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Profile of risk factors for stroke: sex- and age-related differences

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Abstract

The objective of the study was to compare the incidence of key risk factors of stroke in men and women with first-ever stroke.

Material and methods: The study included 511 patients (F/M 304/207 aged 32-100 years with stroke. The incidence of the following diseases was analyzed: arterial hypertension, lipid disorders, coronary artery disease, atrial fibrillation, diabetes mellitus, carotid and/or cerebral artery stenosis and age of the occurrence of stroke.

Results: The age at which first-ever stroke occurred was higher in women ($p<0.001$). Atrial fibrillation occurred significantly more frequently in women in comparison with men , particular among patients >55 years old. Among patients ≤ age of 55, men suffered significantly more often from arterial hypertension, lipid disorders , coronary artery disease and diabetes . Among patients > 55, lipid disorders and diabetes occurred significantly more frequently in women . Age had 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). Among men, there was a higher proportion of patients with carotid/cerebral artery stenosis (p=0,0065) and among women; there were also more patients with cardiogenic stroke (p=0,0014).

Conclusions:

There are sex-dependent differences in the incidence of key risk factors of stroke.
Women more frequently suffer from cardiogenic stroke and men more often from stroke associated with artery diseases.
The lower incidence of cardiovascular system diseases and metabolic disorders in young women can be the reason for the older age at which first-ever stroke occurs.

Introduction

Stroke is a disease with heterogeneous aetiology. Epidemiological studies have shown that there are sex differences in the distribution of traditional risk factors of stroke, its course and long-term effects.[1] Classification systems, such as TOAST and ASCO, help to categorize the causes of stroke, knowing what causes stroke is vitally important for planning secondary prevention.[2, 3] Women are more often found to have cardiogenic stroke; men more often suffer from thromboembolic stroke associated with atherosclerosis in large arteries.[4, 5] A different profile of modifiable risk factors of stroke underlies stroke prevalence rates, its course and post-stroke disability. These elements differ in both men and women. Determining the significance of each risk factor of stroke is of great value for both the choice of treatment and its prognosis. This is because the interaction between certain risk factors of stroke has an impact not only on the occurrence of cerebral ischaemia, but also on the results of the treatment applied. In all probability, the higher effectiveness of thrombolysis in women is associated with the presence of fibrin-rich cardiogenic emboli as well as higher endogenous fibrinolytic activity.[6, 7, 8] The objective of the study was to compare the incidence of key risk factors of stroke in men and women with first-ever stroke.

Material and methods

The prospective study included 511 patients (304 women and 207 men) aged 71.1 years (median: 72 years, min. 32 years, max. 100 years, SD = 11.49 years, Q25% = 63 years, Q75% = 79 years), who were hospitalized due to their first stroke in 2011 at the Stroke Unit of Department of Neurology . There were 304 women and 207 men in the studied population. The occurrence of selected diseases and established risk factors of stroke such as age, arterial hypertension, lipid disorders, coronary artery disease (CAD), atrial fibrillation (AF), diabetes mellitus (DM) and carotid and/or cerebral arteries atherosclerotic change was analyzed. 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. Duplex Doppler examination of the carotid and cerebral arteries were performed in order to assess blood flow parameters. The presence of atherosclerotic plaque and morphology was examined. The NASCET criteria were used to assess the degree of arterial stenosis. Stenosis > 50% of cerebral arteries and > 70% stenosis of carotid arteries was considered haemodynamically significant. All patients underwent daily glycaemic profile tests, and tests to examine total cholesterol concentrations, HDL, LDL and triglyceride levels. A-S-C-O scale was used to assess the main causes of stroke.[3] 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. The analyses were carried out with respect to the group of men and women, and then after dividing them into two age groups: 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 that two qualitative characteristics are independent. Multiple logistic regression was performed in order to assess the impact of sex and age (≤ and > 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.

P-value < 0.05 ($p < 0.05$) was adopted as the statistically significant difference between the two samples.

Results

The age at which stroke occurred for the first time was higher in women than in men (the average age was 72.76 vs. 68.65, respectively). The difference was statistically significant ($p < 0.001$).

