Acute small subcortical infarctions on diffusion weighted MRI: clinical presentation and aetiology

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J Neurol Neurosurg Psychiatry 2005;76:1520–1524. doi: 10.1136/jnnp.2005.063594

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Received 16 January 2005
Revised version received
21 March 2005
Accepted 21 March 2005

Objective: To determine the clinical presentation and aetiology of small subcortical infarctions as found on diffusion weighted magnetic resonance imaging (DWI). DWI is both sensitive and specific in the early detection of acute ischaemic brain lesions irrespective of pre-existing vascular damage.

Methods: Ninety three patients were identified showing subcortical or brainstem DWI lesions <1.5 cm in diameter within a maximum of 7 days from the onset of stroke symptoms. The patients' clinical status on admission was reviewed according to the Oxfordshire Community Stroke Project (OCSP). The results of procedures searching for cerebrovascular risk factors, large artery disease, and potential sources of cardiac embolism were included to determine stroke aetiology. Magnetic resonance imaging scans were also reviewed for concomitant changes that could support the aetiological classification.

Results: Only 41 (44.1%) patients presented clinically with a lacunar syndrome according to OCSP criteria. The nine (9.7%) patients who showed two or more DWI lesions in different vascular territories were also significantly more likely to have potential sources of cardiac embolism (5/9, 55.6% v 20/84, 23.8%). Hypertension was significantly more prevalent in the group of patients who showed a microangiopathy related imaging pattern, but this pattern did not exclude the presence of large artery disease or a possible cardioembolic source of stroke.

Conclusion: Identification of small subcortical infarctions as the cause of stroke appears quite uncertain based on clinical characteristics only. DWI adds significant aetiological information but does not obviate the search for other potentially causative mechanisms.

Small subcortical infarctions are currently assumed to have several aspects in common as proposed by the concept of "lacunar stroke".¹ First, histopathologic studies found that ischaemic subcortical lesions <1.5 cm in diameter result predominantly from occlusion of small penetrating arteries, which is presumed to be due to microatheroma or lipohyalinosis in the penetrating vessel or due to an atheroma lining the parent vessel.^{2–6} Early reports also suggested that the occlusion of a penetrating artery may be due to embolism,^{3–5} but subsequent investigations could not confirm a significant contribution of cardiac embolism to lacunar infarction.^{7–8} Second, small subcortical infarctions have been linked to distinct clinical syndromes: pure motor stroke, pure sensory stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome, and sensory motor stroke.⁹ Third, patients suffering from lacunar stroke are considered to have a better prognosis compared to patients with non-lacunar stroke.¹ As a consequence, the concept of lacunar stroke has entered stroke classifications such as that proposed by the Oxfordshire Community Stroke Project (OCSP)¹⁰ or criteria used for the description of stroke aetiology and subsequent patient selection for treatment trials such as the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.¹¹

The assumptions mentioned above were derived from clinico-pathological correlations and studies that used computerised tomography for cerebral imaging, which is rather insensitive for detecting small subcortical lesions, at least in the acute stage. The advent of magnetic resonance imaging (MRI) markedly improved this situation. However, focal signal abnormalities similar to acute lesions may be seen on MRI in a variety of clinical settings and even with normal ageing. This often complicates the delineation of acute subcortical infarcts especially in the presence of pre-existing tissue damage.^{12–13} In this context, the introduction of diffusion weighted MRI (DWI) has been a further

significant step forward. Restricted diffusion is typically seen only during the first few days of infarction and thus allows a good separation of acute from old lesions including chronic white matter damage.¹⁴ The addition of DWI to standard MRI protocols not only enables identification of the acute, clinically relevant lesion but may also provide aetiological insights. The detection of multiple acute subcortical ischaemic lesions by DWI has been considered to be suggestive of embolism.^{15–17} This view was challenged recently by a report proposing that diffuse damage to small vessels might also cause multiple subcortical DWI lesions.¹⁸

In view of the potential of DWI for acute stroke imaging, we have attempted to collect further information regarding the concepts of lacunar stroke by studying consecutive patients who presented with an acute neurological deficit and were shown to have small subcortical infarcts on DWI. This was prompted primarily by (a) the observation of a frequent clinical misclassification of these lesions and (b) uncertainties regarding the aetiological implications of finding one or more small subcortical ischaemic lesions in relation to an acute stroke syndrome.

