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Source / Izvornik: **Archives of Psychiatry Research : An International Journal of Psychiatry and Related Sciences, 2023, 59, 13 - 20**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.20471/may.2023.59.01.02

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:862734

Original paper

Archives of Psychiatry Research 2023;59:13-20
DOI:10.20471/may.2023.59.01.02

Why She? A Retrospective Study on Sex Inequality Related to Subarachnoid Haemorrhage

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Abstract - Subarachnoid haemorrhage (SAH) is the only type of stroke with female predominance. We conducted a retrospective analysis of SAH patients throughout a decade and tried to establish any reason for such remarkable sex difference. We conducted a retrospective analysis of subarachnoid haemorrhages treated in Istria County between 2010 and 2021. Some of those patients were referred to a comprehensive stroke centre and we collected those data too. We also collected data regarding the outcome recorded at follow up exams of patients treated for SAH in that period. A total of 193 patients with subarachnoid haemorrhage were found in observed period. We found a lower incidence regarding general population but with a tendency to increase, compared with data from other studies. Among all SAH, 113 were female, which makes a Risk Ratio (RR) of 1.44. The highest RR in females was in aneurysmal subarachnoid haemorrhages, 2.06. We obtained a similar high RR of 2.03 in the case of female ruptured multiple intracranial aneurysms (IA), clearly with a worse outcome. Conversely, the RR in non-aneurysmal subarachnoid haemorrhages and perimesencephalic subarachnoid haemorrhages was lower in the case of female sex and amounted 0.67. We noticed similar sex inequality as shown in other studies, so we can also state that women are at higher risk of IA rupture then men. The reason has to be multifactorial. As found in this study, women have different predilection sites of IA rupture compared with men so we strongly believe that certain hemodynamic forces may lead to aneurysm growth and rupture. As we also confirmed IA rupture is age dependent more in women than in men. As shown in other studies, oestrogen level might be the reason for that. Future studies should further establish and prove these risk factors for IA aneurysm rupture and improve preventive measures.

Key words: aneurysm; subarachnoid haemorrhage; female; mesencephalon; risk factors

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Introduction

Within the wide spectrum of cerebrovascular diseases in female population, aneurysmal subarachnoid haemorrhage has the highest incidence [1-3]. The incidence of SAH in Europe is about 10 - 12 / 100.000 inhabitants. Croatian population has equal incidence of 10 / 100.000. Mortality in both sexes is around 26.5 % within the first month and additional 5.6 % till the end of the first year [4].

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Some cerebrovascular risk factors can increase the risk of formation but mostly increase the risk of growth and aneurysm rupture [5]. This risk is more pronounced in females [1]. Those are in order of importance: age, blood pressure, smoking and excessive alcohol consumption [5]. Regarding age, it was studied that oestrogen deficiency correlates with IA growth and rupture [2]. This correlates with the rise of female SAH in the fifties. One review concerning female risk factors for SAH found an increased risk of SAH among postmenopausal women compared with premenopausal women of the same age [6]. Reproductive factors play a role in aetiology of SAH [7]. Anatomical variants and hemodynamic stress, such as high blood pressure or strong wall shear stress, on ICA walls may participate to IA formation and growth [2]. Risk of IA formation and later rupture is multifactorial [3,8]. Familial factor may also increase the risk [1,9].

Subjects and Methods

We retrospectively identified all patients hospitalized due to subarachnoid haemorrhage in General Hospital Pula in the period between 2010. and 2021. Cases were further stratified by type of SAH (aneurysmal, perimesencephalic, other) and sex. Data obtained from medical records included previous history (where available), aneurysm location and number of aneurysms, temporal interval between symptom initiation and hospital admission, type of procedure to close ruptured aneurysm, complications, initial assessment scores: Glasgow coma score (GCS), Hunt Hess (HH) and modified Fisher score (mFisher), functional outcome measured as modified Rankin score.

We tried to establish which factors concerning medical history or treatment have impact on patient's clinical outcome. In order to analyse impact of these factors on outcome we used multivariate logistic regression analysis. Outcome was measured as independent variable with two categories: good, meaning modified Rankin scale (mRankin) 0 - 2, or poor outcome, mRankin scale 3-6. Categorical data, such as presence of infarction in male and female sex, was analysed through chi-square test. Data was analysed with the program Statistics version 14.0.015 (TIBCO Software inc). Statistical significance was set at p 0.05 or less, confidence interval was 95 %.

