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Chemo brain: myth or clinical reality? Literature review and clinical case

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ABSTRACT

The review presents a psychopathological phenomenon new for the Russian psychiatry. It combines various cognitive and psychopathological entities (hallucinations, delusions, consciousness disorders) occurring in cancer patients as a result of chemotherapy. In foreign literature, such entities are generalized under such common terms as chemo brain, chemo fog, and post-chemotherapy cognitive impairment (PCCI). Chemo Brain is a symptom complex developing after treatment with various groups of chemotherapeutic drugs and caused by certain functional and structural brain changes. This article collates the data on etiology, pathogenesis, clinical features and interventions in case of disorders generally known as Chemo Brain. In addition, it discusses chemotherapeutic drugs most often inducing the Chemo Fog phenomenon (Cisplatin, Doxorubicin, Methotrexate, 5-fluorouracil), and a clinical Chemo Brain case with severe cognitive impairment and a confusion episode. A 74-year-old female patient undergoing chemotherapy for sigmoid colon carcinoma and metastases experienced a sharp deterioration of memory, self-care, and mobility after a routine chemotherapy round. The patient had been treated with a cocktail of chemotherapy drugs for 3 years and had several surgeries. With acute memory impairment, she consulted the internal medicine department. The doctors were puzzled with her symptoms. Having received advice of various medical specialists and the corresponding treatment, the patient showed improvement of both cognitive and motor functions. The review emphasizes the need for further clinical research of Chemo Brain drug treatment.

Keywords: chemo brain; chemo fog; cognitive impairment; chemotherapy.

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Синдром «химического мозга»: миф или клиническая реальность? Обзор литературы и клинический случай

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АННОТАЦИЯ

В обзоре представлен новый для российского сегмента психиатрии психопатологический феномен, объединяющий различные когнитивные и психопатологические образования (галлюцинации, бред, синдромы расстроенного сознания), возникающие у лиц с онкологическими заболеваниями, перенёсших химиотерапевтическое лечение, в зарубежной литературе объединённых под названиями «chemobrain» («химиомозг»), «chemofog» («химический туман»), «post-chemotherapy cognitive impairment» — PCCI (когнитивные нарушения, связанные с химиотерапией). Синдром «химического мозга» представляет собой симптомокомплекс, развивающийся после лечения различными группами химиотерапевтических препаратов и имеющий под собой определённые функциональные и морфологические изменения в головном мозге. В данной статье осуществлён сбор данных, касающихся этиологии, патогенеза, особенностей клинической картины и способов коррекции группы расстройств, объединённых термином «химиомозг». Кроме того, рассмотрены химиотерапевтические препараты, наиболее часто провоцирующие развитие феномена «химического тумана» (цисплатин, доксорубицин, метотрексат, 5-фторурацил), а также представлен клинический случай развития синдрома «химического мозга» с выраженными когнитивными нарушениями и эпизодом спутанности сознания. У пациентки 74 лет, получавшей химиотерапевтическое лечение в связи с карциномой сигмовидной кишки и метастазами, после очередного курса химиотерапии отмечалось резкое ухудшение памяти, нарушения в самообслуживании и свободном передвижении. За 3 года лечения пациентка получила «коктейль» из химиотерапевтических препаратов, а также перенесла несколько хирургических операций. С остро возникшими нарушениями памяти она обратилась в терапевтическое отделение, озадачив своими симптомами врачей. После консультаций врачей-специалистов различных профилей и полученного лечения у пациентки отмечалась положительная динамика как в когнитивной, так и в двигательной сфере. В обзоре подчёркнута необходимость дальнейших клинических исследований в области фармакотерапии синдрома «химического мозга».

Ключевые слова: химиомозг; химический туман; когнитивные нарушения; химиотерапия.

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«Химик ми» синдромы: мифмы әллә клиник чынбарлыкмы? Әдәбиятка күзәтү һәм клиник очрак

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АННОТАЦИЯ

Күзәтүдә психиатриянең Россия сегменты өчен яңа булган психопатологик феномены тәкъдим ителә, ул химиотерапия узган онкологияле авыруларда барлыкка килә торган төрле когнитив һәм психпатологик тайпылышларны (галлюцинацияләр, саташулар, какшаган аң синдромнары) берләштерә- чит ил галимнәре хезмәтләрендә «chemobrain», «химик ми», «chemofog» («химик томан»), post-chemotherapy cognitive impairment — PCCI (химиотерапия белән бәйле когнитив тайпылышлар) исемнәре астында берләштереп бирелә. «Химик ми» синдромы химиотерапия препаратларының төрле группалары белән дәваланганнан соң үсә торган һәм баш миендә билгеле бер функциональ һәм морфологик үзгәрешләргә ия булган симптом комплексы булып тора. Әлеге мәкаләдә этиологиягә, патогенезга, клиник картина үзенчәлекләренә һәм «химиомозг»термины белән берләштерелгән тайпылышлар төркемен төзәтү ысулларына кагылышлы мәгълүматлар җыелды. Моннан тыш, «химик томан» феноменын (цисплатин, доксорубицин, метотрексат, 5-фторурацил) үстерүгә еш этәрүче химиотерапевтик препаратлар каралды, шулай ук ачык когнитив тайпылышлар һәм аң буталу эпизоды белән «химик ми» синдромы үсешенең клиник очрагы тәкъдим ителде. Сигмовид эчәк карциномасы һәм метастазлар белән бәйле рәвештә химиотерапевтик дәвалау алган 74 яшьлек пациентканың чираттагы курсыннан соң хәтере кискен начарлану, үз-үзенә хезмәт күрсәтүдә һәм ирекле хәрәкәт итүдә бозылу күзәтелгән. 3 ел дәвалану вакытында пациентка химиотерапевтик препаратлардан «коктейль» алган, шулай ук берничә хирургик операция кичергән. Хәтерендә кискен бозылу белән ул терапия бүлегенә мөрәҗәгать итте, табибларны үзенең симптомнары белән аптырашта калдырды. Төрле профильдәге табиб-белгечләр консультацияләреннән соң һәм алынган дәвалаудан соң пациенткада когнитив һәм хәрәкәт өлкәсендә уңай динамика күзәтелә. Күзәтүдә «химик ми»синдромы фармакотерапиясе өлкәсендә алга таба клиник тикшеренүләр кирәклеге ассызыкланды.

Төп сүзләр: химик ми; химик томан; когнитив тайпылышлар; химиотерапия.

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BACKGROUND

The World Health Organization reports that cancer is one of the leading causes of mortality worldwide, accounting for nearly 10 million deaths in 2020. The global structure of cancer by localization is as follows: breast cancer (2.26 million cases), lung cancer (2.20 million cases), colorectal cancer (1.93 million cases), prostate cancer (1.41 million cases), skin cancer (1.20 million cases), and stomach cancer (1.09 million cases) [1]. According to the Russian Ministry of Health, in Russia there are 3.94 million patients with cancer, with about 600,000 cases of newly diagnosed cancer annually and 278,000 of cancer deaths in 2021 [2].

Current cancer screening and early diagnosis programs increase the likelihood of a good response to treatment, reduce the severity of the disease, allow the use of less expensive therapies, and increase the chances of survival and life expectancy of patients. In addition, advances in modern therapies for cancer patients have resulted in a steadily increasing number of cancer survivors. Globally, the median 5-year survival rate for breast cancer increased from 75% in the 1975 to 1977 cohort to 91% in the 2008 to 2014 cohort [3]. The American Cancer Society reports that by 2026, the number of cancer survivors in the United States will exceed 20 million, nearly doubling from 2012 [4, 5]. As of 2023, cancer mortality rate in the Russian population has decreased by almost 6% compared to 2018 [2]. This has increased interest in assessing the health-related quality of life in patients with cancer, as well as the psychosocial consequences associated with cancer and its treatment.

