RISK FACTORS AND MECHANISMS OF ISCHEMIC STROKE DEVELOPMENT IN WOMEN

(Literature review)

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ANNOTATION. Stroke is a cause of permanent disability. The disease can occur in people of any age. In women, stroke often occurs between the ages of 18 and 65. Various factors can provoke a stroke. Unlike men, members of the weaker sex are subject to more pronounced hormonal changes. Hormone imbalance is one of the predisposing conditions. Currently, cerebral stroke is one of the most serious medical and social problems in the world.

Keywords: Stroke, risk factors, women, cerebral circulation disorders

Introduction: Brain Circulatory Disorders (CCD) are at the top of the list of the most significant social problems in terms of prevalence. Annually, 15 million cases of stroke are registered in the world; in Russia this figure exceeds 450,000. Stroke is one of the main causes of patients' disability, regardless of age, gender, ethnicity and country of residence [1, 2].

It should be emphasized that high prevalence of arterial hypertension (AH) and major cardiovascular diseases, such as atherosclerosis (AS) and coronary heart disease (CHD), along with decreasing life expectancy of patients, lead to a constant increase in the total structure of cerebrovascular pathology of the specific weight of acute forms of stroke, primarily ischemic stroke [1]. Stroke is 1.25 times more common in men than in women [3-5]. However, due to women's longer life expectancy, the total number of women who die of stroke is higher [6,10]. Ischemic stroke develops 4 times more often in women and 5 times more often in men than hemorrhagic stroke, and the morbidity of men aged 75-80 years exceeds the

morbidity of women of the corresponding age by 500 cases per 100,000 population [11].

Stroke is the second leading cause of death in the population over 65 years of age, with 60% of all stroke deaths occurring in women (3.2 million deaths per year). In Europe and the USA, cardiovascular disease mortality in women is 1.5 times higher than cancer mortality. More than 500,000 women die from cardiovascular disease in the United States each year, which is approximately 1 death per minute [12].

By 2015, the socioeconomic burden of stroke increased by 22% in terms of mortality and by 31% in terms of potential life years lost due to premature death and disability (Disability-adjusted life year - DALY). According to recent data, 58% of all cases of stroke develop in patients under the age of 70 [12]. Currently, there is a large number of studies devoted to the study of the specifics of risk factors for stroke in men and women. However, contradictory literature data and lack of a unified view on the problem of gender-oriented approach to stroke prevention determine the relevance of the problem.

Gender is an uncorrelated risk factor for stroke. According to the definition of the World Health Organization (WHO), sex is a set of traits by which a specific division of individuals or cells is made, based on their morphological and physiological features and allowing the combination in the process of sexual reproduction of hereditary predispositions of parents in the descendants. In the literature, there is a terminological distinction between the concepts of "biological sex" and "gender," which in addition to biological identity is understood as a set of social and behavioral factors [13].

The most significant non-specific for gender risk factors for stroke development are: AH, heart disease, including atrial fibrillation, smoking, carbohydrate and lipid metabolism disorders, excessive alcohol consumption, excessive body weight, low physical activity and sedentary lifestyle, and emotional stress [14, 15]. However, given their reproductive status, women have a different frequency and significance of risk factors than men. The risk factors of IHD development that are more frequent in women than in men include: AH, atrial

fibrillation, diabetes mellitus, abdominal obesity, migraine with aura, emotional stress and depression. Exclusively for women are such factors as age at menarche, pregnancy, gestational diabetes mellitus, preeclampsia, changes in hormonal status, use of combined oral contraceptives and hormone replacement therapy [16, 17].

Arterial hypertension. Both systolic and diastolic blood pressure (BP) levels are closely associated with stroke development [18]. The risk of stroke in patients with BP over 160/95 mm Hg increases approximately 4-fold compared to those with normal BP (below 140/90 mm Hg), and at BP over 200/115 mm Hg. - by a factor of 10.

AH is the most important and correctable risk factor for the development of IAC in both men and women. However, the prevalence of AH differs depending on age and sex. For example, AH is more common in men than in women under the age of 60, while after 60 the prevalence of AH in women is higher than in men (66.5 and 63.1%, respectively).

