed ipsilateral WMM infarcts or ipsilateral MCA territory infarcts, suggesting an embolic pathogenesis. This finding suggests that although the short term prognosis of WMM infarcts is excellent, embolic WMM infarcts frequently recur. Therefore, a preventive strategy, focusing on inhibition of recurrent embolism, is warranted in patients with WMM infarcts accompanying cortical embolic

signals. Because activated platelets play a crucial role in embolic events, a strategy for reducing microemboli, such as a conventional antiplatelet drug²⁰ or GPIIb/IIIa-receptor antagonist, may be applicable.²¹ In addition, a plaque stabilisation strategy such as administering statin^{22,23} or an angiotensin II receptor blocker may be helpful.²⁴

Some limitations to our study should be mentioned. First, caution is always required when interpreting retrospective data obtained from a database because of selection bias. The exclusion criteria in our study may also have resulted in selection bias. Second, limitations and technical points must be considered when vascular investigations are carried out using different tools. However, recent studies suggested that MR angiography and CT angiography, as a non-invasive method, had good discriminatory power as regards significant stenosis and occlusion of ICA or MCA.²⁵ Third, the long term prognosis of embolic WMM infarcts should be interpreted cautiously since the number of patients under follow up is small.

In summary, this study demonstrates that WMM infarcts are associated with an embolic pathogenesis and most are associated with LAD. In addition, WMM infarcts accompanying cortical embolic signals warrant a search for underlying embolic sources in the heart or large artery.

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