Cardiovascular diseases in patients 65 years and younger with non-cardiogenic stroke

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Abstract

Introduction: Approximately 10–15% of patients with stroke are under 65 years of age. The aim of the study was to determine types of stroke In people below 65. We analysed the incidence and types of associated cardiovascular diseases in patients with non-cardiogenic stroke.
Material and methods: In this prospective study patients (aged ≤ 65) with stroke underwent physical examination, computed tomography of the head, blood tests, electrocardiogram, echocardiography, and transcranial and carotid artery ultrasound. Classification of stroke was performed according to the ASCOD scale. Analysis considered the incidence of heart diseases in patients with non-cardiogenic stroke and the incidence of heart diseases recognised as a cause of cerebral embolism in patients with cardiogenic stroke.
Results: The study included 611 patients with stroke at the age of 27–65 (mean: 57.2 ±6.7; M/F 380/231). Stroke of heterogeneous aetiology was observed in 321 patients, cardiogenic stroke in 78, and stroke caused by small vessel and carotid artery disease in 73 and 72 patients, respectively. The most common heart diseases in non-cardiogenic stroke patients included persistent foramen ovale, coronary heart disease and past myocardial infarction. The most common causes of cardiogenic embolism were cardiomyopathy, atrial fibrillation and interatrial septal defect.
Conclusions: Aetiologically heterogeneous stroke and cardiogenic stroke are the most commonly observed among young stroke patients. Cardiomyopathy and atrial fibrillation are the most common sources of cerebral embolism in young patients with cardiogenic stroke. Nearly 1/5 of patients with a non-cardiogenic stroke have congenital or acquired structural changes in the heart.

Key words: cardiovascular diseases, stroke, young.

Introduction

Among all patients with ischaemic stroke, approximately 10–15% of patients are under 65 years of age [1–7]. Cardiogenic and cryptogenic strokes are the most common forms of acute cerebral ischaemia in this age group, and they constitute 20–47% and 30% of patients, respectively [1, 2, 7, 8]. However, it is believed that approximately 40% of the strokes which were considered cryptogenic are finally cardiogenic [9]. Risk factors associated with lifestyle and dissection of the carotid and vertebral artery are more

important in the younger age group, in contrast to atherosclerosis, which becomes one of the main causes of brain ischaemia, starting in the seventh decade of life.

Knowledge of the prevalence of traditional risk factors for cardiogenic stroke and heart diseases in young patients with non-cardiogenic stroke is important in the prevention of that potentially devastating disease, especially in light of reports of an increasing number of young patients with stroke [10].

The aim of the study was to determine which aetiology types of stroke occur most commonly in people below the age of 65.

Detailed analysis was aimed at a subgroup of patients with non-cardiogenic stroke in which incidence and types of associated cardiovascular diseases were subject to assessment.

Material and methods

Six hundred eleven patients aged ≤ 65, who had their first ischaemic and/or haemorrhagic stroke diagnosed according to the WHO criteria and based on radiological images (computed tomography (CT) and/or magnetic resonance (MRI) of the head), were included in the prospective study within the period of November 2011 to February 2014 [11]. Five hundred sixty-one patients with completed ischaemic stroke or reversible ischaemic neurological deficit and 50 patients with haemorrhagic stroke were qualified for the study. Patients with post-traumatic haemorrhage, including subarachnoid haemorrhage, were excluded from the study. All patients were hospitalised in the acute phase of stroke in the Department of Neurology of the University Hospital, where diagnostics and therapy were conducted in accordance with the current guidelines [12, 13]. Each patient was interviewed and underwent physical internist examination, neurological examination and CT scan of the head on the first day of hospitalization which was the first day of stroke. During hospitalization, all patients underwent blood tests: blood count, ionogram, creatinine, creatinine clearance, bilirubin, troponin I (TnI), creatine kinase MB-fraction, C-reactive protein, anticardiolipin antibodies, antinuclear antibodies, protein C and S, antithrombin III, international normalized ratio, activated partial thromboplastin time, electrocardiogram (ECG), transthoracic (TTE) and transoesophageal echocardiography (TEE), ultrasound of the carotid and cerebral arteries, and 3-fold blood pressure measurement during each day of hospitalization. All patients underwent daily glycaemic profile tests and tests to examine total cholesterol concentrations, HDL, LDL and triglyceride levels. Twenty-four-hour ECG monitoring was performed in patients with previous negative history of atrial fibrillation/flutter (593 individuals). Four hundred and eleven patients underwent MRI of the head and 318 patients underwent angio-MRI of the carotid and cerebral arteries. Blood tests for the presence of coagulation factor pathology (VII, VIII, V Leiden mutation and prothrombin gene GA20210A) were performed in patients with no definite cause of stroke after initial evaluation (at least 4 months after the onset of stroke).

