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Post-stroke depression: predictors and prophylaxis

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Abstract

The purpose of the study was to evaluate the effectiveness of prevention of post-stroke depression in patients with acute cerebrovascular accident

It was shown that the incidence of PID in patients with ischemic stroke exceeds 30%. In assessing the role of various risk factors among the examined patients with PID, the prevalence of male patients (OR = 1.3 (1.1-1.5)), under the age of 55 (1.7 (1.3-1.9)), with indications in the history of episodes of depression in the past (1.6 (1.4-1.8)), as well as alcohol abuse (1.2 (1.0-1.3)). In 31 (58.5%) there was a localization of focal ischemia in the frontal lobe of the dominant hemisphere. The use of both SIRS and an antidepressant with multimodal effect - vortioxetine was sufficiently effective in PID, but vortioxetin showing the best results - from 8,8±0,1 points to 6,2±0,1 points. The paper considers the expediency of the use of vorothoxetine in order to prevent PID in patients with ischemic stroke.

Key words: postnatal depression, ischemic stroke, diagnosis, treatment

Постінсультна депресія: предиктори та профілактика

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Метою дослідження була оцінка ефективності профілактики постінсультної депресії у пацієнтів з гострим порушенням мозкового кровообігу

Показано, що частота ПІД у хворих на ішемічний інсульт перевищує 30%. При оцінці ролі різних чинників ризику серед обстежених пацієнтів з ПІД виявлене переважання осіб чоловічої статі (ОШ=1,3 (1,1-1,5)), у віці до 55 років (1,7 (1,3-1,9)), з вказівками в анамнезі на епізоди депресії в минулому (1,6 (1,4-1,8)), а також на зловживанням алкоголем (1,2 (1,0-1,3)). У 31 (58,5%) мала місце локалізація фокусу ішемії у лобній долі домінантної півкулі. Застосування як СІЗЗС, так й вортіоксетину виявилося достатньо ефективним при ПІД, при чому вортіоксетин показав найкращі результати - з 8,8±0,1 балів до 6,2±0,1 балів. В роботі розглядається доцільність застосування вортіоксетину з метою профілактики ПІД у хворих на ішемічний інсульт.

Ключові слова: постінсультна депресія, ішемічний інсульт, діагностика, лікування

Постинсультная депрессия: предикторы и профилактика

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Целью исследования была оценка эффективности профилактики постинсультной депрессии у пациентов с острым нарушением мозгового кровообращения

Показано, что частота ПОД у больных с ишемическим инсультом превышает 30%. При оценке роли различных факторов риска среди обследованных пациентов с ПИД обнаружено преобладание лиц мужского пола (ОШ = 1,3 (1,1-1,5)), в возрасте до

55 лет (1,7 (1,3-1,9)), с указаниями в анамнезе на эпизоды депрессии в прошлом (1,6 (1,4-1,8)), а также на злоупотребление алкоголем (1,2 (1,0-1,3)). В 31 (58,5%) имела место локализация фокуса ишемии в лобной доли доминантного полушария. Применение в качестве СИОЗС, так и вортиоксетина оказалось достаточно эффективным при ПИД, причем вортиоксетин показал лучшие результаты - с 8,8±0,1 баллов в 6,2±0,1 баллов. В работе рассматривается целесообразность применения вортиоксетину с целью профилактики ПИД у больных с ишемическим инсультом.

Ключевые слова: постинсультная депрессия, ишемический инсульт, диагностика, лечение

Post-stroke depression (PID) is a pathological condition that is constantly encountered by specialists working with acute cerebrovascular abnormalities [7, 13, 15, 16]. According to the DSM-V criteria for diagnosing a depression, The individual must be experiencing five or more symptoms during the same 2-week period and at least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day.

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.

3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.

4. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).

5. Fatigue or loss of energy nearly every day.

6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day.

7. Diminished ability to think or concentrate, or indecisiveness, nearly every day.

8. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

To receive a diagnosis of depression, these symptoms must cause the individual clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms must also not be a result of substance abuse or another medical condition [4].

