GENDER DISTRIBUTION OF RISK FACTORS IN ISCHEMIC STROKE IN HOSPITAL OF PSYCHIATRY AND NEUROLOGY FROM BRAŞOV

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Abstract: *Some age-adjusted statistics considers that the distribution of risk factors for stroke differs between men and women. The aim of this study is to assess the gender distribution of risk factors among patients with acute IS. In this purpose we have conducted a retrospective study which included 437 patients with ischemic stroke (233 men and 204 women) admitted to Hospital of Psychiatry and Neurology from Braşov from April 2013 till March 2014. Most of demographic and clinical characteristics differed by sex. We found that women were more likely to have a history of atrial fibrillation, excess weight or hypercholesterolemia, while men were more likely to have a history of hypertension, hypertriglyceridemia and disturbances of carbohydrate metabolism, and were more likely to drink and smoke.*

Key words: *ischemic stroke, atrial fibrillation, diabetes mellitus, dyslipidemia, smoking.*

1. Introduction

Ischemic stroke (IS) is a disease more prevalent in developed countries. While IS mortality rate is declining in western countries, worldwide it is observed an increasing along with the level of socioeconomic development. In particular, IS mortality rates in Eastern Europe have been increasing, such that now the highest rates are found in countries such as Bulgaria, Romania, and Hungary [30]. In Romania stroke is the second cause of death among women and the third among men, and the main cause of disability for adults over 40 years [27, 30]. As the proportion of elderly people in the population increases, the number with IS may be expected to increase. Some age-adjusted statistics considers that IS mortality rate that is higher in males than females, but women would have a higher IS mortality rate [29]. The aim of this study is to assess the gender distribution of risk factors among patients with acute IS.

2. Patients and methods

In this purpose we have conducted a retrospective study which included 437 patients with acute IS (233 men and 204 women; sex ratio M/F 1.142) admitted to Hospital of Psychiatry and Neurology from Braşov from April 2013 till March 2014.

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In every patient IS was confirmed by computed tomography scan. In cases where it was possible, Doppler ultrasound of carotid arteries and echocardiography were performed. For etiological classification of IS the Trial of Org 10172 in Acute Stroke Treatment (TOAST) Classification system was applied [1]. The topographic subtype of IS in Oxfordshire Community Stroke Project Classification (OCSP) (total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar circulation syndrome (LACS), and posterior circulation syndrome (POCS)) was aplied [2]. Due to insufficient data collection (retrospective study), the National Institutes of Health Stroke Scale (NIHSS) score could not be applied to assess the severity of IS, instead being used modified Rankin scale (mRS) [23, 24] to assess the degree of disability on admission and discharge from hospital. We assessed gender differences in the distribution of the known stroke risk factors (age, environmental factors, current smoking, alcohol abuse, atrial fibrillation (AF), hypertension, excess weight, dyslipidemia, disturbances of carbohydrate metabolism), stated prior to stroke.

Blood sampling was performed after overnight fasting for determination of serum triglycerides, total cholesterol, and fasting plasma glucose. Oral glucose tolerance test and determination of glycated hemoglobin A1c were additionally performed in cases of abnormal levels of fasting blood glucose. Body mass index and waist circumference were calculated in each patient. Diagnosis of obesity was made in patients with BMI ≥ 30 kg/m^2. Hypertension was defined as values ≥ 140 mmHg systolic blood pressure (SBP) and/or ≥ 90 mmHg diastolic blood pressure (DBP), or documented history of hypertension when the blood pressure values are normal in case the patient undergoing an antihypertensive treatment [16]. The diagnostic criteria for diabetes mellitus (DM) used in this study were: a fasting plasma glucose level of 126 mg/dl or higher, or a 2-hour plasma glucose level of 200 mg/dl or higher during a 75 g oral glucose tolerance test, or a random plasma glucose of 200 mg/dl or glycated hemoglobin A1C $\geq 6.5\%$ [28]. The data were collected from the clinical observation sheets of the hospital.

Comparisons between male and female patients were made using chi-square analysis for dichotomous variables or Pearson's chi-square test for categorical variables. Continuous variables were tested using Student's t-test. The level of significance was set at $p < 0.05$.

