



Barow, E. et al. (2019) Clinical characteristics and outcome of patients with lacunar infarcts and concurrent embolic ischemic lesions. *Clinical Neuroradiology*, (doi: [10.1007/s00062-019-00800-5](https://doi.org/10.1007/s00062-019-00800-5))

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Deposited on 14 May 2019

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Clinical characteristics and outcome of patients with lacunar infarcts and concurrent embolic ischemic lesions

Acknowledgments

WAKE-UP received funding from the European Union Seventh Framework Program [FP7/2007-2013] under grant agreement n°278276 (WAKE-UP).

Abstract

Purpose: Lacunar infarcts are thought to result from occlusion of small penetrating arteries due to microatheroma and lipohyalinosis, pathognomonic for cerebral small vessel disease (CSVD). Concurrent embolic ischemic lesions indicate a different stroke mechanism. The purpose of this study was to examine clinical characteristics and outcome of patients with lacunar infarcts and concurrent embolic infarcts on diffusion weighted imaging (DWI).

Methods: All patients screened for the WAKE-UP trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke; ClinicalTrials.gov number, NCT01525290) were reviewed for acute lacunar infarcts and concurrent embolic lesions on baseline DWI. Clinical characteristics and outcome were compared between lacunar infarct patients with and without concurrent embolic lesions.

Results: Of 244 patients with an acute lacunar infarct, 20 (8.2%) had concurrent acute embolic infarcts. Compared to patients with a lacunar infarct only, patients with concurrent embolic infarcts were older (mean age 69 vs. 63 years; $p = 0.031$), more severely affected (median National Institutes of Health Stroke Scale [NIHSS] score 5 vs. 4; $p = 0.046$), and - among those patients randomized - had worse functional outcome at 90 days (median modified Rankin Scale [mRS] 3 vs. 1; $p = 0.011$).

Conclusions: About 8% of lacunar infarct patients show concurrent embolic lesions suggesting stroke etiology other than CSVD. These patients are more severely affected and have a worse functional outcome illustrating the need for a thorough diagnostic workup of possible embolic sources even in patients with imaging-defined diagnosis of lacunar infarcts.

Introduction

Lacunar infarcts are defined as small subcortical ischemic lesions in the territory of thin penetrating arteries and account for about 20% to 30% of all ischemic strokes [1, 2]. With regard to pathophysiology, lacunar infarcts are considered to result from occlusion of small penetrating arteries due to microatheroma and lipohyalinosis, both pathognomonic findings in cerebral small vessel disease (CSVD) [3]. Based on this assumption, the diagnosis of a lacunar stroke from an occlusion of a single penetrating artery may result in limited diagnostic efforts as to potential embolic sources of stroke.

In a small proportion of patients with acute lacunar infarcts, additional cortical infarcts can be observed, suggesting an embolic etiology [4-6]. This challenges the generality of the assumption that local small vessel pathology is the leading cause of lacunar infarction [5].

We investigated individual data of patients screened for the WAKE-UP trial (efficacy and safety of MRI-based thrombolysis in wake-up stroke) [7]. We sought to examine the frequency of concurrent embolic lesions, and to explore whether the two patient groups differed in clinical characteristics and functional outcome.

Methods

Study design

WAKE-UP was a multicenter-randomized, double blind, placebo-controlled trial to study MRI-based intravenous thrombolysis in unknown onset stroke. The detailed trial protocol and the results of the original paper are described elsewhere [7]. For this secondary analysis, we investigated individual data of all screened patients for acute lacunar infarcts and simultaneous acute embolic ischemic lesions on screening MRI, performed within 4.5 hours of symptom recognition [7]. Patients or their legal representatives provided written informed consent according to national and local regulations. There was an exception from explicit informed consent in emergency circumstances in some countries. The trial was approved for each study site by the competent authorities and the corresponding ethics committee. Acute ischemic lesions were identified as a hyperintense signal on DWI and a reduced apparent diffusion coefficient (ADC) in the corresponding brain region. According to the neuroimaging criteria of the STRIVE position paper, we defined lacunar infarcts as acute subcortical lesions in the territory of penetrating arteries, located in the deep grey or white matter of the cerebral hemispheres or brainstem and with a maximum diameter of 20 mm on axial plane on DWI [2].