Critics of this approach point out that when a stroke is present in a patient, it may be a phenomenon of weakness, anosognology, or cognitive dysfunction, which complicates the use

of classical criteria. In addition, in acute stroke department, it is not always possible to observe the dynamics of manifestations of depression for two weeks, since in most countries of the world the term of stay in a stroke unit does not exceed 10 days. Therefore, in neurology, somewhat simplified perception of the concept of PSD is taken - this is a depression that occurs after a stroke and can not be explained by the presence of other diseases. In the literature, the concept of "vascular depression" is becoming popular, to cases which involve all manifestations of depression against the background of cerebrovascular disease. The reason for vascular depression is often called a malfunction of the prefrontal system and the ponto-thalamic-cortical pathways. The main manifestations of PSD include constant grief, a sense of hopelessness, helplessness, the patient could believe that he is a burden for the family, loses interest in life, motivation for action, may have passive or active suicidal intentions. By the time of occurrence, all species are distributed in the early (in the first three months after the stroke) and late (more than three months) [7, 17].

PSD can occur at any time after a stroke, but most often it registers after 3-6 months. Most often PSD are found in institutions of rehabilitation [8]

Risk factors include age up to 60, female sex, more often single people who are depressed, widows and widowers, persons abusing alcohol and other psychoactive substances. Significant role is played by the severity of stroke (severe motor deficiency, severe aphasia), stroke localization, small vessel disease (SVD), post-stroke emotional disorder (PSEI), hyperhomocysteinemia, and lack of social support. It is important to take into account episodes of depression in history. In recent years, much attention has been paid to the genetic factor (polymorphism 5-HTTLPR, STin2 VNTR, SERT) [7, 8, 15]

Some authors believe that lesions of the left frontal lobe in the right-handed, basal nuclei, and dominum hemisphere as a whole are an important predictor of PSD [6, 8, 17, 18]. However, none of the systematic reviews and meta-analyzes confirm this view. In the fundamental review of domestic experts are analyzed and other potential predictors: biochemical, neuroimaging, clinical anamnestic, etc. [9].

There is some evidence in favor of the fact that small vessel disease (SVD) is an important risk factor for postnatal depression [6, 8]. Modern neuroimaging techniques allow us to verify the damage to the white matter of the brain, lacunar infarcts and cerebral microventilations, which are considered pathognomonic for small vessel disease [6]. The accumulated data array allows the association of SVD with the emergence of depression and cognitive impairment. In patients with PSD the deterioration of function restoration, social

disadaptation, reduced quality of life, increased cognitive impairment, increased mortality [10].

To date, there is a significant number of diagnostic tools for PSDs, but the lack of unified approaches to psychometric evaluation of the severity of depression leads to significant heterogeneity of the accumulated data on the epidemiology of the disease. Another problem that is acutely faced by specialists in stroke departments is the issue of the safety of funds that are prescribed for PSD. One of the most complicated issues is the risk of side effects in a comorbid stroke patient, as well as insufficient high compliance in the treatment of PSD. Most antidepressants have an effect on the function of an electrical conduction system of heart that increases the risk of fatal arrhythmias [3, 11] in the context of hypomagnesaemia and hypokalemia, [3, 11], for an SSRI there is an actual risk of bleeding, especially when anticoagulants and disaggreants are receiving the disease [5, 14]. In addition, with the administration of antidepressants, control of blood pressure is complicated and other undesirable effects may occur. Unfortunately, 30% of patients give up the antidepressant treatment immediately after discharge from the hospital [3]

The purpose of the study was to evaluate the effectiveness of prevention of post-stroke depression in patients with acute cerebrovascular accident

Material and methods

The study was performed on the basis of the stroke unit of the neurological department of the Center for Reconstructive and Restorative Medicine (University Clinic) of the Odessa National Medical University during 2016-2018. Under supervision, there were 217 patients with acute cerebrovascular accident with ischemic type. The examination and treatment were carried out in accordance with the requirements of the order No 602 dated August 03, 2012 "On approval and implementation of medical-technological documents on the standardization of medical care for ischemic stroke" [1]. Additionally, the severity of depressive manifestations was evaluated using the HADS-D scale in patients with preserved speech function (n = 159). There was conducted an analysis of clinical results with the use of various antidepressants. The term of catamnestic observation was 6 months. Statistical processing was performed using the software Statistica 10.0 (Dell StatSoft Inc., USA)