3. Results

Most of demographic and clinical characteristics in our population differed by gender. The mean age of female patients was 2.77 years higher than in male patients (mean age 72.15 and 69.38 years, respectively) (p=0.0149) (table 1). The prevalence of IS according to age had a bimodal trend in our population. While up to age of 70 years the prevalence of IS was higher in men, after the age of 70 years it was higher in women (Fig. 1).
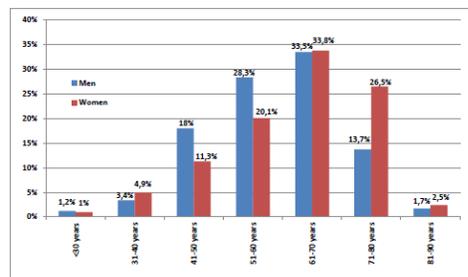

Fig. 1. *Distribution by age and sex of ischemic stroke*

The majority of both male and female patients were from urban area (80.57% and

78.87%, respectively). Men were more likely to smoke, abuse alcohol, or have a history of ischemic stroke compared to women (Table 1). AF was more common among women compared to men (30.40% vs. 25.32%) (OR 1.29; 95% CI 0.84-1.96). Hypertension occurred more frequently in males than females (87.12% and 86.27%, respectively) (OR 1.07, 95% CI 0.62-1.87), but in contrast, the mean values of SBP and DBP measured at the time of admission were higher in women than in men but the difference was not statistically significant (Table 1). Regardless of the degree of excess weight it was higher in women (OR 1.1, 95% CI 0.67-1.81) (Table 1). While hypercholesterolemia was more frequently noted in women (37.25% vs. 33.90%) (p=0.0201), hypertriglyceridemia was more common among men (24.89% vs. 18.62%) (p=0.0009). The prevalence of disturbances of carbohydrate metabolism were higher in men than in women (41.20% and 39.71%, respectively; OR 1.06; 95% CI 0.72-1.56), in most cases being recorded type 2 non insulin requiring DM (22.75%. and 20.59%, respectively).

Table 1

Demographic and clinical characteristics of ischemic stroke patients (n=437)

Characteristics of ischemic stroke patients	Male		Female		P value
	n	%	n	%	
Total	233	53.32%	204	46.68%	-
Mean age (±SD)	69.38 (63.36-75.4)		72.15 (60.14-84.16)		0.0149
Environment					
Rural	34	19.43%	30	21.12%	0.0112
Urban	141	80.57%	112	78.87%	
Current smoker	55	23.60%	20	9.80%	<0.001
Alcohol abuse	34	14.60%	6	2.94%	<0.001
Hypertension	203	87.12%	176	86.27%	0.0385
Grade 1	14	6.0%	10	4.90%	0.0281
Grade 2	83	35.62%	76	37.25%	0.0354
Grade 3	106	45.49%	90	44.11%	0.0375
SBP mean values (±SD) (mm Hg)	153.76 (128.73-178.79)		154.8 (124.99-184.61)		0.7038
DBP mean values (±SD) (mm Hg)	84.35 (74.08-94.62)		85.82 (72.08-99.56)		0.2249
Atrial fibrillation	59	25.32%	62	30.40%	0.0067
Excess weight					
Overweight	4	1.72%	4	1.96%	0.0403
Obesity class I	19	8.15%	20	9.8%	0.0262
Obesity class II	7	3.00%	12	5.88%	0.0044
Obesity class III	1	0.43%	1	0.49%	0.0418
Hypercholesterolemia	79	33.90%	76	37.25%	0.0201
Hypertriglyceridemia	58	24.89%	38	18.62%	0.0009
Disturbances of carbohydrate metabolism	96	41.20%	81	39.71%	0.0365
Impaired Glucose Tolerance	28	12.01%	27	13.23%	0.0346
Type 2 Non Insulin Requiring Diabetes Mellitus	53	22.75%	42	20.59%	0.0271
Type 2 Insulin Requiring Diabetes Mellitus	15	6.43%	12	5.88%	0.0387
History of ischemic stroke	76	32.62%	56	27.45%	0.0055

SD – standard deviation; SBP – systolic blood pressure; DBP – diastolic blood pressure

In terms of etiology of IS, women predominantly had cardioembolic IS (29.41% in women vs. 24.89% in men; p=0.0094) due to the higher prevalence of AF, while in men prevailed IS secondary to large-artery atherosclerosis (49.35% in men vs. 47.55% in women; p=0.0345) (table 2), IS secondary to small-vessel occlusion (6.4% vs. 3.92%; p=0.0033) and IS of other determined etiology (3.43% vs. 2.45%; p=0.0226) (table 2). In 15.88% of men and 16.67% of women the etiology of IS cannot be determined due to either an incomplete evaluation or the cause of a stroke cannot be determined with confidence in patients with two or more potential causes of IS.