Concurrent embolic ischemic lesions were diagnosed in cases of territorial or small punctuate cortical lesions (for examples see Fig. 1). Two neurologists, blinded to clinical information, assessed the imaging data.

Vascular risk factors were recorded, and neurological deficits on admission were assessed using the NIHSS. For differentiation of clinical signs indicating cortical involvement individual NIHSS items were evaluated additionally. We determined neglect and aphasia as clinical signs of cortical involvement by any score >0 on NIHSS items 9 (“Language/aphasia”) and 11 (“Extinction/inattention”). Outcome parameters were assessed in randomized patients only. The mandatory imaging criterion for randomization to treatment with alteplase or placebo was a mismatch between an acute ischemic lesion visible on DWI and no corresponding parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR), indicating a stroke onset most likely within the previous 4.5 hours. As initially defined in the WAKE-UP trial primary outcome measure was functional outcome assessed by the modified Rankin scale (mRS) at 90 days after stroke. Further outcomes included favorable outcome (mRS 0-1), mortality, death or dependence (mRS score 4-6), and symptomatic intracranial hemorrhage (SICH) according to the SITS-MOST criteria [8].

Statistical analysis

Clinical characteristics and outcome were compared between patients with a lacunar infarct only and those with concurrent ischemic lesions other than lacunar infarcts using the non-parametric Mann-Whitney test for continuous outcomes, the Fisher exact test for categorical outcomes, and the Mantel-Haenszel Chi-square test for ordinal outcomes. Statistical analyses of outcome parameters in lacunar infarcts were performed for randomized patients with available information on clinical endpoints. As all analyses were considered exploratory, all tests were carried out with a two-sided alpha level of 5% without correction for multiple comparisons.

Results

Of 1362 patients enrolled and screened by MRI in WAKE-UP, 1085 patients had an acute ischemic lesion on DWI. Of these, 244 (22.5%) patients presented with an imaging-defined lacunar infarct (108 were randomized after screening with MRI, 136 were screen failures as they did not meet all inclusion and exclusion criteria). In 20 (8.2%) lacunar infarct patients concurrent ischemic lesions other than lacunar infarcts were observed. Six patients had single concurrent embolic lesions, while 14 patients presented with multiple simultaneous embolic

lesions. Occlusion of an intracranial cerebral artery was present on time-of-flight MR-angiography in three patients with a lacunar infarct and concurrent multiple embolic infarcts, and two of them had simultaneous territorial infarcts.

Patients with concurrent embolic infarcts were significantly older (mean age 69 vs. 63 years; $p = 0.031$), more severely affected (median NIHSS score 5 vs. 4; $p = 0.046$), and showed a trend of a higher prevalence of cortical symptoms such as aphasia and/or neglect (35.0% vs. 16.1%; $p = 0.059$) than those with a lacunar infarct only (see table). Other baseline parameters and risk factors were comparable between the two groups.

Information on functional outcome was available in 105 (43.0%) of 244 patients with lacunar infarcts (100 patients with a single lacunar infarct and five patients with concurrent embolic infarcts). Patients with concurrent embolic infarcts had a worse functional outcome at 90 days after stroke (median mRS 3 vs. 1; $p = 0.011$). Favorable outcome (mRS score 0-1) was observed in 55 (55%) patients with a single lacunar infarct but in none of the patients with concurrent embolic lesions.

SICH was observed in a single patient with a lacunar infarct only, leading to a fatal outcome. Dependence (mRS 4-5) occurred in six patients (6%) with a lacunar infarct only, and in one lacunar infarct patient (20%) with concurrent embolic lesion.

Discussion

In the present subgroup analysis of patients enrolled in the WAKE-UP trial, 8% of lacunar infarct patients showed concurrent acute embolic infarcts on DWI. Lacunar stroke patients with concurrent embolic lesions were older, more severely affected with a higher prevalence of cortical symptoms, and, among the subgroup of randomized and followed up to day 90, had a worse functional outcome than patients with a lacunar infarct only. The distribution of lacunar and nonlacunar infarcts was similar both in randomized (21.5%) as well as non-randomized patients with ischemic lesions on DWI (23.4%), and was also comparable to distributions reported previously [1, 9].