On the basis of the existing patients' records and test results, the presence of diseases and conditions that are generally recognized as certain and probable risk factors for stroke was found during hospitalization.

The following criteria were used to diagnose the conditions below:
- Arterial hypertension – the patient was diagnosed or treated for arterial hypertension before the stroke or his/her in-hospital blood pressure values were above 160/90 mm Hg.
- Diabetes – the patient was diagnosed or treated for diabetes before the stroke, any in-hospital glycaemia was above 200 mg/dl, fasting plasma glucose measured on 2 different days was above 126 mg/dl or the 2-hour oral glucose tolerance test (OGTT) glucose was above 200 mg/dl.
- Coronary heart disease (CHD) – diagnosis established before hospitalization, history of typical symptoms and typical ECG changes (prior myocardial infarction, ischaemic abnormalities in ECG) or typical echocardiographic findings (regional wall motion abnormality, reduced ejection fraction).
- Atrial fibrillation (AF) or flutter – arrhythmias documented earlier or present in ECG during current hospitalization.
- Lipid disorder – LDL level > 130 mg/dl in patients without ischaemic heart disease or > 100 mg/dl in patients with coronary artery disease or triglyceride level > 150 mg/dl or the patient has already been treated for hyperlipidaemia (statins, fibrates, ezetimibe).
- Myocardial infarction – increase in TnI on the second day of stroke by at least 25% in relation to the baseline assay, CK-MB > 25 UI (on the first day of stroke), ST-T elevation or depression in the ECG ≥ 0.1 mV or formation of a new pathological Q-wave.
- Haemodynamically significant stenosis > 50% stenosis of cerebral arteries and/or > 70% stenosis of carotid arteries (the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria were used to assess the degree of arterial stenosis).
- Valve disease – post-rheumatic narrowing of the mitral valve, mechanical or biological prosthetic valve, a valve after reconstructive surgery.

The above conditions were in the end confirmed by a cardiologist or internal medicine specialist.

Assessment of the prevalence of selected risk factors for stroke was performed in the study

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group, and after considering the age categories (≤ 55 and > 55 years of age).

Phenotypic classification of stroke was performed in accordance with the ASCOD scale [14]. In this phenotype-based classification, every patient was characterized by ASCOD: A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause, D for dissection of carotid and vertebral artery. Each of the 5 phenotypes was graded 1, 2, or 3: 1 for 'definitely a potential cause of the index stroke', 2 for 'causality uncertain', 3 for 'unlikely a direct cause of the index stroke (but disease is present)'. When the disease was completely absent, the grade was 0; when grading was not possible due to insufficient work-up, the grade was 9. Aetiopathogenesis of stroke based on this scale was attributed to that factor which obtained 1 point in a certain phenotype, definitely a potential cause of stroke.

The incidence of migraine and thrombophilia was compared between patients with persistent foramen ovale (PFO) and without PFO.

Persistent foramen ovale (with or without atrial septal aneurysm) was present in 8 patients in category A, 22 in category S, 31 in category C, and 41 and 5 patients in categories O and D, respectively.

Statistical analysis

Statistical analysis was performed using Statistica v.5.0. The χ^2 test was used for comparison of non-parametric data. Parametric data were compared using Student's t-test for unpaired data.

Results

The study included 611 patients with stroke at the age of 27–65 (mean age: 57.2 ±6.7), including 380 males (62.19%) and 231 females. Ischaemic stroke was observed more frequently (in 561 patients, 91.8%) than haemorrhagic stroke.