The most frequent form of AH in women is isolated systolic A.G. High systolic BP and increased BP variability after the onset of menopause are the main causes of left ventricular hypertrophy, heart failure and stroke [1, 9]. According to the NHANES III study [20], the incidence of BP in women aged 55-56 years is 46-53% and 68% in those over 65 years.

According to the results of a survey of the Russian national representative sample standardized by age, the prevalence of AH in men is 39.2%, in women - 41.1% [2,11]. A screening study conducted among men 40-59 years showed that BP 160/95 mm Hg or higher was found in 30% of men 40-49 years and in 38% of men 50-59 years. At the same time, 65% of men with AH did not exceed 180/105 mm Hg and only 12% had 200/115 mm Hg or higher . Atrial fibrillation is found in a significant proportion of the population and is associated with about ½ of all strokes due to thromboembolism from different parts of the heart.

The risk of developing atrial fibrillation over the age of 55 years is 23.8% in men and 22.2% in women [2,3]. However, due to the longer life expectancy of women and the increasing number of cases of atrial fibrillation with age, the absolute number

of women with atrial fibrillation is higher than men [2,4]. The CHA2DS2-VASc scale considers "large" and "clinically significant" risk factors for stroke in patients with atrial fibrillation. The "big" factors include ischemic stroke, transient ischemic attacks, history of embolism, and age older than 75 years. Each "big" factor is scored at 2. All other risk factors (cardiovascular disease, age 65 to 74 years, and female gender) are classified as "clinically significant," and each is scored 1 [2,5].

Smoking increases the risk of stroke by 1.5-fold, and smoking cessation is accompanied by a decrease in this risk. After stopping smoking for 2-4 years, the risk of cardiovascular disease is reduced by half, but it remains elevated for another 10 years (according to some data, for 20 years) [6]. The prevalence of smoking is higher among men. However, with the same number of cigarettes, smoking has a greater negative effect on women's health [7]. Disorders of carbohydrate metabolism. Diabetes mellitus, which is a risk factor for ICD, increases the probability of ICD development 5-fold in women and 2-3-fold in men [9]. In addition, the adverse role of insulin resistance has been shown, which is observed when the response of insulin-sensitive organs and tissues (liver, muscle, adipose tissue) to insulin action at its sufficient concentration is reduced. Insulin resistance leads to decreased glucose uptake by tissues, resulting in hyperglycemia [3,10].

The prevalence of diabetes mellitus among stroke patients is 32.5% in women and 32.7% in men [3,11].

The so-called metabolic syndrome (MS) is often formed in carbohydrate metabolism disorders, which is characterized, along with hyperinsulinemia, by increased plasma triglyceride levels, decreased content of antiatherogenic high-density lipoproteins (HDL), AH and central obesity. In general, the syndrome of multiple metabolic disorders leads to accelerated development of atherosclerosis [3,12]. The incidence of MS increases progressively 6 years before the onset of menopause and for 6 years after the onset of menopause. The rate of this increase is independent of age and other risk factors. The menopausal increase in testosterone activity is the main hormonal factor associated with the development of M.S. The decrease in estrogen

levels is an insignificant risk factor for M.S. It is more likely that testosterone has a direct negative effect on the risk of cardiovascular complications [3,4].

Disorders of lipid metabolism. It is known that AS is a significant factor leading to the development of both myocardial infarction and ischemic stroke. Currently, great importance is given to the estimation of the ratio of separate fractions of lipoproteins: low-density lipoproteins (LDL) and HDL, lipoprotein (a) and triglycerides.

Lipid metabolism disorders differ in men and women. In the former, the main significance in atherogenesis is an increased level of LDL, in the latter it is more important to reduce HDL. Cholesterol (cholesterol) levels in women at a young age are lower than in men of the same age. During menopause, the levels of cholesterol and LDL increase by 10 and 14%, respectively [5].

Alcohol. Excessive alcohol consumption (more than 60 g of ethanol per day) increases the risk of stroke [3, 6]. Adverse effects of large doses of alcohol are associated with the development and severe course of AH, cardiomyopathy, heart rhythm disturbances. In women, the risk of IHD increases at a 2-fold lower alcohol dose than in men.

Excessive body weight (body mass index more than 25 kg/m2) is associated with increased BP, carbohydrate and lipid metabolism disorders. Central obesity with abdominal fat deposition is particularly unfavorable in the prognosis of cardiovascular disease.