Lacunar infarcts are considered pathognomonic for CSVD and, according to the lacunar hypothesis, are mainly caused by occlusion of small penetrating arteries due to microatheroma and lipohyalinosis, secondary to hypertension and diabetes [3]. Though embolism is not assumed as being part of the pathophysiology of lacunar infarcts, in fact, C. Miller Fisher was the first to suggest an embolic mechanism as a possible stroke cause in lacunar infarcts. In his autopsy series of ten patients with capsular infarcts, in two patients the perforating

arteries supplying the infarcted area did not show any pathologies [10]. As atheroma and lipohyalinosis would be considered constantly present pathological changes of the vascular structure, Fisher therefore speculated that in those two cases the stroke might have been caused by embolic material that presumably has disappeared over time. Further autopsy studies followed and Fisher's findings were confirmed in an autopsy case of a woman with multiple lacunar and cortical infarcts due to cholesterol emboli from atheromatous changes in the aortic arch [11].

The possibility of embolism as a relevant cause of lacunar infarcts is also supported by animal experiments. Contrary to the assumption that embolic material is unlikely to enter penetrating arteries due to their sharp angles with the parent vessel, models of various generated embolic sources in rodents and primates demonstrated that embolic material can enter small perforating arteries and, thereby, cause lacunar infarcts [12, 13]. Furthermore, animal studies supporting the hypothesis that lacunar infarcts result from microatheroma or lipohyalinosis due to hypertension and diabetes are lacking [14]. Finally, with the introduction of MRI with DWI as a highly sensitive diagnostic tool to detect even small acute ischemic brain lesions, simultaneous presence of acute lacunar and cortical infarcts was observed, suggesting an underlying embolic mechanism as common etiology rather than CSVD [6], e.g., cardiac or aortic embolism, or pathologies of the internal carotid or the basilar artery [4, 5, 15-17].

Importantly, the lacunar hypothesis of CSVD as major underlying etiology has resulted in often limited diagnostic workup with regard to embolic sources in patients with an imaging diagnosis of lacunar infarction. However, patients with imaging-defined lacunar infarcts show a higher rate of other risk factors that might indicate a mechanism different than CSVD and it is not possible to identify the stroke cause from the size, shape or location of an ischemic lesion considered lacunar [18]. Indications for a stroke mechanism other than CSVD can be derived from clinical symptoms referring to cortical involvement, cardiac or vascular comorbidities suggesting an embolic mechanism of infarct, and advanced brain imaging such as MRI. Therefore, especially in the context of concurrent acute embolic infarcts in patients with lacunar stroke, an extensive search for other stroke mechanisms such as cardiac embolism or large artery atherosclerosis should be undertaken, as effective secondary prevention relies on the identification of the underlying etiology.

There are limitations to our analysis. As our study is a secondary exploratory analysis and the number of patients with available information on clinical outcome is small, any results should be considered hypothesis-generating. In addition, the WAKE-UP study protocol did not require the evaluation of stroke etiology based on a comprehensive diagnostic workup. Information on clinical evaluation required by the trial protocol, was

limited to the standard assessment of stroke symptoms based on the NIHSS. Although scores >0 on NIHSS items “Language/aphasia” and “Extinction/inattention” likely indicate cortical involvement, we do not have available results of a detailed neurological examination and we lack information on the final clinical assessment of stroke etiology. Diagnosis of lacunar infarcts was based on imaging findings only, following the STRIVE consensus criteria.

In line with previous autopsy and MRI studies, the finding of a relevant proportion of concurrent acute embolic ischemic lesions in patients with lacunar infarcts suggests that embolism needs to be considered as potential stroke etiology, even in patients with imaging-defined acute infarcts consistent with a lacunar infarct. The choice of the modality for imaging of acute stroke patients depends on numerous factors including availability as well as the individual patient’s characteristics. CT is currently the prevailing modality for acute stroke imaging. However, MRI as first imaging modality for acute ischemic stroke has shown to be both feasible [19] as well as cost-effective [20]. In lacunar stroke, the use of DWI to detect multiple acute infarcts may provide helpful information on stroke etiology and may improve the planning of diagnostic tests and effective preventive strategies.

