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N. P. Ilyaev[1], O. A. Maksakova[1], O. S. Zaitsev *[1, 2], D. I. Pitskhelauri[1], A. P. Troitskiy[1], G. L. Kobiakov[1], A. A. Poddubskiy[1], S. A. Maryashev[1], A. E. Bykanov[1]

[1] — Federal State Autonomous Institution «National Medical Research Center for Neurosurgery Named After N. N. Burdenko», Moscow, Russia

[2] — Privolzhsky Research Medical University, N. Novgorod, Russia

PRIMARY CEREBRAL LYMPHOMA. MENTAL DISORDERS AFTER BIOPSY (CASE REPORT)

Abstract

The article reviews the literature on the diagnosis and treatment of primary lymphomas of the central nervous system and describes a case of mental disorder before and after surgery in a patient with lymphoma of the third ventricle. Using an interdisciplinary approach, psychopathological dynamics is analyzed taking into account the structural and functional state of the brain, which allowed to clarify the possible causes of mental disorders and methods of treatment. Acute onset of confusion and headache was associated with disorders of the liquor outflow, due to the localization of the tumor. The reason for the disintegration of consciousness after surgery was brain hypoxia and the instability of connections between cerebral structures associated with it. The peculiarity of the consciousness recovery could be determined by premorbid personal traits.

Key words: *brain lymphoma; third brain ventricle; biopsy; disintegration of consciousness; mental disorders, psychopathology; psychopharmacotherapy*

Conflict of interests

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Lymphoma is a disease of lymphoid and myeloid tissue. Primary lymphoma of the central nervous system (PLCNS) is a rare form of non-Hodgkin lymphomas that occurs in the central nervous system and does not extend beyond it. The incidence of this pathology is 4–7 cases per 1,000,000 people [1–3]. PLCNS was first isolated as a nosological unit more than 80 years ago [4], then it was classified as sarcoma from reticular cells and microglioma. Improvement of diagnostic methods made it possible to finally confirm the lymphoid nature of PLCNS and contributed to an improvement in its detectability [5], which led to an increase in scientific and practical interest in this disease, including in special literature reviews [6, 7].

Localization of PLCNS is very diverse: single or multiple foci in the brain and spinal cord, eyeballs, in the structures of the anterior optic tract [8] and in

*Contacts: Oleg S. Zaitsev, e-mail: OZaitsev@nsi.ru

cerebral meninges. Most often, cerebral lymphoma is supratentorial, in 15% of cases — infratentorial. In 60% of cases, the tumor is localized in the paraventricular zone (thalamus, basal ganglia, corpus callosum). Frontal lobes are involved in 20% of cases, temporal lobes — 18%, parietal — 15% and occipital — in 4% of cases [9].

At the initial detection, foci of various sizes are found, most often — clearly visible formations more than 2 cm in diameter. Visualization with contrast enhancement reveals a dense, homogeneous formation in immunocompetent patients and less formed, heterogeneous — in HIV-associated PLCNS. Peritumoral edema and a local mass effect are observed less frequently than with intracerebral neoplasms of a different etiology; in addition, calcifications or hemorrhages in the tumor are not typical for PLCNS [10].

It is believed that in the pathogenesis of lymphoma, both unfavorable external factors and a decrease in the effectiveness of the immune system play a role. Among the possible predisposing factors are the effects of radiation and vinyl chloride gas, tobacco, as well as the use of products containing carcinogens. Immunodeficiency conditions that contribute to the occurrence of lymphomas can be caused by HIV infection, Epstein—Barr virus, the effects of radiation therapy and organ transplantation.

People with intact immunity are more likely to suffer PLCNS after the age of 50 years. Symptomatically, the disease manifests itself fairly quickly. Apparently, in the early stages of its growth, any specific symptoms are absent. Primary symptoms occur when the local volume of the tumor tissue increases due to increased intracranial pressure, eye damage, compression of the surrounding brain tissue or conduction pathways. In general, pathological signs are determined by the volume and localization of intracranial lesions, however, there are some differences in the manifestations of this disease from intracranial tumors of a different genesis. So, in contrast to gliomas, meningiomas, and secondary tumor lesions of the central nervous system, structural epilepsy relatively rarely develops in PLCNS. At the same time, focal neurological symptoms, personality changes, headaches and drowsiness are observed in most cases [11]: focal neurological deficit is detected in 70% of cases of PLCNS, up to 43% of patients show behavioral or neuropsychiatric changes that, due to their nonspecificity, delay diagnosis; in 33% of cases there are signs of increased intracranial pressure (headache, nausea and vomiting), in 14% — epileptic seizures, in 4% — visual impairment.

Cerebral lymphoma often manifests with local symptoms. Cognitive and personality changes, as with other intracerebral tumors, can be observed at different locations (frontal lobes, corpus callosum, periventricular structures). Symptoms due to the mass effect (headache, nausea, vomiting) are less common than with gliomas and metastases.