Central obesity is defined by the ratio of waist circumference to hip circumference. Central obesity is said when the ratio is more than 0.85 in women and more than 1.0 in men. The best method to assess body fat is to have an X-ray or MRI scan of the abdomen.

Over the past 25 years, the number of overweight people in the European Union has increased 3-fold. According to WHO, the prevalence of obesity in Russia is 46.5% in men and 51.7% in women. In central (abdominal) obesity, the incidence of stroke is higher in women [3,7].

Hormonal status. Changing hormonal status is the most important factor influencing the risk of stroke in men and women.

Hormonal status in women. Early appearance of the first menstruation (menarche) in girls under the age of 12 years increases the risk of cardiovascular diseases and stroke . According to the British study "One Million Women", a U-shaped association between age of menarche and risk of stroke was revealed. The risk of stroke in women with menarche before the age of 10 years was higher compared to women with menarche at the age of 13 years. However, women who had menarche at age 17 years or older also had a higher risk of stroke compared with women who had menarche at age 13 years [3,9].

Women of childbearing age, unlike men, have a low risk of stroke. However, after the onset of menopause, the probability of developing IAC significantly increases [4,11]. The results of clinical studies have established that the positive effect of estrogens in women consists in the increase of cardiac output, HDL cholesterol, blood fibrinolytic potential, reduction of total peripheral vascular resistance, reduction of thromboxane A2 formation, activity of renin-angiotensin-aldosterone blood system components, LDL oxidation .

Pregnancy is a peculiar factor increasing the risk of ICH development. According to different authors, the incidence of stroke is 30 per 100,000 pregnant women. An increase in estrogen levels during pregnancy leads to an adaptive increase in platelet activity, an increase in clotting factors, a decrease in fibrinolysis and an increase in endothelial procoagulant activity.

The development of pregnancy complications (AH, diabetes mellitus, induced termination of pregnancy, habitual pregnancy failure, preeclampsia, preterm birth, and low, not corresponding to gestational age fetal weight at birth) indicates the presence of cardiovascular disease, metabolic disorders, hemostasis activation and endothelial dysfunction in women [4,15]. Preeclampsia and eclampsia are considered the most significant risk factors for both ischemic and hemorrhagic stroke, occurring in 24-48% of women in late pregnancy. In recent years, the need and safety of adequate antihypertensive therapy for AH during pregnancy have been substantiated.

In obesity, late age of primiparous women, multiple pregnancies as a result of in vitro fertilization, IAH develops in 40% of cases, and in 10-20 years the risk of AH increases by 3-4 times, the risk of stroke, CHD, venous thrombosis and pulmonary embolism and pulmonary arteries by 2 times [48]. A high risk of ischemic stroke during pregnancy and delivery is noted 2 days before delivery, on day 1 and within 6 weeks after delivery.The oral contraceptives used in the 1970s contained more than 50 mcg of estrogen, and their use was associated with an increased risk of stroke, especially in women with AH and smokers. Combination contraceptives containing low doses of estrogen (less than 30 mcg) currently in use are not risk factors for stroke, but this applies only to healthy women under the age of 35 who do not smoke and have normal BP [5,10]. Migraine with aura at any age and migraine without aura at the age over 35 years increase the risk of stroke with hormonal contraception by 7-10 times. There is evidence that these drugs may increase the predisposition to venous thrombosis. This probably occurs mainly in women with hereditary thrombophilia.

The menopausal period in women spans the period from 45 to 60 years of age and is characterized by the gradual cessation of menstrual function and then the hormonal function of the ovaries against the background of general age-related changes in the body. The premature development of menopause is considered to be before the age of 40-42 years, while the late development of menopause occurs after the age of 55 years. There is evidence that early menopause (before 40 years), late menopause (after 55 years) and surgical menopause (bilateral oophorectomy performed at a young age) increase the risk of IAC [12].

One of the main protective factors in women of reproductive age is 17β-estradiol. Estradiol stimulates angiotensinogen formation in the liver, leading to increased aldosterone synthesis and sodium and water retention. These adverse effects of aldosterone are prevented by progesterone, which competitively binds to mineralcorticoid receptors in the kidneys [6]. Estrogens increase nitric oxide and prostacyclin levels, reduce endothelin synthesis and thus contribute to vasodilatory effects. They also have antioxidant effect and decrease functional activity of

platelets.With the onset of menopause, the decrease of progesterone and estradiol is abrupt, while testosterone level decreases slowly and smoothly. Low estrogen level is a trigger factor for a number of metabolic disorders (obesity, dyslipidemia, insulin resistance, etc.), united by the term "postmenopausal MS".