METHODS

We identified 1304 acute ischaemic stroke patients who were admitted to our hospital between August 2001 and December 2003. Brain MRI including DWI was performed on these patients when their clinical condition was stable enough to

Abbreviations: DWI, diffusion weighted magnetic resonance imaging; ECG, electrocardiogram; ICA, internal carotid artery; LACS, lacunar syndrome; MRI, magnetic resonance imaging; OCSP, Oxfordshire Community Stroke Project; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; TACS, total anterior circulation syndrome; TEE, transoesophageal echocardiography; TOAST, Trial of Org 10172 in Acute Stroke Treatment; TTE, transthoracic echocardiography; WMH, white matter hyperintensities

undergo examination, when there were no contraindications to MRI (for example, a cardiac pacemaker), and the patient agreed to scanning. The respective case records were screened for patients who fulfilled the following criteria: neurologic deficit present on admission and persisting for at least 24 h, MRI performed between 0 and 7 days after the onset of clinical symptoms, and subcortical or brainstem DWI lesions <1.5 cm in diameter. Patients with additional cortical involvement on DWI were not included. Based on these criteria, we identified a total of 93 patients. The clinical examination of patients on admission was documented in a standardised scheme according to predefined in-house guidelines. A primary diagnosis of vascular territory involved, that is, anterior, median, posterior cerebral artery, or basilar artery, was made based on the clinical examination. For our retrospective study, an investigator (CE) who was blinded to the patients' age, gender, complaints, history, cerebrovascular risk factors, the primary diagnosis of vascular territory, cerebral imaging, and all other results from diagnostic procedures, reviewed the documented clinical examinations and classified the patients according to the OCSP.¹⁰

DWI was performed as part of a routine MRI protocol for stroke patients on a 1.5 T system (Gyrosan NT, Philips Medical Systems, Eindhoven, The Netherlands) as follows: TR 4600, TE 81, slice thickness 5 mm, gap 1.0 mm, number of excitations (NSA) 2, field of view (FOV) 200 mm, rectangular field of view (RFOV) 100%, matrix 128×128. All scans were reviewed by a trained neurologist with MRI experience (TS) unaware of the clinical or other information. Cerebral white matter hyperintensities (WMH) on conventional MRI were rated using a modification of the Fazekas scale¹⁹ which was developed recently as part of a multinational European study on age related white matter changes²⁰ as follows: no WMH (grade 0), punctate (grade 1), early confluent (grade 2), and confluent (grade 3) WMH.

We further attempted to define imaging criteria that might serve to better separate true microangiopathy related cases of subcortical infarction from those of other possible aetiologies. We thus defined a microangiopathy related imaging pattern to consist of the presence of only a single lesion on DWI plus grade 2 or 3 WMH and no previous infarctions other than lacunar on conventional MRI (fig 1). Conversely, all other patients, that is, patients who showed multiple lesions on DWI, or grade 0/1 WMH, or previous non-lacunar infarctions, were felt to show a pattern not suggestive of microangiopathy (fig 2).

The following vascular risk factors were identified as defined by preadmission history or the need for medication at discharge: hypertension, hypercholesterolaemia, and diabetes mellitus. Cigarette smoking of at least 1 pack year (a vascular risk factor) within the past 5 years was recorded. Duplex sonography of carotid and vertebral arteries, transcranial Doppler sonography, and electrocardiograms (ECG) were performed in all patients. The severity of internal carotid artery (ICA) stenosis was graded according to established morphology and velocity criteria.²¹ TTE was performed in 80 (86.0%) patients. Amongst these, TEE was additionally performed in 21 patients (22.6% of all patients). Magnetic resonance angiography was carried out in 22 (23.7%) patients, and conventional angiography in three (3.2%) patients. Screening for serologic parameters indicating vasculitis (anti-nuclear antibodies, complement complexes, immunoglobulins) was performed in 24 (25.8%) patients, and screening for coagulopathy was carried out in 30 (32.3%) patients.