Conflicts of Interest

EB reports grants from European Union 7th Framework Program during the conduct of the study and grants from the German Parkinson Society and ACTELION Pharmaceuticals Deutschland GmbH, outside the submitted work. FB reports grants from University Medical Center Hamburg-Eppendorf during the conduct of the study. ME reports grants from European Union 7th Framework Program during the conduct of the study. MEn reports grants from European Union 7th Framework Program during the conduct of the study, grants from Bayer and fees paid to the Charité from Bayer, Boehringer Ingelheim, BMS/Pfizer, Daiichi Sankyo, Amgen, GlaxoSmithKlineGSK, Sanofi, Covidien, Ever, Novartis, all outside the submitted work. JBF reports grants from European Union 7th Framework Program during the conduct of the study and personal fees from Bioclinica, Artemida, Cerevast, and Nicolab outside the submitted work. IG reports grants from European Union 7th Framework Program during the conduct of the study. AN reports grants from European Union 7th Framework Program during the conduct of the study. PR reports grants from European Union 7th Framework Program during the conduct of the study. TM reports grants from DFG, BMBF, the Schilling Foundation, Merck-Serono and Grifols, outside the submitted work. VT reports grants from European Union 7th Framework

Program and personal fees and non-financial support from Boehringer Ingelheim, Pfizer/BMS, Bayer, Sygnis, Amgen and Allergan outside the submitted work. KWM reports grants from European Union 7th Framework Program during the conduct of the study, personal fees and non-financial support from Boehringer Ingelheim outside the submitted work. SP reports grants from European Union 7th Framework Program during the conduct of the study. CZS reports grants from Novo Nordisk Foundation and personal fees from Bayer outside the submitted work. CG reports from European Union 7th Framework Program during the conduct of the study, personal fees from AMGEN, Bayer Vital, BMS, Boehringer Ingelheim, Sanofi Aventis, Abbott, and Prediction Biosciences outside the submitted work. GT reports grants from European Union 7th Framework Program during the conduct of the study, personal fees from Acandis, Boehringer Ingelheim, BMS/Pfizer, Stryker, Daiichi Sankyo, grants and personal fees from Bayer, grants from Corona Foundation, German Innovation Fonds and Else Kroener Fresenius Foundation outside the submitted work. All remaining authors declare no competing interests.

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Figure Legend

Fig. 1 Exemplary MRI findings in lacunar infarct patients

Axial diffusion weighted MRI images of a patient with a lacunar infarct in the left posterior corona radiata and a single cortical embolic infarct in the territory of the left anterior cerebral artery (upper row, A), a patient with a lacunar infarct in the left internal capsule and multiple cortical embolic infarcts in the territory of the left middle cerebral artery (middle row, B) and a patient with a lacunar infarct in the left thalamus showing multiple cortical embolic infarcts in the territory of the right posterior and the left middle cerebral artery, and a territorial infarct of the right middle artery (lower row, C). Lacunar infarcts are marked with black arrows, embolic infarcts with thin white arrows and the territorial infarct with a thick white arrow.

Table 1 Baseline data of lacunar infarct patients

Variable	Lacunar Infarcts (n=224)	Lacunar and cortical infarcts (n=20)	p-value
Age - years			
Mean (SD)	63 (11)	69 (9)	0.031
Male sex - number (%)	148 (66)	16 (80)	0.319
Treatment allocated - no. (%)			
Alteplase	54 (24.1)	1 (5)	0.09
Placebo	49 (21.9)	4 (20)	
Not randomized	121 (54.0)	15 (75)	
Time between last seen well and symptom recognition - hours			
Median (interquartile range)	7 (4.8-8.8)	7.5 (5-9)	0.819
Medical history/risk factors - no. (%)			
Arterial hypertension	124 (55.4)	9 (45)	0.525
Diabetes mellitus	41 (18.3)	4 (20)	0.824
Hypercholesterolemia	73 (32.6)	4 (20)	0.315
Atrial fibrillation	5 (2.2)	0	1.0
History of ischemic stroke	26 (11.6)	4 (20)	0.399
NIHSS score			
Median (interquartile range)	4 (3-6)	5 (4.5-8)	0.046
Cortical symptoms - number (%)*	36 (16.1)	7 (35.0)	0.059
DWI lesion volume at baseline - ml			
Median (interquartile range)	0.73 (0.21-1.19)	1.06 (0.33-1.94)	0.134
Time from symptom recognition to MRI - hours			
Median (interquartile range)	3.0 (2.3-3.8)	3.1 (2.2-3.7)	0.748

DWI = diffusion weighted imaging; MRI = magnetic resonance imaging; NIHSS = National Institute of Stroke Scale; *Cortical symptoms were assessed by a score >0 on NIHSS items 9 “Language/aphasia” or 11 “Extinction/inattention”.