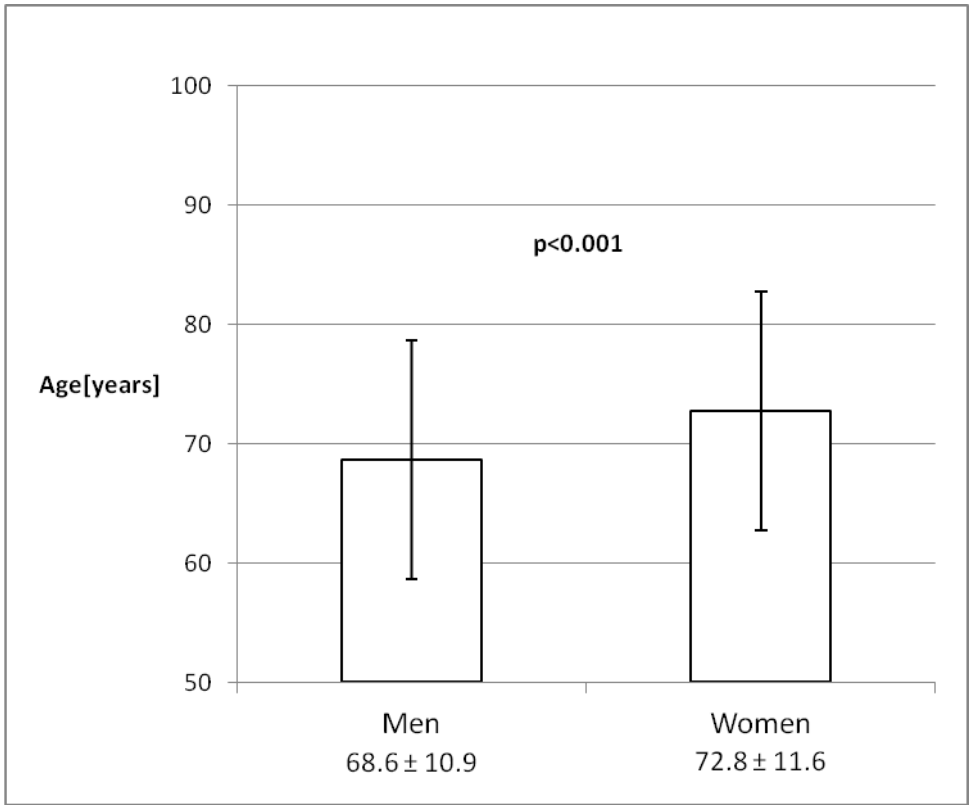

Figure 1. Comparison of the age of first-ever stroke occurence in men and women.

No statistically significant sex differences in the occurrence of arterial hypertension were observed (p = 0.506). After dividing the subjects into two age groups (under and over 55), it was found that, in patients under 55, it occurs significantly more often in men (p = 0.038).

No statistically significant sex differences in the incidence of lipid disorders were observed (p = 0.273). It turned out, however, that in the under-55 group, they occurred significantly more often in men (p = 0.004), and in the older group significantly more often in women (p = 0.043). No significant sex differences were found in the incidence of CAD (p = 0.196), but in the group of patients aged 55 years and younger, the condition occurred significantly more often in men (p= 0.036). AF occurred significantly more frequently in women in comparison with men (p = 0.0007), particular in the over-55 group (p= <0.001). Among stroke patients aged 55 years and younger, DM was found to occur significantly more often among in men (p = 0.018), while in the older group, it was more common in women (p = 0.024). When the subjects were not divided into age groups, no statistically significant differences in the occurrence of this disease were observed (p = 0.076). 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).

According to A-S-C-O among women, there is a considerably higher proportion of patients with cardiogenic stroke than among men (respectively, 34.9% vs. 21.7% p=0,0014). Among men, there is a considerably larger proportion of patients with common or internal carotid artery stenosis in comparison with women (20.3% versus 11.5%, p=0,0065) as well as those exhibiting key causes of stroke other than vascular or cardiogenic (27.1% versus 21.7%, p=0,1643). Sex was important for the 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).

Tab. 1. Comparison of the prevalence of selected risk factors for stroke in men and women.

Parameter	F, n= 304 n(%)	M, n= 207 n(%)	*p*
AH	273(89.80)	182(87.92)	0.506
CAD	152(50.00)	91(44.17)	0.196
LD	156(46.38)	96(51.32)	0.273
DM	137(45.07)	77(37.20)	0.076
AF	101(33.22)	41(19.81)	<0.001

M- male, F- female, AH- arterial hypertension, CAD- coronary artery disease, LD- lipid disorders, DM- diabetes mellitus, AF- atrial fibrillation

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

Parameter	Age ≤ 55			Age > 55		
	M, n= 27 n(%)	F, n= 22 n(%)	*p*	M, n= 180 n(%)	F, n= 282 n(%)	*p*
AH	23 (85.19)	13 (59.09)	0.038	159 (88.33)	260 (92.19)	0.167
CAD	9 (33.33)	2 (9.09)	0.036	150 (88.33)	82 (29.07)	0.122
LD	17 (62.96)	5 (22.73)	0.004	79 (43.89)	151(53.55)	0.043
DM	10 (37.04)	2 (9.09)	0.018	67 (37.22)	135 (47.87)	0.024
AF	4 (14.81)	2 (9.09)	0.538	37 (20.55)	99 (35.10)	<0.001

M- male, F- female, AH- arterial hypertension, CAD- coronary artery disease, LD- lipid disorders, DM- diabetes mellitus, AF- atrial fibrillation