This review collected data describing changes in cognitive function and the brain after chemotherapy. Although the negative cognitive effects following localized therapy, particularly cranial irradiation (radiation therapy), have long been evaluated, more than 60% of patients receiving systemic chemotherapy also develop cognitive impairment that significantly affects their daily life, performance and social relationships, and the long-term effects may persist for many years after discontinuation of therapy [6].

CHEMO BRAIN

Cognitive changes associated with chemotherapy have been mentioned since 1978, when concerns were raised about the impact of chemotherapy on the emotional and cognitive status of cancer patients [7]. However, no due scientific attention was paid to this topic until the mid-1990s [8]. The combination of pathological phenomena in patients who have undergone chemotherapy includes disorders of cognitive functions from minimal impairments of short-term memory and reaction time to altered mental status. In world literature the disorders are united by the terms *chemo brain*, *chemo fog* [9], and *post-chemotherapy cognitive impairment* (PCCI) [10]. In literature in Russian, the terms *chemo brain* and *chemo fog* are quite rare, while the terms *post-chemotherapy neurotoxicity* [11], *post-chemotherapy encephalopathy* [12], and *toxic encephalopathy* [13] are used more often in the context of neurologic complications. Even though the symptoms of chemo brain are largely represented by disorders of various spheres of mental activity, we could not find the point of view of the Russian-speaking psychiatric community regarding this problem.

CLINICAL FEATURES

Most cancer treatments, including traditional chemotherapy, are associated with severe, sometimes prolonged and irreversible side effects. Patients often experience altered mental status during and after treatment with various anticancer agents. Other treatments, including hormonal and targeted therapies, may also contribute to cognitive impairment [14]. In such cases, the most common complaints are fatigue, emotional lability, low mood, anxiety, memory impairment (up to small memory lapses), difficulty concentrating, and episodes of disorientation in time and space [12]. In addition, cognitive impairment is characterized by difficulties in memorization, term selection, information processing, and multitasking. Critical and strategic thinking, creativity, learning, and establishing connections between objects and phenomena are affected. It is worth noting that the severity of deficits varies significantly with personal experience and attitude toward the condition [15]. Overall, different researchers estimated the number of patients experiencing chemo brain after chemotherapy to be as high as 15%–30% of cases. Of these, up to 75% of patients experience symptoms while undergoing treatment, and 35% report behavioral and cognitive symptoms only after treatment has ended [16]. Most patients reported starting chemotherapy unaware of chemo brain as a potential side effect of the treatment. This initial unawareness often led to shock and panic, with many patients mentioning they learned of chemo brain almost by chance. The lack of an accepted concept of the chemo brain syndrome has hindered the adaptation of many patients, with the disorder often having to be hidden from others, causing the feeling of isolation with the problem and the anxiety associated with it to become personal, preventing patients from seeking support. Initial anxiety 2–6 years after treatment is replaced by frustration and acceptance with further diminishing hope of returning to the pre-chemotherapy state. Some studies have shown that cognitive deficits persist for 10 years after treatment, while others have found a significant improvement after 3 years [15].

ETIOLOGY AND MECHANISMS OF DEVELOPMENT

Cognitive impairment associated with chemotherapy develops through several potential mechanisms including damage to the blood–brain barrier, increased oxidative stress

and inflammation in the brain, and impaired neurogenesis, each leading to neuronal dysfunction [17]. Other potential mechanisms have been suggested, including inhibition of hippocampal neurogenesis and direct neuronal damage, as well as activation of secondary glial cells, i.e. microglia and astrocytes, production of proinflammatory cytokines, and defects in myelin-producing cells (oligodendrocyte lineage) [18]. A model of abnormalities in the brain default mode network as a potential biomarker of chemotherapy-induced damage is of interest. This system is believed to be responsible for such processes as implicit learning, autobiographical memory, prediction, analysis of what is happening at the moment, creativity, and self-reflection. A decrease in the level of activity of the default mode network explains the cognitive disorders in this group of patients [19]. Changes in brain activity (signals, cerebral blood flow) in patients with cancer have been observed in all functional networks, including prefrontal, parietal, occipital, temporal, and cerebellar regions. In addition to changes in brain activity, neuroimaging methods reveal decreased gray matter density in frontal, parietal, and temporal regions, and diffusion-weighted MRI data suggest decreased white matter integrity affecting the superior longitudinal fasciculus, corpus callosum, great forceps, and corona radiata, as well as altered structural connectivity throughout the brain network [20]. One study demonstrated evidence of a dramatic reduction in cortical thickness, along with an acceleration of predicted brain age from before treatment and 1 month after chemotherapy in breast cancer patients compared to controls. These results suggest that accelerated aging is one of the underlying mechanisms of chemo brain. These findings are particularly relevant because increasing brain age is associated with an increased risk of developing Alzheimer's disease in individuals with mild cognitive impairment. Notably, cancer survivors diagnosed with chemo brain tend to have a negative correlation of symptoms with time after treatment, suggesting that some recovery does occur. Nevertheless, deficits can be detected up to 10 years after treatment, suggesting permanent cognitive deficits in some of the cases [21].

MEDICINES COMMONLY ASSOCIATED WITH THE CHEMO BRAIN SYNDROME

Here we discuss the drugs most frequently used in cancer treatment protocols, some of which were used as chemotherapeutic treatment in our patient from the case report that we present below.

Platinum-based products (e.g., cisplatin, oxaliplatin) are widely used for chemotherapy. Prolonged treatment with cisplatin leads to neuronal mitochondrial dysfunction, which affects patients' cognitive functions. Multiple neurodegenerative diseases including Parkinson's, Alzheimer's disease, and post-chemotherapy cognitive impairment are associated with neuronal mitochondrial dysfunction [22–28]. Cisplatin penetrates the blood–brain barrier at levels sufficient to cause damage to hippocampal neurons and neural stem cells [29]. Astrocytes can respond to the "help" signal from damaged neurons, resulting in the transfer of mitochondria to them. Here a paradox arises: if astrocytic mitochondrial transfer leads to neuronal recovery, why do patients undergoing chemotherapy still experience neurotoxicity leading to cognitive impairment? One answer may be the fact that the regenerative capacity of astrocytes becomes deficient when patients are treated for long periods of time, which is characteristic of cisplatin chemotherapy [30]. Indeed, the risk of developing a chemo brain increases with the duration of treatment [31–34]. Exposure of mice to a single course of cisplatin treatment did not cause any cognitive deficits, whereas two courses of treatment caused a significant decrease in performance in cognitive function tests.

The use of doxorubicin in the treatment of various types of cancer [35] is associated with decreased long-term hippocampal potentiation, increased lipid peroxidation, and apoptosis [36]. Moreover, despite the low ability of doxorubicin to penetrate the blood–brain barrier, even its short-term administration has been shown to adversely affect hippocampal cell proliferation [37]. In addition, it has been reported that the combination of doxorubicin and cisplatin impairs cognitive function by increasing phosphorylation of proteins of extracellular signal-regulated kinase 1/2 (Erk1/2) and contributes to inflammation [38], production of reactive oxygen species, and further oxidative stress [39].

The primary mechanism of action of 5-fluorouracil (5-FU, capecitabine, etc.) is inhibition of thymidine synthesis and blocking DNA replication. 5-FU penetrates the blood–brain barrier and directly affects mitotic activity in the brain. It is one of the most common chemotherapeutic agents with long-lasting neurotoxicity. Early studies showed that three systemic injections of 5-FU (40 mg/kg) over five days impaired long-term survival of mature neurons for up to six months after 5-FU treatment in young adult mice. This suggests that slower hippocampal cell proliferation rate may not be evident immediately after 5-FU treatment, whereas long-term neuronal survival is affected [40].

