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Research Article

Comparison of the state of brain metabolism and psycho-emotional disorders in patients with postmastectomy syndrome

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BACKGROUND: The most common consequence of the radical treatment of breast cancer is postmastectomy syndrome — a complex of changes in the lymph circulatory system, central and peripheral nervous system, skeletal and muscular apparatus, that significantly reduce the quality of life and working capacity of women. In recent years, special attention has been paid to the study of psycho-emotional disorders in this group of patients. A promising method for preclinical diagnosis of anxiety and depressive disorders in patients with postmastectomy syndrome may be positron emission computed tomography with fluorine-18 labeled glucose — 2(18F)-fluoro-2-deoxy-D-glucose, which makes it possible to deduce typical patterns of changes in glucose metabolism in cerebral structures in various depressive and anxiety states.

AIM: The purpose of this study is to study the relationship between brain metabolism and psycho-emotional status in patients with postmastectomy syndrome.

MATERIALS AND METHODS: In our work, the sample consisted of 28 patients who underwent radical treatment for breast cancer, who underwent an assessment of the psycho-emotional state using the State-Trait Anxiety Inventory and Zung scales for self-assessment of depression. Positron emission tomography was also performed with 18-fluorodeoxyglucose.

RESULTS: The study revealed that 71% of patients showed an increased level of anxiety, and 64% showed signs of depression. Positron emission tomography data revealed the following areas of hypometabolism in patients with anxiety-depressive disorders: parietal cortex, inferior parietal lobule, precuneus, superior temporal gyrus, prefrontal cortex, and posterior cingulate cortex.

CONCLUSION: Thus, typical zones of changes in glucose metabolism in patients with psycho-emotional disorders have been identified, which makes it possible to improve the accuracy of diagnosing these conditions, as well as to develop the most effective ways to prevent and treat them.

Keywords: anxiety; brain metabolism; depression; PET; postmastectomy syndrome; prognosis.

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Научная статья

Сопоставление состояния метаболизма головного мозга и психоэмоциональных нарушений у пациенток с постмастэктомическим синдромом

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Актуальность. Наиболее частым последствием радикального лечения рака молочной железы является постмастэктомический синдром — совокупность изменений со стороны лимфоциркуляторного русла, центральной и периферической нервной системы, скелетно-мышечного аппарата, существенно нарушающих повседневную активность и трудоспособность женщин. В последние годы особое внимание уделяется изучению психоэмоциональных нарушений в данной группе пациенток. Перспективным методом для доклинической диагностики тревожно-депрессивных расстройств у пациенток с постмастэктомическим синдромом может стать позитронно-эмиссионная компьютерная томография с меченной фтором-18 глюкозой — 2(18F)-фтор-2-дезокси-Д-глюкоза, позволяющая обнаружить типичные паттерны изменения метаболизма глюкозы в церебральных структурах при различных депрессивных и тревожных состояниях.

Целью данного исследования является изучение взаимосвязи метаболизма головного мозга и психоэмоционального статуса у пациенток с постмастэктомическим синдромом.

Материалы и методы. В нашей работе выборка составила 28 пациенток, перенесших радикальное лечение рака молочной железы, которым была выполнена оценка психоэмоционального состояния с использованием шкал Спилбергера–Ханина и Цунга для самооценки депрессии, а также позитронно-эмиссионная томография с 18-фтордезоксиглюкозой.

Результаты. Выявлено, что 71 % пациенток демонстрировали повышенный уровень тревоги, у 64 % наблюдались признаки депрессии. Позитронно-эмиссионная томография выявила следующие области гипометаболизма у пациенток с тревожно-депрессивными нарушениями: теменная кора, нижняя теменная долька, прекунеус, верхняя височная извилина, префронтальная кора, задняя поясная кора.

Заключение. Таким образом, выявлены типичные зоны изменения метаболизма глюкозы у пациенток с психоэмоциональными нарушениями, что позволяет повысить точность диагностики данных состояний, а также разработать наиболее эффективные пути их профилактики и лечения.

Ключевые слова: депрессия; метаболизм головного мозга; постмастэктомический синдром; прогнозирование; ПЭТ; тревога.

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BACKGROUND

The high prevalence and severe disabling consequences of radical breast cancer (BC) treatment represent a significant medical and social problem and make the study of this pathology urgent. One consequence is postmastectomy pain syndrome (PMPS), which occurs in >80% of patients [1].