Discussion

The results of epidemiological studies suggest that there are differences between men and women in the incidence of stroke risk factors, aetiology and the course of stroke.[4, 9, 10, 11, 12]

The male sex is associated with a higher incidence of conditions and diseases recognized as risk factors of stroke.[13] Men significantly more often obtain worse Deyo-Charlson index prognostic scores, though the level of post-stroke disability is lower in them.[1] Knowledge related to the differences in the distribution of key risk factors of stroke in men and women is significant for the choice of prevention strategy and the treatment of the acute phase of the disease which can improve long-term prognosis with respect to social functioning after stroke. In our study, women suffered first-ever stroke at an older age in comparison with men. Similar observations were published by other authors as well.[9, 13, 15, 16]

It has been shown that the first-ever stroke occurs 4.3-6 years later in women than in men.[17, 18]

On the other hand, a study by Fukuda et al. (2009) demonstrated an older age at which stroke occurred in men (65.8+/-13.9 vs. 64.1+/-12.0; $p < 0.05$).[1] The discrepancies can result from different inclusion criteria used in the studies, such as whether the authors took into consideration such factors as transient ischaemic attacks and reversible ischaemic neurological deficits or if they excluded them. According to population data, the average age at which stroke occurs for the first time is increasing both in women and men.[19, 20, 21] Over the last 3 decades, a decrease in the incidence of stroke has been observed, which is more pronounced in the male population.[19, 20, 21] There is also data available that does not indicate

any changes in trends regarding the relationship between sex and the age at which stroke occurs for the first time.[17] Analyzing differences between sexes with respect to the prevalence of stroke, the protective impact of oestrogens on cerebral circulation is stressed, though divergent results have been obtained regarding this observation.[22, 23] It is believed that the classic risk factors are less atherogenic in the presence of oestrogens in the period before menopause. The beneficial effects of their action end in the 5th-6th decades of life, and hormone replacement therapy does not reduce the incidence of stroke.[22, 24]

The neuroprotective action of endogenous oestrogens can explain the later development of stroke in women in comparison with men. The most important risk factor of stroke is arterial hypertension. It is found in most patients with stroke.[25] In our study, we observed a higher incidence of arterial hypertension in men aged 55 or younger; however, across the entire analyzed group of patients, without taking age groups into account, the disease was insignificantly more often observed in women. The available study results regarding the epidemiology of arterial hypertension suggest that it occurs more frequently in women.[1, 9, 13, 16, 26]

Studies by Giround et al. (1991) as well as by Hays and Taler (1998) did not demonstrate any gender differences in the incidence of arterial hypertension among patients with stroke.[27, 28] The impact of arterial hypertension manifests itself as disturbances of the regulatory mechanisms of cerebral circulation. These disturbances result from structural changes (hypertrophic and eutrophic remodeling) in the walls of cerebral arteries and arterioles, which lead to a shift in autoregulation towards higher blood pressure. The use of antihypertensive medications in young individuals usually leads to the normalization of the limits of cerebral flow autoregulation. This effect is more difficult to obtain in elderly patients. Though lipid disorders are a recognized risk factor for CAD (Prospective Studies Collaboration, 2007), their influence on the occurrence of stroke has not been conclusively established.[29] The risk of another coronary event or stroke decreased in individuals with a history of myocardial infarction who received statins. This effect was particularly visible in men, in whom the risk declined by 24% (in comparison with the 11% reduction found in women).[30]

In our study, in the group of patients aged 55 and younger, lipid disorders occurred significantly more frequently in men; in the older age group, they were more commonly found in women. The results of epidemiological studies suggest that lipid disorders occur more commonly in men.[5, 16] It was also shown that there is a cause and effect relationship between lipid metabolism disorders and the progression of atherosclerotic lesions in carotid arteries. Concomitant nicotine addiction in men is also significant here.[5] According to the results of the SPARCL study, statins effectively reduce the risk of stroke and other cardiovascular events both in men and women with a recent cerebral infarction or transient ischaemic attack.[31] According to a study by Smith et al. and others, women use statins more seldom.[15, 16] 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%.[32,33,34] AF occurs significantly more frequently in women with stroke, which is confirmed by the results of the presented study and a number of previously published ones.[4, 9, 10, 35, 36, 37] AF is the cause of cardiogenic embolism resulting in cerebral ischaemia, which constitutes 90% of the complications of this form of cardiac dysrhythmia. Both men and women with AF suffered from stroke significantly more often in comparison with individuals without this arrhythmia; however, in women, AF is associated with > 4 times higher risk of stroke in comparison with men.[37] It is believed that all types of AF (paroxysmal, persistent, chronic) are associated with a similar risk of stroke. Using the ASCO stroke classification system in our study, we found a significantly higher incidence of cardiogenic stroke in women, which undoubtedly was associated with the incidence of atrial