Methotrexate is a dihydrofolate reductase inhibitor used for the treatment of leukemia, lymphoma, choriocarcinoma, breast and lung cancer, and other malignant neoplasms [41]. Methotrexate was found to cause depletion of the cellular potential of oligodendrocytes in human and murine white matter, leading to microglia activation [42]. Activated microglia induce a state of neurotoxic reactivity in astrocytes and disrupt oligodendroglial lineage dynamics and myelin plasticity, ultimately leading to abnormal myelination and cognitive impairment. The major delayed complication of methotrexate therapy is leukoencephalopathy [43]. Although this syndrome can be caused by intrathecal or high-dose systemic methotrexate alone, it is exacerbated by radiotherapy, especially if radiotherapy is administered

before or during methotrexate treatment. Symptoms of developing cognitive impairment appear months or years after the treatment. The clinical presentation ranges from mild cognitive impairment to severe progressive dementia [44]. Over time, many patients stabilize or improve after discontinuation of methotrexate, but in some patients the disease may progress and lead to death [45]. Such a diverse course with variants of increased neurotoxicity may be explained by genetic polymorphism, i.e. individual characteristics of methionine metabolism necessary for myelination in a particular patient [44].

One of the main manifestations of paclitaxel-induced neurotoxicity is the phenomenon of endoplasmic reticulum stress [46]. Neurotoxicity is characterized by predominantly symmetrical sensory axonal neuropathy affecting both large and small nerve fibers. Symptoms usually develop 1–3 weeks after treatment initiation [47].

THERAPEUTIC STRATEGIES TO PREVENT OR ALLEVIATE CHEMO BRAIN SYMPTOMS

Inaccurate diagnostic criteria and heterogeneous molecular mechanisms of brain alterations that are not fully understood have hindered effective research into the prevention and treatment of chemo brain. The typical patient receives a "cocktail" of drugs during chemotherapy. In this case, the molecular mechanisms of the chemo brain are a combination of the therapeutic effect and side effects of each drug and their synergism [48].

Inflammatory markers found in patients with Alzheimer's disease and vascular dementia, characterized by cognitive impairment, have prompted the inflammatory hypothesis and attempts to use aspirin in the treatment of the chemo brain syndrome. The anti-inflammatory drug aspirin was previously reported to prevent tumor-induced cognitive impairment in a murine model of metastatic breast cancer not treated with chemotherapy [49], but a similar study in paclitaxel-treated mice showed that aspirin was not effective in preventing or treating post-chemotherapy cognitive impairment [50].

Several epidemiologic studies and a case–control study have shown that diabetic patients receiving metformin may have a lower risk of developing cancer compared to those using other sugar-lowering medications. The reasons for this finding remain unclear and the results require confirmation in controlled studies [51]. This study inspired another one, on the effect of metformin on mice with doxorubicin-induced memory impairment, where no improvement was observed [52].

Research on the microbiota of patients with cancer is promising and represents a new field that is gradually coming to the forefront of clinical research in oncology from different perspectives [53]. A recent microbiological analysis of over 1,500 tumor and adjacent healthy tissue samples from breast, lung, ovarian, pancreatic, bone and brain cancers and melanoma revealed the presence of intracellular bacteria in both cancerous and immune cells. Importantly, each tumor type was characterized by a different composition of the intratumor microbiota [54]. Growing evidence from animal models and clinical trials emphasizes the significant impact of the gut microbiota on the efficacy of cancer therapy, mainly immuno- and chemotherapy. Restoration of microbiota with probiotics and prebiotics or fecal microbiota transplant may represent a new treatment modality for cancer survivors [55].

Fluvoxamine, a selective serotonin reuptake inhibitor widely used in clinical practice as an antidepressant, improves symptoms of depression resulting from an imbalance between pro- and anti-inflammatory cytokines [56], in addition to alleviating endoplasmic reticulum stress response *in vitro* and in animal models. In particular, fluvoxamine mitigates paclitaxel-induced neurotoxicity, partly through induction of Sig-1R in cell models, and reduces the infarction size after focal cerebral ischemia in mice [57].

In general, MAO inhibitor antidepressants have been shown to have anti-inflammatory effects [58], with the evidence of inhibition of anti-inflammatory cytokines and lymphocytes. Thus, antidepressants may have beneficial effects on chemotherapy-induced inflammation and post-chemotherapy cognitive impairment by restoring the balance of cytokines. In addition, the pro-cognitive effects of some antidepressants justify their use in patients with chemo brain [59].

Lithium is a drug that has been used for decades to treat psychiatric disorders, but evidence has recently emerged that it may have neuroprotective effects and is associated with less cognitive deficit in various models of brain injury, including after cranial irradiation [60, 61]. Whole brain radiotherapy in mice reduced neuronal proliferation in the subgranular zone of the dentate gyrus, which led to a long-term reduction in neurogenesis [62]. Lithium was found to protect irradiated hippocampal neurons in mice from apoptosis, which improved learning and memory function [61].

The growing popularity of phytotherapy, despite the great success in the development of synthetic drugs, is also reflected in research papers. Mohamed et al. found that epicatechin, a polyphenolic molecule derived from green tea, has a pronounced neuroprotective effect before doxorubicin injection and then during doxorubicin injections for another two weeks [63]. A similar neuroprotective effect was demonstrated for the pulp of mango fruit (*Mangifera indica*), turmeric rhizome (*Curcuma longa*), and Indian pennywort (*Centella asiatica*) [64]. Resveratrol, a natural nonflavonoid polyphenol present in various plant species including grapes, peanuts, berries, and red wine, exhibits anticancer activity against a wide range of cancers (prostate, skin, liver, ovarian, and lung cancers). An in vivo study showed that oral administration of resveratrol for three weeks, starting one week before treatment with docetaxel, adriamycin, and cyclophosphamide, improved cognitive impairment caused by

these drugs in mice [65]. In search of a potential phytochemical for the treatment of chemo brain, acetylcholinesterase inhibitors, such as donepezil and rivastigmine, actively used for cognitive impairment in dementia, were studied [66]. Therapy with doxorubicin in combination with donepezil fully restored cognitive function, mitigating the pathologic effects caused by doxorubicin without deteriorating the cytostatic effect [67]. The combined use of doxorubicin with galantamine only resulted in improved memory performance in mice [68].

CASE REPORT

Patient G., 74 years old; has a higher education. In 2018, she was diagnosed with de novo cancer of the sigmoid colon and underwent resection of the sigmoid colon. However, despite the surgical intervention, disease progression with metastases to the left lung occurred. The patient underwent resection of the left lung in 2020, followed by 6 courses of palliative chemotherapy (PCT) with XELOX (capecitabine and oxaliplatin) regimen. In January 2022, the patient underwent resection of liver metastases with additional 4 courses of PCT with XELIRI regimen (capecitabine and irinotecan). In May 2022, during the 3rd course of PCT, no evidence of progression of the primary tumor and metastases were revealed. However, in December 2022 negative dynamics in the lungs and liver was observed. From January to February 2023, two courses of immunotherapy with monoclonal antibody nivolumab were administered, with a positive effect. In June 2023, the 4th line of PCT was started (irinotecan and cetuximab). Final diagnosis: cancer of the sigmoid colon (pT4aN0M0; stage IIb, eligible for radical treatment); disease progression; metastases to the lungs and liver. Concurrent diagnoses: type II diabetes mellitus, subcompensated; hypertension, stage II, risk group 4; congestive heart failure, stage C, functional class II; systemic atherosclerosis. A total of 11 courses of chemotherapy with two courses of immunotherapy were performed during the treatment period.