Results

In the structure of the surveyed, men prevailed - 113 (52.0%) persons. The average age was 60.4±1.1 years, the average score on the NIHSS scale was 10.1 ± 0.09. 149 (68.7%) patients received the clinic during the first day after the first clinical manifestations of the

HPMC. Further analysis showed that the risk factors for PSD in the examined patients were as follows (Table 1):

Table 1. Risk Factors of post-stroke depression

The factor	**Frequency**	
	Абс.	%
Female gender	104	47,9
Age less than 60 years	98	45,2
Single marital status	89	41,0
Alcohol abuse	34	15,7
Other addictions	9	4,1
NIHSS>10 балів	110	50,7
SVD	61	28,1
Localization in the dominate hemisphere	97	44,7
Lesion of frontal lobe	37	17,1
Episodes of depression in anamnesis	26	12,0
Other neurological comorbidities	49	22,6

The average length of stay in the hospital was 10.2±0.9 days. Manifestations of PID were identified in 53 (33.3% of the number of respondents) patients whose average age was 54.2±1.5 years.

Further analysis showed that the most commonly used antidepressants were presented by selective serotonin reuptake inhibitors (SSRI: paroxysin, sertraline, escitalopram and citalopram). They were administered in standard doses - 36 or 67.9% of the total number of patients with PSD. Another 17 patients received vortioxetine (32.1%) at a dose of 10-20 mg per day. At the time of the initial survey, the score on the HADS-D scale was an average of 8.8±0.1 points. Six months after discharge, patients continued receiving medications, those receiving SSRI average score on the HADS-D scale was 7.7±0.1 points, and in patients taking vortioxetin - 6.2±0.1 scores (Fig. 1).

