Modifying effect of aortic atheroma on ischemic events recurrence in stroke patients with cervical and intracranial steno-occlusive disease

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Abstract

Background: Large artery atherosclerosis is a major cause of ischemic stroke. Ultrasound can assess aortic, supra-aortic and intracranial vessels. We describe the recurrence rate in patients with cervical/intracranial disease and aortic atheroma.

Methods: We performed a retrospective review of patients’ charts admitted to a Neurology ward with ischemic stroke/transient ischemic attack in a 5-year period. We collected clinical data, aortic, supra-aortic, and intracranial atherosclerotic changes whenever transesophageal echocardiogram was also available. Follow-up data was obtained from charts. Group comparison and recurrence risk estimates were done by Kaplan-Meier curves with Log Rank (LR) and Cox regression with Hazard Ratio (HR), with 95% confidence intervals (95% CI).

Results: Of 1300 patients, 337 underwent transesophageal echocardiogram (mean age 55.7 years; 62.9% male). Stenosis >50% or occlusion was found in 8.0% of carotid arteries, 4.2% of vertebral arteries, and 14.2% of intracranial vessels. Aortic complex plaques were found in 18.2%. Recurrence rate was 10.3% and lethality 1.3%, in 604.7 days of mean follow-up. No difference was found between risk factors of patients with or without recurrence. After 1-year of follow-up more events were seen with cervical/intracranial disease (11.7% vs 2.8%, LR p=0.006). However, cervical/intracranial disease is not predictive of recurrent events in patients without aortic atheroma (LR p=0.607), while the association is strong if aortic atheroma is present (LR p=0.013; HR=4.9; 95% CI 1.2-19.5).

Conclusion: In stroke patients investigated with transesophageal echocardiogram, cervical/intracranial disease had higher 1-year recurrence risk, but not in subjects without aortic atheroma. Presence of aortic atheroma slightly further increases recurrences.

Keywords: Ischemic stroke, Stroke recurrence, Aortic atherosclerosis, Carotid atherosclerosis, Intracranial atherosclerosis.
Introduction

Large artery atherosclerosis has long been identified as one of the most frequent causes of ischemic stroke (IS). Recent epidemiological studies in the European population have shown a prevalence of this stroke etiology ranging from 8.2% to 15.7% [1-3]. Palm et al. [3] identified a further 13.4% of their patients with ‘probable atherothrombotic stroke’, a subgroup introduced to account for those patients with extracranial or intracranial atherosclerosis without significant stenosis in the absence of alternative stroke etiologies. These cases may reflect atherosclerotic changes at a more proximal site in the arterial tree, not routinely imaged.

The major sites for extracranial large vessel atherosclerosis are the carotid bifurcations, particularly near or at the origin of the internal carotid artery, and the proximal segments of the vertebral arteries. The most commonly affected intracranial sites are: the terminal internal carotid bifurcation, the distal segment of the vertebral arteries, the basilar artery and the middle cerebral artery bifurcation [4]. At the aortic level atherosclerotic changes are also a frequent finding. A population based study by Russo et al. [5] identified a high prevalence of aortic plaques of any size, both in the aortic arch (62.2%) and in the descending aorta (60.9%).

Ultrasound imaging, through cervical triplex ultrasound and transcranial Doppler ultrasound, can be used to assess the arterial patency and the presence of atherosclerotic lesions in the extracranial and intracranial vasculature, and should be available for the evaluation of every stroke patient [6]. Another ultrasound technique, the transesophageal echocardiogram (TEE), is the gold standard for evaluation of cardiac sources of embolism and also assessment of atherosclerotic disease at the level of the aorta [7].

The role of TEE in the evaluation of embolism sources has been questioned, because of its limited benefit in modifying the therapeutic approach [8]. Our aim was to evaluate the modifying effect of the presence of aortic atheroma on the recurrence rate of ischemic events in ischemic stroke patients with cervical and intracranial steno-occlusive disease. We describe the recurrence rate of cerebrovascular events and identify associated risk factors.

Methods

This study was carried out at the Stroke Unit of a Portuguese tertiary hospital, which has a direct influence area of 381,799 inhabitants and receives acute stroke patients from an area of almost 500,000 inhabitants.

Patients

In the present study we retrospectively screened all consecutive patients with a final diagnosis of acute IS or transient ischemic attack (TIA), admitted to our Neurology ward during a period of 5 years—from the 1st of July of 2007 until 30th of June of 2012. Patients with cerebral venous thrombosis, subarachnoid hemorrhage, or intracerebral bleeding on admission were excluded. To reach a final diagnosis of stroke or TIA, all patients were assessed by a neurologist to determine the diagnosis of stroke (neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours) with imaging evidence of ischemia or no other likely diagnosis, and TIA (defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction). Stroke subtype was categorized according to the Oxfordshire Community Stroke Project classification [9]. Stroke etiology was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [10]. Patients were included in the study if they underwent TEE as part of the vascular event etiological investigation.

