

Original Research

Etiology and Outcome of Cardioembolic Stroke in Young Adults in Greece

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Introduction: Cardioembolism is the most frequent cause of ischemic stroke in Greece. However, data regarding this stroke subtype in young adults from Greece and the East Mediterranean area are scarce.

Methods: We aimed to determine the source of embolism and evaluate outcomes in a sample of young Greek patients with ischemic stroke of cardioembolic etiology. A series of 245 Greek patients with ischemic stroke at an age up to 45 years were selected from a consecutive series of 2820 first-ever stroke patients admitted to our departments during the period January 1998 to December 2008.

Results: Cardioembolism was diagnosed in 45 cases (18.4%). Almost half of the cases (48.9%) were attributed to congenital anomalies of the interatrial septum, including 13 cases of patent *foramen ovale* (28.9%), 7 cases of atrial septum aneurysm (15.6%), and 1 case with both defects (2.2%). The majority of strokes in our young patient collective were related to medium-risk sources of embolism, while high-risk sources, namely dilated cardiomyopathy, atrial fibrillation and akinetic left ventricular lesions, were found in only 33.3%. The overall probability of 10-year survival was 89.4% (95% confidence interval 79.4-99.4), whereas the probability of a new composite vascular event was 14.3% (95% confidence interval 2.3-26.3) during the same period. The clinical outcome in general was excellent, since the majority of patients (82.2%) showed no significant handicap on follow up.

Conclusions: As in other western countries, it would seem that atrioseptal abnormalities played an important role as a cause of cardioembolism in this young Greek population, whereas atrial fibrillation and other major cardioembolic sources seem to be of minor relevance as compared to stroke in elderly patients.

Ischemic strokes in young adults aged up to 45 years are considered as relatively rare. They account for approximately 1% of all strokes in the community^{1,2} and up to 12% in specialized tertiary centers.³ Compared to the elderly stroke population, stroke in the young in western countries is characterized by a different etiological spectrum, where arterial dissection, procoagulant states, non-atherosclerotic arteriopathies and cardiogenic embolism seem to play a key role.^{4,5} However, recent evidence suggests racial and ethnic differences regarding stroke risk factors and subtypes among young patients.⁶

Cardioembolic stroke is one of the

major ischemic stroke subtypes documented in the elderly worldwide. Cardioembolism seems to be the most frequent cause of cerebral infarction in Greece and atrial fibrillation is considered as the most important source of brain embolism.^{2,7} However, data regarding cerebral ischemia in young adults in Greece and in the East Mediterranean area are scarce, in particular with regard to cardioembolic stroke in the under-45 age group. Therefore, the aim of the present study was to determine the source of embolism and to evaluate outcomes in a sample of young Greek patients with ischemic stroke of cardioembolic etiology.

Methods

Patients with ischemic stroke at an age up to 45 years were selected from a consecutive series of 2820 first-ever stroke patients admitted to our departments during the period January 1998 to December 2008. Patients' data were prospectively collected and documented in the digitalized database of the Athens Stroke Outcome Project, which started in 1998 as a modification of our previous stroke registry⁷ and focuses mainly on early and long-term outcome data.

Diagnostic evaluation

Cerebral ischemia was established in all cases by means of computed tomography (CT) or magnetic resonance imaging (MRI). Extensive cardiac diagnostics were performed in order to identify cardiac sources of embolism (CSE) in patients with suspected cardioembolic stroke. To evaluate possible cardiovascular diseases, the patient's detailed history was documented and a clinical examination was performed on admission. In addition, all patients underwent CT of the brain, standard electrocardiography (ECG) and chest X-ray on admission. Based on our diagnostic protocol, in cases where the initial workup remained inconclusive, the next step of diagnostic investigations included sonographic evaluation of the cervical arteries, as well as transthoracic echocardiography. In cases where no specific cause of stroke and especially no CSE were yet identified, transesophageal echocardiography and 24-hour Holter ECG monitoring were additionally performed. In selected cases, cerebral angiography was used to exclude stenosis and/or ulceration of major arteries in the ipsilateral to infarct large-vessel supply or intracranial arterial disease.

