Potential cardioembolic sources of stroke in patients less than 60 years of age

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Minor potential cardioembolic sources of stroke such as atrial septal aneurysm or patent foramen ovale are important risk factors for cryptogenic stroke. We aimed to determine the prevalence of these abnormalities through an exhaustive aetiological work-up. One hundred and eighteen stroke patients under 60 years of age, who had no evidence of a significant cardiac source of embolism, were classified into four groups following transoesophageal echocardiography and assessment of cervical arteries. Group A comprised 30 patients (25.4%) who had an arteriopathy, probably related to stroke without any cardiac abnormality; group B, had only a potential cardiac source; group C, nine (7.6%) had an obvious arterial source of stroke and incidental cardiac abnormalities; group D, 30 (25.4%) had neither cardiac or arterial source.

Data were analysed with the Chi-square test to compare risk factors between groups, and variance analysis was used to compare age between groups. Significance was assessed as $P<0.05$. Fisher’s exact test was used to test the association between atrial septal aneurysm and patent foramen ovale.

In groups B and D atrial septal aneurysm represented 56.8% of the cardiac abnormalities and was diagnosed in 35.4% of the 79 patients who had an unexplained stroke, and a patent foramen ovale was found in 34.1% of the patients. According to Fisher’s exact test, atrial septal aneurysm was significantly associated with patent foramen ovale ($P<0.001$). On this basis, one fourth of the patients might be said to have had a truly cryptogenic stroke as the aetiological work-up failed to demonstrate any source of stroke. Comparison between groups showed that in 23% of the patients in whom an arterial source was detected, there was also a potential cardioembolic source (group C), vs 62% in patients who had no arterial source (groups B and D) ($P=0.0007$). Our study confirmed the strong association between atrial septal aneurysm, patent foramen ovale and stroke. Although there was a lower incidence of cardiac risk factors for stroke in patients who had cervical artery disease, we suggest that all patients who have a stroke without evidence of a major cardiac source should undergo transoesophageal echocardiography, in order to ensure a better prevention.

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Key Words: Atrial septal aneurysm, patent foramen ovale, cryptogenic stroke, transoesophageal echocardiography.

Introduction

As many as 40% of acute ischaemic strokes have no clearly identifiable cause and are classified as cryptogenic[11], whereas atrial fibrillation, prosthetic heart valves, infective endocarditis, and acute transmural anterior myocardial infarction have all been shown to cause cardioembolic events[12]. In recent years transoesophageal echocardiography has been more successful in identifying potential cardiac sources of cerebral embolism than transthoracic echocardiography[14]. Atrial septal aneurysm and patent foramen ovale have a higher prevalence in patients with cerebral ischaemia of unknown cause[15-18]. Transoesophageal echocardiography findings were considered as incidental in patients who had stroke obviously related to cervical artery diseases[19], but angiographic and transoesophageal assessment revealed some inadequacy in most of the studies.

This study was designed to examine consecutive stroke patients who had no evidence of a strong cardiac source of embolism, as defined by the NINCDS Stroke Data Bank[11,12]. Transoesophageal echocardiography and an exhaustive assessment of the cervical arteries was undertaken to determine accurately the prevalence of potential cardioembolic sources such as atrial septal aneurysm and patent foramen ovale and to determine from the results the frequency of truly cryptogenic stroke.
Subjects and Methods

Between January 1991 and September 1994, 118 of 612 patients referred to our institution with ischaemic stroke were prospectively enrolled into the study. Inclusion criteria were: (1) Age between 20 and 60 years; (2) Transient ischaemic attack or stroke occurring within the previous week. (Two neurologists independently established a definite clinical diagnosis of transient ischaemic attack or stroke.) (3) Patient’s consent to undergo detailed aetiological investigations (see below). (4) Enrolment in the study was restricted to patients who had no evidence of strong cardiac sources of embolism, according to the NINCDS Stroke Data Bank. Patients were considered to have a strong potential cardiac source of embolism if they had a history of valvular surgery; a history or electrocardiographic evidence of atrial fibrillation, atrial flutter or sick sinus syndrome; or echocardiographic evidence of ventricular aneurysm, akinetic segment, mural thrombus, diffuse left ventricular hypokinesis, or cardiomyopathy. According to these criteria, 156 of 612 patients (25-4%) were considered to have a strong cardiac source of embolism. (5) Absence of coagulopathies and systemic disorders favouring stroke. One hundred and forty stroke patients <60 years old met the enrolment criteria, from which 118 were included in the study. The 22 patients who did not enter the study were excluded because either they refused to undergo transoesophageal echocardiography (n = 3) or they were unable to swallow the oesophageal probe (n = 10) as their stroke was associated with dysfunction of corticobulbar pathways. In addition the cardiological investigations were not performed according to our study protocol in nine patients: the echocardiography was performed in another laboratory before the patient was referred to our neurological institution (n = 5); manipulation of the probe did not allow complete evaluation of the interatrial septum or the left atrial appendage (n = 4).

