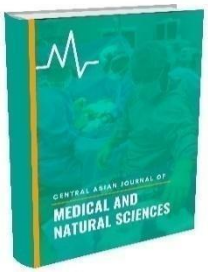
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Neuroimmunological Predictors Of The Risk Of Developing Neurological Disorders In Pre- And Postmenopausal Women After The Onset Of Covid-19.

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Annotation: . In connection with the imbalance of neurotransmitters in the brain, vasomotor symptoms develop. In particular, the concentration of serotonin, norepinephrine, γ-aminobutyric acid and opioid peptides decreases, and the concentration of monoamine oxidase increases. As a rule, such changes occur immediately and significantly reduce the quality of life of women, leading to sleep disturbance, anxiety, depression, migraine, dementia, etc.

Key words: y-aminobutyric acid, menopause, diabetes mellitus, COVID-19, , depression, migraine.

- With the onset of menopause, women start pathological mechanisms that affect many organs. At the same time, more life-threatening conditions, such as osteoporosis, sarcopenia, metabolic syndrome, type 2 diabetes mellitus (DM), and atherosclerosis, develop gradually and subtly. Complications of these diseases can cause premature death.
- It should be noted that the main causes of death in developed countries are cardiovascular diseases, oncology, chronic obstructive pulmonary disease, and diabetes [2]. The priority of fatal diseases differs in women depending on age. If from 50 to 70 years the main causes of death for women are considered to be diseases such as coronary heart disease, stroke and breast cancer, then after 70 years Alzheimer's disease takes the 3rd place.
- The main indication for the appointment of menopausal hormone therapy (MHT) is the relief of vasomotor symptoms (hot flashes). In addition, MHT can reduce the risk of developing cardiovascular diseases. In particular, there is a positive effect on glucose homeostasis through effects on pancreatic O-cells, skeletal muscle, liver, and adipose tissue. This leads to a decrease in the amount of abdominal fat, a decrease in fasting glucose and insulin levels, an improvement in glucose metabolism and insulin sensitivity, and, in general, a decrease in the incidence of type 2 diabetes [3–5].
- When taken orally, estrogens are absorbed in the intestine and delivered to hepatocytes, which allows to achieve supraphysiological concentrations of estrogens in the liver. As a result, there is an increase in the synthesis of high-density lipoproteins (HDL) and the elimination of low-density lipoproteins (LDL) from the bloodstream, as well as increased insulin sensitivity. With transdermal estrogen therapy, such supraphysiological concentrations cannot be achieved, therefore, transdermal therapy does not have a positive effect on lipid and carbohydrate metabolism. It should be noted that of all the gestagens used in MHT, only dydrogesterone significantly increases the concentration of anti-atherogenic HDL in blood plasma [6, 7].
- In 2018, the EMAS (European Menopause and Andropause Society) guidelines on menopause and

diabetes were published, which state the following [6]:

- • MHT has a positive effect on the glycemic profile in women both without and diagnosed with type 2 diabetes;
- • timely started MHT can delay the development of type 2 diabetes;
- • oral MHT is preferred as it has the most pronounced effect on carbohydrate metabolism (unless there are absolute contraindications);
- • if there is a high risk of thrombosis, the use of transdermal forms of MHT can be considered;
- • Of the available and studied gestagens in oral MHT, metabolically neutral ones that do not reduce the positive effect of estrogens on carbohydrate metabolism (such as progesterone and dydrogesterone) are preferred.
- Following these recommendations, new EMAS guidelines on menopause and dyslipidemia were published in 2020, which noted the following [8]:
- • systemic estrogens, when taken orally as part of MHT, induce a significant dose-dependent decrease in total cholesterol, LDL and lipoprotein (a), as well as an increase in HDL concentration;
- • the preferred gestagens in the combined MHT are metabolically neutral - dydrogesterone or progesterone;
- • patients with severe triglyceridemia may be recommended transdermal forms of estrogens in combination with metabolically neutral progestogens (dydrogesterone or progesterone);
- • MHT should be used in conjunction with the main type of therapy for dyslipidemia, nutritional modification and physical activity.