For statistical analysis, the χ^2 test was used to compare risk factors between patient groups and Student's *t* test was performed to compare differences in age between different

Figure 1 Microangiopathy related MRI imaging pattern (single DWI lesion plus grade 2 WMH and no previous infarctions other than lacunar) in a 70 year old male patient presenting with a lacunar syndrome (LACS). Hypertension and smoking were identified as cardiovascular risk factors. Large artery disease was excluded by carotid duplex and transcranial Doppler sonography. Serologic parameters indicating vasculitis were normal. No coagulopathy or atrial fibrillation was found. Transthoracic echocardiography (TTE) was normal.

patient groups. A *p* value of less than 0.05 was considered to indicate statistically significant differences.

RESULTS

We identified 93 patients with subcortical or brainstem DWI lesions <1.5 cm in diameter (63 men, 30 women; mean age 65.7 years, range 28–89). The lesions were located in the vertebrobasilar circulation in 57 (61.3%) patients, thereby affecting areas supplied by pontine perforators in 22 patients and by thalamic, lateral medullary, and midbrain perforators in 18, 10, and 7 patients, respectively. Thirty four (36.6%) patients had lesions in the ICA territory; 23 of these had lesions in the basal ganglia and internal capsule and 11 had lesions in the centrum semiovale. Two (2.1%) of the 93 patients showed lesions in regions of both the anterior and posterior circulation.

A lacunar syndrome (LACS) was found clinically in 41 (44.1%) patients, a posterior circulation syndrome (POCS) in 37 (39.8%), a partial anterior circulation syndrome (PACS) in 14 (15.0%), and a total anterior circulation syndrome (TACS) in one (1.1%) patient. When patients with small subcortical infarcts located only in areas supplied by the anterior circulation (*n* = 34) were considered, we found a LACS in 52.9% of patients. Patients with small infarcts in the posterior circulation (*n* = 57) showed a LACS in 40.4% of cases.

The major cerebrovascular risk factors associated with small vessel disease, that is, hypertension, hypercholesterolaemia, diabetes mellitus, and smoking, were found in 72.0%, 55.9%, 32.3%, and 38.7% of all patients, respectively. No statistically significant differences in the prevalence of these vascular risk factors were found between men and women. Potential sources of cardiac embolism were found in 25 (26.9%) of our patients as follows: atrial fibrillation and

Figure 2 MRI imaging pattern not suggestive of microangiopathy (two DWI lesions, grade 1 WMH) in a 56 year old male patient presenting with a posterior circulation syndrome (POCS). There was a history of smoking, but there was no hypertension, hypercholesterolaemia, or diabetes mellitus. Large artery disease and intracranial vascular abnormalities were excluded by sonography and magnetic resonance angiography. Serologic parameters for vasculitis were negative. Coagulopathy and atrial fibrillation were excluded. Transoesophageal echocardiography (TEE) revealed a patent foramen ovale as a potential source of cardiac embolism.

atrial sludge in 12 patients, patent foramen ovale in seven, ventricular wall hypokinesia in three, ventricular thrombus in one, mitral valve prosthesis with insufficient oral anticoagulation in one, and aortic valve myxoma in one. Large artery disease was found in 25 (73.5%) of 34 patients with a lesion in the ICA territory, that is, plaques or stenosis of the ipsilateral common or internal carotid artery in 24 patients and a plaque in the ascending aorta in one patient. ICA stenosis >50% on duplex ultrasound was found in three of these patients, and intracranial ICA stenosis in one patient. In 16 (28.1%) of 57 patients with a lesion in the vertebrobasilar territory, large artery disease was revealed as follows: dissection or occlusion of vertebral artery in 11 patients, subclavian steal phenomenon in two, basilar artery aneurysm in one, and plaque of ascending aorta in one.