A computed tomographic scan was performed in all patients, and magnetic resonance imaging in selected cases. In addition to transthoracic and transoesophageal echocardiography, the diagnostic work-up included carotid ultrasound in all cases and cerebral angiography in 106 of the 118 patients. Patients underwent electrocardiography and continuous cardiac monitoring during the acute stage. Laboratory studies included systematically, complete blood count, erythrocyte sedimentation rate, protein electrophoresis, glucose, serum cholesterol, and triglyceride levels, and prothrombin and activated partial thromboplastin times; work-up for the procoagulation state was performed in patients younger than 45 years. Risk factors for stroke were also evaluated.

Transoesophageal echocardiography assessment

After undergoing routine transthoracic echocardiography all patients underwent transoesophageal echocardiography (Hewlett-Packard 77025 A); a 5-MHz monoplane transoesophageal echocardiography probe was introduced after topical oropharyngeal anaesthesia with a 2% xylocaine spray. The probe was manipulated to optimize imaging of the left atrium and the atrial septum. Criteria for diagnosis of atrial septal aneurysm were those described by Pearson et al.\(^2\) (1) base width >1-5 cm (2) >1-1 cm excursion into either the left or right atrium or a sum of total excursion into the left or right atrium >1-1 cm. The diagnosis of patent foramen ovale relied on transoesophageal echocardiography using an intravenous administration of 5 cm\(^3\) of an echocardiogram-detectable contrast material. The injection was carried out at rest and after Valsalva manoeuvre. The echocardiographic diagnosis of inter-atrial shunt was based on the appearance of more than five microcavitations in the left atrium within four cardiac cycles of the total opacification of the right atrium. The established two-dimensional criterion for echocardiographic diagnosis of mitral valve prolapse included (1) superior systolic displacement (>2 mm) or billowing of one or both mitral leaflets across the saddle-shaped mitral annular plane in the parasternal long-axis view and (2) displacement of the mitral leaflet in the apical long-axis view. Doppler imaging was used to detect the presence of mitral regurgitation. Only systolic bowing of one or both mitral leaflets in the apical four-chamber view was not considered evidence of mitral valve prolapse.

Arteriopathies were represented by: (a) dissections, (b) atherosclerosis with extra or intracranial stenosis >50% of the corresponding vessels either in the carotid or vertebrabasilar systems, (c) lacunar stroke due to small artery disease when a hypertensive patient had one of the four main lacunar syndromes\(^1\) and a small deep infarct on computed tomography or magnetic resonance imaging in the absence of any large artery disease.

Statistical analysis

Data were analysed with the Chi-square test for the comparison of risk factors between groups. Variance analysis was used to compare age between groups. Significance was assessed as \(P<0.05\). Fisher’s exact test was used to test the association between arterial septal aneurysm and patent foramen ovale. As a result of transoesophageal echocardiography and exploration of the cervical arteries, the patients were classified into four groups. Group A comprised patients who had only large or small artery disease probably related to stroke; Group B had minor potential cardioembolic sources but no evidence of arterial disease; Group C had both arterial and cardiac sources of embolism; group D might have experienced a truly cryptogenic stroke as the aetiological work-up failed to show any abnormality.