After the next course of chemotherapy in August 2023, the patient developed an acute memory loss, self-care problems, and free movement deficits. She presented to the Internal Diseases Department with these complaints. The results of the brain MRI showed moderate external hydrocephalus ex vacuo and atrophic changes in the brain matter (cortical atrophy). Mental status at the time of examination: the patient is slow and confused, looks around, gives one-word answers to some questions (e.g., "what is your name?"). Disoriented in time and place. Motor coordination is disturbed; after sitting up with the help of doctors she remained in a sitting position for some time, but after a few minutes she asked to lie down. Muscle tone is weakened. Conclusion: chemo brain syndrome with severe cognitive impairment and an episode of confusion. The following treatment was recommended: dimethyloxobutylphosphonyl dimethylate solution (2 g IV), memantine hydrochloride (10 mg/day), fluvoxamine (100 mg/day), ethylmethylhydroxypyridine succinate solution (10 mL per 200 mL of 0.9 % NaCl solution IV). After several injections of dimethyloxobutylphosphonyl dimethylate, followed by ethylmethylhydroxypyridine succinate, she slept through the night. In the morning, the patient awoke, productive contact appeared, and orientation in time and space was restored. Purposeful movements were not recovered. The patient said that the previous night (before the administration of therapy) she thought she was in Israel, recognized the doctor, but could not understand why he was there and what he was doing. During the next four weeks, positive dynamics was noted in both cognitive and motor functions of the upper and lower extremities.

The presented case report shows how long the patient journey can be. The patient received a "cocktail" of chemotherapeutics and underwent several surgical procedures over 3 years. She presented to the Internal Diseases Department with acute memory loss, puzzling the doctors with the symptoms. It is worth mentioning the patient's comorbidity in this case. Despite the differences in the point of view of psychiatrists, who emphasize cognitive disorders in chemo brain, and neurologists, who mainly focus on accompanying motor disorders, our patient was prescribed practically the same treatment after appointments with these specialists, which highlights the importance of a multidisciplinary approach. The patient's rapid recovery from cognitive decline was also surprising for us, because the drugs prescribed (fluvoxamine, dimethyloxobutylphosphonyl dimethylate solution) were used off-label, i.e. they are not indicated for the treatment of the chemo brain syndrome, which requires further experimental and clinical research. As the review shows, there is no unified approach to the treatment of chemo brain. However, rapid recovery of cognitive functions was accompanied by a rather long and difficult process of returning to the previous level of motor activity, which was not described previously in this group of patients, and this is what we would like to point out to specialists.

ADDITIONAL INFORMATION

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REFERENCES

1. Ferlay J, Ervik M, Lam F, et al. Global cancer observatory: cancer today. Cancer today Gco. Iarc. Who. Int. 2020. [cited 2024 Aug 22]. Available from: https://gco.iarc.fr/today/en

2. Oncology in Russia. [cited 2024 Jun 18]. Available from: https://tochno.st/problems/oncology

3. de Martel C, Georges D, Bray F, et al. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *Lancet Glob Health.* 2020;8(2):e180–e190. doi: 10.1016/S2214-109X(19)30488-7

4. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA Cancer J Clin.* 2016;66(4):271–289. doi: 10.3322/caac.21349

5. Rowland JH, Kent EE, Forsythe LP, et al. Cancer survivorship research in Europe and the United States: Where have we been, where are we going, and what can we learn from each other? *Cancer.* 2013;119 Suppl 11(0 11):2094-2108. doi: 10.1002/cncr.28060

6. Gutmann DH. Clearing the Fog surrounding Chemobrain. *Cell.* 2019;176(1–2):2–4. doi: 10.1016/j.cell.2018.12.027

7. Levine PM, Silberfarb PM, Lipowski ZJ. Mental disorders in cancer patients: a study of 100 psychiatric referrals. *Cancer.* 1978;42(3):1385–1391. doi: 10.1002/1097-0142(197809)42:3<1385::aid-cncr2820420349>3.0.co;2-0

8. Ahles TA. Brain vulnerability to chemotherapy toxicities. *Psychooncology.* 2012;21(11):1141–1148. doi: 10.1002/pon.3196

9. Argyriou AA, Assimakopoulos K, Iconomou G, et al. Either called "chemobrain" or "chemofog," the long-term chemotherapy-induced cognitive decline in cancer survivors is real. *J Pain Symptom Manage.* 2011;41(1):126–139. doi: 10.1016/j.jpainsymman.2010.04.021

10. Lange M, Joly F, Vardy J, et al. Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. *Ann Oncol.* 2019;30(12):1925–1940. doi: 10.1093/annonc/mdz410

11. Vykhovanets NYu, Aleshechkin PA, Tomash LA. Arly and long-term neurological complications of chemotherapy in oncology (literature review). *Malignant Tumoursis.* 2022;12(4):41–49. EDN: JIYRGG doi: 10.18027/2224-5057-2022-12-4-41-49

12. Kholodova NB, Sotnikov VM, Dobrovolskaia NIu, Ponkratova IuA. Aspects of encephalopathy in oncologic patients after chemotherapy. *S.S. Korsakov Journal of Neurology and Psychiatry.* 2014;114(12):84–88. EDN: TIWRTT doi: 10.17116/jnevro201411412184-88

13. Iozefi D, Vinidchenko M, Demchenko N. Chemobrain, phenomenon of post-chemotherapy cognitive impairment. options of mri imaging and follow up monitoring. *Glavnyi Vrach Uga Russia.* 2017;(3):43–47. EDN: YZBIQZ

14. Lange M, Joly F, Vardy J, et al. Cancer-related cognitive impairment: An update on state of the art, detection, and management strategies in cancer survivors. *Ann Oncol.* 2019;30(12):1925–1940. doi: 10.1093/annonc/mdz410

15. Henderson FM, Cross AJ, Baraniak AR. 'A new normal with chemobrain': Experiences of the impact of chemotherapy-related cognitive deficits in long-term breast cancer survivors. *Health Psychol Open.* 2019;6(1):2055102919832234. doi: 10.1177/2055102919832234

16. Janelsins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatry.* 2014;26(1):102–113. doi: 10.3109/09540261.2013.864260

17. Fernandez HR, Varma A, Flowers SA, Rebeck GW. Cancer chemotherapy related cognitive impairment and the impact of the Alzheimer's disease risk factor APOE. *Cancers (Basel).* 2020;12(12):3842. doi: 10.3390/cancers12123842

18. Murillo LC, Sutachan JJ, Albarracín SL. An update on neurobiological mechanisms involved in the development of chemotherapy-induced cognitive impairment (CICI). *Toxicol Rep.* 2023;10:544–553. doi: 10.1016/j.toxrep.2023.04.015

19. Kesler SR. Default mode network as a potential biomarker of chemotherapy-related brain injury. *Neurobiol Aging.* 2014;35(Suppl 2):S11–S19. doi: 10.1016/j.neurobiolaging.2014.03.036

20. Li M, Caeyenberghs K. Longitudinal assessment of chemotherapy-induced changes in brain and cognitive functioning: A systematic review. *Neurosci Biobehav Rev.* 2018;92:304–317. doi: 10.1016/j.neubiorev.2018.05.019

21. Henneghan A, Rao V, Harrison RA, et al. Cortical brain age from pre-treatment to post-chemotherapy in patients with breast cancer. *Neurotox Res.* 2020;37(4):788–799. doi: 10.1007/s12640-019-00158-z

