

Role of Complex Aortic Atheroma Plaques in the Recurrence of Unexplained Cerebral Infarction

Ramon Pujadas,^a Adrià Arboix,^b Núria Anguera,^a Montserrat Oliveres,^b Joan Massons,^b and Emilio Comes^b

^aServicio de Cardiología, Hospital del Sagrat Cor, Barcelona, Spain.

^bServicio de Neurología, Hospital del Sagrat Cor, Barcelona, Spain.

Introduction and objectives. In a subgroup of patients with cerebral infarction, noninvasive diagnostic explorations fail to disclose the etiology. We studied the clinical course and the usefulness of transesophageal echocardiography to diagnose complex aortic atheroma plaques in patients with cerebral infarction of uncertain cause with recurrence of ischemia.

Patients and method. In a study population of 1840 consecutive patients with a first cerebral infarction evaluated with a screening protocol for transesophageal echocardiography, the etiology remained uncertain in 248 cases. These patients were followed during 1 year of treatment with antiplatelet agents, and transesophageal echocardiography was done if cerebral ischemia recurred. We compared the prevalence of complex aortic atheroma plaques in patients with recurrence and in patients with cerebral infarction of unknown etiology in the French Study of Aortic Plaques in Stroke, in whom there was no recurrence of cerebral infarction.

Results. Recurrent cerebral infarction was documented in 17 of our 248 patients with infarction of unknown etiology (6.9%). Transesophageal echocardiography established the etiology in 15 of these patients (88.2%) with complex aortic atheroma plaques being identified in 14 cases (82.4%). In contrast, in patients with cerebral infarction of unknown etiology in the French study without recurrent cerebral infarction during the first year of follow-up, the prevalence of complex plaques was 21.1% ($P < .0001$).

Conclusions. During the first year of treatment with antiplatelet agents, most patients with cerebral infarction of unknown etiology had no recurrences. In the small subgroup with short-term recurrence, transesophageal echocardiography yielded the etiologic diagnosis in 88.2% of cases: the pathology most frequently involved was complex atherosclerotic disease of the aortic arch.

Key words: Cerebral infarction. Atherosclerotic plaque. Aorta.

Papel de las placas complejas de ateroma aórtico en la recurrencia del infarto cerebral de etiología incierta

Introducción y objetivos. En un subgrupo de pacientes con infarto cerebral, las exploraciones diagnósticas no invasivas no permiten establecer un diagnóstico etiológico. Hemos estudiado su evolución y el valor del ecocardiograma transesofágico en el diagnóstico del ateroma complejo aórtico en pacientes con infarto cerebral de etiología incierta que presentan recurrencia.

Pacientes y método. Al evaluar a 1.840 pacientes consecutivos con un primer infarto cerebral mediante un protocolo restrictivo para la ecocardiografía transesofágica, en 248 no pudo establecerse un diagnóstico etiológico. Durante 1 año de seguimiento con fármacos antiplaquetarios, se practicó un ecocardiograma transesofágico en caso de nuevo episodio isquémico cerebral. Se comparó la prevalencia de placas complejas aórticas en estos pacientes con recurrencia respecto a la de los infartos cerebrales de etiología incierta del French Study of Aortic Plaques in Stroke que no presentaron un segundo infarto cerebral.

Resultados. Presentaron un segundo infarto cerebral 17 de los 248 pacientes con etiología incierta (6,9%). El ecocardiograma transesofágico estableció la etiología en 15 de ellos (88,2%), que fue atribuida a placas complejas de ateroma aórtico en 14 casos (82,4%). En cambio, entre los pacientes del French Study con infarto cerebral de etiología incierta que no presentaron reinfarcto cerebral durante el primer año de seguimiento, la prevalencia de placas complejas aórticas fue del 21,1% ($p < 0,0001$).

Conclusiones. Durante el primer año de seguimiento con antiagregantes, la mayoría de los pacientes con infarto cerebral de etiología incierta no presenta recurrencia. En el subgrupo con recurrencia isquémica cerebral, el ecocardiograma transesofágico permite establecer el diagnóstico definitivo en el 88,2% de los casos; la principal etiología implicada es la ateromatosis avanzada de la aorta torácica.

