Stroke Risk Factors, Course and Long-Term Functional Outcome of First-Ever Stroke in Women

Anetta Lasek-Bal[1*], Jan Szymszal[2], Zofia Kazibutowska[1]

[1]*Department of Neurology, Medical University of Silesia Hospital No. 7, Professor Leszek Giec Upper Silesian Medical Centre, Katowice, Poland;* [2]*Silesian Technical University, Katowice, Poland*

Abstract

BACKGROUND: Recently, many studies regarding stroke in men and women showing differences in its incidence and course have been conducted, but the cause of sex differences remains unclear.

AIM: The objective of study was to assess the incidence of selected stroke risk factors, the course and long-term consequences of first-ever stroke in women.

MATERIAL AND METHODS: 304 women and 207 men with first-ever stroke were studied. We assessed: age at which stroke occurred; presence of hypertension, lipid disorders, coronary disease, atrial fibrillation, diabetes, carotid/cerebral artery stenoses; stroke aetiology, state on days 1 (NIHSS) and 90 (Rankin).

RESULTS: The age at which first-ever stroke occurred was higher in women ($p = 0.030$). Atrial fibrillation occurred more frequently in them ($p = 0.0007$). Hypertension and coronary disease occurred less commonly in women under 55 ($p = 0.038$ and 0.035 respectively). In women < 55, lipid disorders ($p = 0.004$) and diabetes ($p = 0.018$) were observed more rarely, they were more common in > 55 group ($p = 0.042$ and 0.023). In women, carotid artery stenoses were less common ($p = 0.07$), cardiogenic stroke more common ($p = 0.001$). They were in worse neurological state both on day 1 ($p = 0.001$) and 90 ($p = 0.033$) of disease.

CONCLUSIONS: Cardiogenic stroke is significantly more common in women. Women exhibit more severe post-stroke disability, resulting in more frequent use of institutional care.

Introduction

The profile of risk factors for stroke shows a relationship with gender. In recent years, there have been a number of studies regarding stroke in men and women, in which differences in the incidence and the course of ischemic stroke were shown, but the cause of gender differences often remains unclear. Women more rarely suffer from stroke, but only before menopause – differences among the elderly become blurred [1]. They experience ischemic stroke more frequently as a result of cardiogenic embolism, which is associated with a higher mortality rate and severe disability [2]. Post-stroke depression and dementia are more common among women [3, 4]. Differences in response to thrombolytic treatment in the acute phase of stroke and endovascular treatment in secondary prevention are also observed [5-7]. The protective impact of oestrogens on cerebral circulation, modifying the process of atherogenesis, is emphasised [8]. Study results obtained by researchers are often contradictory; this is associated, among other things, with the influence of geographical, race-related and individual factors. In literature, there are few reports raising the issue of the importance of sex in stroke [9]. An analysis of the distribution of risk factors for stroke in women, as well as differences in the course of the acute phase of the disease and its outcome may be helpful in optimising preventive and therapeutic strategies regarding stroke.

The objective of this study was to assess the course and long-term consequences of first-ever ischemic stroke in women and to determine the incidence of selected risk factors for stroke in this group.

Material and Methods

In 2012-2013, 511 patients participated in the prospective study: 304 women (the study group) aged 32-100 years (median 74 years, Q25% = 66 years,

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Q75% = 81 years) and 207 men (the reference group) aged 42-99 years (median 70 years, Q25% = 61 years, Q75% = 77 years). The inclusion criterion for the study was a first-ever symptomatic ischemic stroke or reversible ischemic neurological deficit) diagnosed in accordance with World Health Organisation (WHO) criteria (1980) [10].

Patients with symptoms of a transient ischemic attack or acute intracranial bleeding complicated by ischemic stroke due to angiospasm were not included. Patients meeting the inclusion criteria and consecutively admitted to the Neurology Department for treatment of the acute phase of ischemic stroke participated in the study. The study included patients in whom head computed tomography (CT) scans performed in the first 24 hours of stroke revealed no lesions or new ischemic lesions. Clinically silent "old" vascular foci were found in 86 patients.

The following were recorded in all of the included patients:

- the age at which their first-ever ischemic stroke occurred

- the presence of the following diseases: arterial hypertension (HA), coronary artery disease (CAD), atrial fibrillation (AF), diabetes mellitus (DM) and lipid disorders (based on laboratory tests carried out beforehand and during hospitalisation as well as the conclusions of general medicine consultations).