22. Burté F, Carelli V, Chinnery PF, Yu-Wai-Man P. Disturbed mitochondrial dynamics and neurodegenerative disorders. *Nat Rev Neurol.* 2015;11(1):11–24. doi: 10.1038/nrneurol.2014.228

23. Chiu GS, Maj MA, Rizvi S, et al. Pifithrin-m prevents cisplatin-induced chemobrain by preserving neuronal mitochondrial function. *Cancer Res.* 2017;77(3):742–752. doi: 10.1158/0008-5472.CAN-16-1817

24. Devine MJ, Kittler JT. Mitochondria at the neuronal presynapse in health and disease. *Nat Rev Neurosci.* 2018;19(2):63–80. doi: 10.1038/nrn.2017.170

25. Ren X, Keeney JTR, Miriyala S, et al. The triangle of death of neurons: oxidative damage, mitochondrial dysfunction, and loss of choline-containing biomolecules in brains of mice treated with doxorubicin. Advanced insights into mechanisms of chemotherapy induced cognitive impairment ('chemobrain') involving TNF-α. *Free Radic Biol Med.* 2019;134:1–8. doi: 10.1016/j.freeradbiomed.2018.12.029

26. Ma J, Huo XJ, Jarpe MB, et al. Pharmacological inhibition of HDAC6 reverses cognitive impairment and tau pathology as a result of cisplatin treatment. *Acta Neuropathol Commun.* 2018;6(1):103. doi: 10.1186/s40478-018-0604-3

27. Shirihai OS, Song M, Dorn GW 2nd. How mitochondrial dynamism orchestrates mitophagy. *Circ Res.* 2015;116(11):1835–1849. doi: 10.1161/CIRCRESAHA.116.306374

28. Mattson MP, Gleichmann M, Cheng A. Mitochondria in neuroplasticity and neurological disorders. *Neuron.* 2018;60(5):748–766. doi: 10.1016/j.neuron.2008.10.010

29. Andres AL, Gong X, Di K, Bota DA. Low-doses of cisplatin injure hippocampal synapses: a mechanism for 'chemo' brain? *Exp Neurol.* 2014;255:137–144. doi: 10.1016/j.expneurol.2014.02.020

30. English K, Shepherd A, Uzor NE, et al. Astrocytes rescue neuronal health after cisplatin treatment through mitochondrial transfer. *Acta Neuropathol Commun.* 2020;8(1):36. doi: 10.1186/s40478-020-00897-7

31. Wang XM, Walitt B, Saligan L, et al. Chemobrain: a critical review and causal hypothesis of link between cytokines and epigenetic reprogramming associated with chemotherapy. *Cytokine.* 2015;72(1):86–96. doi: 10.1016/j.cyto.2014.12.006

32. Gutmann DH. Clearing the Fog surrounding Chemobrain. *Cell.* 2019;176(1–2):2–4. doi: 10.1016/j.cell.2018.12.027

33. Asher A. Cognitive dysfunction among Cancer survivors. *Am J Phys Med Rehabil.* 2011;90(5 Suppl 1):S16–S26. doi: 10.1097/PHM.0b013e31820be463
34. Jiang T, Cadenas E. Astrocytic metabolic and inflammatory changes as a function of age. *Aging Cell.* 2014;13(6):1059–1067. doi: 10.1111/acel.12268
35. Thorn CF, Oshiro C, Marsh S, et al. Doxorubicin pathways: pharmacodynamics and adverse effects. *Pharmacogenetics Genom.* 2011;21(7):440–446. doi: 10.1097/FPC.0b013e32833ffb56
36. Alhowail AH, Bloemer J, Majrashi M, et al. Doxorubicin-induced neurotoxicity is associated with acute alterations in synaptic plasticity, apoptosis, and lipid peroxidation. *Toxicol. Mech. Methods.* 2019;29(6):457–466. doi: 10.1080/15376516.2019.1600086
37. Christie L-A, Acharya MM, Parihar VK, et al. Impaired cognitive function and hippocampal neurogenesis following cancer chemotherapy. *Clin. Cancer Res.* 2012;18(7):1954–1965. doi: 10.1158/1078-0432.CCR-11-2000
38. Salas-Ramirez KY, Bagnall C, Frias L, et al. Doxorubicin and cyclophosphamide induce cognitive dysfunction and activate the ERK and AKT signaling pathways. *Behav Brain Res.* 2015;292:133–141. doi: 10.1016/j.bbr.2015.06.028
39. Gaman A, Uzoni A, Popa-Wagner A, et al. The role of oxidative stress in etiopathogenesis of chemotherapy induced cognitive impairment (CICI) — "Chemobrain". *Aging Dis.* 2016;7(3):307–317. doi: 10.14336/AD.2015.1022
40. Sekeres MJ, Bradley-Garcia M, Martinez-Canabal A, Winocur G. Chemotherapy-induced cognitive impairment and hippocampal neurogenesis: a review of physiological mechanisms and interventions. *Int J Mol Sci.* 2021;22(23):12697. doi: 10.3390/ijms222312697
41. Fukuda Y, Li Y, Segal RA. A Mechanistic understanding of axon degeneration in chemotherapy-induced peripheral neuropathy. *Front Neurosci.* 2017;11:481. doi: 10.3389/fnins.2017.00481
42. Gibson EM, Nagaraja S, Ocampo A, et al. Methotrexate chemotherapy induces persistent tri-glial dysregulation that underlies chemotherapy-related cognitive impairment. *Cell.* 2019;176(1–2):43–55.e13. doi: 10.1016/j.cell.2018.10.049
43. Zvonkov EE, Koroleva DA, Gabeeva NG et al. high-dose chemotherapy for primary diffuse large B-cell lymphoma of the central nervous system. Interim results of the CNS-2015 protocol. *Russian Journal of Hematology and Transfusiology.* 2019;64(4):447–461. EDN: ZANTQB doi: 10.35754/0234-5730-2019-64-4-447-461
44. Penzin OV, Shvyrev SL, Zarubina TV. Results of implementation in the clinical practice the prognostic model for assessing the risk development of mielotoxic complications of chemotherapy. *Journal of New Medical Technologies.* 2019;26(1):112–118. EDN: ZALHUT doi: 10.24411/1609-2163-2019-16061
45. Mesheryakova AV, Zorkin EK. Deficiency of the peripheral nervous system in the structure of post-chemotherapeutic complications. Literature review. *International Journal of Humanities and Natural Sciences.* 2017;(9):35–40. EDN: ZHZKZR
46. Tanimukai H, Kudo T. Fluvoxamine alleviates paclitaxel-induced neurotoxicity. *Biochem Biophys Rep.* 2015;4:202–206. doi: 10.1016/j.bbrep.2015.09.014
47. De Man FM, Goey AKL, van Schaik RHN, et al. Individualization of irinotecan treatment: a review of pharmacokinetics, pharmacodynamics, and pharmacogenetics. *Clin Pharmacokinet.* 2018;57(10):1229–1254. doi: 10.1007/ s40262-018-0644-7
48. Nguyen LD, Ehrlich BE. Cellular mechanisms and treatments for chemobrain: insight from aging and neurodegenerative diseases. *EMBO Mol Med.* 2020;12(6):e12075. doi: 10.15252/emmm.202012075
49. Walker AK, Chang A, Ziegler AI, et al. Low dose aspirin blocks breast cancer-induced cognitive impairment in mice. *PLoS One.* 2018;13(12):e0208593. doi: 10.1371/journal.pone.0208593
50. Chang A, Chung NC, Lawther AJ, et al. The anti-inflammatory drug aspirin does not protect against chemotherapy-induced memory impairment by paclitaxel in mice. *Front Oncol.* 2020;10:564965. doi: 10.3389/fonc.2020.564965
51. Chong CR, Chabner BA. Mysterious metformin. *Oncologist.* 2009;14(12):1178–1181. doi: 10.1634/theoncologist.2009-0286
52. Alharbi I, Alharbi H, Almogbel Y, et al. Effect of metformin on doxorubicin-induced memory dysfunction. *Brain Sci.* 2020;10(3):152. doi: 10.3390/brainsci10030152
53. Xavier JB, Young VB, Skufca J, et al. The cancer microbiome: distinguishing direct and indirect effects requires a systemic view. *Trends Cancer.* 2020;6(3):192–204. doi: 10.1016/j.trecan.2020.01.004
54. Nejman D, Livyatan I, Fuks G, et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. *Science.* 2020;368(6494):973–980. doi: 10.1126/science.aay9189
55. Ciernikova S, Mego M, Chovanec M. Exploring the potential role of the gut microbiome in chemotherapy-induced neurocognitive disorders and cardiovascular toxicity. *Cancers (Basel).* 2021;13(4):782. doi: 10.3390/cancers13040782
56. Das A, Ranadive N, Kinra M, et al. An overview on chemotherapy-induced cognitive impairment and potential role of antidepressants. *Curr Neuropharmacol.* 2020;18(9):838–851. doi: 10.2174/1570159X18666200221113842
57. Omi T, Tanimukai H, Kanayama D, et al. Fluvoxamine alleviates ER stress via induction of Sigma-1 receptor. *Cell Death Dis.* 2014;5(7):e1332. doi: 10.1038/cddis.2014.301
58. Wood LJ, Nail LM, Perrin NA, et al. The cancer chemotherapy drug etoposide (VP-16) induces proinflammatory cytokine production and sickness behavior-like symptoms in a mouse model of cancer chemotherapy-related symptoms. *Biol Res Nurs.* 2006;8(2):157–169. doi: 10.1177/1099800406290932
59. Walker FR. A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? *Neuropharmacology.* 2013;67:304–317. doi: 10.1016/j.neuropharm.2012.10.002
60. Rowe MK, Chuang DM. Lithium neuroprotection: molecular mechanisms and clinical implications. *Expert Rev Mol Med.* 2004;6(21):1–18. doi: 10.1017/S1462399404008385
61. Yazlovitskaya EM, Edwards E, Thotala D, et al. Lithium treatment prevents neurocognitive deficit resulting from cranial irradiation. *Cancer Res.* 2006;66(23):11179–11186. doi: 10.1158/0008-5472.CAN-06-2740
62. Rola R, Raber J, Rizk A, et al. Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. *Exp Neurol.* 2004;188(2):316–330. doi: 10.1016/j.expneurol.2004.05.005
63. Mohamed RH, Karam RA, Amer MG. Epicatechin attenuates doxorubicin-induced brain toxicity: critical role of TNF-α, iNOS and NF-κB. *Brain Res Bull.* 2011;86(1–2):22–28. doi: 10.1016/j.brainresbull.2011.07.001
64. John J, Kinra M, Ranadive N, et al. Neuroprotective effect of Mulmina Mango against chemotherapy-induced cognitive decline in