Palabras clave: Infarto cerebral. Placa de ateroma. Aorta.

Correspondence: Dr. R. Pujadas Capmany.
Servicio de Cardiología. Hospital del Sagrat Cor.
Viladomat, 288. 08029 Barcelona. España.
E-mail: rpujadas@ya.com.

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ABBREVIATIONS

ECG: electrocardiogram.

TEE: transesophageal echocardiography.

TTE: transthoracic echocardiography.

INTRODUCTION

In Western populations the incidence of cerebral ischemia has risen with the increase in life expectancy, and is now the direct cause of death in 10% of the general population. Another 10% of deaths are related to the sequelae and complications of cerebral infarction.

Previous studies have established that a cardioembolic mechanism is the cause of more than 20% of episodes of cerebral ischemia, that atrial fibrillation is implicated in two-thirds of these patients, and that it is essential to establish the diagnosis because of the importance of anticoagulation therapy and the growing tendency toward early implementation of this treatment.¹⁻⁸ Over the last decade, it has been shown that morphologically complex atheromatous plaques in the ascending aorta or aortic arch can indicate a high risk of cerebral infarction due to an artery-to-artery embolic mechanism.⁹⁻²⁰ Anticoagulation is also an important option in this situation to control the risk of new embolic events.^{21,22}

Most ischemic episodes associated with a cardioembolic mechanism are diagnosed on the basis of the medical history, physical examination, electrocardiography (ECG), transthoracic echocardiography (TTE), and Holter monitoring in the case of suspected paroxysmal arrhythmia. In clinical practice, most protocols to assess cerebral ischemia include these cardiologic studies, in addition to investigation of systemic diseases, coagulation disorders, specific examination of the cranial arterial system (ultrasonography plus Doppler assessment of the supra-aortic arteries, which can be complemented with angiography or magnetic resonance angiography), and in some cases transcranial Doppler ultrasound with the Valsalva maneuver to rule out a patent foramen ovale with a right-to-left shunt. Late-generation echocardiography units (particularly those with harmonic image technology) allow the diagnosis of some cases of complex aortic arch atheromas using visualization through the suprasternal space with TTE.²³ In many patients, however, particularly the elderly population, visualization is inadequate through this sonographic window. Despite the use of all these examinations in clinical practice, the definite etiopathogenic diagnosis of cerebral infarction cannot be made in 10%-30% of cases.^{7,8,24}

Transesophageal echocardiography (TEE) can overcome many of the limitations of TTE in the evaluation

of patients with cerebral ischemia. In addition to a substantially higher-quality image, TEE provides better visualization of the left atrium and auricular appendage, cardiac prostheses, the presence of endocardial vegetations, thrombi or intracardiac masses, and the characteristics of the septum, including detection of a patent foramen ovale, associated or not with an atrial septal aneurysm. Moreover, it yields valuable information on the presence of complex atheromatous plaques in the aortic arch or ascending aorta. Nevertheless, TEE is a semi-invasive examination with some disadvantages: it carries a certain risk, it is costly and not always available in certain health care settings, and its performance and indications in cerebral ischemia have not been well-defined. The huge volume of this type of patients (particularly among the elderly population) and the limited available health resources make easy access to TEE difficult and inevitably requires restriction of the test to specific patient subgroups.

We studied the clinical progress of patients with unexplained cerebral infarction after assessment with a protocol of diagnostic examinations restrictive for TEE, and investigated over a one-year follow-up period which diseases were implicated in patients who had recurrent cerebral ischemia while receiving antiplatelet treatment. Special attention was placed on the possible role of morphologically complex atheromatous plaques in the ascending aorta or aortic arch as a potential cause of recurrent ischemia in these patients with cerebral infarction of uncertain etiology.