The diagnoses of arterial hypertension were established on the basis of the diagnostic criteria of the Polish Cardiac Society [11]. The diagnosis of ischaemic heart disease was posted earlier, or the data from the patient's medical history or family history reflected the presence of typical symptoms of the disease, or it was stated on the basis of the electrocardiography (ECG) image (past myocardial infarction, characteristics of myocardial ischemia), or ultrasound cardiography (segmental left ventricular dysfunction of contractility, reduced ejection fraction, EF). The diagnosis related to atrial fibrillation was posted when arrhythmia was recognized in the previous patient records or if it was present in the ECG during current hospitalization. The presence of the enumerated diseases, and conditions considered as risk factors for cerebral stroke was based on the tests, and specialist consultations performed during hospitalization and/or after the analysis of existing patients' medical records. During hospitalization, continuous ECG monitoring was carried out for 3 days during the acute period of the disease. ECG-holter test was carried out once; transthoracic echocardiography, and 3-fold measurement of arterial blood pressure was taken during each day of hospitalization.

The concentrations of total cholesterol >200 mg/dl (>5.18 mmol/L), LDL >100 mg/dl (2.59 mmol/L), HDL <35mg/dl (0.91 mmol/L) and triglycerides >135 mg/dl (1.53mmol/L) were assumed to be abnormal.

- the presence of haemodynamically significant stenoses of the carotid and/or cerebral arteries found on ultrasound examinations performed on the 1st and 8th days of the disease using an EnVisor system, manufactured by Philips, and a PIONEER device, manufactured by EME. Stenoses considered being significant haemodynamically: ≥ 70% of the carotid artery and/or ≥ 50% of the cerebral artery ipsilaterally to the cerebral ischemia (the NASCET criteria were used).

- the neurological state in the first 24 hours of stroke according to the NIHSS (National Institutes of Health Stroke Scale) [12]

- the neurological state at day 90 following the onset of the disease according to the Rankin scale [13]

- the anatomical location of the cerebral vascular event, specified as: vessels supplying the internal carotid artery or the basilar artery

A-S-C-O scale was used to assess the main causes of stroke. In this phenotype-based classification, every patient was characterized by A-S-C-O: A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause. Each of the 4 phenotypes was graded 1, 2, or 3. One 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.

Multiple logistic regression was performed in order to assess the impact of sex and age (under and over 55 years) on the occurrence of HA, CAD, DM, lipid disorders; log-linear models were used in order to assess the impact of sex on the cause of stroke according to the ASCO scale.

The statistical suite Statistica v. 7.1 PL by StatSoft and MedCalc v. 12.04 by MedCalc Software were used in multiple factor assessment.

The analyses were carried out with respect to the whole group of men and women, and then after dividing each of them into two age subgroups: under and over 55 years. It is consistent with the categories used in a number of studies, which the authors of the presented report refer to. The following tests were used during the statistical analysis: the D'Agostino-Pearson test – to verify the consistency of the distribution of the examined characteristic (age) with the normal distribution; the Mann-Whitney test – for intergroup comparisons, the Chi-square test – to verify the independence of two qualitative characteristics. A value of $p < 0.05$ was accepted as statistically significant.

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Results

The age at which first-ever ischemic stroke occurred was significantly higher in women (median 74 years, SD = 11.57 years, Q25% = 66 years, Q75% = 81 years) compared to men (median 70 years, SD = 10.92 years, Q25% = 61 years, Q75% = 77 years) (Table 1).

Table 1: Comparison of prevalence of selected risk factors and concerning course of stroke in women and men.

Parameters		Female (F) n (%)	Male (M) n (%)	F vs M p
Median age at of first-ever stroke		74 $Q_{25\%}$ = 66 $Q_{75\%}$ = 81	70 $Q_{25\%}$ = 61 $Q_{75\%}$ = 77	<0.001
NIHSS on 1st day		7.12	5.63	0.001
Atrial fibrillation		101 (33.22)	41 (19.81)	<0.001
Arterial hypertension		273 (89.80)	182 (87.92)	0.506
Coronary Heart Disease		152 (50.00)	91 (44.17)	0.195
Diabetes		137 (45.07)	77 (37.20)	0.076
Lipid disturbances		156 (46.38)	96 (51.32)	0.272
	A	35 (11.5%)	42 (20.3%)	0.006
	S	97 (31.9)	64 (30.9%)	0.813
	C	106 (34.9%)	45 (21.7%)	0.001
	O	66 (21.7%)	56 (27.1%)	0.164
Anatomical location of stroke	ICA	235 (77.30)	151 (72.95)	
	BA	69 (22.70)	56 (27.05)	0.26
mRankin > 3 points on 90th day, n		72	35	0.033
Using the services of residential care facilities, n		53	20	0.02
Mortality, n		68	45	0.74

NIHSS- National Institutes of Health Stroke Scale; ICA- internal catrotid artery; BA- basilar artery; A- S- C- O- (phenotypic) classification of stroke: A for atherosclerosis, S for small-vessel disease, C for cardiac pathology, O for other causes.