Results

We studied 76 men and 42 women. The mean age of the patients was 47 ± 8.9 (range 23–59) years. Sixteen
patients had transient ischaemic attacks whereas 102 had stroke. The ischaemic event involved the carotid circulation in 73 patients (61.9%), vertebrobasilar territory in 42 (35.6%) and remained unknown in three cases. Combining transoesophageal echocardiography and exploration of the cervical arteries allowed classification into four groups (Fig. 1). Group A comprised 30 patients, six of whom had a cervical artery dissection (carotid 4, vertebral 2), 18 had large vessel atherosclerosis and six small artery disease. Group B comprised 49 patients who had cardiac abnormalities but no evidence of arterial disease. Group C, comprised nine patients who had both arterial and cardiac sources of embolism. These patients are described in Table 1. In three patients it was impossible to decide with certainty whether the arteriopathy or the cardiac lesion was responsible for the ischaemic event. Conversely, six patients had a cervical artery dissection clearly related to stroke. Among them five had an atrial septal aneurysm which was associated with a patent foramen ovale in two cases. However, according to Fisher's exact test, atrial septal aneurysm was not significantly associated with cervical artery dissection \((P=0.31)\). The remaining patient who experienced a dissection also had mitral valve incompetence. Group D comprised 30 patients who had experienced a truly cryptogenic stroke as the aetiological work-up failed to show any abnormality.

A cardiac abnormality was found in 58 patients (49%), of which transthoracic echocardiography failed to detect 43%. Atrial septal aneurysm represented 56.8% of these cardiac abnormalities, and was diagnosed in 35.4% of the 79 patients who had an unexplained stroke (groups B and D). A patent foramen ovale was found in 34% of the patients who had a cryptogenic stroke (groups B and D). A patent foramen ovale was found as a unique abnormality in 13.7% of the patients who had a potential cardiac source of embolism (groups B and C). According to Fisher's exact test, atrial septal aneurysm was significantly associated with patent foramen ovale \((P<0.001)\). A mitral valve prolapse was found in 13 patients, and was a unique abnormality \((n=9)\) in 15.5% of the patients who had a potential cardiac source of embolism and was associated with atrial septal aneurysm and patent foramen ovale in four patients. An important thickening and redundancy of the mitral valve leaflets was observed in eight patients, four of whom also had an atrial septal aneurysm associated with patent foramen ovale. In five cases mitral valve prolapse did not have a particular aspect. Potential cardioembolic sources are listed in Fig. 2. Mitral valve incompetence was observed in four patients, with moderate regurgitation in three patients and severe in one case. Comparison between groups showed that the patients in whom an arterial source was detected (groups A and C) also had a potential cardioembolic source in 23% of the

<table>
<thead>
<tr>
<th>Transoesophageal echocardiography findings</th>
<th>Large artery disease</th>
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<tbody>
<tr>
<td>Patient 1. Mitral valve incompetence</td>
<td>Right siphon stenosis</td>
</tr>
<tr>
<td>Patient 2. Atrial septal aneurysm and patent foramen ovale</td>
<td>Internal carotid artery (ICA)</td>
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<tr>
<td>Patient 3. Atrial septal aneurysm and patent foramen ovale</td>
<td>Vertebrobasilar system</td>
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<td>Patient 4. Atrial septal aneurysm</td>
<td>Left vertebral artery</td>
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<td>Patient 5. Atrial septal aneurysm</td>
<td>Extracranial dissection</td>
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<td>Patient 6. Atrial septal aneurysm</td>
<td>Left extracranial vertebral artery dissection</td>
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<tr>
<td>Patient 7. Mitral valve incompetence</td>
<td>Right ICA dissection</td>
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<tr>
<td>Patient 8. Aortic arch atheroma</td>
<td>Left ICA dissection</td>
</tr>
<tr>
<td>Patient 9. Patent foramen ovale</td>
<td>Right ICA dissection</td>
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</tbody>
</table>

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Discussion

The diagnosis of cryptogenic infarcts is more common than atherosclerotic stenosis or thrombosis\(^{[1]}\). Although 10 to 40% of strokes are believed to be cardioembolic in origin\(^{[12,13]}\), the cardiac source frequently remains unidentified. Direct imaging of potential sources of cardiac embolism with transthoracic echocardiography has a low sensitivity\(^{[14,15]}\), but this can be improved by transoesophageal echocardiography\(^{[6,16]}\). The common prevalence of atrial septal aneurysm in transoesophageal echocardiography studies ranges from 3 to 10\%\(^{[15,17]}\), but this latter is higher in patients undergoing transoesophageal echocardiography for unexplained stroke. Although the use of a monoplane transoesophageal echocardiography probe may have limited the number of positive studies, atrial septal aneurysm in the present study was found in 35.4\% of the patients; this frequency is in accordance with a recent related study using a single plane probe\(^{[6]}\).