PATIENTS AND METHODS**General Population Studied and Examination Protocol**

Between January 1987 and December 2001, 1840 consecutive patients with a first-ever episode of ischemic cerebral infarction and neurological deficit lasting more than 24 hours, admitted to the Neurology Service of Hospital Sagrat Cor (Barcelona, Spain), were able to undergo a prospective protocol of diagnostic examinations with recording of data in an extensive, previously described database.^{4,24,25} This hospital stroke registry compiled 167 variables, including demographic data, cardiovascular risk factors, clinical findings, topography, diagnostic studies, and evolution. For inclusion in the study, patients were required to have been admitted to hospital during the first 48 h after a first episode of stroke; transient episodes during the prior four weeks, were, however, also accepted.

On the day of admission, demographic information for all patients was recorded, as well as relevant data related to the medical history, neurological examination, general analyses (hemogram, biochemistry, electrolytes, and urine), 12-lead ECG, and chest x-ray. Neurological examinations were performed daily up to

the patient's hospital discharge or death. With regard to the diagnostic examinations, the study protocol contemplated cranial computed tomography (CT) for all patients, plus magnetic resonance (MR) imaging when deemed necessary. In all patients, Doppler ultrasonography of the supra-aortic arteries was performed, optionally associated with angiography or magnetic resonance angiography. In addition to the ECG on admission, cardiological study included one TTE in all cases and one or more 24-hour Holter recordings when the clinical records suggested a history of arrhythmia. In addition to the cardiological study, TEE with injection of saline contrast material and the Valsalva maneuver to assess foramen ovale patency was done in patients with an inconclusive diagnosis after TTE, artificial valves, endocarditis and whenever an etiological diagnosis of cerebral infarction could not be established after performing the usual examinations in the following cases: *a*) the patient was more than 60 years old; *b*) TTE had shown atrial septal disease; or *c*) paradoxical embolism (peripheral venous thrombosis or pulmonary embolism during the month before or after cerebral ischemia) was clinically suspected.

Classification of Cerebral Infarction

Ischemic cerebral infarction was classified according to the criteria of the Study Group for Cerebrovascular Disease of the Spanish Society of Nephrology²⁶ and included 3 groups of clinicopathological entities and 2 clinical neurological syndromes. The clinicopathological entities were: *a*) atherothrombotic cerebral infarction; *b*) cerebral infarction due to a cardioembolic mechanism; and *c*) cerebral infarction of infrequent cause, including cerebral venous disease, hematological disease, coagulation disorders, vasculitis, infections, migraine with aura, aortic disease, trauma, and hypertensive encephalopathy. Patients who did not fulfill the criteria of a clinicopathological entity were classified into 2 other groups according to the clinical neurological syndrome they presented: *a*) lacunar cerebral infarction, and *b*) unexplained cerebral infarction, in cases in which the inclusion criteria were not met for any of the 4 previous groups.

Diagnostic Criteria in the Subgroups of Cerebral Infarction

Cerebral infarction was classified as atherothrombotic when an ulcerated plaque, thrombotic material, or $\geq 50\%$ stenosis was detected in the cranial artery related to the anatomical topography of the lesion.²⁶

To establish the diagnosis of cerebral infarction having a cardioembolic mechanism, we used the criteria recommended by the Study Group for Cerebrovascular Disease of the Spanish Society of Nephrology,²⁶ which are similar to those used in the classification of the