The clinical picture of PMPS is represented by lymphocirculatory disorders, chronic pain syndrome, psychoemotional disorders, restricted mobility in the shoulder joint on the side with surgical intervention, and cerebrovascular disorders. Among psycho-emotional disorders in women with PMPS, depressive and anxiety symptoms are the most common. PMPS has a pronounced negative effect on the daily activities and performance of women and reduces their quality of life [2]. A traumatic life experience, such as undergoing radical treatment of PMPS, is accompanied by agitation, insomnia, appetite loss, anxiety about death, generalized anxiety, and decreased mood. The above symptoms gradually disappear; however, in 25%–70% of women, anxiety and depression persist many years after treatment [3–5]. Remote chronic pain is diagnosed in 20%–60% of women treated for early-stage RA [6–7]. According to the International Association for the Study of Pain, pain as a psychosomatic sensation is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Chronic pain is defined as maladaptive, lacking biological value, persisting beyond the expected healing period, not amenable to conventional treatment, and lasting >6 months. Recurrence is a specific feature of chronic pain, and anxiety and depression play important roles in its perception. The presence of chronic pain in women who underwent mastectomy is associated with anxiety and depressive symptoms [3, 7]. Psycho-emotional disorders lead to the patient's limitation or rejection of the previous lifestyle, physical activity, and interests.

Studies of patients with depression using fluorine-18glucose-labeled positron emission computed tomography (18F-FDG PET/CT) have revealed metabolic abnormalities in some specific brain regions, including the prefrontal, temporal, cingulate cortex, striatum, precuneus, and hippocampus [8–10]. These changes are explained by the hypothesis suggesting the presence of limbic–cortical–striatal–pallidal–thalamic connections in the brain. The disruption of the connections along with the dysfunction of the above-described brain areas can lead to the development of depression. The frontal lobe plays an important role in attention, perception, planning ability, goal-directed behavior, working memory, and executive function. Disturbances in this area can be responsible for the development of the majority of the symptoms of depression. Alterations in frontal lobe function likely underlie depression and are also closely associated with symptoms of major depressive disorder (MDD) [11]. The anterior cingulate cortex and corpus striatum are major components of the limbic system that play an important role in episodic memory functioning, emotion processing, and cognition. Most studies in patients with MDD have found hypometabolism in the striatum and anterior cingulate; however, data from the literature are often contradictory [11–14].

Current evidence suggests that patients with high anxiety levels have metabolic changes in the prefrontal cortex bilaterally (hypometabolism in most studies), hippocampus, caudate nucleus, shell (hypometabolism on the left), and amygdala (usually hypermetabolism). Other metabolic changes identified include hypometabolism in the orbitofrontal cortex, anterior cingulate cortex, and hypermetabolism in the insula (predominantly on the right) [15–17].

Thus, 18F-FDG PET/CT showed high sensitivity in detecting anxiety–depressive disorders and allowed the identification of metabolic mechanisms of their development. In addition, this method has great potential as a method of the preclinical diagnosis of psycho-emotional disorders.

Identification of the pathogenetic mechanisms and predictors of the development of psycho-emotional disorders in patients with the postmastectomy syndrome will make it possible to form strategies for the prevention and treatment of clinically significant anxiety and depression, which will allow for the reduction of the disabling consequences of BC treatment.

Thus, this study aimed to investigate the relationship between brain metabolism and cognitive impairment, psycho-emotional status, and quality of life in patients with postmastectomy syndrome.

MATERIALS AND METHODS

An open single-center study recruited 28 patients with postmastectomy syndrome who had previously undergone radical treatment for breast malignancy. The inclusion criteria were as follows: age 25–50 years (mean age, 45.8 years ± 3 months), history of radical treatment of BC (mastectomy, radiation, and/or chemotherapy), comprehensive examination to exclude metastasis, and continued tumor growth. The exclusion criteria were as follows: history of acute cerebral circulatory failure, myocardial infarction, craniocerebral trauma, advanced oncologic diseases, decompensation of chronic diseases, and psychiatric diseases. Most patients underwent radical Madden mastectomy (n = 22), sectoral resection (n = 4), and breast reconstruction (n = 2). Complex treatment (surgery, radiation, and chemotherapy) of BC was performed in 5 patients, a combination of surgical treatment and chemotherapy in 19, and a combination of radiation therapy and surgical intervention in 4. According to TNM classification of cancer stages, stage I (T1N0M0) was detected in 4 patients, IIA (T2N0M0) in 15, IIB (T2N1M0) in 3, IIIA (T0N2M0) in 4, and IIIB (T4N2M0) in 2.

