Editorial

Complex Atheromatosis of the Aortic Arch: An Emerging Diagnosis in Cerebral Ischemia of Unknown Cause

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Abstract: Complex atheromatosis of the aortic arch has been increasignly recognized as a cause of cerebral infarction in patients with stroke of uncertain etiology. The incorporation of transesophageal echocardiographic studies in routine clinical practice allows direct visualization of cardiac and vascular structures previously inaccessible, including atherosclerotic plaques in the aortic arch. Large atheromatous plaques, which protrude strikingly into the aortic arch lumen and have obvious mobile components are associated with a high probability of being the etiology of embolism. Aortic arch atheromatosis should be considered a dynamic process entailing a non-negligible risk of recurrent cardiovascular events. Therefore, adequate diagnosis and optimal treatment is mandatory for secondary prevention of cerebral ischemic infarction and progression of aortic arch atheromas.

Keywords: Aortic arch atheromatosis, Transesophageal echocardiography, Cerebral infarction, Aortic atheromas, Atherosclerotic plaques.

INTRODUCTION

Approximately between 15% and 42% of all cases of cerebral infarction collected in the main hospital-based stroke registries are cases of ischemic stroke of unknown origin [1-3]. The most frequent etiological subtypes of focal cerebral ischemia are cardioembolic infarctions, atherothrombotic infarctions, and lacunar infarctions, which account for 55-75% of all cerebral ischemic infarcts [1-3, 4]. Cerebral infarcts of unusual cause account only for 5-10% of all infarcts and are usually associated with hematological diseases, arterial dissection, inflammatory or infectious arteritis as well as a large list of miscellaneous entities, with stroke as the presenting manifestation or complicating the natural course of the disease [5]. Finally, there is a group of stroke patients in whom the etiology of cerebral ischemia is unknown because appropriate diagnostic procedures are not performed, presence of two possible pathological conditions responsible for stroke concomitantly, or despite performance of a battery of adequate diagnostic work-up studies, the cause of stroke remains unclear. Patients included in the last group are those with true cerebral infarction of undetermined cause in which the use of more extensive complementary diagnostic studies may be required (such as transesophageal echocardiography, 24-hours Holter monitoring, magnetic resonance angiography, screening of hematological disorders with prothrombotic risk, testing for factor V Leiden, protein C or S deficiency, antithrombin III deficiency, etc.) [6].

In this subgroup of patients with cerebral ischemic stroke of essential etiology, complex atheromatosis of the aortic arch is currently an emerging diagnosis.

CEREBRAL ISCHEMIA AND COMPLEX ATHEROMATOSIS OF THE AORTIC ARCH

It has been reported that aortic plaques of ≥ 4 mm thick are the second most prevalent embolic risk factor for stroke after atrial fibrillation, and are present in 16% to 20% of all stroke and transient ischemic attack (TIA) patients. Also, the presence of aortic atheromatous plaques is a risk for new and recurrent stroke [7].

In patients with ischemic cerebral infarction in which routine diagnostic examinations are negative to identify the cause of stroke, it is useful to perform a transesophageal echocardiographic study, with the objective to exclude the presence of complex atheromatous plaques in the aortic arch, particularly in patients with concurrent risk factors for atheromatosis (advanced age, smoking, hypertension, diabetes) [6]. The use of transesophageal echocardiography has contributed to optimize the diagnosis of complex aortic arch atheromatosis. At present, the association between ischemic stroke and complex aortic arch atheromatosis is well established, mainly in the following circumstances: 1) when the atheroma is located proximal to the ostium of the left subclavian...
artery, 2) when the plaque is > 4 mm thick or with mobile component (aortic debris), and 3) when there is evidence of ulceration and hypogenicity (which probably indicate a high lipid content in the plaque) [8]. An analysis of different reviews shows that the presence of complex atheromatosis of the aortic arch is an independent predictor of any new arterial cerebral and peripheral vascular events [8].

Complex aortic arch atheromatosis is a proven cause of cerebral ischemia. In the recent clinical study of Wang et al. [9] of 116 patients with cerebral infarction, 70 had aortic atherosclerotic plaques (5.7% in the ascending aorta, 77.1% at the arch, 17.1% in the descending aorta), and 64/70 had carotid atherosclerotic plaques too (46 were unstable). Moderate/severe aortic atherosclerotic plaques and unstable carotid plaques are significant causes of embolic cerebral infarction without stenosis of the internal carotid arteries [9]. In the study of Sharifkazemi et al. [10], aortic atheroma was present in 25% of elderly ischemic stroke patients (underwent transesophageal echocardiography) without significant carotid artery stenosis.

Complex atheromatosis of the aortic arch was also frequent in patients with TIA: about 14% of TIA patients had severe aortic arch atheromatosis with at least one plaque over than 4 mm [11] similarly to what is observed in patients with cerebral infarction.

In a clinical study carried out in 248 patients who were discharged from the hospital with the diagnosis of cerebral infarction of unknown cause and receiving conventional platelet anti-aggregant therapy, after 1 year of follow-up, 17 patients (6.9%) presented a recurrent cerebral infarct. The transesophageal echocardiography established the diagnosis of complex atheromatosis of the aortic arch in 14 cases (82.4%) [12].

In a study of 71 patients with a first ever lacunar infarct (9 of uncertain etiology) it was observed that 7 patients presented simple aortic plaques and 13 complex aortic atheroma plaques (18.3%). Of the 71 patients, 9 presented lacunar infarctions of unknown cause (12.6%), that is, none of them had hypertension, diabetes, or any other vascular risk factor, and did not meet criteria of cardioembolism, atherothrombosis or ischemia of unusual cause. The frequency of complex atheromatosis of the aortic arch was more frequent in lacunar stroke of unknown etiology (3 of 9 cases; 33%) than in the remaining lacunar stroke patients (10 of 62 cases; 16.3%). These results indicate that complex aortic arch atheromatosis should be ruled out in essential lacunar infarct patients [13].