Clinical characteristics of the patients and the age-related risk factor profile (≤ 55 and > 55 years of age) are shown in Table I. Analysis of the dis-

Table I. Clinical characteristics of patients

Parameter	N (%)	Age ≤ 55 (n = 195)	Age > 55 (n = 416)	P-value
IS	561 (91.8)	173 (88.7%)	388 (93.3%)	0.0557
ICH	50 (8.2)	22 (11.3%)	28 (6.7%)	0.0557
CHD	34 (5.6)	10 (5.1%)	24 (5.8%)	0.7473
MI*	13 (2.1)	1 (1.0%)	11 (2.6%)	0.1962
Cardiomyopathy	32 (5.2)	11 (5.6%)	21 (5.0%)	0.8643
VD	4 (0.7)	1 (0.5%)	3 (0.7%)	0.7660
AF	26 (4.3)	9 (4.6%)	17 (4.1%)	0.7627
IE	6 (1.0)	5 (2.6%)	1 (0.2%)	0.0066
LVT	10 (1.6)	3 (1.5%)	7 (1.7%)	0.8958
PFO	55 (9.0)	21 (10.8%)	34 (8.2%)	0.2959
PFO + ASA	52 (8.5)	11 (5.6%)	41 (9.9%)	0.0818
DM	101 (16.5)	32 (16.4%)	69 (16.6%)	0.9564
AH	117 (19.1)	38 (19.5%)	79 (19.0%)	0.8843
LD	132 (21.6)	37 (19.0%)	95 (22.8%)	0.2796
CAD/PAD	17 (2.8)	6 (3.1%)	11 (2.6%)	0.7618
Cigarette smoking	66 (10.8)	20 (10.3%)	46 (11.1%)	0.7661
ICA or VA dissection	15 (2.5)	5 (2.6%)	10 (2.4%)	0.9050
History of migraine	82 (13.4)	27 (13.8%)	55 (13.2%)	0.8327
Family history of stroke	89 (14.6)	24 (12.3%)	65 (15.6%)	0.2786
OCP use	20 (3.3)	19 (9.7%)	1 (0.2%)	0.0008
Thrombophilia	23 (3.8)	5 (2.6%)	18 (4.3%)	0.2859
Collagenosis/APS	20 (3.3)	5 (2.6%)	15 (3.6%)	0.5000

*Acute MI in 4 patients; IS – ischaemic stroke, ICH – intracranial haemorrhagia, CHD – coronary heart disease, MI – myocardial infarct, VD – valve disease, AF – atrial fibrillation, IE – infective endocarditis, LVT – left ventricle thrombus, PFO – patent foramen ovale, ASA – atrial septum aneurysm, DM – diabetes mellitus, AH – arterial hypertension, LD – lipid disorders, CAD – carotid artery disease, PAD – peripheral artery disease, ICA – internal carotid artery, VA – vertebral artery, OCP – oral contraceptive pill, APS – antiphospholipid syndrome.

tribution of risk factors for stroke including age categories revealed a significantly more frequent occurrence of infective endocarditis in subjects aged ≤ 55 than in older subjects.

The most frequently observed strokes were strokes of 'other' aetiology (heterogeneous); less frequently observed were cardiogenic strokes, followed by strokes caused by small vessel disease, carotid artery disease and/or cerebral artery disease, and by dissection of the carotid or vertebral artery. In 37 (6.05%) patients the cause of stroke was not established, so their strokes were classified as cryptogenic (Table II).

The most common heart diseases in patients with established non-cardiogenic cause of stroke included structural defects of the interatrial septum (persistent foramen ovale and/or atrial septal aneurysm (ASA)), coronary arterial disease and past myocardial infarction (MI). The most common sources of established or potential cardiogenic embolism among patients with cardiogenic stroke were cardiomyopathy, atrial fibrillation and interatrial septal communication. Distribution of heart diseases in patients with cardiogenic stroke and stroke related to another cause is shown in Table III.

There were no statistically significant differences in the occurrence of migraine and thrombophilia between the patients with PFO and without PFO (Table IV).

Discussion

The distribution of risk factors for stroke and the aetiological type indicate the relationship of sex and age. In people under the age of 65 the most commonly observed are cardiogenic and cryptogenic strokes [1–7]. In the present study, 57% of patients had 'other' strokes (heterogeneous according to ASCOD categories), with 14% of patients diagnosed with cardiogenic stroke and 6% of patients with cryptogenic stroke. The study results indicate that consistent implementation of the diagnostic plan allows us to determine the cause of stroke in 94% of young patients, which is crucial for the introduction of optimal secondary prevention. As the reports suggest, more than 10% of patients develop recurrent vascular events within 5 years [2]. According to Ji *et al.*, in nearly 90% of young patients with stroke it is possible to determine the cause during examinations using modern diagnostic tests (including a test for rare disorders of the coagulation system) [7].