mouse model of mammary carcinoma. *Sci. Rep.* 2022;12(1):3072. doi: 10.1038/s41598-022-06862-9

65. Jaiswara PK, Shukla SK. Chemotherapy-mediated neuronal aberration. *Pharmaceuticals (Basel).* 2023;16(8):1165. doi: 10.3390/ph16081165

66. Howes MJ, Perry E. The role of phytochemicals in the treatment and prevention of dementia. *Drugs Aging.* 2011;28(6):439–468. doi: 10.2165/11591310-000000000-00000.

67. Ongnok B, Khuanjing T, Chunchai T, et al. Donepezil protects against doxorubicin-induced chemobrain in rats via attenuation of inflammation and oxidative stress without interfering with doxorubicin efficacy. *Neurotherapeutics.* 2023;20(2):602–603. doi: 10.1007/s13311-023-01347-7

68. Alsikhan RS, Aldubayan MA, Almami IS, Alhowail AH. Protective effect of galantamine against doxorubicin-induced neurotoxicity. *Brain Sci.* 2023;13(6):971. doi: 10.3390/brainsci13060971

СПИСОК ЛИТЕРАТУРЫ

1. Ferlay J., Ervik M., Lam F., et al. Global cancer observatory: cancer today. Cancer today Gco. Iarc. Who. Int. 2020. Режим доступа: https://gco.iarc.fr/today/en Дата обращения: 22.08.2024.

2. Онкология в России. Режим доступа: https://tochno.st/problems/oncology Дата обращения: 22.08.2024.

3. de Martel C., Georges D., Bray F., et al. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis // Lancet Glob Health. 2020. Vol. 8, N 2. P. e180–e190. doi: 10.1016/S2214-109X(19)30488-7

4. Miller K.D., Siegel R.L., Lin C.C., et al. Cancer treatment and survivorship statistics, 2016 // CA Cancer J Clin. 2016. Vol. 66, N 4. P. 271–289. doi: 10.3322/caac.21349

5. Rowland J.H., Kent E.E., Forsythe L.P., et al. Cancer survivorship research in Europe and the United States: Where have we been, where are we going, and what can we learn from each other? // Cancer. 2013. Vol. 119, Suppl 11(0 11). P. 2094–2108. doi: 10.1002/cncr.28060

6. Gutmann D.H. Clearing the Fog surrounding Chemobrain // Cell. 2019. Vol. 176, N 1–2. P. 2–4. doi: 10.1016/j.cell.2018.12.027

7. Levine P.M, Silberfarb P.M, Lipowski Z.J. Mental disorders in cancer patients: a study of 100 psychiatric referrals // Cancer. 1978. Vol. 42, N 3. P. 1385–1391. doi: 10.1002/1097-0142(197809)42:3<1385::aid-cncr2820420349>3.0.co;2-0

8. Ahles T.A. Brain vulnerability to chemotherapy toxicities // Psychooncology. 2012. Vol. 21, N 11. P. 1141–1148. doi: 10.1002/pon.3196

9. Argyriou A.A, Assimakopoulos K., Iconomou G., et al. Either called "chemobrain" or "chemofog," the long-term chemotherapy-induced cognitive decline in cancer survivors is real // J Pain Symptom Manage. 2011. Vol. 41, N 1. P. 126–139. doi: 10.1016/j.jpainsymman.2010.04.021

10. Lange M., Joly F., Vardy J., et al. Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors // Ann Oncol. 2019. Vol. 30, N 12. P. 1925–1940. doi: 10.1093/annonc/mdz410

11. Выхованец Н.Ю., Алёшечкин П.А., Томаш Л.А., и др. Ранние и отдалённые неврологические осложнения химиотерапии в онкологии (обзор литературы) // Злокачественные опухоли. 2022. Т. 12, № 4. P. 41–49. EDN: JIYRGG doi: 10.18027/2224-5057-2022-12-4-41-49

12. Холодова Н.Б., Сотников В.М., Добровольская Н.Ю., Понкратова Ю.А. Особенности проявления энцефалопатии, возникшей после химиотерапии онкологических заболеваний // Журнал неврологии и психиатрии им. С.С. Корсакова. 2014. Т. 114, № 12. P. 84–88. EDN: TIWRTT doi: 10.17116/jnevro201411412184-88

13. Иозефи Д.Я., Винидченко М.А., Демченко Н.С. Проблема токсической энцефалопатии, ассоциированной с химиотерапией у онкологических больных, обзор возможностей магнитно-резонансной визуализации и нейроонкологического мониторинга // Главный врач Юга России. 2017. № 3. С. 43–47. EDN: YZBIQZ