The more prevalent clinical subtype of IS in both gender was PACS (55.79% in men vs. 60.78% in women; p=0.0086) (Table 3). Women underwent especially from PACS while TACS were more common in men explaining higher mortality among them.

Table 2

Etiological subtypes of ischemic stroke in TOAST classification

Etiological stroke subtype	Male		Female		P value
	n	%	n	%	
Large-artery atherosclerosis (embolus/thrombosis)	115	49.35%	97	47.55%	0.0345
Cardioembolism	58	24.89%	60	29.41%	0.0094
Small-vessel occlusion (lacune)	15	6.44%	8	3.92%	0.0034
Stroke of other determined etiology:	8	3.43%	5	2.45%	0.0226
Nonatherosclerotic vasculopathies	3	1.28%	3	1.47%	0.0408
Hypercoagulable states	3	1.28%	1	0.49%	0.0049
Hematologic disorders	2	0.85%	1	0.49%	0.0231
Stroke of undetermined etiology	37	15.88%	34	16.67%	0.0395

Table 3

Topographic subtypes of ischemic stroke in Oxfordshire Community Stroke Project Classification (OCSP)

Clinical syndrome	Male		Female		P value
	n	%	n	%	
Total anterior circulation syndrome	23	9.97%	18	8.82%	0.0342
Partial anterior circulation syndrome	130	55.79%	124	60.78%	0.0086
Posterior circulation syndrome	59	25.32%	52	25.49%	0.0422
Lacunar circulation syndrome	15	6.44%	8	3.92%	0.0034
Unclassified stroke	6	2.57%	2	0.98%	0.0008

There was no difference between the genders in terms of mean mRS at admission (3.93 vs. 3.75; p>0.5). 78.9% of men and 71.56% of women had a mRS ≥4 (Fig. 2). At discharge from the hospital (mean period of hospitalization of 14 days), the mean mRS had an improvement more evident in men than in women (3.11 vs. 3.19; p>0.5) (Fig. 3). The mortality rate by IS was significantly higher in men (11.58% vs. 9.8%) (p=0.0242) being noted especially among patients over age of 70 years.
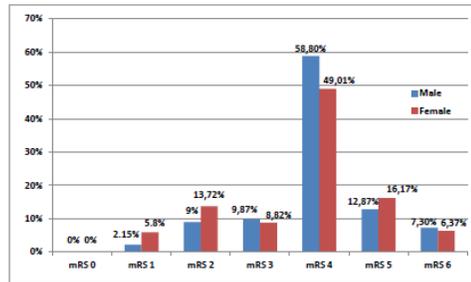
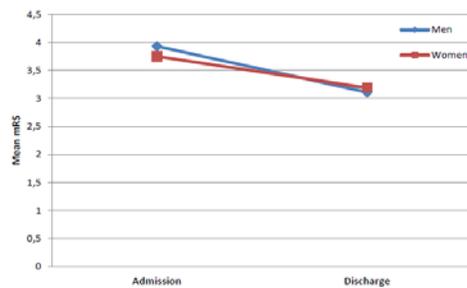Fig. 2. *The extent of disability after modified Rankin Scale (mRS)*

Fig.3. *The evolution of the mean modified Rankin Scale (mRS) from admission to discharge according to gender*

4. Discussion

The prevalence of IS in Romania has been shown to be higher than reported prevalence in the world [30]. This is due to the increased prevalence of modifiable risk factors for IS: hypertension, AF, history of coronary artery disease, obesity, DM, dyslipidemia, sedentary life, smoking, alcohol abuse. Various studies published over the past decades have clearly documented that men and women with IS have different characteristics [6], [10], [12], [15], [29].

The incidence of IS increases significantly with age in both men and women, but there are sex differences in the incidence by age subgroups. Women are, on average, older than men at stroke onset (72.15 vs. 69.38 years). Previous studies showed that IS risk almost is doubled for each successive decade after age of 55 [18]. In our study the incidence of IS was higher in men up to age 70, as after 70 years to be more frequently in women. Although women have a lower lifetime risk of IS than men, because women are over-represented in the older age groups, women had a higher risk of IS in this group of age due to the presence of risk factors that increase with age, such as AF and hypertension, but there are also sex differences in cardiovascular risk profiles throughout the decades of mid-life. We found that women were more likely to have a history of AF, excess weight or hypercholesterolemia, while men were more likely to have a history of hypertension, hypertriglyceridemia and disturbances of carbohydrate metabolism, and were more likely to drink and smoke.