We found two or more DWI lesions in 14 of our patients (15.1%). Further review of DWI images revealed that in five of these patients showing two lesions each, the lesions were probably a consequence of the occlusion of the same small vessel as follows: a probable common trunc of bilateral thalamo-subthalamic paramedian arteries causing bilateral paramedian thalamic lesions^{22, 23} as revealed in two patients, adjacent small DWI lesions in the internal capsule in another two patients, and adjacent lesions in the pons in one patient suggesting occlusion of a single penetrating artery. The remaining nine patients (9.7% of all patients) showed two or more DWI lesions in different vascular territories. In addition to ECG and ultrasound, all nine also had TTE and, additionally, four of them had TEE. Magnetic resonance angiography was performed in two and conventional

angiography in one of these patients with normal results. Screening for serologic parameters indicating vasculitis or coagulopathy was carried out in four and five of the patients, respectively, with normal results. The characteristics of these patients in comparison to all other patients are given in table 1. No statistically significant differences were found between these patient groups concerning gender, clinical syndrome, or vascular risk factors. Potential sources of cardiac embolism were detected significantly more often in the group of patients with multiple DWI lesions in different vascular territories.

We found 36 (38.7%) patients with a microangiopathy related imaging pattern. These patients were significantly older, the ratio of both genders was shifted significantly towards women, and hypertension was significantly more prevalent in this group. The prevalence of other vascular risk factors, large artery disease, or potential sources of cardiac embolism was not statistically different between the groups of different imaging patterns (table 1).

DISCUSSION

Clinical examination of stroke patients is not sufficient to differentiate lacunar infarcts from other stroke subtypes. In our study, only 44.1% of patients in whom a small subcortical infarction was found on DWI presented clinically with a LACS. This is in line with earlier studies which pointed out the limitations of stroke classification by clinical criteria only. In a previous observation using DWI and perfusion weighted imaging, lacunes could also not be reliably diagnosed on the basis of clinical findings only.²⁴ Other studies have shown that only 75% of patients are correctly classified clinically by the OSCP classification,²⁵ and that a significant proportion of patients presenting with a LACS show cortical lesions on cerebral imaging.²⁶ In our analysis, overlap of a LACS with other stroke syndromes persisted even when we considered only supratentorial small subcortical infarcts. As clinical classifications are frequently used for patient description and for selection for stroke trials, it is important to recognise this limitation in the accuracy of clinical classification of stroke subtypes. Apparently, patient selection for examination of therapeutic interventions targeted at specific stroke subtypes should be based on DWI.

Clearly, the retrospective design of our study imposes some limitations and the investigated cohort is not representative of the overall stroke population. Referral of patients to MRI was based solely on the discretion of the treating neurologist and may therefore have been prone to selection bias regarding age, stroke severity, or results from other examinations. However, it is the policy of our department to routinely obtain MRI in all stroke patients, and there were no specified guidelines to exclude patients from routine MRI other than those given in the Methods section. All ischaemic stroke patients who underwent MRI also had DWI sequences. The retrospective classification of patients according to the OSCP may have been influenced by the quality of the documentation of the patients' symptoms and signs, but a systematic bias towards a specific clinical syndrome seems unlikely.

For a targeted diagnostic procedure and specific secondary prevention, a clear association between infarct patterns and aetiology is desirable. In this context, small vessel disease and related risk factors, such as hypertension, have been implicated as the major causes of lacunar stroke. Hypertension is a predominant risk factor in our cohort of patients. Reported frequency rates of hypertension in patients with lacunar stroke vary from 24% to 97%, with a mean of approximately 70%,²⁷ which is similar to our results. Not unexpectedly, we found hypertension to be especially prevalent in the subgroup of patients with an overall imaging pattern suggestive of microangiopathy.

Table 1 Characteristics of patients with multiple v single DWI lesions and of patients with a microangiopathy related imaging pattern compared to those without (*p<0.05; **p<0.001)