The imbalance of hormonal status causes the development of obesity with redistribution of fat to the upper half of the body [5,7]. A decrease in somatotropic hormone levels also contributes to the progression of obesity. Somatotropic hormone deficiency causes insulin resistance and hyperinsulinemia. In insulin resistance, endothelial dysfunction occurs - the synthesis of endothelin 1, thromboxane and catecholamines increases, nitric oxide and prostacyclin levels decrease, which causes A.G. Hyperinsulinemia leads to increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system. Low levels of dehydroepiandrosterone, an adrenal hormone that is involved in estrogen and testosterone synthesis, have been found to be associated with a high risk of ischemic stroke [8].

A number of epidemiological studies have found that estrogen-rich hormone therapy in healthy menopausal women increases the risk of ischemic stroke, myocardial infarction and A.G. Its use leads to hemostasis activation and blood hypercoagulation. Estradiol increases the content of fibrinogen, clotting factors VII, VIII and X, and decreases the level of anticoagulants (antithrombin III, protein S). The use of hormone replacement therapy increases the risk of stroke. According to the Womens Health Initiative study, the risk of stroke increases by 31% when combined hormone therapy is used and by 37% when estrogen is used [14].

Thus, factors that increase the risk of stroke in women include: early (≤10 years) or late (≥17 years) age at menarche; AH and gestational diabetes mellitus in pregnancy; preeclampsia and eclampsia; habitual pregnancy failure; premature delivery and fetal weight at birth that is inappropriate for gestational age; late onset of pregnancy; induced termination of pregnancy; multiple pregnancies; early (<45 years) and late (>55 years) age at menopause; low dihydroepiandrosterone levels; use of combined contraceptives or hormone replacement therapy (oral and transdermal forms of

estrogen). The onset of early menopause, natural or surgery-related, increases the risk of cardiovascular disease by 2-fold.

Hormonal status in men. Several retrospective studies examining gender differences in stroke incidence have demonstrated that men, compared with women, have a higher risk of stroke over most of their lives. Young and middle-aged men have a higher incidence of stroke. Over the age of 54 years, the incidence of stroke in men and women is similar [6,10]. Gender differences observed at young age are explained by differences in hormonal status and the protective role of estrogens in women, whose levels decrease sharply after menopause.

The process of age-related changes in androgen status in men is accompanied by a decrease in testosterone levels. According to the Massachusetts study of elderly men, the level of total testosterone begins to decrease at the age of 50-55 years by 0.8-1.6% per year. It is known that the physiological effects of testosterone are largely determined by its biologically active free fraction, and, consequently, the development of clinical manifestations of androgen deficiency is associated with a decrease in free testosterone. A significant contribution to the decrease in the level of the biologically active testosterone fraction is made by the globulin that binds sex steroids, the level of which increases with age [6,11]. In 2005, the International Society for the Study of the Aging Male (ISSAM) proposed the term "age-related hypogonadism". Hypogonadism is diagnosed when the level of total testosterone is less than 12 nmol/L or free testosterone less than 225 pmol/L. The incidence of hypogonadism among men aged 40-49 years is 8%, 50-59 years - 29%, 60-69 years - 44%, over 70 years - 70% or more [6,13].

According to a 29-year prospective study of the Copenhagen City Heart Study [64], in men with low testosterone levels (less than 10 nmol/L) the relative risk of ischemic stroke is 1.34, which is associated with increased body mass index in 21% of cases and with AH in 14%.

Conclusions: Thus, a combination of risk factors. Often, both men and women have several risk factors for acute MI simultaneously, each of which may be expressed moderately. In this regard, the risk of acute stroke, which may be high due to the

mutual influence of factors, is determined by special scales based on the results of long-term follow-up of large cohorts. According to WHO, when 1 or 2 factors occur, the risk of stroke is 6%, and 3 factors or more - 19%. The Freming scale allows estimating the individual risk of stroke (%) over the next 10 years.

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