National Institute of Neurological Disorders and Stroke (NINDS).²⁷ According to these recommendations, the patients had to meet all of the following 6 criteria: *a*) sudden onset of the neurological syndrome, with maximum clinical manifestations since the initial phase; *b*) absence of a clinical lacunar syndrome; *c*) deficit lasting more than 24 h; *d*) documented (CT and/or MR imaging) evidence of cortical involvement, with a medium-size (maximum diameter, 15-30 mm) or large (>30 mm) infarction; *e*) absence of ulceration, thrombosis or $\geq 50\%$ stenosis in the ipsilateral supra-aortic arteries; and *f*) identification of a heart disease traditionally associated with a risk of embolism. These include the heart diseases reported in the main published series involving cardioembolism^{3,5,6} and those included in the major treatises on cardiology.²⁸ The protocol contemplated the following as possible cardioembolic substrates: presence of risk-associated arrhythmia (persistent or permanent atrial flutter or paroxysmal atrial fibrillation, rheumatic valvular disease, cardiac prostheses, degenerative non-rheumatic left valvular disease with calcification of the leaflets, seen as dense, bright echoes of ≥ 1 mm, with a limitation of valvular motion)²⁹ generating grade III/IV or IV/IV regurgitation, or at least mild stenosis (maximum aortic valve gradient >20 mm Hg, mitral valve area <2.5 cm²); ischemic heart disease (acute myocardial infarction, left ventricular aneurysm, left ventricular ejection fraction $<40\%$ in the absence of acute infarction or aneurysm, and akinesia or dyskinesia affecting at least 2 contiguous segments in the absence of the 3 above-mentioned subgroups of ischemic heart disease); dilated hypertrophic, restrictive, infiltrative, or obliterative cardiomyopathy; considerable calcification of the mitral annulus (calcification thickness ≥ 5 mm as measured by two-dimensional echocardiography from the apical four-chamber view)^{30,31}; mitral prolapse (systolic displacement of one or both valve leaflets into the atrium, as seen in the longitudinal parasternal section)³²⁻³⁶; cardiac tumors; endocarditis; interventricular communication; interatrial communication; aneurysm of the interatrial septum defined according to the criteria of Hanley et al³⁷ (base width of the aneurysm ≥ 15 mm, associated with either protrusion beyond the plane of the atrial septum ≥ 15 mm or phasic excursion of the atrial septum ≥ 15 mm during the cardiorespiratory cycle); and patent foramen ovale with or without an associated atrial septal aneurysm.

Cerebral infarction of unusual cause was diagnosed according to the data on cerebral venous diseases, hematological diseases, coagulation disorders, systemic vasculitis, central nervous system infections, migraine with aura, aortic involvement, trauma, and hypertensive encephalopathy.

The diagnosis of lacunar infarction was based on neuroimaging findings associated with the presence of a characteristic clinical syndrome (pure motor hemipar-

resis, pure sensory syndrome, sensorimotor syndrome, ataxic hemiparesis, or clumsy hand-dysarthria).

Patients in Each Cerebral Infarction Subgroup

Among the 1840 patients with a first-ever cerebral infarction, 553 (30.1%) met criteria of atherothrombotic infarction, 484 (26.3%) lacunar infarction, 468 (25.4%) cardioembolic infarction, and 87 (4.7%) infarction of unusual cause.

Patients With Unexplained Cerebral Infarction

Among the 1840 patients with a first-ever cerebral infarction, the examination protocol used was unable to establish an etiological diagnosis in 248 cases of non-lacunar infarction (13.5%). This subgroup, which was the subject of the present study, received antiplatelet treatment during 1 year of follow-up. When a new ischemic cerebral episode occurred, all diagnostic examinations performed in the initial protocol were repeated, and additionally TEE with saline contrast injection and the Valsalva maneuver was carried out.

Classification of Thoracic Aorta Atheromatous Plaques

The atheromatous plaques in the thoracic aorta documented on TEE were classified according to the modified criteria of the French Study of Aortic Plaques in Stroke Group as follows: grade I, plaques <4 mm thick; grade II, plaques \geq 4 mm thick; and grade III, plaques of any thickness with an added component of unequivocally mobile intra-aortic debris.^{15,21} Complex atheromatous plaques, which in all probability were responsible for the episodes of unexplained recurrent cerebral ischemia according to the high-risk evidence reported in previous studies,⁹⁻²¹ were considered to be those meeting the criteria of grades II or III and necessarily located in the ascending aorta or the aortic arch (proximal to the ostium of the left subclavian artery).

Control Group

To assess the importance of complex atheromatous plaques detected by TEE, we compared the prevalence of this finding in our patients with unexplained cerebral infarction who presented a second episode with a control group of patients with unexplained cerebral infarction who did not present a second episode during the first year of follow-up in the French Study of Aortic Plaques in Stroke.¹⁵ This study included 331 consecutive patients over the age of 60 with cerebral infarction. In all cases TEE was carried out during the 2 weeks after the stroke, with special attention to the presence of plaques in the thoracic aorta. Follow-up

was 2 to 4 years (mean follow-up was 2.4 years, corresponding to 788 patients/year).