The psycho-emotional state was assessed by collecting anamnesis (complaints during questioning) using Spielberger–Hanin and Zung scales for the self-assessment of depression.

The anxiety level was assessed using the Spielberger–Hanin State-Trait Anxiety Inventory scale, which is an informative way to self-assess anxiety level at the moment (reactive anxiety as a state) and personality anxiety (a stable characteristic of a person) [18]. Depression was assessed using the Zung scale, which has high sensitivity and specificity for the self-assessment of depression, while assessing the degree of depressive disorder in patients, and is used for depression screening [19].

18F-FDG PET/CT was performed to study the state of brain tissue metabolism. According to the degree of drug accumulation in the brain tissue, this method allows for identifying zones with normal metabolism, hypometabolism, and hypermetabolism, which allows the evaluation of the functional state of different parts of the brain.

Statistical analysis was performed using comparative analysis in the Statistica 10.0 program with the evaluation of nonparametric methods (Fisher's exact criterion).

The study was performed in compliance with the principles of the Declaration of Helsinki of the World Medical Association and approved by the Ethical Committee of the Almazov National Medical Research Center of the Russian Ministry of Health (conclusion dated 31.10.2019). All patients received an explanation of the purpose of the study, and all of them gave informed consent.

RESULTS

According to the results of questionnaires, 20 out of 28 (71%) patients showed high anxiety levels and 18 out of 28 (64%) had signs of depression. A combination of anxious and depressive changes was detected in 10 (36%) patients (Table 1).

Among patients with anxiety ($n = 20$), 14 (50% of all patients and 70% of patients with high anxiety) had hypometabolism in the parietal cortex, and 13 (46% of all patients and 65% of patients with high anxiety) had hypometabolism in the inferior parietal lobule (9 in both hemispheres and 4 in the left hemisphere). Hypometabolism in the precuneus was detected in 5 patients (3 on the right and 2 on both sides, which was 18% of all patients and 25% of patients with high anxiety levels). Hypometabolism in the superior temporal gyrus was detected in 4 patients (3 on the left and 1 bilaterally, which was 14% of all patients and 20% of patients with high anxiety levels). Hypometabolism in the prefrontal cortex was detected bilaterally in 2 patients, which was 7% of all patients and 10% of patients with high anxiety levels. Hypometabolism in the posterior cingulate cortex was detected in 2 patients, which was 7% of all patients and 10% of patients with high anxiety levels (Table 2).

Among patients with depression ($n = 18$), 13 (46% of all patients and 72% of patients with depression) have hypometabolism in the parietal cortex (9 bilaterally and 4 on the left); among them, hypometabolism in the inferior parietal lobule was found in 11 (8 bilaterally and 3 on the left, representing 39% of all patients and 61% of patients with depression). Hypometabolism in the precuneus was detected in 6 patients (2 bilaterally and 4 on the right), representing 21% of all patients and 33% of patients with depression. Hypometabolism in the superior temporal gyrus was detected in 6 patients (4 on the left and 2 bilaterally), which was 21% of all patients and 33% of those with depression. Hypometabolism in the prefrontal cortex was detected in 4 patients (2 on the right, 1 bilaterally, and 1 on the left), which was 14% of all patients and 22% of those with depression. Hypometabolism in the posterior cingulate cortex was detected in 3 patients, which was 11% of all patients and 17% of patients with depression (Table 3).

When comparing the frequency of metabolic zone changes in patients with depression and anxiety using Fisher's exact test, no statistically significant differences were found ($p > 0.05$). The lack of differences when comparing groups can be explained by small quantitative sampling.