In patients with ischemic stroke of uncertain etiology dense mitral annular calcification is an important marker of complex aortic atheroma. In the study of Pujadas et al. [14], dense mitral annular calcification ≥ 5 mm was found in 58.3% of patients with complex atheromatosis of the aortic arch as compared with 16.3% in those without complex aortic arch atheromatosis (P < 0.001). Plaques with mobile component (grade III) were documented in 28% of patients with dense mitral annular calcification and in 9.9% of patients without dense mitral annular calcification (P < 0.01) [14]. The association of dense mitral annular calcification and complex aortic atheroma may explain in part the high prevalence of ischemic stroke and peripheral embolism in patients with mitral annular calcification.

In the study of Okuzumi et al. [15], mobile and ulcerative aortic plaques were observed in 18% of patients with unexplained ischemic stroke. In this study, advanced age and the low-density lipoprotein (LDL)-cholesterol/high-density lipoprotein (HDL)-cholesterol ratio of 2.23 were substantially higher and closely associated with mobile and ulcerative aortic plaques. A study of 63 patients with cryptogenic stroke using diffusion-weighted MR imaging (DWI) and multidetector row CT revealed the presence of vulnerable aortic arch atheromatosis in 23.8% of the cases [16]. These patients had more risk of having a DWI pattern characterized by multiple, small, scattered lesions in multiple vascular territories [16].

All these studies show that complex atheromatosis of the aortic arch is associated with ischemic stroke of unknown cause, stroke recurrence and all vascular events [17, 18].

Magnetic resonance imaging (MRI) can be useful to assess the characteristics of the aortic atheroma plaque and its components (presence of calcification, lipid composition, presence of thrombi). However, MRI is contraindicated in patients with prosthetic valves, carriers of pacemakers and defibrillators as well as in claustrophobic patients and is less effective in the detection of mobile thrombi as compared to transesophageal echocardiography (TEE) [17]. High-resolution helicoidal computed tomography would be of particular interest in the study of areas not visualized by TEE (the distal ascending aorta) [17].
TREATMENT

In the ARCH clinical trial (Aortic Arch Related Cerebral Hazard) patients with ischemic stroke and aortic arch plaques > 4 mm treated with aspirin (75 to 150 mg/day) plus clopidogrel (75 mg/day) had a non-significant 24% reduction in the rate of recurrent stroke (including intracerebral hemorrhage), myocardial infarction, peripheral embolism, and vascular death compared with patients on warfarin therapy (INR 2-3) [19] After a median follow-up of 3.4 years, the primary end point (which included cerebral infarction, myocardial infarction, peripheral embolism, vascular death, or intracranial hemorrhage) occurred in 7.6% on patients treated with aspirin plus clopidogrel and in 13.6% on warfarin therapy ($P = 0.2$). It was observed more intracranial hemorrhages in the long treatment aspirin plus clopidogrel therapy, and the authors suggested a short-term term use (3 months) of the combination, followed by long-term clopidogrel monotherapy. The authors also recommended that future trials are required to clarify the optimal therapy for ischemic stroke attributed to aortic arch atheromatosis (for example to compare an antiplatelet strategy with one of the new anticoagulants) [19].

Patients with atherosclerosis in the aortic arch should also be treated with statins (to achieve a LDL-cholesterol level of 70 to 80 mg/dL). Statins reduce vascular wall thickness, increasing the luminal area, and are used as secondary stroke prevention even in the presence of normal levels of cholesterol. Also, treatment of associated cardiovascular risk factors is mandatory (e.g. blood pressure-lowering agents to reduce high blood pressure < 130/85 mm Hg).

However, in patients with complex aortic atheromatosis plaques with mobile components, which constitute the subgroup of patients at the highest risk of embolism, therapeutic options are not well defined, and in the absence of randomized trials comparing the efficacy of different antithrombotic strategies in this specific patient population, it seems that therapeutic anticoagulation is the first-line treatment according to experts recommendations.

Data supporting the indication of surgical treatment for complex atheromatosis of the aortic arch are currently lacking. Aortic arch endarterectomy should be restricted to cases of embolic recurrences resistant to anticoagulation treatment at therapeutic doses [17].

PROGNOSIS

Complex atheromatosis of the aortic arch should be viewed as a marker of a very severe atherosclerotic disease involving not only the aorta but also coronary, peripheral and carotid/vertebral arteries [8]. In a recent study carried out in 149 hospitalized patients with first-ever cerebral infarction of unknown origin, thick aortic arch plaques was a factor in the prediction of poor prognosis [20].
Aortic arch atheromatosis is a dynamic process with progression noted in 29% of patients [18]. Progression of complex atheromatosis of the aortic arch is associated with the presence of recurrent vascular events. A study of TEE in 117 patients with stroke/TIA with aortic arch atheroma at 12 months follow-up of the vascular event, showed the aortic arch atheroma progression in 28% of them (n=33). This subgroup of patients presented a higher prevalence of complex mobile plaque and vascular events (myocardial infarct, TIA, stroke, vascular death) than the subgroup without progression (55% vs. 8%).

It is important to establish an adequate diagnosis of complex atheromatosis of the aortic arch to indicate the optimal treatment for both secondary prevention of cerebral ischemia and progression of the aortic atheromatosis.

ACKNOWLEDGMENTS

The authors are grateful to Drs. J. Massons, M. Oliveres, E. Comes and R. Pujadas for critical review of the manuscript and Dr. Marta Pulido for editing the manuscript and editorial assistance.

FUNDING

None.

CONFLICTS OF INTEREST

None to be declared.

REFERENCES