Hypertension, the most powerful and modifiable risk factor of IS, was found in 87.12% of men and 86.27% of women, but female patients had higher mean SBP and mean DBP. These results underline the importance of programs prevention of hypertension, as demonstrated by a review of 17 randomized controlled trials in which the control of hypertension was followed by a decrease of 38% in the incidence of IS [4].

DM, recognized as the second most common risk factor for IS, was found in 27.91% of our patients. In a previous study conducted in Romania for a period of three years (2008-2010) the incidence of DM in patients with IS was 14.63% [18]. Conversely, the incidence of IS in patients with DM ranged from 16.64‰ to 27.15‰, compared to the general population where the incidence of IS in the same period was between 5.21‰ and 6.9‰ [3].

Our investigations found a higher prevalence of hypercholesterolemia in women and hypertriglyceridemia in men. Elevated cholesterol has typically been a

weak risk factor for all types of IS; it is also a notable risk factor for atherosclerotic disease of the carotid artery. In a meta-analysis, cholesterol levels of more than 5.7 mmol/L were associated with a relative risk of IS of 1.3 [19]. According to some authors, each increase of 1 mmol/L in total cholesterol is associated with a 25% greater risk of IS [26]. Combination of DM, hypertension and low high-density lipoprotein cholesterol was associated with an 11-fold increase in atherosclerotic disease in women, whereas men with this cluster of conditions had a fourfold increase in this outcome [13]. The use of HMG-CoA reductase inhibitors has been reported to produce about a 30% relative risk decreasing of IS [21]. In contrast, the use only of dietary or fibrates provides evidence that lowering cholesterol levels does not reduce the risk of IS [5].

Obesity has received increased attention as a possible risk factor for IS, but the data are inconsistent [8, 9]. The association of obesity was relatively low in our study, only 13.7% of cases. In a case-control study in Norway [8] subjects with BMI >29.24 had the highest risk of IS and those with BMI between 23.23 and 25.06 had the lowest risk. The atherogenic effect of obesity has been suggested as a pathophysiologic mechanism responsible for the increased risk of cerebrovascular disease in overweight people [11].

23.60% of men and 9.8% of women with IS were current smokers. The significance of current cigarette smoking for IS is demonstrated by the results of most studies [14, 22, 25]. The mechanisms by which cigarette smoking is thought to increase the probability of IS include increased fibrinogen levels [7], platelet adhesiveness [17], and reduced cerebral blood flow [20], due mainly to atheroma formation associated with smoking and higher blood viscosity [7] in chronic smokers.

AF is the most frequent persistent cardiac arrhythmia and a major risk factor for IS among older adults. Over 30% of all IS in our female patients and over 25% of male patients were associated with AF. Only 20% of patients with permanent AF were following an appropriate anticoagulant therapy. In spite of incontestable evidence in all age groups in favour of anticoagulant therapy for AF, many patients are reluctant to follow this therapy, a fact that was also shown in our study by high rate of cardioembolic IS.

Minimal gender differences were observed in topographic subtypes of IS within our patients. In general, men have been found to have more TACS explaining higher mortality rate among them [6]. We found no significant sex differences in degree of disability on admission or discharge from hospital, but men had a more evident improvement of mean disability grade compared to women. Assessing the degree of disability according to IS subtype was observed that lacunar strokes had milder deficits compared with other subtypes. Although mortality may not be higher in women, a series of studies have found that women who survive stroke have less favourable outcomes than men [6], [10], [15].

Our study has some limitations given that it took into account a population-based sample of patients admitted to hospital only for the period of one year. Another limitation was the impossibility to perform all investigations concerning risk and etiological factors of IS in all patients.

5. Conclusion

In conclusion, these differences in the risk factors distribution between men and women and suggested that gender may have effect on IS outcome and the preventive strategies should be different in the two sexes. Although some biological differences such as hormonal state and

longer lifespan may explain some differences, there is still much that is not understood. Controlling dyslipidemia and AF should be a priority in women, whereas lifestyle changes and controlling the hypertension are required in men. Gender is likely a marker for multiple medical, genetic, and socioeconomic factors that will require further study to elucidate.

Acknowledgement

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