Atrial fibrillation occurred significantly more frequently in women than in men (p < 0.001), which resulted from significantly more common atrial fibrillation in women over 55 years (p = 0.0007) (Tables 1, 2). The percentage of haemodynamically significant carotid artery stenoses was lower in women (11.51% vs. 20.37% in men, p = 0.07). The neurological state in the first 24 hours of the disease, according to the NIHSS, was found to be more severe in women than in men (the mean score in women: 7.12; the mean score in men: 5.63; p = 0.001) (Table 1). Women obtained statistically significantly higher scores on the Rankin scale at day 90 following the onset of stroke (>3 points in 72 women and in 35 men; p=0.033) and more often used the services of residential care facilities in comparison with men (17.36% vs. 9.71%) (Table 1). Women significantly often suffered from cardiogenic stroke (34.9% vs 21.7%; p = 0.001) (Table 1). The impact of the classic risk factors for stroke, atrial fibrillation, arterial hypertension, lipid disorders and diabetes, depended on age to a large extent in both groups. Arterial hypertension and ischemic heart disease occurred significantly more rarely in women aged under 55 age group (p = 0.038 and p = 0.035, respectively) (Table 2). Similarly, lipid disorders (p = 0.004) and diabetes (p = 0.018) were significantly less observed in women in the same age group; however, among older patients, both diseases were significantly more common in women (p = 0.042 and p = 0.023, respectively) (Table 2).

Table 2: Comparison of the prevalence of selected risk factors for stroke and parameters of stroke in men and women ≤ and > 55 years of age.

		Female ≤ 55 years	Male ≤ 55 years	p	Female >55 years	Male >55 years	p
n		22	27		282	180	
Atrial fibrillation		2	4	0.538	99	37	0.000
Arterial hypertension		13	23	0.038	260	159	0.167
Coronary Heart Disease		2	9	0.035	82	150	0.122
Diabetes		2	10	0.018	135	67	0.023
Lipid disturbances		5	17	0.004	151	79	0.042
Anatomical location of stroke	ICA	22	17		213	134	
	BA	0	10	0.002	69	46	0.79

ICA- internal catrotid artery; BA- basilar artery.

In women aged under 55 years, in comparison with men, stroke located within the blood vessels supplying the basilar artery was significantly more rare (p = 0.002) (Table 2). Age had a statistically significant effect on the incidence of HA (OR = 3.46,CI 1.69-7.07, p = 0.0006), CAD (OR = 3.40,CI 1.69-6.84, p = 0.0006), AF (OR = 2.73,CI 1.13-6.62, p = 0.025), DM (OR = 2.29,CI 1.16-4.53, p = 0.016). Neither sex nor age mattered in relations to the occurrence of lipid disorders (significance level for model p = 0.47). Female gender was important for the cardiogenic mechanism of cerebral stroke (p = 0.0018). There was no statistically significant effect of age on the patho-mechanism of cerebral ischemia (p = 0.1992).

Discussion

Atrial fibrillation occurs more commonly in older individuals and in women. Among individuals aged 60 years and younger, the incidence of AF is estimated at 0.1-0.2%, while in individuals over the age of 80 years, it is 9.1–11% [14-16]. The older age of women at the onset of first-ever ischemic stroke may explain why this arrhythmia causes cerebral ischaemia more often in women than in men. In the presented study, like other authors, we found a significantly higher incidence of AF in women. Humphries observed a higher heart rate during AF in the acute phase of stroke in women [17]. The increase in heart rate and parasympathetic nervous system dysfunction may result from the older age of women with AF and arrhythmogenic thyroid diseases, which are more common among them [18]. The female gender has been recognised as a negative parameter in the CHA_2DS_2VaSc score, which stratifies the annual stroke risk in patients with AF [19].