We present the results of a study constituting part of a project related to stroke in young patients. The aim of that study was to determine the type and incidence of cardiovascular diseases in young subjects with non-cardiogenic stroke. Analysis was conducted in the context of the results presented previously and related to cardiogenic stroke in young subjects [15].

In the whole group of patients under study, the following stroke risk factors were found most of-

Table II. ASCOD phenotyping of ischaemic stroke (*n* = 561)

Phenotyping	Number	Percentage
A	72	12.8
S	73	13.0
C	78	13.9
O	321*	57.2*
D	15	2.6

A – Arteries with atheromatosis, S – small vessel disease, C – Cor, O – other (*cryptogenic stroke included, n = 37, 6.05% of all), D – dissection (of internal carotid artery or vertebral artery).

Table III. Type and frequency of associated cardiovascular diseases in patients with stroke of different aetiology

Parameter	A (*n* = 72)	S (*n* = 73)	C (*n* = 78)	O (*n* = 321)	D (*n* = 15)
MI	1 (1.3%)	5 (6.8%)	4* (5.1%)	3 (0.9%)	0
IE	0	0	6 (7.6%)	0	0
AF	0	0	26 (33.3%)	0	0
LVT	0	0	9 (11.5%)	1 (0.3%)	0
PFO/PFO + ASA	8 (11.1%)	22 (30.1%)	21 (26.9%)	51 (15.8%)	5 (33.3%)
CHD	9 (12.5%)	6 (8.2%)	7 (8.9%)	9 (2.8%)	3 (20%)
Cardiomyopathy	1 (1.3%)	0	30 (38.7%)	0	1 (6.7%)
VD	0	0	3 (3.8%)	1 (0.3%)	0

*Acute MI, A – arteries with atheromatosis, S – small vessel disease, C – Cor, O – other, D – dissection (of internal carotid artery or vertebral artery), MI – myocardial infarct, IE – infective endocarditis, AF – atrial fibrillation, LVT – left ventricle thrombus, PFO – patent foramen ovale, ASA – atrial septum aneurysm, CHD – coronary heart disease, VD – valve disease, AH – arterial hypertension, LD – lipid disorders, CAD – carotid artery disease, PAD – peripheral artery disease, ICA – internal carotid artery, VA – vertebral artery, APS – antiphospholipid syndrome.

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Table IV. Coincidence of PFO with migraine and thrombophilia

Parameter	Patients with PFO (*n* = 107)	Patients without PFO (*n* = 504)	*P*-value
Migraine	13 (12.1%)	69 (13.7%)	0.6711
Thrombophilia	6 (5.6%)	17 (3.4%)	0.2701

SI – stroke infarct, ICH – intracranial haemorrhage, MI – myocardial infarct, IE – infective endocarditis, AF – atrial fibrillation, LVT – left ventricle thrombus, PFO – patent foramen ovale, ASA – atrial septum aneurysm, CHD – coronary heart disease, VD – valve disease, AH – arterial hypertension, LD – lipid disorders.

ten: lipid disorders, arterial hypertension, diabetes, family burden of stroke and nicotinism. These observations are consistent with the previously published data related to the profile of risk factors in young patients with stroke [1, 2, 4, 7, 16–21].

In the present study, 86% of patients with stroke were classified as cases of non-cardiogenic aetiology (including cryptogenic stroke in 7.6% of patients in this group). Structural defect of the interatrial septum, CHD and past MI in this group turned out to be the most common cardiovascular diseases. Isolated PFO or PFO concomitant with ASA in the present study was reported in 11–33% of patients in various categories of stroke aetiology. The prevalence of PFO according to the results of echocardiography and autopsy is dependent on age, and it affects approximately 15–35% of subjects [22–25]. Persistent foramen ovale was classified according to ASCOD as a factor of uncertain significance for cerebral ischaemia. Many study results, including the CLOSURE, RESPECT and PC trials, did not explicitly confirm a cause-and-effect link between PFO and stroke [26–28]. However, it must be mentioned that there is a relationship between the inter-atrial septum pathology and acute cerebral ischemia in patients without traditional risk factors for stroke [29]. Research is needed to explicitly determine the role of a PFO in cerebral ischemia and to be able to specify the eligibility criteria for PFO occlusion in patients with cryptogenic stroke. In this study, the presence of a single (PFO or ASA) or double interatrial septal defect was not a decisive factor to divide strokes into separate aetiology categories. Different dominant causes of acute cerebral ischaemia (or lack thereof in the case of cryptogenic stroke) were identified in each case; PFO with ASA and ASA were recognised as additional pathologies. Their role may be important for the co-existence of additional factors, regardless of the difficulties in determining the source of paradoxical embolism. Paradoxical embolism probably is not a dominant mechanism of cerebral ischaemia in patients with PFO. The importance of cardiac rhythm disorders due to structural changes in the interatrial septum

