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Coexisting Large and Small Vessel Disease in Patients with Ischemic Stroke of Undetermined Cause

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Key Words
Atherosclerosis · Small vessel disease · Stroke · CT angiography

Abstract
Background and Purpose: Large artery atherosclerosis (LAA) and small vessel disease (SVD) share common risk factors for stroke. We aimed at investigating the association of SVD with cerebral LAA as well as with atherosclerosis in patients with stroke likely to originate from aortic plaques. ***Methods:*** We investigated 71 consecutive patients (48 men, mean age 64.2 ± 13 years) with ischemic stroke of undetermined cause according to the ASCO classification, who received ECG-triggered CT angiography for best available atherosclerotic plaque detection in the aorta. ***Results:*** Aortic atherosclerotic plaques were detected in 54 patients (76.1%). The presence of SVD significantly correlated with the presence of aortic plaques ($p < 0.001$), as well as LAA ($p < 0.001$) and risk factors such as arterial hypertension ($p = 0.032$) and diabetes mellitus ($p = 0.017$). ***Conclusions:*** Aortic plaques are common in patients with stroke of undetermined cause. If so, SVD and LAA are often coexisting, which demonstrates the close link of macro- and microangiopathy, at least in cases of severe risk factors of atherosclerosis.

Introduction

Large artery atherosclerosis (LAA) and small vessel disease (SVD) can both act as a cause of ischemic stroke, but they also share similar risk factors in the pathophysiology of atherosclerosis. Although causing different stroke patterns once silent stages become vulnerable plaques (also reflected in separate stroke subtype classification scores [1]), mild or moderate co-manifestations are commonly overlapping. Until now, limited data from pathoanatomical studies are available on the association of both subtypes of stroke with aortic arch atherosclerosis [2]. This study aimed at comparing atherosclerosis of the aorta as a potential source of stroke with coexisting LAA of the carotid arteries and cerebral SVD in acute ischemic stroke patients, who – due to mild and moderated degrees of LAA and/or SVD – could not be classified to either of these etiological subtypes (i.e. 'undetermined' subtype).

Patients and Methods

Seventy-one consecutive patients (48 men, 23 women, mean age 64.2 ± 13 years, age range 32–85 years) admitted to our Stroke Center for acute ischemic stroke were studied. The diagnosis of ischemic stroke was based on clinical features and MRI brain imaging. All patients underwent a thorough stroke work-up

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Table 1. Associations of the presence of SVD according to ASCO **(a)** and Fazekas **(b)** with aortic plaques, LAA and risk factors

a

Parameters	All patients (n = 71)	SVD according to ASCO			
		S0 (n = 27)	S2 (n = 1)	S3 (n = 43)	p value
Aortic plaques					
No plaques	17 (23.9)	14 (51.9)	0	3 (17.6)	*<0.001*
All plaques	54 (76.1)	13 (48.1)	1 (100)	40 (74.1)	
Grade 1	32 (45.1)	7 (25.9)	1 (100)	24 (55.8)	0.652
Grade 2	22 (31)	6 (22.2)	0	16 (37.2)	
Risk factors					
Arterial hypertension	54 (76.1)	16 (59.3)	1 (100)	37 (86.0)	*0.032*
Hyperlipidemia	34 (47.9)	12 (44.4)	0	22 (51.2)	0.540
Diabetes	18 (25.4)	2 (7.4)	0	16 (37.2)	*0.017*
Vascular diseases					
Carotid atherosclerosis	52 (73.2)	12 (44.4)	0	40 (93.0)	*<0.001*
Carotid stenosis ≥50	18 (25.4)	4 (14.8)	0	14 (32.6)	0.212
Coronary heart disease	10 (14.1)	1 (3.7)	0	9 (20.9)	0.120
Peripheral artery disease	5 (7.0)	1 (3.7)	0	4 (9.3)	0.647

b

Parameters	All patients (n = 71)	SVD according to Fazekas				
		0 (n = 27)	I (n = 21)	II (n = 11)	III (n = 12)	p value
Aortic plaques						
No plaques	17 (23.9)	14 (51.9)	2 (9.5)	0	1 (8.3)	0.586
All plaques	54 (76.1)	13 (48.1)	19 (90.5)	11 (100)	11 (91.7)	
Grade 1	32 (45.1)	7 (25.9)	14 (66.7)	7 (63.6)	4 (25)	0.127
Grade 2	22 (31)	6 (22.2)	5 (27.8)	4 (36.4)	7 (8.3)	
Risk factors						
Arterial hypertension	54 (76.1)	16 (59.3)	17 (80.9)	10 (90.9)	11 (91.7)	0.606
Hyperlipidemia	34 (47.9)	12 (44.4)	9 (42.9)	5 (45.5)	8 (66.7)	0.396
Diabetes	18 (25.4)	2 (7.4)	8 (38.1)	4 (36.4)	4 (33.3)	0.963
Vascular diseases						
Carotid atherosclerosis	52 (73.2)	12 (44.4)	19 (90.5)	10 (90.9)	11 (91.7)	0.993
Carotid stenosis ≥50	18 (25.4)	4 (14.8)	7 (33.3)	3 (27.3)	4 (33.3)	0.933
Coronary heart disease	10 (14.1)	1 (3.7)	4 (19.0)	3 (27.3)	2 (16.7)	0.800
Peripheral artery disease	5 (7.0)	1 (3.7)	2 (9.5)	0	2 (16.7)	0.379

Percentages refer to the number of the corresponding category (column).