Cervical and transcranial color ultrasound technique

Cervical carotid and vertebral color ultrasonography examinations were performed with a GE Vivid 7 Ultrasound System equipped with an 8-MHz linear probe. Transcranial color-coded sonography examinations were performed with the same equipment, fitted with a 3.5-MHz sectorial probe, without ultrasound contrast material. A standardized evaluation protocol was employed and images from all vessels were obtained and stored.

Carotid stenosis was estimated using flow velocities and Doppler spectrum analysis, according to the criteria defined by von Reutern et al. [11]. For vertebral evaluation, peak systolic velocities, artery morphology and symmetry with the contralateral vertebral artery were considered.

The peak systolic flow velocity thresholds considered for a ≥50% intracranial artery stenosis were 220 cm/s for the middle cerebral artery, 155 cm/s for the anterior cerebral artery, 145 cm/s for the posterior cerebral artery, 140 cm/s for the basilar artery and 120 cm/s for the vertebral artery [12].

Transesophageal echocardiography

TEE was performed with a Hewlett-Packard multiF plane probe at 5 MHz, rotating the image plane by up to 180°. Images with the significant findings for each patient were printed.

Aortic atherosclerosis was classified as simple or complex considering the size and morphology of the plaques. Simple aortic plaques were defined as an intimal thickening of less than 4 mm. Complex aortic plaques were defined as plaques protruding more than 4 mm, with visible surface ulceration, or presence of mobile components regardless of atheroma size [13].

Stroke risk factors

The medical records were reviewed for risk factor information. Arterial hypertension was defined as current
treatment with antihypertensive medication or a history, or present diagnosis, of hypertension according to the 2003 World Health Organization criteria as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Dyslipidemia was defined as on lipid-lowering medication or total cholesterol level ≥190 mg/dL, low-density lipoprotein level ≥110 mg/dL, or triglycerides level ≥150 mg/dL. Diabetes mellitus was defined as treated with oral anti-diabetic drugs or insulin or a history, or present diagnosis, according to the 1999 World Health Organization criteria as fasting plasma glucose ≥126 mg/dL. A patient was defined as a smoker if currently smoking, or past history of regular smoking of ≥1 cigarettes per day or daily use of tobacco (cigar or pipe). Recorded cardiovascular diseases included coronary heart disease, previous myocardial infarction, and atrial fibrillation.

All patients underwent a routine range of laboratory and other diagnostic testing. On admission laboratory tests were ordered, including serum glucose, serum creatinine, hematocrit, platelet count, and International Normalized Ratio (INR). Other baseline variables that were obtained for each patient included fasting serum glucose, fasting serum cholesterol (total, HDL, and LDL), and fasting triglycerides, among other routine smoking of ≥1 cigarettes per day or daily use of tobacco (cigar or pipe). Recorded cardiovascular diseases included coronary heart disease, previous myocardial infarction, and atrial fibrillation.

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Evaluation of outcome

Patients were followed-up through the information available from registries of medical appointments in the outpatient clinic or emergency room admissions. Study outcomes were assessed at maximum follow-up time available. Subsequent vascular events, their type (IS, TIA), and time of occurrence were recorded. TIA and IS as outcome events were diagnoses according to the same definitions as the baseline TIA or stroke. If the outcome was fatal, both the date and cause of death were recorded. The causes of death were divided into neurological (recurrence of stroke), and other causes. Death after stroke was defined as case-fatality in the following 30 days after the event. We defined combine vascular events as any of TIA, IS of fatal stroke.

Statistical analysis

The statistical analyses were performed using the software SPSS version 19.0 and MedCalc version 12.3. We report descriptive statistics with rates and 95% confidence intervals (95% CI). Comparisons between groups were made with chi-square test, with a two-tailed level of significance of 0.05. We calculated recurrence risk by Kaplan-Meier curves with Log Rank (LR), and Cox proportional hazards model was used for univariate and multivariate risk factor analyses. Hazard Ratios (HR) are presented, along with 95% CI.

Results

Study cohort

From 1300 patients screened, 337 (25.9%) had undergone TEE examination and were entered in the study. Clinical characteristics of the study cohort are shown in Table 1. Stroke etiologies according to the TOAST criteria are shown in Table 2.