for cerebral ischaemia, the so-called 'atrial vulnerability', is stressed. Coexistence of AF with PFO has been shown in approximately 1/5 of young patients with stroke [1].

Possible genetic determinants of the pathology of interatrial septum and heart structure are suggested; in susceptible individuals these may lead to brain ischaemia in the course of embolic mechanism and vasoactive reactions observed in women with migraine [30, 31]. Recently a potential significant relationship between increased mean platelet volume and PFO has been discussed [32]. A summation effect of interatrial septal anomaly and other factors is probable; these include haemostatic and genetic factors, and factors associated with brain vessels which lead to brain ischaemia. In the present study no significant relationship was observed between PFO and migraine or thrombophilia.

Other cardiovascular diseases observed in the present study among patients with non-cardiogenic stroke are CHD and past MI. Partially shared are the risk factors for stroke and acute coronary syndrome. As the INTERSTROKE and INTERHEART studies suggest, these have a different degree of correlation with acute ischaemia of the brain and heart [33, 34]. It is caused by a more differentiated pathomechanism of stroke, while acute coronary syndromes are mainly caused by atherosclerosis. According to the results of INTERSTROKE, 10 modifiable risk factors are responsible for 90% of the risk of cerebral stroke. Arterial hypertension certainly deserves attention; it may be responsible for 50% of all cerebral strokes, and pharmacological control over the system pressure values significantly reduces that risk [35–37]. Coronary heart disease was found in nearly 6% of patients in the whole study group, which is consistent with the results of the Scandinavian investigators [1].

In the present study, cardiogenic stroke is the second cause of ischaemic stroke, after the most frequent 'other' category. The most common causes of established or potential embolism included cardiomyopathy, atrial fibrillation and interatrial septal defect. Similar results were obtained in a study conducted in 15 European stroke departments [38]. Among young patients with cardioembolism, the most frequent high-risk sources were atrial fibrillation/flutter (15.1%) and cardiomyopathy (11.5%) [38].

Atrial fibrillation is observed in 1–5% of young patients with stroke [1, 7, 16]. Acute cerebral ischaemia in patients with AF results from the embolic material generated in the left atrium or left atrial appendage. A cardiogenic stroke is characterized by severe course, a higher degree of post-stroke disability and a higher mortality rate compared to

strokes of other aetiology [39, 40]. In the present study, AF was found in 4.3% of patients.

The coexistence of several potential causes of cerebral ischaemia is observed in 1/4 of patients with stroke [41]. Most often these are heart diseases, carotid atherosclerosis and/or small vessel disease, and factors related to lifestyle in young patients [1, 41]. In the present study, in 1/5 of the patients stroke was attributed to large artery atherosclerosis and small vessel disease. The incidence of vascular diseases is significantly influenced by the fact that in the study group 68% of patients were > 55 years of age. These factors in patients with cardiac embolism could additionally increase susceptibility to stroke.

In conclusion, aetiologically heterogeneous stroke and cardiogenic stroke (according to the causative classification system of stroke) are the most commonly observed among young patients with stroke. Cardiomyopathy and atrial fibrillation are the most common sources of cerebral embolism in young patients with cardiogenic stroke. Nearly 1/5 of patients with a documented or highly probable non-cardiogenic cause of stroke have stroke-concomitant congenital or acquired structural changes in the heart. The most common cardiac pathologies in patients with non-cardiogenic stroke include interatrial septal anomalies and coronary heart disease.

Conflict of interest

The authors declare no conflict of interest.

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