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Brain magnetic resonance imaging findings in cryptogenic stroke patients under 60 years with patent foramen ovale

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ABSTRACT

Purpose: To compare magnetic resonance imaging (MRI) brain feature in cryptogenic stroke patients with patent foramen ovale (PFO), cryptogenic stroke patients without PFO and patients with cardioembolic stroke.
Materials and methods: The ethics committee required neither institutional review board approval nor informed patient consent for retrospective analyses of the patients' medical records and imaging data. The patients' medical files were retrospectively reviewed in accordance with human subject research protocols. Ninety-two patients under 60 years of age were included: 15 with cardioembolic stroke, 32 with cryptogenic stroke with PFO and 45 with cryptogenic stroke without PFO. Diffusion-weighted imaging of brain MRI was performed by a radiologist blinded to clinical data. Univariate, Fischer's exact test for qualitative data and non-parametric Wilcoxon test for quantitative data were used.
Results: There was no statistically significant difference found between MRI features of patients with PFO and those with cardioembolic stroke ($p < .05$). Patients without PFO present more corticosubcortical single lesions ($p < .05$) than patients with PFO. Patients with PFO have more often subcortical single lesions larger than 15 mm, involvement of posterior cerebral arterial territory and intracranial occlusion ($p < .05$) than patients with cryptogenic stroke without PFO.
Conclusion: Our study suggests a cardioembolic mechanism in ischemic stroke with PFO.

1. Introduction

Patent foramen ovale (PFO) is an established cause of stroke in patients under 60 years of age with a stroke with no clearly definable underlying cause, the cryptogenic strokes [1]. When found in association with atrial septal aneurysm (ASA), it is known to increase the risk of stroke [2]. The prevalence of this interatrial abnormality is 22–38% [3] in the general population and possibly as high as 46% in younger cryptogenic stroke patients [4]. However, the precise mechanism of stroke with PFO remains uncertain and widely discussed [1]. Potential mechanisms include paradoxical embolism [5], direct embolism of thrombi formed within the PFO or ASA [6], and thrombosis caused by atrial arrhythmias such as paroxysmal atrial fibrillation [6]. It seems relevant to determine the pathophysiology of these strokes with PFO, mainly so as to figure out the best therapeutic options for preventing recurrent events.

Magnetic resonance imaging (MRI), more specifically diffusion-weighted imaging (DWI), is able to detect and date acute ischemic brain lesions [7] and distinguish different stroke mechanisms [8]. Neuroimaging data suggestive of cardiogenic embolism has been reported in previous studies. This namely includes multiple acute ischemic brain lesions on DWI involving several arterial

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territories in the anterior and posterior circulations [7], superficial infarct, large subcortical infarct [9], infarct larger than one half of the cerebral hemisphere, hemorrhagic transformation within 2 weeks of stroke onset, as well as intracranial occlusion [10].

Some prior studies have assessed brain MRI features of cryptogenic stroke with PFO alone [10,11] and with ASA [12]. The aim of our study was twofold. Our primary objective was to determine whether brain MRI findings in cryptogenic stroke patients with PFO were similar to those in patients with cardioembolic stroke, which would suggest a cardioembolic mechanism for cryptogenic stroke with PFO. Our second objective was to analyze whether imaging features differed between cryptogenic stroke with and without PFO.

2. Materials and methods

This study was designed as a retrospective review. Neither institutional review board approval nor informed patient consent was required by the ethics committee of our institution (University Hospital of Saint-Etienne) for retrospective analyses of the patients' medical record and imaging data.

2.1. Patients

The ethics committee required neither institutional review board approval nor informed patient consent for retrospective analyses of the patients' medical records and imaging data. The patients' medical files were retrospectively reviewed in accordance with human subject research protocols.

Inclusion criteria were as follows: age under 60 years, recent ischemic stroke and transient ischemic attack (TIA) $\leq$6 weeks with or without lesions on DWI (if no lesions on MRI, stroke diagnosis was established by the neurologist depending on neurologic deficit type), and cardioembolic origin or no definite cause of stroke after an extensive standardized etiological work-up including blood tests, 12-lead ECG at admission followed by 24-h ECG monitoring, cervical ultrasound, transthoracic $\pm$ transesophageal echocardiography, and neurologic investigation via MRI and MR angiography. Criteria derived from the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [13] were used to rule out definite causes of stroke. Patients with strokes due to large-artery atherosclerosis (TOAST I) and small-vessel occlusion (TOAST III) were excluded from participation, while patients with PFO but no other definite stroke cause were included in a special group entitled "cryptogenic stroke with PFO". Nine patients were excluded: five with incomplete data, two with MRI conducted too late and no lesions on DWI, and two initially included in the cardioembolic stroke group but actually exhibiting PFO. In total, 92 patients were included between January 2009 and December 2010 and separated into three groups; a cardioembolic stroke group (TOAST II) including 15 patients (CE group), a cryptogenic stroke with PFO group (TOAST Vb) including 32 patients (PFO group) and a cryptogenic stroke without PFO (TOAST Vb) including 45 patients (non-PFO group).