including neurological examination, brain MRI (with diffusion-weighted, T_1, T_2, T_2* and FLAIR sequences), vascular imaging (Doppler/Duplex), 24-hour monitoring of blood pressure and ECG, as well as cardiac imaging (TTE or TEE). Stroke was defined as of undetermined cause according to the TOAST and ASCO classification systems [1, 3]. No patient had a grade 1 in any of the four ASCO categories. For best available stroke subtyping, all patients received CT angiography (CTA) of the aorta in search of atherosclerotic plaques with emboligenic potential, as part of our routine stroke work-up in cases where the stroke cause could not otherwise be determined [4, 5]. All patients were informed in detail as to the CTA procedure and gave their written informed consent. Risk factors (arterial hypertension, hyperlipidemia, diabetes mellitus) as well as the presence of clinically manifested coronary heart disease (CHD) and peripheral artery disease (PAD) were documented. Carotid atherosclerosis and stenosis (≥50% of lumen reduction), as diagnosed in Duplex/Doppler imaging, were also registered.

CTA was performed using a first-generation 64-channel dual-source CT system (Somatom Definition, Siemens Medical Solutions, Germany). The CTA datasets were evaluated by consensus by two experienced radiologists, who were blinded to all other

exams and test results. The thoracic aorta was divided into three segments – ascending aorta, aortic arch (beginning with the brachiocephalic artery and ending distal to the left subclavian artery) and descending aorta. For each segment, the presence of the atherosclerotic plaques was documented and assessed on a 3-point scale (grade 0: not present, grade 1: mild, grade 2: severe). For comparison with other parameters, a simplified classification was used, taking the highest grade in any of the three aortic segments to describe the plaque burden of the whole aorta.

Cerebral SVD was classified using the degrees of the Fazekas scale (0: not present, 1: mild, 2: moderate, 3: severe) [6]. To demonstrate the relation of SVD to the acute stroke, the ASCO score was used, with 3 different grades (S0, S2, S3; no patient had S1 or S9).

LAA was diagnosed in cases where carotid atherosclerosis with plaques (with or without significant stenosis) was detected in duplex vascular imaging.

The Spearman and Kendall-Tau correlation tests as well as phi coefficients were used to compare parameters. $p < 0.05$ was considered to indicate statistical significance.

Results

Among the 71 patients, 37 (52.1%) had infarcts in the anterior and 20 (28.2%) in the posterior circulation only, while 14 patients (19.7%) had infarcts in both circulations. There were 5 patients (7%) with lacunar and 17 (23.9%) with territorial infarcts, while in 49 cases (69%), the stroke morphology was suggestive of emboligenic infarcts. Following the aortic imaging, ASCO classification, which takes into consideration plaques in the aortic arch, was changed according to the plaque findings in 14 cases (66.7%): the ASCO category 'A' (atherothrombosis) grade was changed from '0' to '3' in 1 patient and from '3' to '2' in 13 patients. Results relating to large and small vessel disease are summarized in the table 1. LAA was present in 52 (73.2%) patients. There were 16 (22.5%) cases with an A2 and 36 (50.7%) with an A3 grade in the ASCO score. A carotid stenosis ≥50% was present in 18 (25.4%) patients. SVD was also quite common, in a total of 44 (61.9%) patients (ASCO: S0: 27; 38%, S2: 1; 1.4%, S3: 43; 60.6%). Aortic plaques were found in more than three quarters of the patients (54; 76.1%), in most cases (50; 70.4%) in the aortic arch, followed by the descending (45; 63.4%) and the ascending (28; 39.4%) aorta. Grade 1 plaques were found in 32 (45.1%) patients, whereas there were 22 (31%) patients with grade 2 plaques. The correlation of SVD with the presence (but not the grading) of aortic plaques was highly significant ($p < 0.001$; phi = 0.513). However, the grading of SVD did not show any significant correlation with the presence or grading of aortic plaques. The presence of LAA in form of carotid atherosclerosis was correlated significantly with SVD ($p < 0.001$; phi = 0.566), in contrast to coronary heart and peripheral artery disease, where no correlation was found.

Of the three investigated risk factors, arterial hypertension and diabetes mellitus significantly correlated with the presence of SVD ($p = 0.032$; phi = 0.311 and $p = 0.017$; phi = 0.338, respectively).

Discussion

In a patient group with cryptogenic strokes, LAA and SVD are common. Although the strokes cannot be classified into one etiological category with high evidence, these diseases (as well as vascular risk factors) are present, which is reflected in the ASCO score. Significant aortic plaques are also common (76.1%) in this patient group, confirming recent observations [4, 7].

Correlation of SVD with risk factors such as arterial hypertension and diabetes is not surprising. However, the correlation of aortic plaques with the presence of SVD is stronger than might have been expected and has not been described before, although numerous reports about associations of LAA (in the form of carotid atherosclerosis) and SVD are known from pathological (postmortem) studies and described in patients with particular associated risk factors or diseases such as diabetes or vasculitis [2, 8–13]. Our study demonstrates this association of macro- and microangiopathy in this group of ischemic stroke patients considering large (carotid arteries) and very large vessels (aorta). This is most likely due to a usually high burden of vascular risk factors in patients with stroke of undetermined etiology (≥2 score levels in ASCO). These findings suggest that patients with LAA can have higher risk or prevalence of SVD and vice versa. Consequently, they are endangered not only by macroangiopathic but also by microangiopathic ischemia. As macro- and microangiopathy commonly overlap, diagnostic work-up, therapeutic decisions and prognosis estimations should be probably focused on severe manifestations, rather than the mere presence, of either type of angiopathy.

Disclosure Statement

None.

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