14. Lange M., Joly F., Vardy J., et al. Cancer-related cognitive impairment: An update on state of the art, detection, and management strategies in cancer survivors // Ann Oncol. 2019. Vol. 30, N 12. P. 1925–1940. doi: 10.1093/annonc/mdz410

15. Henderson F.M., Cross A.J., Baraniak A.R. 'A new normal with chemobrain': Experiences of the impact of chemotherapy-related cognitive deficits in long-term breast cancer survivors // Health Psychol Open. 2019. Vol. 6, N 1. P. 2055102919832234. doi: 10.1177/2055102919832234

16. Janelsins M.C., Kesler S.R., Ahles T.A., Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment // Int Rev Psychiatry. 2014. Vol. 26, N 1. P. 102–113. doi: 10.3109/09540261.2013.864260

17. Fernandez H.R., Varma A., Flowers S.A., Rebeck G.W. Cancer chemotherapy related cognitive impairment and the impact of the Alzheimer's disease risk factor APOE // Cancers (Basel). 2020. Vol. 12, N 12. P. 3842. doi: 10.3390/cancers12123842

18. Murillo L.C., Sutachan J.J., Albarracín S.L. An update on neurobiological mechanisms involved in the development of chemotherapy-induced cognitive impairment (CICI) // Toxicol Rep. 2023. Vol. 10. P. 544–553. doi: 10.1016/j.toxrep.2023.04.015

19. Kesler S.R. Default mode network as a potential biomarker of chemotherapy-related brain injury // Neurobiol Aging. 2014. Vol. 35, Suppl 2. P. S11–S19. doi: 10.1016/j.neurobiolaging.2014.03.036

20. Li M., Caeyenberghs K. Longitudinal assessment of chemotherapy-induced changes in brain and cognitive functioning: A systematic review // Neurosci Biobehav Rev. 2018. Vol. 92. P. 304–317. doi: 10.1016/j.neubiorev.2018.05.019

21. Henneghan A., Rao V., Harrison R.A., et al. Cortical brain age from pre-treatment to post-chemotherapy in patients with breast cancer // Neurotox Res. 2020. Vol. 37, N 4. P. 788–799. doi: 10.1007/s12640-019-00158-z

22. Burté F., Carelli V., Chinnery P.F., Yu-Wai-Man P. Disturbed mitochondrial dynamics and neurodegenerative disorders // Nat Rev Neurol. 2015. Vol. 11, N 1. P. 11–24. doi: 10.1038/nrneurol.2014.228

23. Chiu G.S., Maj M.A., Rizvi S., et al. Pifithrin-m prevents cisplatin-induced chemobrain by preserving neuronal mitochondrial function // Cancer Res. 2017. Vol. 77, N 3. P. 742–752. doi: 10.1158/0008-5472.CAN-16-1817

24. Devine M.J., Kittler J.T. Mitochondria at the neuronal presynapse in health and disease // Nat Rev Neurosci. 2018. Vol. 19, N 2. P. 63–80. doi: 10.1038/nrn.2017.170

25. Ren X., Keeney J.T.R., Miriyala S., et al. The triangle of death of neurons: oxidative damage, mitochondrial dysfunction, and loss of choline-containing biomolecules in brains of mice treated with doxorubicin. Advanced insights into mechanisms of chemotherapy induced cognitive impairment ('chemobrain') involving TNF-α // Free Radic Biol Med. 2019. Vol. 134. P. 1–8. doi: 10.1016/j.freeradbiomed.2018.12.029

