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Clinical short communication

Cerebral microbleeds and white matter hyperintensities in cardioembolic stroke patients due to atrial fibrillation: single-centre longitudinal study

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ABSTRACT

Cerebral microbleeds (CMBs) are a potential predictor of future stroke risk with clinical relevance for antithrombotic treatments, especially in ischaemic stroke patients with atrial fibrillation. However, prospective data on CMBs and risk of stroke in this particular stroke population remain scarce. We therefore performed a single centre longitudinal study to investigate CMBs and white matter hyperintensities (WMH) and the risk of future stroke. Consecutive acute stroke patients, admitted during 2008–2012 for presumed cardioembolic stroke due to non-valvular atrial fibrillation with available follow-up for the occurrence of recurrent stroke were included in our study. The rate of future stroke between patients with vs. without CMBs and moderate to severe WMH at baseline MRI was compared in separate survival and multivariable Cox regression analyses. A total of 119 cardioembolic stroke patients (49% female, median age: 76; IQR: 68–82 years) were included. CMBs were found at baseline in 26/119 (21.8%; 95% CI: 14.8–30.4%) patients. Moderate to severe WMH were present in 27/119 (22.7%; 95% CI: 15.5–31.3%) cases. During a median follow-up time of 17 months (IQR: 3–50 months), 17 of 119 patients experienced a symptomatic stroke: 14 patients had an ischaemic stoke and 3 had intracerebral haemorrhage. The overall incidence rate for ischaemic stroke and intracerebral haemorrhage was 4.2 (95% CI: 2.3–7.1) and 0.9 (95% CI: 0.5–2.6) per 1000 patient-year of follow-up respectively. In multivariable Cox regression analysis the hazard ratio for total CMB number and the risk of stroke during follow-up was 1.05 (95% CI: 0.99–1.11; $p = 0.137$, per each additional CMB increase), after adjusting for CHAD2S. A similar regression analysis demonstrated that moderate to severe WMHs were independently associated with increased risk of symptomatic stroke at follow-up, after adjusting for CHAD2S (HR: 2.99; 95% CI: 1.01–8.30; $p = 0.036$). Despite the small sample size, our study provides useful data to guide power calculations and likely effect sizes relevant for ongoing and future larger studies and clinical trials.

1. Introduction

Cerebral microbleeds (CMBs) are a key MRI biomarker of small vessel disease with potentially clinical relevance for future stroke risk [1,2]. They are detected as small, rounded, hypointense lesions on haemosiderin-sensitive MRI sequences, including gradient-recalled echo T2*-weighted MRI (T2*-GRE) and susceptibility-weighted imaging (SWI) [3,4]. With the widespread use of these sequences, CMBs have been increasingly brought to the attention of clinicians since they are quite common: they are found in about 30% of patients with ischaemic stroke, 60% of patients with intracerebral haemorrhage (ICH) [5], and in up to 40% of the healthy population over the age of 80 [6,7]. A systematic review and meta-analysis pooled data from ten cohorts including 3067 patients with ischemic stroke or transient ischemic attack, and evaluated CMBs and future stroke risk [8]. CMBs were consistently found to confer an increased risk of any recurrent stroke (OR: 2.25; 95%CI: 1.70–2.98; $p < 0.0001$), including future ischaemic stroke (OR: 1.55; 95%CI, 1.12–2.13; $p < 0.0001$) and symptomatic ICH (OR: 8.52; 95%CI: 4.23–17.18; $p = 0.007$) [8].

These risk estimates are crucial to inform clinical decisions, especially regarding whether to prescribe antithrombotic treatments in individuals with CMBs [9,10]. This increasingly common clinical dilemma is especially challenging in ischaemic stroke patients with atrial fibrillation and CMBs, who generally require anticoagulation treatment [11]. However, prospective data on CMBs and risk of stroke in this particular stroke population remain scarce. We therefore performed a single centre longitudinal study to investigate CMBs and white matter hyperintensities (WMH), another established marker of small vessel disease, and the risk of future stroke. Our aims were to: (a) determine the prevalence of CMB in patients with atrial fibrillation hospitalized

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for ischaemic stroke; (b) explore the incidence of future stroke (including recurrent ischemic stroke and incident ICH) in this population; and (c) investigate whether the presence of CMBs and WMH are associated with future risk of stroke.

2. Methods

2.1. Study population and baseline data collection

We included consecutive acute stroke patients, admitted to our hospital between January 2008 and August 2012, for presumed acute cardioembolic stroke due to non-valvular atrial fibrillation with available follow-up for the occurrence of recurrent stroke. Non-valvular atrial fibrillation was investigated on electrocardiogram (including Holter electrocardiogram). The cause of symptomatic ischaemic stroke for which the patient was hospitalized was determined to be cardioembolic due to atrial fibrillation, based on a comprehensive evaluation including brain CT and MRI, digital subtraction angiography, carotid ultrasound, electrocardiographic monitoring and echocardiogram (including transoesophageal echocardiogram) during hospital admission. >2 physicians with Japanese Board Certifications in Neurosurgery and in Stroke classified stroke types based on all available clinical and imaging findings. Standard evaluations for concomitant carotid disease or alternative aetiologies were systematically performed.

Patients who died within 2 weeks of the baseline ischaemic stroke (n = 16), patients with transient neurological symptoms and those without neuroimaging signs of associated infarct on brain CT and MRI, were not considered for the study. We excluded patients without MRI (due to pacemakers, etc.) and patients with unclear findings on MRIs due to motion or metal artifacts.