Statistical Analysis

Comparisons between continuous variables were made with Student's *t* test. Comparisons between proportions used the Chi-square or Fisher exact test, depending on the size of the sample. Significance was set at a *P*-value of <.05.

RESULTS

Demographic Characteristics of Unexplained Cerebral Infarction

Mean age \pm standard deviation (SD) of the 248 patients with unexplained cerebral infarction was 71.4 \pm 13 years, with a predominance of men (60.1%). The most frequent cardiovascular risk factor was hypertension (34.0%), followed by hypercholesterolemia (17.7%), smoking (13.3%), diabetes mellitus (6.9%), ischemic heart disease (2.8%), and peripheral arterial disease (1.4%).

Clinical Evolution

Over 1 year of treatment with antiplatelet agents, 20 of 248 patients (8.1%) with unexplained cerebral infarction presented a new ischemic episode (a second infarction in 17 cases and a transient ischemic attack in 3 cases).

All cases of recurrent ischemia occurred during the first 4 months of follow-up and none of the patients had undergone TEE study previously in the first diagnostic assessment. Among the 17 patients who had a second infarction, the new episode was the cause of death in one patient and there was some degree of residual disability in four cases.

Comparison of patients with unexplained cerebral infarction who presented a new ischemic episode (*n*=20) or not (*n*=228) showed no significant differences with regard to age, sex, or prevalence of cardiovascular risk factors.

Transesophageal Echocardiography

Transesophageal echocardiography with administration of saline contrast material and use of the Valsalva maneuver was carried out in all patients who experienced a second cerebral ischemic episode. This examination established the probable cause of the ischemic event in 16 of the 20 cases (80.0%) of recurrent cerebral ischemia and among them, in 15 of the 17 patients (88.2%) with a second cerebral infarction.

The most noteworthy finding was complex atheromatous plaques in the ascending aorta and/or aortic

arch, in 15 of the 20 cases (75%) of recurrent cerebral ischemia, and among them, in 14 of the 17 patients (82.4%) with a second cerebral infarction. In 10 of the 15 patients (66.6%) with complex plaques, plaque thickness was found to be ≥ 4 mm and they were additionally associated with unequivocally mobile atherothrombotic debris; in the remaining 5 patients, only plaques ≥ 4 mm thick were detected. Lastly, in one patient with recurrent cerebral infarction, substantial concentric left ventricular hypertrophy, mild ejection fraction depression and sinus rhythm, TEE showed spontaneous echo contrast in a dilated left atrium with thrombosis of the auricular appendage.

Comparability With the Control Group

The consecutive patient populations with cerebral infarction included in our study (n=1840) and in the French Study of Aortic Plaques in Stroke (n=331)¹⁵ did not differ significantly with respect to mean age (75.4 vs 75.7 years), distribution by sex (with a predominance of women: 55.6% vs 52.9%), or mean prevalence of the seven main cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes, smoking, atrial fibrillation, history of myocardial infarction, and presence of peripheral arterial disease; 25.5% vs 28.8%). Both studies used the same classification to assign aortic plaque complexity. Similar to our study (where TEE was not systematically performed in all patients), in the French Study the classification *unexplained cerebral infarction* was given to patients in which an etiological diagnosis could not be established regardless of whether they presented aortic plaques, and antiplatelet agents were also administered during the follow-up of these patients. In addition, the 2 subgroups of patients with unexplained cerebral infarction presented a similar incidence of recurrent infarction during antiplatelet follow-up (in the French study, episodes of transient ischemia were not included in the analysis). In our study 17 cases of a second infarction were recorded (6.85 events per 100 patients per year of follow-up), versus 13 in the French Study (5.71 events per 100 patients per year of follow-up). Hence, these 2 populations of consecutive cerebral infarction patients were acceptably comparable, as was the incidence of recurrent infarction during antiplatelet therapy follow-up in the 2 subgroups of unexplained infarction derived from each of the general populations.