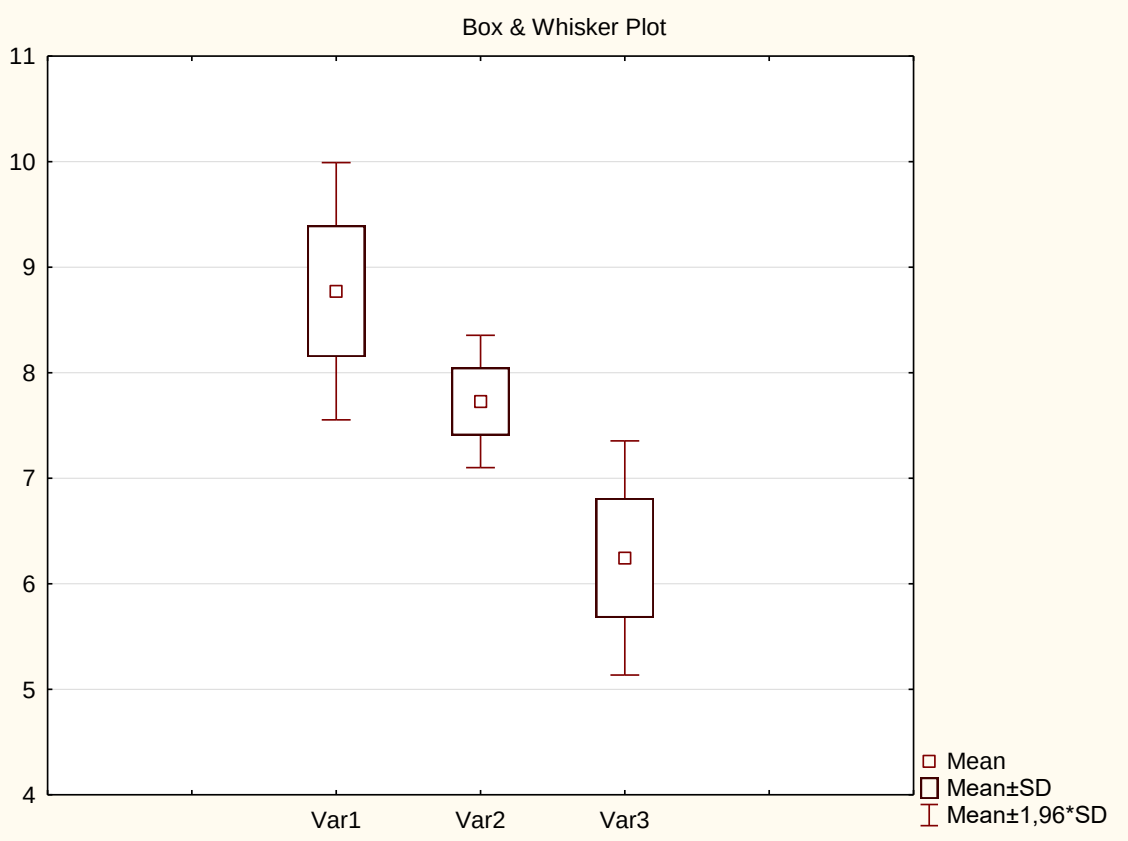

Fig. 1 Dynamics of indicators on the scale of HADS-D

Thus, the use of both SSRI and antidepressant with multimodal effect (vortioxetin) was sufficiently effective at PSD, but vortioxetin showed the best results. The reasons for this phenomenon are possible features of the pharmacodynamics of the drug [12, 17].

In assessing the role of various risk factors among the examined patients with IDU, the prevalence of male patients (OR = 1.3 (1.1-1.5)), under the age of 55 (1.7 (1.3-1.9)), with indications in the history of episodes of depression in the past (1.6 (1.4-1.8)), as well as alcohol abuse (1.2 (1.0-1.3)). In 31 (58.5%) there was a localization of focal ischemia in the frontal lobe of the dominant hemisphere.

At present, various pathogenetic models of the occurrence of PSD [13, 17] are discussed. One of the most popular is the concept of the effect of inflammatory response and activation of the cytokine cascade. The position of Robinson-Bloom's hypothesis, according to which the deficiency of neutrons (serotonin, dopamine and norepinephrine), and also the model of hyperproduction of glutamate [7, 9, 13], are the main cause of depression. The cytokine model is in good agreement with the above concepts. Caused by cytokines damage to tissues in the ischemia zone leads to cell death through mechanisms such as glutamate exitotoxicity, increase of free radicals production.

Timely start of treatment can significantly improve prediction and prevent the occurrence of associated depressive disorders

Unfortunately, most of the patients today do not receive adequate treatment. Nowadays, there are both medicamental and non-medicated means for treatment, but there is no clear algorithm for their use. This is particularly due to the complexity of the pathophysiology of depression in post-stroke patients. In the pathogenesis of post-stroke depression, a significant decrease in the content of monoamines - serotonin and norepinephrine. The stroke of the serotoninergic pathways from the caudal and spinal nuclei of the suture to the hypothalamus, almond-shaped complex, striped body, hippocampus and cerebellar cortex causes a decrease in serotonin levels in many parts of the brain. To some extent, this is confirmed by a decrease in the content of metabolites of monoamines in cerebrospinal fluid, as well as by changes in receptor reactivity in the left temporal region [8, 9, 12].

Regarding the role of the axis of the hypothalamus-pituitary-adrenal gland, its activation following a stroke is associated directly with the presence of a hearth of ischemia and with the use of corticosteroids in the treatment of stroke and comorbid states. Today there is enough evidence that proinflammatory cytokines can cause increased activity of the glands of the internal secretion. Significant role in this play changes in synapthogenesis and neurogenesis, which determine the phenomenon of neuronal plasticity [12].

A key point in ensuring the success of treatment and rehabilitation measures at PID is the level of motivation and participation of the patient. With expressed emotional and volitional violations, rehabilitation is significantly complicated. This ultimately leads to a decrease in the effectiveness of rehabilitation, prolongation of stay in the hospital, poor social rehabilitation, deterioration of the prognosis [2, 3]

The first-line therapy for PSD is now considered SSRI, which appeared in the arsenal of neurologists in the 80's of the last century. In therapy of PSD there is most commonly used paroxetine, fluoxetine, fluvoxamine, sertraline, citalopram and escitalopram, with each of these drugs having additional mechanisms besides the serotonin reuptake inhibition. For example, fluoxetine has an effect as 5HT2C antagonist; paroxetine has a weak anticholinergic effect; sertraline has the ability to influence the metabolism of dopamine by inhibiting DAT and σ1. Fluvoxamine affects the binding of σ1; and citalopram has an antihistaminergic effect that is absent in escitalopram. In addition, SSRI have a different effect on the cytochrome-P450, which is important for interactions between drugs. The slightest adverse effects are made by sertraline and citalopram [10].