DISCUSSION

The results revealed a high frequency of hypometabolism in the parietal cortex in patients with depression (50%) and anxiety (46%), particularly the inferior parietal lobe, accounting for 46% and 39%, respectively. The inferior parietal lobe is a hetero-modal convergence zone of different brain neuronal networks that

Table 1. Number and proportion of patients with psycho-emotional disorders

Patient group under study	Anxiety	Depression	Combination of anxiety and depression
Number of patients	20	18	10
% of total	71	64	36

Table 2. Zones of hypometabolism in patients with high anxiety levels

Area of altered metabolism	Number of patients	% of total number of patients	% of patients with anxiety
Dark crust	14	50	70
Inferior parietal lobe	13	46	65
Precuneus	5	18	25
Upper temporal gyrus	4	14	20
Prefrontal cortex	2	7	10
Posterior cingulate cortex	2	7	10

Table 3. Zones of hypometabolism in patients with depression

Area of altered metabolism	Number of patients	% of total number of patients	% of patients with depression
Dark crust	13	46	72
Inferior parietal lobe	11	39	61
Precuneus	6	21	33
Upper temporal gyrus	6	21	33
Prefrontal cortex	4	14	22
Posterior cingulate cortex	3	11	17

play a central role in the realization of key cognitive operations at different levels of the neural processing hierarchy. These cognitive functions include lower- (spatial attention) and higher-level processes that are of greater importance in humans, such as semantic memory and social interaction. Changes in the metabolism of this brain region are not highly specific. Hypometabolism in this area in patients with depression and anxiety may reflect impaired social functioning, creating difficulties in understanding and interacting with others.

Hypometabolism in the precuneus was found predominantly in patients with depression (21% among all patients) and to a lesser extent in patients with anxiety (18%). The precuneus can be conceptualized as a brain region that provides access to the hippocampus for spatial and related information from the parietal cortex. Higher functional connectivity of the precuneus with the lateral orbitofrontal cortex has been studied in patients with depression. This supports the theory that in depression the reward rejection system in the lateral orbitofrontal cortex has a relatively enhanced interaction with areas that represent the inner self, including the precuneus, which may be associated with low self-esteem in patients with depression.

Another frequent finding is hypometabolism in the superior temporal gyrus (predominantly on the left) in patients with anxiety (14%) and depression (21%). In addition to the well-known function of audio information processing and participation in speech perception, this area of the cerebral cortex analyzes socially relevant information, being part of the "social brain" along with the inferior parietal lobe of the left hemisphere (e.g., determining gaze direction and body language). The altered metabolism of this area in depression is a common finding, which may be due to impaired recognition of socially relevant information.

Hypometabolism in the prefrontal cortex (predominantly bilateral) was observed in 7% of patients with anxiety and 14% with depression. The prefrontal cortex plays an important role in attention, perception, planning ability, goal-directed behavior, working memory, and executive function. Disturbances in this area may be responsible for the development of the majority of the symptoms of depression. Alterations in frontal lobe function may likely underlie depression and are closely associated with MDD symptoms, as evidenced by numerous studies.

In addition to the aforementioned changes, hypometabolism in the posterior cingulate cortex was noted in patients with anxiety and depression (7% and 11%, respectively). The posterior cingulate cortex is involved in topographic and topokinetic memory, i.e., orientation of the body in space. This area also plays a role in recognizing familiar faces and surroundings. The posterior cingulate cortex is part of the default mode network (i.e., the neural network of the brain that is most active outside of specific tasks) and is involved in the attention system. This network generates slow waves and synchronizes different parts of the brain (medial prefrontal cortex, posterior cingulate cortex, precuneus, inferior parietal cortex, etc.). As assumed, the disruption of the synchronization between different parts of the default mode network and stable generation of slow waves can lead to affective disorders, particularly anxiety spectrum disorders, because of the resulting hyperactivity of the amygdala body [20].

Despite the lack of significant correlations in the statistical analysis, the results of this study are consistent with the literature data.

CONCLUSION

Thus, the use of neuropsychological testing methods, careful assessment of complaints, and the use of PET/CT to assess brain metabolism can improve the diagnostic accuracy of psycho-emotional disorders in patients with postmastectomy syndrome. The use of specialized questionnaires and examination of brain tissue metabolism will make it possible to diagnose preclinical psycho-emotional disorders early. A significant proportion of patients with PMPS have affective disorders. Depression and anxiety occupy the leading positions in prevalence. Characteristic changes in brain metabolism are detected in the majority of patients with psycho-emotional disorders. This result opens the possibility for early objectivized diagnosis of psycho-emotional disorders and is of undoubted scientific interest for further research. Prompt and accurate diagnosis is a direct path to effective treatment.

ADDITIONAL INFORMATION

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Authors' contribution. All authors contributed substantially to the study and article, read and approved the final version before publication.

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