Role of Complex Atheromatous Plaques

In our patients with unexplained cerebral infarction who presented a second episode, the prevalence of complex aortic plaques (14 of 17 patients; 82.4%) was significantly higher than that found in the French Study patients with unexplained infarction who did not

experience recurrence during the first year of follow-up (20 of 95 patients; 21.1%) ($P < .0001$). Comparison between our patients with uncertain cause and reinfarction and patients in the French Study with uncertain cause who did not present recurrence over the entire follow-up period also showed a significant difference in the prevalence of complex plaques (82.4% vs 18.0%; $P < .0001$).

DISCUSSION

There is a growing incidence of cerebral ischemic events in Western populations, and in 10%-30% of patients it is impossible to establish the etiopathological diagnosis with the commonly used non-invasive cardiovascular examinations.^{7,8,24} It is evident that the problem of unexplained cerebral ischemia is a major clinical challenge. Even though there are no randomized studies defining the most appropriate treatment in this situation, antiplatelet drugs are generally prescribed in clinical practice.

Transesophageal echocardiography has broadened the diagnostic potential in the assessment of ischemic stroke. Nevertheless, because of the relative complexity of this technique, the slight risk involved and its limited availability, the indications for TEE have not been well established in cerebral ischemia²² and its use is restricted in the large elderly population, where this disease is mainly centered. With the application of our protocol of diagnostic examinations, TEE was performed in only 4.0% of patients with cerebral infarction. The etiological diagnosis could not be established in 248 patients (13.5%), who received empirical treatment with antiplatelet agents.

Over the last decades increasing evidence has pointed to the importance of aortic arch atherosclerotic disease as a source of cerebral embolism.⁹⁻²⁰ Several studies have documented a strong association between TEE-detected plaques protruding from the aortic arch and the risk of stroke.⁹⁻¹³ The association with ischemic cerebral infarction is particularly strong when the thickness of the protruding aortic arch plaque reaches ≥ 4 mm.^{13,15} This finding increases by four-fold the risk of presenting a new cerebral infarction.¹¹⁻¹⁵ The highest risk corresponds to patients with morphologically complex plaques. The presence of a mobile atherothrombotic component (aortic debris) can increase the risk of stroke up to 17 times¹⁴ and also increase the risk of death.²¹ Because of the prognosis in these patients and the fact that prompt anticoagulation therapy can reduce embolic events, it is clearly important to establish the diagnosis of this entity.^{21,22}

In the present study, complex plaques (those to which it is highly probable that recurrent unexplained cerebral events can be attributed) were classified as grades II or III proximal to the left subclavian (≥ 4 -mm thick, or any thickness together with mobile atherothrombotic debris).

rombotic intra-aortic debris),^{15,21} findings documented in 15 of the 20 patients with unexplained cerebral infarction with recurrent ischemia over one year of follow-up. As the control group we used patients with unexplained cerebral infarction who did not experience recurrence, included in the French Study of Aortic Plaques in Stroke.¹⁵ This population of consecutive patients with cerebral infarction proved to be acceptably comparable to our cohort. In addition, there was a similar incidence of second cerebral infarction in the subgroups of uncertain etiology derived from each of the total populations. Such a comparison between different population groups has certain limitations and the results should be interpreted with caution. Nonetheless, in the absence of other etiological findings that could explain the ischemic events occurring in these patients, the much higher prevalence of complex aortic plaques in our patients with a recurrent event, as compared to those of the French Study without recurrence, suggests that this disease plays a true causal role and is associated with a high risk of new ischemic events, despite administration of antiplatelet agents.

CONCLUSIONS

In a considerable percentage of patients with cerebral infarction, assessment by routine non-invasive examinations does not result in an etiological diagnosis. Although at mid-term most of these patients do not present new ischemic cerebral events while under antiplatelet treatment, a small subgroup (8.1%) present early recurrence of cerebral ischemia. Our study suggests a central causal role for complex atheromatous plaques of the aorta in patients with unexplained cerebral infarction who present a recurrent event during the first year of treatment with antiplatelet drugs, and indicates the usefulness of TEE for establishing the diagnosis in this situation. This information can have relevant clinical interest, since it is necessary to investigate antithrombotic options that will reduce the incidence of new embolic events in these patients.

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