Diagnostic criteria

Stroke of cardioembolic origin was diagnosed following the Trial of Org 10172 in Acute Ischemic Stroke Treatment (TOAST) criteria when a high or a medium-risk CSE was identified in the absence of any other stroke etiology.⁸ Atrial fibrillation or sick sinus syndrome, mechanical prosthetic valves, mitral valve stenosis with atrial fibrillation, recent myocardial infarction within the previous 4 weeks, aneurysms or akinetic segments of the left ventricular wall, left atrial or ventricular mural thrombus, idiopathic dilated cardiomyopathy, bacterial endocarditis and atrial myxoma are considered as high-risk CSE. Interatrioseptal wall abnormalities, such as patent *foramen*

ovale (PFO) and/or aneurysms of the atrial septum (ASA), are the most important medium-risk CSE.⁸

Risk factors and outcome parameters

Traditional stroke risk factors, such as arterial hypertension, atrial fibrillation, diabetes mellitus, hypercholesterolemia, cigarette smoking, coronary heart disease, heart failure, alcohol abuse, and a positive family history for ischemic heart disease and stroke were documented based on our previously established criteria.⁷ In addition to the Scandinavian Stroke Scale, which was initially applied in the Athens Stroke Registry,⁷ the widely used National Institute of Health and Stroke Scale Score (NIHSS) was now applied for assessing the neurological severity on admission and discharge in all patients enrolled in the Athens Stroke Outcome Project.⁹ Patients were regularly followed up, at least once annually, by both authors in the setting of our departments' outpatients' clinic. During the follow-up visits, the following outcome data were documented: overall death and cause of death, clinical handicap, and composite cardiovascular events (recurrent stroke, newly manifested ischemic heart disease, acute peripheral vascular disease, sudden death). Clinical handicap was assessed using the modified Rankin Scale score (mRS range 0-5, 0= fully independent to 5= totally dependent).¹⁰

Statistical analysis

Continuous data are presented as mean \pm SD and categorical data as percentages. The Kaplan-Meier product limit method was used to estimate the probability of survival and of the composite cardiovascular events at 10 years after the index event.

Results

From our series of 2820 consecutive first-ever stroke patients, a total of 245 (8.7%) were aged up to 45 years at the time of symptom onset (mean age 35.3 ± 6.7 years; range: 17-45 years) and were thus enrolled in this study. Cardioembolic stroke was diagnosed in 45 (18.4%) cases. Males (62.2%) outnumbered females. An extensive cardiac evaluation was performed during hospitalization, including ECG and transthoracic echocardiography in all cases, transesophageal echocardiography in 27 (60%) and 24-hour Holter monitoring in 12 (26.7%) patients. In addition, brain imaging studies (CT or MRI) and ultrasound of the

cervical arteries were performed in all study patients. A CSE was suggested by the documented history of cardiac disease in 15 (33.3%) cases and finally confirmed by ECG and transthoracic echocardiography in 5 and 10 cases, respectively. Two patients (4.4%) were identified as having CSE using 24-hour Holter monitoring, while a further 7 (15.6%) and 21 (46.7%) cases were confirmed by means of transthoracic and transesophageal echocardiography, respectively. Anticoagulation was applied in 41.5% of all patients, while the rest were treated with antiplatelet agents. A total of 11 patients underwent PFO/ASA closure, while two patients with dilated cardiomyopathy underwent heart transplantation (one successfully, one died within a month).

Risk factors and cardiac sources of embolism

The most commonly documented risk factors in this group of young cardioembolic stroke patients were active smoking (46.7%), dyslipidemia (20%), atrial fibrillation (20%), dilated cardiomyopathy (17.8%), valvular heart diseases (13.3%) and myocardial infarction (11.1%). Hypertension was present in only 2.2% and diabetes in 6.7% of all patients, while previous transient ischemic attacks were reported in 6.7% of all cases. Cardiac sources of brain embolism, as identified by our diagnostic workup, are presented in Table 1. Congenital anomalies of the interatrial septum were the most frequent sources of cardioembolism (48.9%), followed by myocardial wall abnormalities (26.7%). Dilated cardiomyopathy was responsible for 8 (17.8%) cases of cardioembolic stroke. Valvular heart diseases (13.3%) and atrial fibrillation (11.1%) were less frequent sources of embolism in our group of young patients. More than one possible CSE was found in six patients. It should be noted that, according to the TOAST criteria for risk stratification of CSE, cardioembolic stroke was associated with a medium-risk CSE in the majority of cases (67%) (Table 1).

Stroke severity and outcome

In terms of stroke severity, our patients suffered relatively mild strokes, as assessed on admission by the NIHSS score (range: 0-24). More than half of them (53.3%) had a mild neurological deficit (NIHSS 0-3). A moderate (NIHSS 4-9) or severe neurological impairment (NIHSS \geq 10) was documented in 33.3% and 13.3% of all cases with cardioembolic stroke, respectively. The majority of patients improved during hospitalization.