Since the first report of atrial septal aneurysm by Lang and Posse\(^{[18]}\), Silver and Dorsey\(^{[19]}\) have found this anomaly in 1% of adult necropsies performed over a 4-year period. Three mechanisms of stroke may be suggested in patients with atrial septal aneurysm: (1) Paradoxical emboli in patients with a patent foramen ovale. (2) Occurrence of a thrombus within the atrial septal aneurysm, as suggested by autopsy\(^{[20]}\), surgical\(^{[21]}\) or transoesophageal echocardiography findings\(^{[17]}\). (3) Association with arrhythmia.

Various mechanisms of the formation of atrial septal aneurysm have been postulated. Aneurysmal formation of the septum primum has usually been attributed to a haemodynamic abnormality, such as the presence of elevated right or left atrial pressure resulting from an associated cardiac disorder\(^{[22]}\). In addition, defective connective tissue of the septum primum has been suggested, especially in patients with myxomatous mitral valve prolapse\(^{[23,24]}\). Degeneration of the mitral valve might result in weakness of the atrial septum and could lead to outpouching of the atrial septum. Connective tissue disorders such as Marfan's syndrome have been associated with atrial septal aneurysm\(^{[25]}\), and arterial dissection might also be involved. Statistical analysis showed that the coexistence of cervical artery dissection and atrial septal aneurysm in our study is an incidental finding. Moreover we found no clinical picture suggesting a connective tissue disorder in patients who had a dissection. Longitudinal transoesophageal echocardiography studies in patients who experienced spontaneous cervical artery dissection might be needed to estimate this association before pointing to a common pathological basis rather than to chance association of two disorders without causal linkage.

The incidence of patent foramen ovale in the normal population is close to 25\%, according to a recent echocardiographic study\(^{[26]}\). Lechat \textit{et al.}\(^{[7]}\) found a patent foramen ovale in 54\% of patients with unexplained stroke vs 21\% in patients who had a definitive cause. Our study confirmed the strong association between atrial septal aneurysm, patent foramen ovale and stroke\(^{[8]}\). However the prognostic implications of

Table 2 Age and risk factors for stroke according to groups (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean age (years)</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Cigarette smoking</th>
<th>Hypercholesterolaemia</th>
<th>Oral contraceptive</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>52.3 ± 6.7*</td>
<td>52.9*</td>
<td>66.7*</td>
<td>23.7</td>
<td>37.8</td>
<td>7.7</td>
</tr>
<tr>
<td>B</td>
<td>47.8 ± 8.4</td>
<td>17.6</td>
<td>16.7</td>
<td>52.6</td>
<td>40.5</td>
<td>61.5*</td>
</tr>
<tr>
<td>C</td>
<td>45.8 ± 7.1</td>
<td>5.9</td>
<td>0</td>
<td>7.9</td>
<td>8.1</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>41.7 ± 9.3</td>
<td>23.5</td>
<td>16.7</td>
<td>15.8</td>
<td>13.5</td>
<td>30.8</td>
</tr>
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Mean age \(^*P=0.005\). Hypertension \(^*P=0.005\). Diabetes mellitus \(^*P=0.006\). Oral contraceptive \(^*P=0.03\).
these abnormalities is subject to debate. Lindgren et al.\textsuperscript{26} have suggested that the prevalence of minor potential cardiac sources increase with age in both control subjects and patients with stroke and that the overall frequency of minor cardiac sources did not differ between stroke patients and normal subjects. Although the finding of a minor cardiac source should be used with caution, we think, according to a previous study\textsuperscript{6}, that the situation in younger stroke patients might be different. However, longitudinal prospective and large scale studies are needed to evaluate the prognosis of these abnormalities.

Because of the high incidence of concomitant carotid artery disease in patients with a potential cardiac source of embolism, the definitive cause of stroke in these patients cannot be clearly established. Bogousslavsky et al.\textsuperscript{27} found that 19% of patients with carotid-territory transient ischaemic attacks had a potential cardiac source of embolism associated with appropriate carotid artery disease. Rem et al.\textsuperscript{28} found that 49% of patients with a possible cardiac source of cerebral embolism also had a vascular lesion in an appropriate carotid artery. In our study, 23% of the patients had both a minor potential cardioembolic source and an arterial source of embolism; however, a clear relationship between stroke and arterial source could only be established in patients with an arterial dissection. Despite the lower incidence of these abnormalities in patients who had cervical artery disease, we suggest that systematic transoesophageal echocardiography screening should be carried out in any patient who has a stroke without a major cardiac source.

References