2.2. Clinical and imaging data

Clinical and imaging data for all patients was collected and reviewed by a radiologist blinded to patient group distribution. All MRI examinations were reviewed using Syngo fastView (Siemens AG 2004–2008). Clinical and imaging data was then recorded in Excel (version 2007, Microsoft Corporation, Seattle, USA). All data were derived from a register submitted to the local ethics review board and reported to the appropriate French authorities.

2.2.1. Clinical data

The following information was systematically recorded: age; sex; risk factors for stroke; history of migraine according to the International Headache Society criteria [14]; past vascular events such as stroke, deep venous thrombosis, or pulmonary embolism; stroke severity assessed using the NIHSS (National Institute of Health Stroke Scale) [15] at admission.

2.2.2. Echocardiography

The presence of PFO with or without ASA was assessed via transesophageal echocardiography with a contrast study performed at rest and during provocative maneuvers (Valsalva and cough test) using 5-MHz multiplane transducers. Examinations were conducted by an experienced sonographer. The contrast study was considered positive if $\geq$3 microbubbles appeared in the left atrium, either spontaneously or after provocative maneuvers, within three cardiac cycles after complete opacification of the right atrium [2]. ASA was diagnosed when the atrial septum exhibited an excursion of $\geq$11 mm into the left or right atrium, or both [6].

2.2.3. Magnetic resonance imaging

Imaging was performed mainly using diffusion-weighted imaging. In total, 64 patients (69.6%) were examined using 1.5 T MRI, and three different systems were used: one Philips (Achieva) and two Siemens (Avanto and Magnetom Symphony). Twenty-nine patients (30.4%) were examined using a 3 T system (Siemens Verio). DWI parameters for the three most commonly used MRI systems were as follows: for the 1.5 T MRI (Philips Achieva), repetition time/echo time = 3706/85 ms; field of view = 230 $\times$ 230; matrix = 164 mm $\times$ 256 mm; *b* values of 0 and 1000 s/mm^2; thickness/gap = 5/0.5 mm. For the 1.5 T MRI (Siemens Avanto), repetition time/echo time = 5000/80 ms; field of view = 230 $\times$ 230; matrix = 192 mm $\times$ 192 mm, *b* values of 0 and 1000 s/mm^2; thickness/gap = 5/0.5 mm. For the Siemens Verio 3 T MRI, repetition time/echo time = 9900/81 ms; field of view = 260 $\times$ 260; matrix = 160 mm $\times$ 160 mm; *b* values of 0 and 1000 s/mm^2; thickness = 3 mm.

Time from onset of symptoms to MRI examination was recorded.

Ischemic lesions on DWI were classified as single lesions (corticosubcortical, cortical, or subcortical larger than 15 mm or diameter <15 mm), multiple lesions in one vascular territory (small scattered lesions <15 mm or confluent lesions $\geq$15 mm with an additional lesion), or multiple lesions in several vascular territories (unilateral anterior circulation, posterior circulation, bilateral anterior circulations, or anterior and posterior circulations). The vascular territories of the anterior circulation were defined as anterior cerebral artery, middle cerebral artery, and anterior choroidal artery; for the posterior circulation as posterior cerebral artery, circumferential branches of the basilar artery, and cerebellar arteries (superior, middle, and inferior). The topography of ischemic lesions by vascular territory and by circulation was determined with reference to published templates [16,17] and recorded for each patient. Arterial intracranial occlusion was evaluated via MR angiography (three-dimensional time of flight). Hemorrhagic transformation and features of previous stroke were also assessed.

2.3. Statistical analysis

Commercially available software (SAS, version 9.2) was used for statistical analysis. We first performed a descriptive analysis of clinical and imaging data, followed by a univariate analysis to compare Group 1 to Group 2, and Group 3 to Group 4. Fischer's exact test was used for qualitative data, and a non-parametric Wilcoxon test for quantitative data. MRI mean delay standard deviations were