Atherosclerotic disease of the carotid arteries was found in 170 patients (50.4%), of which 9 had ulcerated lesions (2.7%), 9 had hemodynamically significant stenosis (2.7%), and 18 patients had unilateral carotid occlusion (5.3%). The vertebral arteries were involved in the atherosclerotic process in 14 patients (4.2%), with 7 cases of occlusion (2.1%). The intracranial vessels showed significant disease in 48 patients (14.2%), with 31 cases of severe stenosis (9.2%), and 17 cases of occlusion (5.0%). Globally, 69 patients (20.5%) presented with stenosis ≥50% of either carotid, vertebral or intracranial arteries.

Aortic atherosclerotic plaques of any size were found in 157 patients (46.6%). Thickness equal to or above 4 mm was seen in 34 subjects (10.1%) and other complex plaque morphology (ulcerations and/or mobile components) was observed in 27 subjects (8.1%). Aortic atheroma was more frequently seen in the aortic arch (108 patients, 32.1% of the total population, 68.8% of the patients with plaques), irrespective of other sites being affected. In 43 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Population (n=337)</th>
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<tbody>
<tr>
<td><strong>Men, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>212 (62.9%)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>232 (68.8%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>69 (20.5%)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>170 (50.4%)</td>
</tr>
<tr>
<td>Coronary heart disease, n (%)</td>
<td>33 (9.8%)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>33 (9.8%)</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet drugs, n (%)</td>
<td>57 (16.9%)</td>
</tr>
<tr>
<td>Anticoagulants, n (%)</td>
<td>10 (3.0%)</td>
</tr>
<tr>
<td>Antihypertensive drugs, n (%)</td>
<td>139 (41.2%)</td>
</tr>
<tr>
<td>Lipid-lowering drugs, n (%)</td>
<td>77 (22.8%)</td>
</tr>
<tr>
<td>Anti-diabetic drugs, n (%)</td>
<td>45 (13.4%)</td>
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</tbody>
</table>
(12.8%) the plaques were exclusively located on the descending portion of the aorta.

Combined disease of the aorta and supra-aortic vessels was present in 47 patients (13.9%).

Table 3 shows the cohort clinical characteristics by presence of atherosclerotic disease of either the supra-aortic and intracranial vessels, or aortic atheroma.

Diabetes loosely associated with the presence of cerebral and pre-cerebral arteries stenosis and occlusion (p=0.082), while other risk factors didn’t.

Increasing plaque thickness occurred with advancing age and men more often had complex plaques. Patients with complex plaques had higher prevalence of traditional risk factors. On multivariate analysis, age equal or above 55 years (OR=7.1; 95% CI 3.2-15.6) remained associated with complex atheroma, and smoking (OR=4.7; 95% CI 2.1-10.3) compared with 2.8% in the group without supra-aortic stenosis or occlusion, with a recurrence rate of 11.7%, piled in the group with cervical and intracranial arteries stenosis or occlusion (p=0.013). Antihypertensive drugs were more frequently used in those with aortic atheroma and anti-diabetic drugs in those with complex aortic plaques compared to those with no or simple plaques respectively (p=0.032 and p=0.036).

**Risk of combined vascular events**

Mean follow-up was 604.7 days (median 468 days, interquartile range 702 days, total range 15 to 1901 days) in 310 patients, while 27 patients were lost to follow-up. Losses to follow-up occurred when patients missed their scheduled appointments, when contacts were missing or were unreliable and no vital information could be retrieved from record linkage with other hospitals. The median survival time was not significantly different in all the presented comparisons. Overall, 32 endpoints (10.3%) occurred, of which 3 were fatal (lethality rate of 1.3%). No difference was found between risk factors prevalence for patients with or without recurrence. Two-thirds of the recurrent events happened during the first year of follow-up. Recurrences according to TOAST classification are shown in Table 4.

In this first year of follow-up more new events happened in the group with cervical and intracranial arteries stenosis or occlusion, with a recurrence rate of 11.7%, compared with 2.8% in the group without supra-aortic disease. This difference is significant, with a LR p=0.006,
and remains so even after adjustment for diabetes (HR=4.4, 95% CI 1.4-13.9).

After 1 year of follow-up, more new events were also seen in the aortic atheroma group (7.1% in the presence of complex plaques, 5.7% if simple plaques and 1.8% in the group without plaques, LR p=0.097). The difference between groups with and without plaques is significant at 1 year (6.3% vs 1.8%, LR p=0.013), but fades with time until end of follow-up. Kaplan–Meier curves for vascular events are showed in the Figure 1.

Events in patients with cervical and intracranial steno-occlusive disease by aortic atheroma status

To address the influence of aortic atheroma in the survival of patients with cervical and intracranial arteries stenosis or occlusion, we performed a stratified analysis using aortic atheroma presence to define each stratum.