All this indicates the importance of the use of MHT for the prevention of the development of cardiovascular diseases and type 2 diabetes, while oral forms of drugs and the most inert gestagen dydrogesterone should be preferred.

However, the use of sex hormones can also lead to undesirable consequences in the form of venous thromboembolic complications (VTEC), since hormone therapy is one of the risk factors for the development of thrombophilia along with obesity, dehydration, age (over 40 years), pregnancy, the postpartum period, oncological process, etc. Currently, in the context of the COVID-19 pandemic, there is a lot of controversy about the advisability of using hormonal drugs due to a possible increase in the risk of developing VTEC. Is it really?

To begin with, it should be noted that the main mechanism for the development of the pathological process in COVID-19 is damage to the endothelium of the vascular wall, which leads to DIC (DIC - disseminated intravascular coagulation) [9]. The mechanism of its development is associated with three main pathogenetic pathways, which are closely related to each other and form a kind of vicious circle. First of all, we are talking about cytopathic damage by the virus to endothelial cells of small and large vessels, which have ACE2 and CD147 molecules. It is with them that SARS-CoV-2 is able to interact against the background of developing viremia [10, 11].

In addition, the so-called “cytokine storm” occurs, which damages vascular endothelial cells and causes an inflammatory reaction with the attraction of various immune cells (leukocytes, macrophages, lymphoid elements) to the site of the lesion and an increase in the aggregation of blood cells. . The mechanism of development of a cytokine storm is due to an uncontrolled reaction of innate immunity with the release of an excessive amount of pro-inflammatory cytokines that have a damaging effect on tissues, including the lungs and blood vessels. In particular, in the blood serum of patients, an increased content of such pro-inflammatory cytokines as interleukin-10 (IL-10), IL-18, tumor necrosis factor a, IL-6, IL-8 and IL-10 is detected [11].

And finally, there is a picture of systemic vasculitis in the form of damage to small and medium-sized vessels. At this stage, the appearance of antiphospholipid antibodies, exacerbating DIC, is possible. Virus-induced autoimmune reactions can increase the severity of the condition [11]. With COVID-19, DIC is accompanied by the development of fibrin thrombi both in the microvasculature and in larger vessels - the veins of the lower extremities, which leads to the occurrence of pulmonary embolism, primary thrombosis of the pulmonary and coronary arteries, arteries and veins of the head brain and intestines, right parts of the heart [12, 13].

However, it should be noted that in relation to the severity of the clinical course and mortality from

COVID-19, there is a certain gender peculiarity - these indicators are higher in men. According to some data, 60% of hospitalized patients are men. Among patients who require a stay in the intensive care unit, men also predominate (66%). According to data obtained by Italian scientists, male pattern baldness (androgenetic alopecia) is associated with more frequent SARS-CoV-2 infection and a more severe outcome of COVID-19, i.e. androgens, being a key factor in this form of alopecia, can cause sex differences in the course of this disease [14].

In addition, as mentioned above, the virus enters cells using the ACE2 receptor, which is facilitated by TMPRSS2 (transmembrane protease, serine 2 - type 2 transmembrane serine protease), an androgen-dependent enzyme. For example, prostate cancer patients who have significantly elevated androgen levels also have significantly increased TMPRSS2 activity, leading to more severe COVID-19 and a greater risk of death compared to men with other cancers. At the same time, androgen deprivation therapy had a protective effect in patients with prostate cancer, reducing the likelihood of infection even to a greater extent than in other types of cancer. Dingetal. noted that women of reproductive age had less severity of COVID-19 and better outcomes than men of the same age. The difference disappeared when postmenopausal women were compared with men of the same age. This is probably due to the important role of female sex hormones, and primarily estradiol, which is considered the most significant factor that has a protective effect by regulating the activity of pro-inflammatory cytokines [7]. It is important to note that the higher the estrogen concentration, the lower the secretion of pro-inflammatory cytokines and the better the humoral immunity [8].