Demographic and clinical data at the time of baseline presentation (age, sex, vascular risk factors including hypertension, diabetes mellitus, previous symptomatic ischaemic stroke or ICH) were obtained from prospective databases and by medical records review using standardized data collection forms as previously described in detail [12]. All elements required for calculation of the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (INR), Elderly (>65 years), Drugs/alcohol concomitantly) and the CHADS-2 (congestive heart failure, hypertension, age = 75 years, diabetes mellitus, stroke) scores were systematically collected. Labile INR was defined as <60% time in the therapeutic range (2–3 inclusive) and calculated based on INR data from regular outpatient visits during follow-up (only for patients on warfarin).

Antithrombotic treatment (anticoagulation, antiplatelet, both or neither) at discharge and during follow-up (including treatment modification and duration) was recorded. As per our stroke centre practice, anticoagulation with warfarin or NOACs started several days to one week after the onset of cardioembolic stroke, before discharge. In case of moderate to severe haemorrhagic transformation of the infarcted area, heparin administration was stopped for about one week, and then patients were started on warfarin or NOAC. With good INR stabilization with warfarization, patients could be subsequently discharged.

All study procedures were approved by the Ethics Committee of Kushiro City General Hospital (IRB 2004-1).

2.2. MRI acquisition and analysis

MRIs were performed during the baseline hospitalization for ischaemic stroke and included the following sequences: T2*-weighted gradient-recalled echo (T2*-GRE), fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). T2*-w, FLAIR, and DWI MRI sequences, acquired using a 1.5-T scanner, were obtained in the axial plane with the following parameters (TR/TE/excitations): 450/26/2, 8800/141/1, and 5000/84/2, respectively, a flip angle of 20°, a section thickness of 6.5 mm with a slice gap of 1.0 mm, and a matrix size of 256 × 205.

CMBs were evaluated by a single trained rater on T2*-GRE according to current consensus criteria [3,13] and the Microbleed Anatomical Rating Scale (MARS) [14]; CMBs were divided into 2 subgroups, those in lobar areas and those in deep areas. Periventricular and deep WMH were visually assessed on axial FLAIR images on the four-point Fazekas rating scale (WMH: grade 1, punctuate; grade 2, early confluence; and grade 3, confluent; and PVH: grade 1, caps or lining; grade 2, bands; and grade 3, irregular extension into the deep white matter) [15]. Grades ≥2 in the Fazekas scale were regarded as moderate to severe WML.

2.3. Follow-up

Follow-up data were obtained from regular patient visits complimented by a systematic review of prospective databases and by medical and hospital records review as previously described [12]. The main outcome events were symptomatic ischaemic stroke and symptomatic ICH confirmed on CT or MRI scans. Outcome events were assessed using all clinical and radiological information available, blinded to the presence of CMBs and WMH at baseline MRI. Follow-up took place until November 2015 at the latest, and stroke recurrences were evaluated in all patients included in the study (i.e. no patients were lost during follow-up). Of note, any patients with symptoms suggestive of stroke would have come for evaluation in our centre, hence no events were missed. At each follow-up visit, antihypertensive drug therapies were titrated to achieve a target BP <140/85 mmHg and an INR 1.60–2.60 for patients ≥70 years old, and 2.0–3.0 for the patients with age < 70 years old in line with the Japanese Guidelines for the Management of Stroke (2009 and 2015). The time point for last follow-up was the last point of contact with the patient. If no clinical outpatient visit happen until the end of the study time period for follow-up (November 2015), a telephone interview was performed to verify the patient status.

2.4. Statistical analysis

Categorical variables were analysed using Pearson's χ^2 or Fisher exact test, and continuous variables by the 2-sample *t*-test (for normal distributions), and Wilcoxon rank sum (for non-normal distributions). Kaplan–Meier survival analysis was used to determine the time until future stroke. The rate of future stroke between patients with vs. without CMBs and moderate to severe WMH was compared in separate analyses using the log-rank test. We investigate whether (a) the number of CMBs and (b) moderate to severe WMH are associated with the risk of stroke using Cox regression, adjusting for CHADS2 score as a single variable in the risk model. Significance level was set at 0.05. Stata software (Version 13, StataCorp.) was used.

3. Results

A total of 119 cardioembolic stroke patients due to AF (49% female, median age: 76; IQR: 68–82 years) were identified and met the inclusion criteria for the study. These patients were all systematically followed-up clinically for the occurrence of symptomatic stroke. CMBs were found at baseline in 26/119 (21.8%; 95% CI: 14.8–30.4%) patients. Moderate to severe WMH were present in 27/119 (22.7%; 95% CI: 15.5–31.3%) cases. The demographic and clinical characteristics of patients with vs. without CMBs are summarised in Table 1. The presence of CMBs was associated with congestive heart failure (31% vs. 15%; p = 0.068) and moderate to severe WMH (42% vs. 17%; p = 0.007). More patients in the CMB-negative group had a history of diabetes mellitus (12% versus 33%; p = 0.030) and were taking statins (4% vs. 24%; p = 0.024). Of those patients with CMB, 9 had a single lesion, 8 had 2–4 CMBs and 9 patients had ≥5 CMBs. CMB had a mixed distribution (i.e. involving both deep and lobar areas) in 11/26 cases, a strictly