26. Ma J., Huo X.J., Jarpe M.B., et al. Pharmacological inhibition of HDAC6 reverses cognitive impairment and tau pathology as a result of cisplatin treatment // Acta Neuropathol Commun. 2018. Vol. 6, N 1. P. 103. doi: 10.1186/s40478-018-0604-3
27. Shirihai O.S., Song M., Dorn G.W. 2nd. How mitochondrial dynamism orchestrates mitophagy // Circ Res. 2015. Vol. 116, N 11. P. 1835–1849. doi: 10.1161/CIRCRESAHA.116.306374
28. Mattson M.P., Gleichmann M., Cheng A. Mitochondria in neuroplasticity and neurological disorders // Neuron. 2018. Vol. 60, N 5. P. 748–766. doi: 10.1016/j.neuron.2008.10.010
29. Andres A.L., Gong X., Di K., Bota D.A. Low-doses of cisplatin injure hippocampal synapses: a mechanism for 'chemo' brain? // Exp Neurol. 2014. Vol. 255. P. 137–144. doi: 10.1016/j.expneurol.2014.02.020
30. English K., Shepherd A., Uzor N.E., et al. Astrocytes rescue neuronal health after cisplatin treatment through mitochondrial transfer // Acta Neuropathol Commun. 2020. Vol. 8, N 1. P. 36. doi: 10.1186/s40478-020-00897-7
31. Wang X.M., Walitt B., Saligan L., et al. Chemobrain: a critical review and causal hypothesis of link between cytokines and epigenetic reprogramming associated with chemotherapy // Cytokine. 2015. Vol. 72, N 1. P. 86–96. doi: 10.1016/j.cyto.2014.12.006
32. Gutmann DH. Clearing the Fog surrounding Chemobrain // Cell. 2019. Vol. 176, N 1–2. P. 2–4. doi: 10.1016/j.cell.2018.12.027
33. Asher A. Cognitive dysfunction among cancer survivors // Am J Phys Med Rehabil. 2011. Vol. 90, N 5, Suppl 1. P. S16-S26. doi: 10.1097/PHM.0b013e31820be463
34. Jiang T., Cadenas E. Astrocytic metabolic and inflammatory changes as a function of age // Aging Cell. 2014. Vol. 13, N 6. P. 1059–1067. doi: 10.1111/acel.12268
35. Thorn C.F., Oshiro C., Marsh S., et al. Doxorubicin pathways: pharmacodynamics and adverse effects // Pharmacogenetics Genom. 2011. Vol. 21, N 7. P. 440–446. doi: 10.1097/FPC.0b013e32833ffb56
36. Alhowail A.H., Bloemer J., Majrashi M., et al. Doxorubicin-induced neurotoxicity is associated with acute alterations in synaptic plasticity, apoptosis, and lipid peroxidation // Toxicol. Mech. Methods. 2019. Vol. 29, N 6. P. 457–466. doi: 10.1080/15376516.2019.1600086
37. Christie L.-A., Acharya M.M., Parihar V.K., et al. Impaired cognitive function and hippocampal neurogenesis following cancer chemotherapy // Clin Cancer Res. 2012. Vol. 18, N 7. P. 1954–1965. doi: 10.1158/1078-0432.CCR-11-2000
38. Salas-Ramirez K.Y., Bagnall C., Frias L., et al. Doxorubicin and cyclophosphamide induce cognitive dysfunction and activate the ERK and AKT signaling pathways // Behav Brain Res. 2015. Vol. 292. P. 133–141. doi: 10.1016/j.bbr.2015.06.028
39. Gaman A., Uzoni A., Popa-Wagner A., et al. The role of oxidative stress in etiopathogenesis of chemotherapy induced cognitive impairment (CICI) — "Chemobrain" // Aging Dis. 2016. Vol. 7, N 3. P. 307–317. doi: 10.14336/AD.2015.1022
40. Sekeres M.J., Bradley-Garcia M., Martinez-Canabal A., Winocur G. Chemotherapy-induced cognitive impairment and hippocampal neurogenesis: a review of physiological mechanisms and interventions // Int J Mol Sci. 2021. Vol. 22, N 23. P. 12697. doi: 10.3390/ijms222312697
41. Fukuda Y., Li Y., Segal R.A. A mechanistic understanding of axon degeneration in chemotherapy-induced peripheral neuropathy // Front Neurosci. 2017. Vol. 11. P. 481. doi: 10.3389/fnins.2017.00481
42. Gibson E.M., Nagaraja S., Ocampo A., et al. Methotrexate chemotherapy induces persistent tri-glial dysregulation that underlies chemotherapy-related cognitive impairment // Cell. 2019. Vol. 176, N 1–2. P. 43–55.e13. doi: 10.1016/j.cell.2018.10.049
43. Звонков Е.Е., Королёва Д. А., Габеева Н. Г., и др. Высокодозная химиотерапия первичной диффузной В-крупноклеточной лимфомы центральной нервной системы. Промежуточные результаты протокола CNS2015 // Гематология и трансфузиология. 2019. Т. 64, № 4. С. 447–461. EDN: ZANTQB doi: 10.35754/0234-5730-2019-64-4-447-461
44. Пензин О. В., Швырёв С.Л., Зарубина Т.В. Результаты внедрения в клиническую практику прогностической модели для оценки риска развития миелотоксических осложнений химиотерапии // Вестник новых медицинских технологий. 2019. Т. 26, № 1. С. 112–118. EDN: ZALHUT doi: 10.24411/1609-2163-2019-16061
45. Мещерякова А. В., Зоркин Е.К. Поражение периферической нервной системы в структуре постхимиотерапевтических осложнений. Обзор литературы // Международный журнал гуманитарных и естественных наук. 2017. № 9. С. 35–40. EDN: ZHZKZR
46. Tanimukai H., Kudo T. Fluvoxamine alleviates paclitaxel-induced neurotoxicity // Biochem Biophys Rep. 2015. Vol. 4. P. 202–206. doi: 10.1016/j.bbrep.2015.09.014
47. De Man F.M., Goey A.K.L., van Schaik R.H.N., et al. Individualization of irinotecan treatment: a review of pharmacokinetics, pharmacodynamics, and pharmacogenetics // Clin Pharmacokinet. 2018. Vol. 57, N 10. P. 1229–1254. doi: 10.1007/ s40262-018-0644-7
48. Nguyen L.D., Ehrlich B.E. Cellular mechanisms and treatments for chemobrain: insight from aging and neurodegenerative diseases // EMBO Mol Med. 2020. Vol. 12, N 6. P. e12075. doi: 10.15252/emmm.202012075
49. Walker A.K., Chang A., Ziegler A.I., et al. Low dose aspirin blocks breast cancer-induced cognitive impairment in mice // PLoS One. 2018. Vol. 13, N 12. P. e0208593. doi: 10.1371/journal.pone.0208593
50. Chang A., Chung N.C., Lawther A.J., et al. The anti-inflammatory drug aspirin does not protect against chemotherapy-induced memory impairment by paclitaxel in mice // Front Oncol. 2020. Vol. 10. P. 564965. doi: 10.3389/fonc.2020.564965
51. Chong C.R., Chabner B.A. Mysterious metformin // Oncologist. 2009. Vol. 14, N 12. P. 1178–1181. doi: 10.1634/theoncologist.2009-0286
52. Alharbi I., Alharbi H., Almogbel Y., et al. Effect of metformin on doxorubicin-induced memory dysfunction // Brain Sci. 2020. Vol. 10, N 3. P. 152. doi: 10.3390/brainsci10030152
53. Xavier J.B., Young V.B., Skufca J., et al. The cancer microbiome: distinguishing direct and indirect effects requires a systemic view // Trends Cancer. 2020. Vol. 6, N 3. P. 192–204. doi: 10.1016/j.trecan.2020.01.004
54. Nejman D., Livyatan I., Fuks G., et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria // Science. 2020. Vol. 368, N 6494. P. 973–980. doi: 10.1126/science.aay9189
55. Ciernikova S., Mego M., Chovanec M. Exploring the potential role of the gut microbiome in chemotherapy-induced neurocognitive disorders and cardiovascular toxicity // Cancers (Basel). 2021. Vol. 13, N 4. P. 782. doi: 10.3390/cancers13040782
56. Das A., Ranadive N., Kinra M., et al. An overview on chemotherapy-induced cognitive impairment and potential role of antidepressants // Curr Neuropharmacol. 2020. Vol. 18, N 9. P. 838–851. doi: 10.2174/1570159X18666200221113842
57. Omi T., Tanimukai H., Kanayama D., et al. Fluvoxamine alleviates ER stress via induction of Sigma-1 receptor // Cell Death Dis. 2014. Vol. 5, N 7. P. e1332. doi: 10.1038/cddis.2014.301

58. Wood L.J., Nail L.M., Perrin N.A., et al. The cancer chemotherapy drug etoposide (VP-16) induces proinflammatory cytokine production and sickness behavior-like symptoms in a mouse model of cancer chemotherapy-related symptoms // Biol Res Nurs. 2006. Vol. 8, N 2. P. 157–169. doi: 10.1177/1099800406290932
59. Walker F.R. A critical review of the mechanism of action for the selective serotonin reuptake inhibitors: do these drugs possess anti-inflammatory properties and how relevant is this in the treatment of depression? // Neuropharmacology. 2013. Vol. 67. P. 304–317. doi: 10.1016/j.neuropharm.2012.10.002
60. Rowe M.K., Chuang D.M. Lithium neuroprotection: molecular mechanisms and clinical implications // Expert Rev Mol Med. 2004. Vol. 6, N 21. P. 1–18. doi: 10.1017/S1462399404008385
61. Yazlovitskaya E.M., Edwards E., Thotala D., et al. Lithium treatment prevents neurocognitive deficit resulting from cranial irradiation // Cancer Res. 2006. Vol. 66, N 23. P. 11179–11186. doi: 10.1158/0008-5472.CAN-06-2740
62. Rola R., Raber J., Rizk A., et al. Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice // Exp neurol. 2004. Vol. 188, N 2. P. 316–330. doi: 10.1016/j.expneurol.2004.05.005
63. Mohamed R.H., Karam R.A., Amer M.G. Epicatechin attenuates doxorubicin-induced brain toxicity: critical role of TNF-α, iNOS and NF-κB // Brain Res Bull. 2011. Vol. 86, N 1–2. P. 22–28. doi: 10.1016/j.brainresbull.2011.07.001
64. John J., Kinra M., Ranadive N., et al. Neuroprotective effect of Mulmina Mango against chemotherapy-induced cognitive decline in mouse model of mammary carcinoma // Sci Rep. 2022. Vol. 12, N 1. P. 3072. doi: 10.1038/s41598-022-06862-9
65. Jaiswara P.K., Shukla S.K. Chemotherapy-mediated neuronal aberration // Pharmaceuticals (Basel). 2023. Vol. 16, N 8. P. 1165. doi: 10.3390/ph16081165
66. Howes M.J., Perry E. The role of phytochemicals in the treatment and prevention of dementia // Drugs Aging. 2011. Vol. 28, N 6. P. 439–468. doi: 10.2165/11591310-000000000-00000
67. Ongnok B., Khuanjing T., Chunchai T., et al. Donepezil protects against doxorubicin-induced chemobrain in rats via attenuation of inflammation and oxidative stress without interfering with doxorubicin efficacy // Neurotherapeutics. 2023. Vol. 20, N 2. P. 602–603. doi: 10.1007/s13311-023-01347-7
68. Alsikhan R.S., Aldubayan M.A., Almami I.S., Alhowail A.H. Protective effect of galantamine against doxorubicin-induced neurotoxicity // Brain Sci. 2023. Vol. 13, N 6. P. 971. doi: 10.3390/brainsci13060971

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