Table 1. Etiology of cardioembolic stroke among Greek stroke patients aged up to 45 years.

Cardiac source of embolism ¹	n=45	%
Congenital abnormalities:		
Patent <i>foramen ovale</i>	13	28.9
Atrial septum aneurysm	7	15.6
Patent <i>foramen ovale</i> and atrial septum aneurysm	1	2.2
Right ventricle dysplasia	1	2.2
Total	22	48.9
Valvular heart disease:		
Rheumatic valvular disease without atrial fibrillation	4	8.9
Mitral valve prolapse	2	4.4
Total	6	13.3
Myocardial wall abnormalities:		
Dilated cardiomyopathy ²	8	17.8
Left ventricular akinetic segment ²	2	4.4
Left ventricular hypokinetic segment	2	4.4
Total	12	26.7
Arrhythmias:		
Atrial fibrillation ²	5	11.1

¹Six patients had more than one possible cardiac source of embolism.

²High-risk source of cardioembolism according to the TOAST criteria.⁸

Early and late stroke outcomes are presented in Table 2. Only one death occurred during hospitalization. A man with known dilated cardiomyopathy and an admission NIHSS score of 24 died 10 days after stroke onset due to massive brain edema. At discharge the majority of patients (71.1%) had no or only a slight handicap (mRS score 0-1), whereas moderate (mRS 2-3) or severe (mRS 4-5) handicap was documented in 20% and 6.7%, respectively. After hospital discharge, during the follow-up period (mean duration 54.9 months, range 1-120 months) three further patients died. Dilated cardiomyopathy was the cause of cardioembolism in all three cases. One of these patients died after heart transplantation within the first month after stroke. Severe recurrent stroke one month after hospital discharge was the cause of death in the second case. The last death occurred 33 months after cardioembolic stroke, as a result of dilated cardiomyopathy due to acute pulmonary edema. The 10-year survival rate was 89.4% (95% confidence interval, CI 79.4-99.4%) for the entire patient group and 52.5% (95% CI 12.5-92.5%) for patients with dilated cardiomyopathy. Five further vascular events were documented during follow up: 3 recurrent strokes and 2 myocardial infarctions. The overall rate of composite vascular events was 14.3% (95% CI 2.3-26.3). However, the clinical outcome in general was excellent, since 82.2% of the entire patient population were independent of any kind of help and support in their daily activities (mRS 0-1) at the time of their last follow-up visit.

Table 2. Stroke severity and outcomes in young patients who suffered a cardioembolic stroke.

Cardiac source of embolism	Total number of patients	Mild stroke on admission (%)	Independent at discharge (%)	Independent at last follow up (%)	Probability of recurrent vascular events ¹	Probability of 10-year survival ¹
All cases	45	53.3	71.1	82.2	14.3	89.4
Congenital abnormalities	22	45.5	63.8	90.9		
Valvular heart disease	6	66.7	66.7	83.3		
Myocardial wall abnormalities	12	50.0	75.0	58.3		
Arrhythmias	5	80.0	100.0	100.0		

¹Estimated by Kaplan-Meier limit method. Rates in blank cells were not calculated because of the small number of events.

Discussion

Cardioembolism was identified as the cause of stroke in 18.4% of our young ischemic stroke patients. According to the results of previous studies examining ischemic stroke subtypes among elderly Greek patients, cardioembolic strokes accounted for 27.8-32.1% of all cerebral infarctions.^{2,7} The majority of these strokes (65%) were attributed to atrial fibrillation. Compared to older subjects, it seems that cardioembolism in Greece is a somewhat less frequent cause of stroke among patients aged less than 45 years. It should be noted that, in this specific subgroup, only 11.1% of cases were etiologically related to atrial fibrillation, whereas almost half of all strokes occurred on a substrate of congenital atrial septum defects. This finding suggests totally different etiological spectra of cardioembolism for young and old Greek stroke patients.

According to previous hospital- and population-based studies from various countries in Europe, Asia and America – which did not, however, all classify stroke following the TOAST criteria – the incidence of cardioembolism ranged between 14.0% and 32.7%.^{3,5,6,11-17} The documented rates of cardioembolism in two studies from Iran and Tunisia were considerably higher; both reported cardioembolic stroke as the most frequent stroke subtype among young individuals with rheumatic valvular heart disease and prosthetic valves.^{18,19} Only one study reported a remarkably low rate of cardioembolic stroke of 5.2%.⁴ This discrepancy may be well explained by the fact that, according to the latter study's protocol, patients with isolated low-risk cardiopathies, PFO and interatrioseptal aneurysms were classified in the group of stroke of undetermined etiology.