Results

First, we analysed the crude number of SAH and determined the incidence through the years. We did compare those numbers with the incidence in female population. The mean incidence in observed twelve-year period was 7.7 / 100 000 for general population and for female population 8.8 / 100 000. As you can see the incidence is about 20 % lower than in the region. Greater incidence in female population is well known by numerous studies

Table 1. Incidence of subarachnoid haemorrhage trough the 2010-2021 period

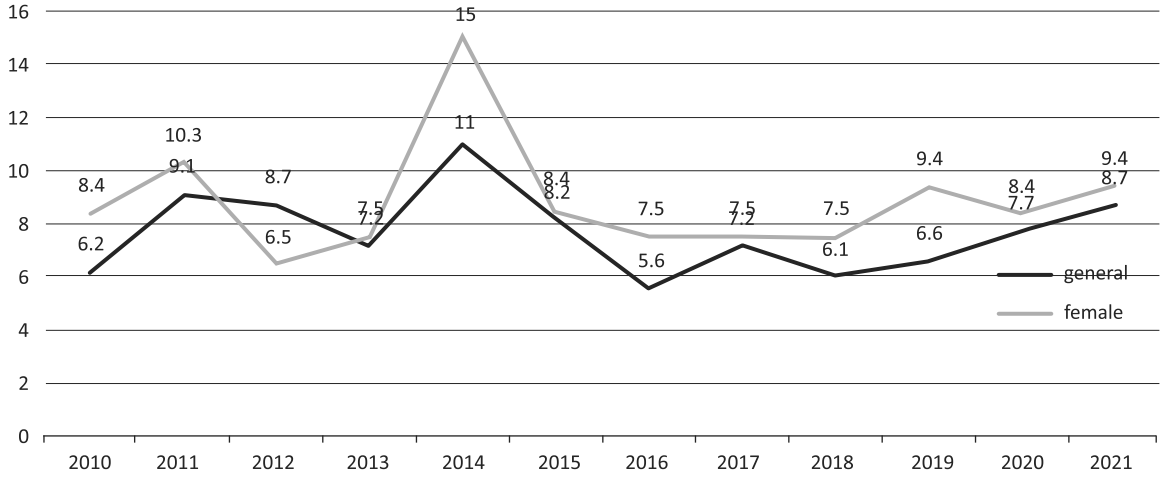
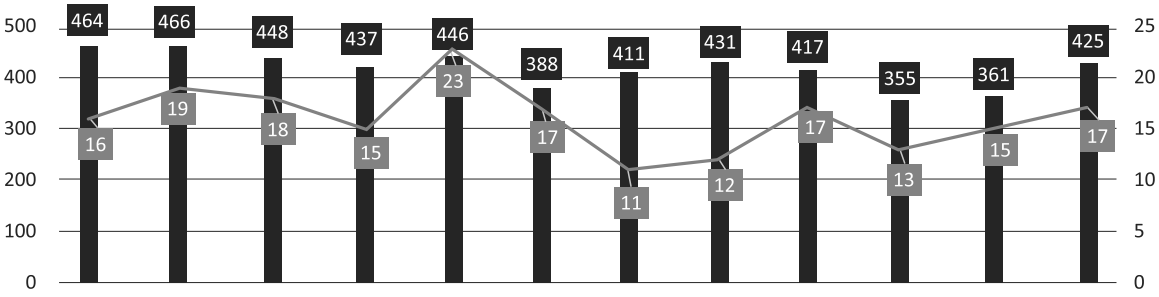


Table 2. Number of strokes trough the 2010-2021 period (upper line) and number of subarachnoid haemorrhage (SAH) (lower line)



[1,2,6-8]. Meanwhile, throughout the past decades the incidence in global population tends to decrease but in our County in the last years the incidence is rising [10]. The greatest incidence for men and women was in 2014 and we can't find any apparent reason (Table 1).

In general, comparing SAH with stroke we didn't find big differences, although there is a rising trend in incidence in both, through last years. The average percentage of SAH among all strokes is 4.2 %. This is slightly under the average of 5 - 6 % in the United States [11] (Table 2).

In those 12 years we had 193 patients with SAH. There were 131 (68 %) patients with ruptured aneurysmal subarachnoid haemorrhage. 41 (21 %) were non-perimesencephalic subarachnoid haemorrhages (nonPMSAH) and 21 (11 %) were perimesencephalic subarachnoid haemorrhage (PMSAH). Our analyses didn't prove an increasing number of non-aneurysmal subarachnoid haemorrhage (NASAH) as stated in some studies. Maybe this might be related with increased use of anticoagulation therapy [12]. In term of outcome aneurysmal SAH had a worst outcome compared with nonPM SAH. The best outcome had the PM SAH (Table 3).