Considering only the patients without aortic atheroma, disease at the cervical and intracranial level no longer predicts recurrent events (1.9% in those without disease compared to 3.7% with cervical/intracranial disease, LR p=0.607). Considering the group of patients with aortic atherosclerotic disease, the recurrence of events is greater in the presence of important stenosis or occlusion of the cervical and intracranial arteries (4.0% in those with only aortic disease paralleled to 18.2% for those with disease at both sites, LR p=0.013; HR=4.9; 95% CI 1.2-19.5). In this last group of patients women had more supra-aortic steno-occlusive disease (p=0.021), while other risk factors were balanced. Adjustment for gender did not change this risk estimate (HR=4.7; 95% CI 1.1-19.7). Figure 2 shows the Kaplan–Meier curves for vascular events.

Discussion

We report on the risk of recurrent cerebral vascular events in ischemic stroke and TIA patients with cervical and intracranial steno-occlusive disease, analyzing the modifying

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Table 3. Stroke Recurrences by the TOAST classification of subtypes of acute ischemic stroke.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients without recurrent events (n=278)</th>
<th>Patients with recurrent events (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-artery atherosclerosis, n (%)</td>
<td>60 (21.6%)</td>
<td>10 (31.2%)</td>
</tr>
<tr>
<td>Cardioembolism, n (%)</td>
<td>52 (18.7%)</td>
<td>3 (9.4%)</td>
</tr>
<tr>
<td>Small-vessel occlusion, n (%)</td>
<td>27 (9.7%)</td>
<td>2 (6.2%)</td>
</tr>
<tr>
<td>Stroke of other determined etiology, n (%)</td>
<td>21 (7.6%)</td>
<td>3 (9.4%)</td>
</tr>
<tr>
<td>Stroke of undetermined etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two or more causes identified, n (%)</td>
<td>10 (3.6%)</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Negative or incomplete evaluation, n (%)</td>
<td>108 (38.8%)</td>
<td>13 (40.7%)</td>
</tr>
</tbody>
</table>

TOAST = Trial of Org 10172 in Acute Stroke Treatment
effect of aortic atheroma in this outcome. We investigated the presence of plaques in the carotid, vertebral and intracerebral arteries causing hemodynamically significant stenosis (≥50%) or occlusion, which have been associated with high early recurrence risk [14]. Likewise, we examined for the presence of aortic atheroma, another well known risk factor for stroke, independent from the traditional vascular risk factors, but which pathophysiology remains uncertain. It is hypothesized that aortic plaques may cause stroke via an atheroembolic mechanism, while other authors consider atherosclerosis at the aortic level as just another marker of generalized atherosclerosis [15-16]. Controversy remains as there is continuing evidence for increased risk of recurrent stroke and death in patients with stroke and large aortic plaques, with plaques of complex morphology conferring a slight additional increase in risk [17]. There are also population-based studies where the incidental detection of plaques in the aortic arch or proximal descending aorta was not associated with future vascular events [5].

In our cohort, the individual presence of either cervical and intracranial steno-occlusive disease or complex aortic atheroma was an independent predictor of subsequent vascular events, including stroke, during the first year of follow-up. But when combining these subgroups of patients, predictive value for recurrence only remains significant in patients with cervical and intracranial significant stenosis or occlusion if there is concomitant disease at the aortic level. This means that the presence of aortic atheroma slightly further increased the number of future recurrences, supporting its pathological role as a stroke mechanism, as opposed to a plain atherosclerotic marker.

Our study has some limitations. The main limitation is the relatively small sample size, which may have affected the statistical power to detect significant risk factors associated with vascular events recurrence. Moreover, given the small number of events, we could not prove an association with atherosclerotic changes at any site beyond the first year of follow-up.

Regarding medication with antihypertensive, antidiabetic or anticoagulant drugs, we also had important imbalances between groups. Nevertheless, these drugs were more frequent in patients with vessel stenosis or occlusion, or aortic atheroma and that should have decreased the risk of recurrence. We found the opposite results, so if any confounding effect of medication is to be expected; it would be to decrease the strength of our estimates and not to increase it.

Our study shows that aortic atheroma interacts with cervical or intracranial atherosclerotic changes, increasing the risk of recurrent events. However we cannot determine with this type of study if the aortic plaques are themselves implied causally in the etiology of recurrences or if they are a signal of more advanced and/or aggressive atherosclerotic systemic disease. Further studies are needed to evaluate whether systematic screening for aortic atheroma or more aggressive treatment strategies in patients with vascular atherosclerotic disease at multiple sites diminish recurrences, and to establish better preventive strategies to limit the occurrence of repeated events

Abbreviations
CT: Computed tomography; HR: Hazard Ratios; INR: International Normalized Ratio; IS: Ischemic stroke; LR: Log Rank; TEE: Transeophageal echocardiogram; TIA: Transient ischemic attack; TOAST: Trial of Org 10172 in Acute Stroke Treatment

Competing interests
The authors declare no conflict of interest.
References