Regarding the underlying cardiac pathology leading to cardiogenic brain embolism, we found that almost half of all our cases (48.9%) were attributed to congenital interatrioseptal defects, namely PFO and ASA. This result is comparable with those from

young Swedish (51.3%) and Finnish (46%) stroke patients.^{11,17} Paradoxical embolism on a substrate of PFO was also found as the most frequent cause of cardioembolic stroke according to the results of two studies from the USA, which evaluated young black Americans and young Americans of northern European ancestry.^{5,13} However, the reported percentages (27.3% and 20.3%, respectively) were significantly lower than those documented in both Scandinavian studies^{11,17} and in our Greek population. On the other hand, a series of studies from Asian and other less developed or developing countries show a clear predominance of rheumatic heart disease, prosthetic valve and mitral valve prolapse as causes of cardiogenic cerebral embolism,^{12,16,18-20} suggesting a different etiological spectrum of cardioembolism for western countries. The changing pattern of infective and rheumatic cardiomyopathies may well explain this discrepancy between more and less developed countries.²¹ However, with the exception of only a single study from India,⁶ where 83.3% of all cardioembolic strokes were related to major sources of cardioembolism, it should be noted that in all the aforementioned studies, almost half, if not the majority, of cardioembolic strokes were attributed to medium-risk embolic sources.

The fact that several studies from different, albeit developed, countries indicate interatrioseptal defects as being the most frequent cause of cardioembolic stroke in young patients suggests that theoretically – according to the TOAST criteria – medium-risk sources of embolism are in reality associated with almost half of such strokes in patients younger than 45. It might, therefore, become a matter of debate whether interatrioseptal defects should really be considered as medium-risk sources of cardioembolism in young adults, or whether the 'traditional' TOAST classification of high- and medium-risk sources of cardioembolism needs particular review for this specific age subgroup.

One might question whether the higher rate of PFO and ASA in developed countries is true, or just reflects a better and more complete diagnostic workup in comparison to less developed countries. On the other hand, with the almost complete eradication of infective endocarditis and rheumatic heart disease in western countries, especially in Europe,²¹ the growing importance of congenital defects of the atrial septum as a cause of stroke in young adults is justified. According to our findings, the severity of strokes due to PFO and/or ASA is considered to be low. Outcome was excellent, with no permanent disability, stroke recurrence or deaths in our group of patients. However, the setting of this study does not allow any conclusions regarding treatment (medical therapy or PFO closure).

The overall outcome in this specific patient group is surprisingly good. The probability of recurrent vascular events was very low and the probability of 10-year survival was almost 90%. Young patients with cardioembolic stroke due to atrial fibrillation showed mild neurological deficits and remarkably good courses compared to older individuals, who are known to present more severe clinical syndromes and permanent handicaps.²² In contrast, patients with dilated cardiomyopathy had the worst prognosis, despite suffering from a mild rather than a severe stroke at admission. Half of our patients with dilated cardiomyopathy died during this 10-year period, despite improvements in management during the last decades.^{23,24} Randomized clinical studies comparing antithrombotics with anticoagulants for stroke prevention were not available today in patients with dilated cardiomyopathy. In a recent clinical trial (WATCH), in patients with heart failure, warfarin was not superior to aspirin or clopidogrel for reducing mortality or composite cardiovascular events.²⁵

Our results also show that an extensive cardiological workup is justified, especially when evaluating young stroke patients. A stepwise diagnostic approach in terms of CSE assessment seems reasonable in order to avoid unnecessary tests and conserve resources. In all young ischemic stroke patients, transthoracic echocardiography should be performed in addition to a detailed documented history and routine ECG. If the initial workup remains inconclusive and a cardioembolic mechanism is suspected, further evaluation with transesophageal echocardiography and 24-hour Holter ECG monitoring is indicated. Our study is not population based and the relatively small sample size limits the extent to which we may draw conclusions from our findings.

In summary, it seems that causes of cardioembolism and clinical outcome in young adults differ significantly from those in the elderly. In developed countries, where infective and rheumatic heart diseases are clearly of minor importance nowadays, congenital defects of the atrial septum, such as PFO and ASA, seem to be the leading cause of cardioembolic strokes. However, regardless of the country of origin, a detailed cardiological evaluation in order to exclude even minor sources of cardioembolism is warranted when dealing with young stroke survivors. Further studies are needed in order to verify our observations and evaluate cardioembolic stroke at young ages in more detail.

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