It should be emphasized that estrogens in general are of great importance in maintaining immunity in women: with the onset of menopause and in the postmenopausal period, the incidence of various infections increases significantly. This is due, among other things, to the fact that estrogen receptors are present in almost all cells of innate and acquired immunity, which is a significant factor in the complex immune response [9].

In addition, estrogens play an important role in the regulation of lipid mediators and peptides involved in the processes necessary for an adequate immune response, increasing the likelihood of a successful outcome in the fight against any infectious agent, including SARS-CoV-2 [2]. Thus, androgens can activate TMPRSS2, while estrogens, on the contrary, can suppress the expression of ACE2, which is used to enter the host cell [8].

It was also found that not only estrogens, but also progesterone, which can have a direct antiviral effect, perform a protective function against COVID-19 [21, 2]. Apparently, therefore, severe cases of coronavirus infection in pregnant women, in which the concentration of estrogen and progesterone is significantly increased, are extremely rare.

Estrogens may play a role in protecting against the effects of SARS-CoV-2 on highly vascularized organs such as the heart, lungs, etc. [13].

And yet, what if a woman takes MHT during the COVID-19 pandemic? In this case, according to the position of international associations, it is necessary to adhere to the following points:

• if COVID-19 is asymptomatic or mild, then no special strategies, including changes in MHT, are required;

• if COVID-19 occurs in a moderate form that does not require hospitalization, then MHT can not be canceled and it is not necessary to switch to transdermal therapy [4];

• For women with severe COVID-19 during hospitalization, most communities recommend that hormonal therapy (both combined oral contraceptives and MHT) be discontinued until recovery and mobility is restored [6].

As noted above, the role of MHT in preventing the development of such formidable diseases as atherosclerosis, diabetes, dementia, osteoporosis, etc., is very significant, and even in the era of coronavirus infection, it is impossible to refuse it, especially considering the fact that female genital hormones not only do not increase the risk of developing and aggravating COVID-19, but also have certain protective and anti-inflammatory mechanisms. Nevertheless, one should not forget about Virchow's triad, which describes the main pathogenetic mechanisms that contribute to the development of thrombosis in the vascular bed: damage to the vascular wall, changes in the nature of blood flow, shift of hemostasis towards thrombus formation.

Since SARS-CoV-2 damages the vascular endothelium and triggers one of the triad mechanisms, it is necessary to approach the choice of hormonal drugs with great care in order to prevent additional thrombophilic conditions that can provoke VTEC. First of all, this applies to combined oral contraceptives, since the synthetic estrogens and gestagens included in their composition have a rather high thrombogenic activity.

When choosing MHT preparations, one should not abandon the oral form, since, unlike the transdermal one, it adequately protects a woman from many diseases. When prescribing MHT, it is important to use inert progestogens that do not reduce the positive properties of estrogens, including such as reducing the inflammatory response and increasing immunity in COVID-19. Dydrogesterone is the most inert progestogen, while III and IV generation progestogens do not have a selective effect only on the endometrium and may increase the risk of VTEC, especially in the context of coronavirus infection.

Additional evidence for this can be the data of a British study, which demonstrated that the risk of venous thrombosis was minimal when using a combination of estradiol and dydrogesterone as MHT, in contrast to other progestogens, the use of which significantly increased this risk [7].

Thus, the use of MHT can not only eliminate vasomotor symptoms in postmenopausal women, but also prevent the development of atherosclerosis, type 2 diabetes, vascular and degenerative dementia, osteoporosis, etc. However, the effectiveness of the oral form is 5-6 times higher than that of the transdermal form . The COVID-19 pandemic is not a contraindication to the appointment and continuation of MHT, on the contrary, the restoration of the estrogen background in postmenopausal women contributes to the preservation of immunity, a decrease in the activity of pro-inflammatory cytokines and inhibition of the development of a cytokine storm. To maintain the positive qualities of estrogens under the conditions of COVID-19, it is necessary to use the most inert progestogens in MHT, the most preferred of which is dydrogesterone.

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