	Multiple DWI lesions in different vascular territories	Single DWI lesion or two lesions due to occlusion of the same small vessel	Microangiopathy related imaging pattern	Imaging not suggestive of microangiopathy
Number of patients	9	84	36	57
Age, years (range)	55.9 (38–70)*	66.7 (28–89)	71.8 (47–88)**	61.9 (28–89)
Gender	8 men 1 woman	55 men 29 women	19 men 17 women*	44 men 13 women
Clinical syndrome	3 LACS 6 POCS	38 LACS 31 POCS 14 PACS 1 TACS	12 LACS 14 POCS 10 PACS	29 LACS 23 POCS 4 PACS 1 TACS
Hypertension	7 (77.8%)	60 (71.4%)	31 (86.1%)*	36 (63.2%)
Hypercholesterolaemia	5 (55.6%)	47 (55.9%)	24 (66.7%)	28 (49.1%)
Diabetes mellitus	3 (33.3%)	27 (32.1%)	14 (38.9%)	16 (28.1%)
Smoking	5 (55.6%)	21 (25.0%)	10 (27.8%)	26 (45.6%)
Large artery disease	4 (44.4%)	37 (44.0%)	16 (44.4%)	25 (43.9%)
Possible source of cardiac embolism	5 (55.6%)*	20 (23.8%)	6 (16.7%)	19 (33.3%)

DWI offers the advantage of differentiating acute from chronic small subcortical and brainstem ischaemic lesions with unprecedented accuracy. Therefore, DWI has been claimed to have the potential to improve early diagnosis of stroke aetiology according to the TOAST criteria, especially by identifying multiple acute lesions in different vascular territories.^{17–28} However, the assumption that such lesions are strongly suggestive of an embolic aetiology has been questioned recently by a report of 10 patients with multiple DWI lesions in whom a cardioembolic source could only be identified in one patient.¹⁸ In contrast to this observation, we found a possible cardioembolic source in five out of nine individuals (55.6%) with multiple small acute DWI lesions in truly different vascular territories. This may be explained in part by the fact that our study included data from TEE and/or TTE in all our patients with multiple DWI lesions, whereas Chowdhury *et al*¹⁸ obtained TTE in only three of their patients. In addition, these authors overlooked a mean interval of 17.7 days (range 2–45 days) from the onset of stroke symptoms to MRI for the identification of multiple lesions on DWI and noted that the lesions appeared to have occurred consecutively rather than simultaneously. As we analysed individuals within the first 7 days of stroke, multiple lesions in our patients are likely to have occurred simultaneously or at least within a short time interval only.

Various issues have to be considered regarding our observation of a rather high rate of possible cardioembolic pathologies and of large artery disease in this sample selected for small subcortical infarcts. Some of the detected cardiac pathologies presumably have a rather low probability of causing cerebral emboli, and even atrial fibrillation may not have been causally related to our patients' strokes. Yet the fact that small subcortical infarcts may indeed be due to an embolic aetiology cannot be dismissed.^{15–29–32} Furthermore, in attempting to optimise the prevention of further strokes, it appears plausible to appropriately treat all conditions with a high cardioembolic risk even if the association with the index stroke is not absolutely certain.

Whether carotid artery stenosis is causative or coincidental in lacunar stroke is a matter of ongoing debate.³³ Large trials have reported a milder degree of ICA stenosis in patients with lacunar stroke,^{34–35} which may suggest that large artery disease is coincidental in lacunar stroke. However, another study has found a higher incidence of ICA stenosis on the ipsilateral side in lacunar stroke,³⁶ thereby suggesting a causal relationship. In our study, the severity of large artery stenosis was mild in most cases. We found only three patients

with ICA stenosis >50% and one patient with intracranial ICA stenosis in a total of 34 patients with a small subcortical lesion in the ICA territory.

In conclusion, MRI with the addition of DWI provides important information regarding stroke subtype and aetiology. Concomitant morphological features as proposed in our study may help to further differentiate true small vessel disease from other stroke subtypes. In this regard, the impact of age related cerebral white matter changes on vascular events is currently under investigation in a prospective multicentre trial.²⁰ Large artery disease and potential sources of cardiac embolism may be not only coincidental but also causally related to small subcortical infarctions, thus underscoring the need for complete diagnostic evaluation in all stroke patients irrespective of their clinical presentation.

ACKNOWLEDGEMENTS

We thank P Ofner, Institute for Medical Informatics, Statistics and Documentation, Graz Medical University, and E Flooh, Department of Neurology, Graz Medical University, for skilful assistance with statistical calculations.

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Competing interests: none declared

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