Using multivariate logistic regression of two outcome categories, we examined the influence of initial clinical scales on the out-

Table 3. Numbers and percentage of subgroups of SAH, divided in two categories of outcome

aSAH	mRS	
51 (39 %)	0-2	
80 (61 %)	3-6	
PM SAH	mRS	nonPM SAH
19 (90,5 %)	0-2	22 (54 %)
2 (9.5 %)	3-6	19 (46 %)

aSAH: aneurysmal subarachnoid haemorrhage, PMSAH: perimesencephalic subarachnoid haemorrhage, nonPMSAH: non perimesencephalic subarachnoid haemorrhage

Table 4. Statistical significance of initial scales assessment to predict outcome

	Logistic regression	$\chi^{2''}$= 60.45 p < 0.001
Num.	Predictive variables	p
1	GCS	0.256
2	HH	0.017 (Female: 0.002)
3	mFISHER	0.179

Table 5. Number and percentage of an infarct after subarachnoid haemorrhage and the outcome

Outcome	Without infarct N. (%)	Infarct N. (%)	Hi-quadrat	p
0-2	77 (82.8)	16 (17.2)	14.1	0.001
3-6	58 (58)	42 (42)		

Table 6. Statistical significance some other variables predicting the outcome

	Logistic regression	$\chi^{2''}$= 36.328 p < 0.001
Num.	Predictive variables	p
1	Age	0.377
2	Aneurysm	0.434
3	Blood pressure	0.023
4	Type of treatment	<< 0.001

come. In our study only the Hunt Hess scale was statistically more significant in predicting the outcome (Table 4). We wanted to know if an infarct occurring during early stage of treatment, which is most likely related to vasospasm (DCI), can influence the outcome. More patients with brain ischemia had poor outcome. A brain infarct after SAH occurred in 30 % of patients with SAH (Table 5).

Further on, through multivariate logistic regression analysis we studied impact of arterial hypertension, age at admission, aneurysm size and treatment type on outcome. We found that arterial hypertension significantly influences outcome (regardless if it was noted for the first time on admission or previously treated). There were three treatment types: surgical, endovascular treatment and conservative. Type of treatment also had significant impact on outcome, with endovascular treatment being connected to better clinical outcome. Age and size of aneurysm didn't significantly predict the outcome (Table 6).

Now back to our main topic within those 193 patients with SAH. There were 80 (41 %) men and 113 (59 %) women. The average age was 58 years (18 - 87). Death rate was 28 % in the first year (Table 7). Please note the statistically relevant sex differences within subtypes of SAH. Women tend to have aneurysmatic SAH more often and rarely non aneurysmatic SAH compared to men.

Sex differences are noted with age too. Note the peak incidence around 50 - 55 years in women and again later on at the age of 80 (Table 8). The reason for the peak in elderly might be well explained within the risk factors for cerebrovascular disease and longevity [13]. Although we didn't prove a statistical significance between sex and outcome, we did find a difference where women had worse outcome compared to men. As we said the difference wasn't statistically relevant (Table 9). Following categories didn't show statistically significant sex related differences. There was no statistically significant difference by sex with regard

Table 7. Sex and different subarachnoid hemorrhage subtypes

Sex/ subtypes of SAH	aSAH N. (%)	NASAH N. (%)	PMSAH N. (%)	Hi- -quadrat	p
male	43 (53.8)	25 (31.2)	12 (15)	12.58	0.002
female	88 (77.9)	16 (14.2)	9 (7.9)		

Table 8. Age related differences - sex comparison

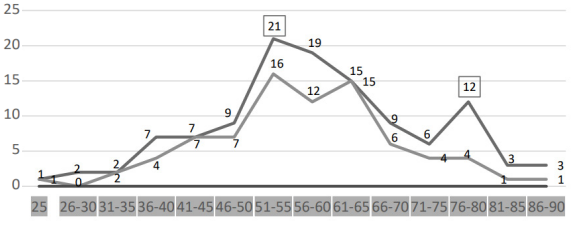


Table 9. Sex differences compared with outcome

Sex	mRS 0-2 N. (%)	mRS 3-6 N. (%)	Hi-quadrat	p
male	41 (51.2)	39 (48.3)	0.33	0.568
female	52 (46)	61 (54)		

Table 10. Sex differences compared with the type of treatment

Sex/type of treatment	Coil N. (%)	Clips N. (%)	Conservative N. (%)	Hi--quadrat	p
male	15 (18.8)	18 (22.5)	47 (58.7)	7.42	0.024
female	39 (34.5)	28 (24.8)	46 (40.1)		

to epileptic seizure (p 0.54), EVD placement (p 0.65), arterial hypertension (p 0.89), aneurysm size (p 0.19).