The most studied are citalopram, escitalopram, fluoxetine and sertraline, however, direct comparisons between these drugs were not performed, and the choice of antidepressant in this group remains at the discretion of the physician. Recently, publications on the security issues of the SSRI have become worse. It is known that they can cause dyspeptic manifestations, headache, sexual dysfunction and insomnia. There is also a risk of hemorrhagic transformation and / or intracranial hemorrhage in their association with the effect on platelet aggregation [14]. In addition, for many antidepressants of this group, the effect on prolongation of QTc is characteristic, which should be taken into account in the treatment of patients with rhythm disorders [11]. Regarding the effect on survival, the idea now that the use of SSRIs reduces mortality in stroke patients is prevalent [3].

In recent years, the prescribing of other antidepressants has increased with PID. SNRI (serotonin reuptake inhibitors and norepinephrine reuptake inhibitors) were put into practice in 1993 after the approval of venlafaxine FDA. Other available SNRI are milnacipran and duloxetine. SNRIs have shown a similar risk of intracranial bleeding over SSRI [10] and may be useful in severe pain due to their noradrenergic effects [17].

Mirtazapine, a tetracyclic antidepressant that enhances noradrenergic and serotonergic neurotransmission due to the blockade of central alpha2 adrenergic auto- and heteroreceptors, is also considered an effective means of preventing and treating PSD [10] but may cause sedation and weight gain.

Reuptake inhibitors of norepinephrine reuptake inhibitors showed greater efficacy in patients with PSD compared to citalopram [10, 17].

Bupropion may be useful for its activation through a possible dual mechanism of action (inhibition of reuptake of both dopamine and norepinephrine) [10], but there is still no data on its efficacy in PID.

The possibility of using agomelatine, nefiracetam, pioglitazone, methylphenidate, modafinil, vitasodone, levominacipran and other drugs is discussed. [13]

The mechanism of action of vortioxetin is believed to be related to its multimodal activity, which is a combination of two pharmacological mechanisms: direct modulation of receptor activity and inhibition of serotonin transporter (5-HT). Preclinical data show that vortionoxetine is an antagonist of 5-HT3, 5-HT7 and 5-HT1D receptors, a partial 5-HT1B receptor agonist, a 5-HT1A receptor agonist, and a 5-HT1 receptor agonist, inducing neurotransmitter modulation in several systems, including serotonin, norepinephrine, dopamine, histamine, acetylcholine, GABA and glutamate. Such multimodal activity provides antidepressant and anxiolytic effects, as well as improving cognitive function, learning and

memory. In addition, warioxetin does not affect either the pharmacokinetics or the pharmacodynamics of anti-blocking and anticoagulant drugs, as well as blood pressure and heart parameters [10]. This allows us to consider this drug as promising for the prevention of PID in patients with ischemic stroke in conditions of institutions and units of the angioneurological profile.

Conclusions:

1. Frequency of early PSD in patients with ischemic stroke exceeds 30%

2. In assessing the role of various risk factors among the examined patients with the prevalence of male prevalence (OR = 1.3 (1.1-1.5)), under the age of 55 (1.7 (1.3-1 , 9)), with indications in the history of episodes of depression in the past (1.6 (1.4-1.8)), as well as alcohol abuse (1.2 (1.0-1.3)). In 31 (58.5%) there was a localization of focal ischemia in the frontal lobe of the dominant hemisphere.

3. The use of both SSRI and vortioxetine was sufficiently effective at PID, with the fact that valyoxetine showed the best results - from 8,8±0,1 points to 6,20,1 points

4. The expediency of the use of vortionoxetin in order to prevent PSD in patients with ischemic stroke is considered.

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