fibrillation. Cardioembolic strokes usually have a severe course and worse prognosis. The presence of AF in women is associated with a significantly higher cardiac mortality.[37] As studies indicate, women use aspirin and oral anticoagulant therapy (OAT) more rarely, which may be a cause of exposure to cerebral ischaemia independently of the risk factor profile.[15, 16] On the other hand, the results of a study by Humphries et al. (2001) showed a 3-times higher risk of iatrogenic bleeding after OAT in women in comparison with men.[38] Age, atrial fibrillation and arterial hypertension are important risk factors for both stroke and CAD, the difference being that they show a stronger correlation with stroke.[39] In the presented study, CAD was observed more often in men under the age of 55 than in women from the same age group. Helroy-Leduc et al., like other authors, also demonstrated the higher incidence of CAD in men with stroke in comparison with women (18.1% vs. 15.3%; $p < 0.001$).[9, 16] In recent years, the prognostic value of resting heart rate for the occurrence of myocardial infarction and stroke in individuals with CAD exhibiting a certain dependence on sex has been emphasized.[40] The role of the sympathetic nervous system is suggested. Diabetes mellitus is an independent risk factor for cardiovascular diseases as well as in patients with stroke, it is an independent risk factor for complications during hospitalization.[41] In our study, in the group of patients with stroke, aged 55 years and younger, DM was found more often in men, whereas in individuals over 55, it was more common in women. In other studies, results indicating a higher incidence of DM in men were also obtained.[9, 16, 42] There are also reports suggesting that DM occurs more frequently in women or that there is no sex dependence.[1, 43] In a study of the Danish population, it was found that type 2 diabetes doubles the risk of stroke in men, but its impact is significantly stronger in women.[43] DM is associated with a 3.2-fold increase in the risk of cerebral ischaemia due to cerebrovascular reactivity impairment secondary to damage to small arteries.[44] The consequences of diabetes are negatively affected by the profile of diseases accompanying it, these are independent risk factors for stroke and are part of the metabolic syndrome. Women use hypoglycaemic treatment less often.[16] The impact of sex on the incidence, course and outcome of stroke is analyzed with respect to the hormone profile, especially with regards to steroid hormones. A hypothesis concerning the role of oestrogen was proposed on the basis of the results of experimental cerebral ischaemia in rodents. 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 ischaemia.[45, 46] The regulatory impact of estradiol on cerebral blood flow and its dilating effects are emphasized.[47] Oestrogens also exhibit anti-inflammatory action.[48] Exposure to ovarian oestrogens seems to have a beneficial influence on cerebral circulation and a protective one regarding cardiogenic stroke. The female hormone profile probably has a neuroprotective effect, which manifests itself in the later occurrence of first-ever stroke. The neuroprotective effect of endogenous oestrogens ends after menopause.[17]

The results of the present and previously published studies indicate that the female sex is significantly more often associated with cardiogenic stroke (category “C” in A-S-C-O) and the male sex with thromboembolic stroke secondary to atherosclerosis of carotid and/or cerebral arteries (category “A” in A-S-C-O). Cerebral embolism, generated from a thrombus in the left atrium, is the cause of ischaemia of the brain in patients with atrial fibrillation. Due to the usually large size of the embolic material, the trunk of the large artery is closed, which results in a large area of ischaemia causing a significant neurological deficit. The incidence of large carotid artery disease is more common in men than women.[49,50] In the present study, we also observed a higher incidence of carotid artery stenosis and/or cerebral vascular disease among men. Large artery stenosis is more commonly diagnosed among Caucasians than the representatives of the black race. Arterio-arterial embolism and haemodynamic failure

underlie the pathomechanism of cerebral stroke in patients with haemodynamically significant arterial stenosis.

The influence of race on the occurrence of risk factors, and the mechanism of cerebral stroke is also meaningful.

The group of patients participating in the presented study was uniform, and it represents the Caucasian race. At all ages, blacks are at a considerably higher risk of incident stroke compared with whites, although the effect is most marked in younger age groups. This is most likely due to blacks having a greater burden of stroke risk factors rather than there being any substantial race differences in the associations between risk factors and stroke outcomes.[51]

There is general agreement that both the aetiology and pathomechanism of stroke differ depending on age and gender.[52,53,54]

Understanding sex- and age differences can be helpful in choosing a management strategy both at the stage of controlling key risk factors of cerebral ischaemia and at the stage of its treatment.

Limitations:

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

Conclusions

There are sex-dependent differences in the incidence of risk factors of stroke. Women more

frequently suffer from cardiogenic stroke and men more often from stroke associated with artery diseases.

The lower incidence of cardiovascular system diseases and metabolic disorders in young women can be the reason for the older age at which first-ever stroke occurs.

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