In our study, we found haemodynamically significant carotid and cerebral artery stenoses less often in women. It is consistent with the results of the available research which indicates a higher incidence of symptomatic peripheral artery disease in men [20-22]. The impact of the risk factors for atherosclerosis, including modifiable ones, which are associated with lifestyle and more often observed in men, is noticeable. The analysis of the incidence of other, apart from AF and carotid artery disease, risk factors for stroke did not reveal significant differences

between men and women. They were, however, observed after dividing the study groups into age subgroups. We found a significantly lower incidence of arterial hypertension in women in comparison with men in the fewer than 55 age group; no significant difference was found in older patients. Arterial hypertension is the cause of alterations in the structure of the walls of cerebral arteries and arterioles, this leads to haemodynamic changes associated with a shift in the limits of autoregulation towards higher blood pressure. The available literature on the epidemiology of arterial hypertension describes its higher incidence in women or men, or the lack of gender-related differences [20, 23-26].

Literature data suggest a lower incidence of lipid disorders in women, which is also consistent with our observations regarding patients aged up to 55 years. We found a reversal of this relationship in older individuals. According to Zang et al., abnormal LDL levels are a risk factor for stroke in both genders, while elevated total cholesterol is associated with the risk of stroke only in women [27]. The use of statins decreases the risk of stroke and other cardiovascular events both in men and in women [28]. As previous studies have shown, women more rarely use lipid-lowering therapy [29, 30]. The analyses were carried out not taking age categories into account.

We observed age-dependent differences in the incidence of diabetes – significantly less common in women aged less than 55 years and significantly more common among older female patients in comparison with men in the same age group. The consequences of diabetes are negatively affected by the profile of disorders accompanying it which are categorised as elements of the metabolic syndrome. In a study of the Danish population, it was found that type 2 diabetes doubles the risk of stroke in men, but its negative impact is significantly stronger in women [31]. Women use hypoglycaemic agents less often [30].

Analysing risk factors for stroke, we found a lower incidence of arterial hypertension, ischemic heart disease, and diabetes and lipid disorders in women aged up to 55 years. It may have an influence on the older age at which first-ever stroke occurs in them. In our study, the mean difference was 4.1 years. Similar observations regarding the difference in age at which the disease occurred have been presented by other authors [4, 20, 24, 29, 31]. In women aged under 55 years, in comparison with men, ischemia occurring in the blood vessels supplying the basilar artery was significantly more rare (p = 0.002). According to single reports, women more frequently suffer from cerebral infarction in the area supplied by the arteries of the anterior Circle of Willis [32]. According to other authors, the location of the area of cerebral ischemia is not related to gender [33-35].

In our study, we observed more severe neurological conditions in women both in the acute phase of stroke and three months later. Similar results were presented by other authors [20, 33, 36]. The presence of risk factors, including atrial fibrillation, has an undoubted impact on the neurological condition during stroke. Literature data indicate that cardiogenic stroke has a more severe course, which usually results from the large size of embolic material generated in the heart. Lower limb osteoarthritis, obesity, lower extremity venous insufficiency and osteoporosis can limit the effects of rehabilitation and improvement in ability in women. Our female patients used the services of residential care facilities due to post-stroke disability far more frequently than men.

The impact of gender on the incidence, course and outcome of stroke is analysed while taking the hormone profile into consideration. A hypothesis concerning the role of oestrogen as a neuro- and vasoprotective factor was proposed on the basis of the results of experimental cerebral ischemia in rodents [8]. In female animals, occlusion of the middle cerebral artery leads to the appearance of smaller infarction foci. After ovariectomy, the size of the foci is comparable between members of both sexes; however, oestrogen substitution leads to a reduction in the size of the area affected by ischemia [37, 38].

The regulatory impact of estradiol on blood flow, its dilating, antithrombotic and anti-inflammatory effects are emphasised [8, 39]. Oestrogens reduce the tone of the smooth muscles of blood vessel walls, increase the production of endothelial nitric oxide, and have a stabilising effect on the blood-brain barrier [8]. The neuroprotective activity of endogenous oestrogens expires after menopause, and the importance of hormone replacement therapy for the incidence of stroke is unknown [40]. Although that many studies show a beneficial effect of endogenous estrogen on the vasculature; there are a few studies with the contrary results. Pappa at al. identified an independent association of endogenous estradiol levels with stroke severity and short-term mortality and outcome [41]. In recent years, attention is drawn to estrogen in the context of its proinflammatory role and its interaction with aging [42].

Limitations: This study has some limitations: the lack of analysis of smoking, alcohol consumption and oral contraceptive as risk factors for stroke.

The results of the presented study allow us to draw the following conclusions:

- Cardiogenic stroke is more common in women.

- Women exhibit a higher level of post-stroke disability, which results in more frequent use of residential care.

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