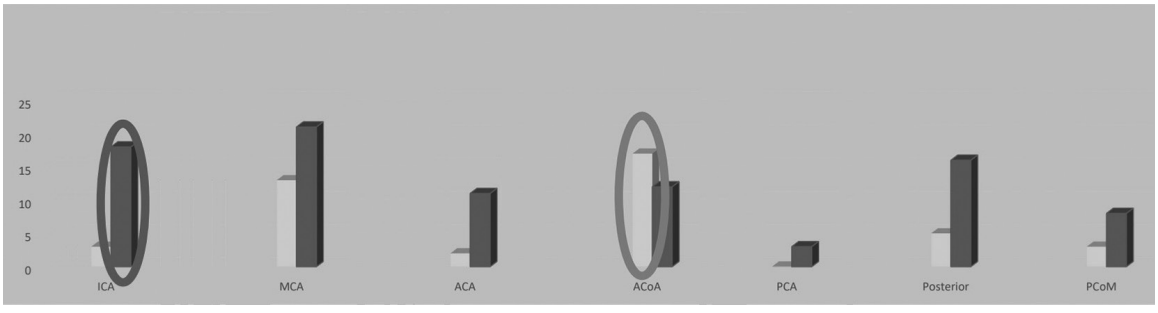
With regard to sex, there was a significant difference in the type of treatment. Women were more often treated surgically or by endovascular treatment then men (Table 10). There is a statistically significant sex difference regarding the number of aneurysms with female predominance. Women tend to have multiple aneurysms (Table 11).

We found differences even regarding the site of aneurysm between sex. The most frequent site of a ruptured aneurysm in women was the MCA, followed by ICA and then the posterior circulation. In male group the most frequent aneurysm was the ACom followed by the MCA. According to available data, this distribution is similar with other works [2] (Table 12). Finally, we would like to mention the migraine prevalence in our patients with SAH. Among 193 cases of SAH, we found 8

Table 11. Sex compared with multiple aneurysm

Sex/N. of aneurysm	N.0 (%)	N.1 (%)	N.2 (%)	N.3 (%)	N.4 (%)	N.5 (%)	N.6 (%)	Hi-quadrat	p
male	37 (46.2)	33 (41.2)	7 (8.8)	3 (3.8)	0 (0)	0 (0)	0 (0)	15.56	0.008
female	24 (21.2)	73 (64.6)	11 (9.7)	3 (2.7)	1 (0.9)	0 (0)	1 (0.9)		

Table 12. Sex compared with the site of aneurysm



patients having a history of migraine. The majority were women, 7:1. Seven of those had aneurysmal SAH and just one non aneurysmal subarachnoid haemorrhage. This data is concordant with findings in literature [14].

Discussion

The dilemma of a non-aneurysmal SAH is still controversial. We had a greater number of such patients compared to other reports. According to some data in up to 15 % of patients with spontaneous SAH initial vascular imaging wasn't able to identify the structural cause for the haemorrhage [15]. Please take in consideration also the variable MSCTA sensitivity for different aneurysm sizes [16]. We still cannot give an answer to question why women have more aSAH and worse outcome, and vice versa why men have more PM SAH. Progress has been made on three different topics: atherosclerosis, oestrogen deficiency and wall shear stress which were well presented by Fréneau and associates earlier this year [2]. As some studies stated, migraine prevalence is possibly increased in patients with unruptured intracranial aneurysm and is comparable in patient with TIA or stroke [14]. According to our results 4.1 % of our SAH patients had a history of migraine. It is possible that this number is even greater, as parts of previous medical history data for our population were missing. We think that patients with a history of migraine should be investigated for an intracranial aneurysm detection.

In our population we found an increasing number of cases of subarachnoid haemorrhage as well as the number of non-aneurysmal SAH. The best outcome was found in perimesencephalic SAH, as suspected, while patients with aneurysmal SAH had the worst outcome. The best outcome predictive tool at admission was the Hunt Hess scale. Other variables with significant influence on outcome were history of hypertension, the presence of brain infarct after SAH and the type of treatment the patient received.

When we analysed female sex in particular, we found that more women had SAH compared with men. Women more often had ruptured aneurysmal SAH. The outcome was age dependent, as older patients had worse outcome. A peak of incidence has been detected after the age of 50. In comparison with men, more than double female patients with SAH had multiple aneurysms and then a worse outcome. Number of women treated conservatively was lower than men.

Acknowledgements

None.

Conflict of interest

None to declare.

Funding Sources

None

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