Psychopathological symptoms are usually observed in combination with focal neurological deficit [12]. Some observations have shown a predominance of mental disorders in PLCNS. Melinz et al. (2002) described a patient with mania [13]. R. Fisher and C. Harper in 1983 [14] observed a case with PLCNS affecting the limbic system, which was manifested by depression and periodic vomiting. In recent work, Chinese colleagues showed that at the early stages, primary lymphoma can affect mood: the main and dominant symptom of the patient was depression, which was treated with drug therapy for a long time before the correct diagnosis was established [15].

Due to the relative rarity of primary cerebral lymphoma, a standard for managing patients with this pathology does not currently exist. To this day, the issue of the possibility and necessity of radiation therapy as a first-line treatment has been under discussion.

Patients with PLCNS sometimes require the administration of drugs to correct neurological disorders. However, caution is needed here: for example, the prophylactic use of antiepileptic drugs should be avoided, not only because of the lack of evidence of the efficacy of such prevention, but also because of the likelihood of increased toxic effects of chemotherapy.

Surgical methods are used mainly for diagnostic purposes through stereotactic biopsy. The radical removal of primary cerebral lymphoma does not increase life expectancy, but can lead to neurological disorders. When the tumor is localized in hard-to-reach places (brain stem), an open biopsy is more preferable. Surgical treatment is used for decompression with a rapid increase in the severity of the condition associated with impaired cerebrospinal fluid outflow and intracranial hypertension

[16]. As recently as 20 years ago, it was believed that the prognosis for primary lymphoma is unfavorable: life expectancy of patients ranged from two months to two years [17]. However, this pessimistic forecast is currently being revised [18].

The use of modern chemotherapy methods has significantly improved treatment outcomes. With the introduction of specific chemotherapy, there was a possibility of long-term complete remissions in more than 50% of cases [19].

The choice of chemotherapeutic drugs is determined by their activity and ability to penetrate the blood—brain barrier. Combined chemoradiotherapy provides higher patient survival [20].

The risk of relapse for patients receiving combination therapy is approximately 50%. Most relapses occur within the first 2 years from the end of the initial therapy, but later relapses are possible — within 5 years after completion of treatment. The risk of relapse is higher (more than 10%) in patients with systemic lymphoma, eye lymphoma and leptomeningitis [21]. The tumor recurs either at the site of the primary focus, or in other parts of the brain. Relapses worsen the prognosis, but with continued treatment, the chances of achieving a second remission are quite high. Some patients remain sensitive to therapy, despite numerous relapses. In patients with previous total head irradiation, there is a high risk of toxic damage to the nervous system. In elderly patients, the risk of developing a progressive neurological syndrome characterized by dementia, ataxia and dysuria is especially high. Typically, symptoms of a neurotoxic damage appear within the first year of treatment.

Despite the relatively large number of studies on the diagnosis and treatment of primary cerebral lymphoma, we have not been able to find any publications devoted to or describing mental disorders in this pathology or as a result of its treatment. It is generally recognized that the primary lymphatic tumor of the brain does not have specific psychopathological features, its symptoms are determined by localization. Without laying claim to participate in the diagnosis of the disease, the psychiatrist is faced with both the psychopathological manifestations of the disease and the consequences of the therapeutic effect. The relative rarity of the disease means every case when "something went wrong" is recorded.

Case Report

Female patient P., 53 years old, right-handed.

A trained doctor, she worked as the head of the laboratory.

She grew and developed in accordance with age; family history was without psychopathological disorders.

According to relatives, she aspired to be a leader and was responsible. At the same time, her husband noted that she "was tyrannical, with a bad temper, she took everything into her own hands, commanded everyone."

According to the discharge record presented, the disease first appeared in the form of strong and prolonged chills. She did not seek medical help. Five days later, dizziness appeared, followed by vomiting. Two days later, relatives noticed lethargy, impaired memory, disorientation in place and time. In the evening, she was admitted by the ambulance team in the intensive care unit of the local hospital. After 18 days, she was transferred to the intensive care unit of the N. N. Burdenko National Medical Research Center of Neurosurgery."

Via spiral computed tomography (SCT) of the brain before surgery (see Fig. 1A), a slight displacement of the middle structures of the brain to the right up to 2 mm was revealed. The lateral ventricles are asymmetric, D > S. The tumor tissue deforms the third ventricle. Convexital subarachnoid spaces of the cerebral hemispheres are not expanded. Basal cisterns are traceable.

An emergency biopsy of a tumor of the third ventricle, microsurgical third ventriculostomy was performed urgently. There were no complications with surgery. Access to the anterior horn of the right lateral ventricle was through interhemispheric access. An obvious presence of an insignificant amount of a tumor was found in the anterior part and in the area of the pituitary funnel; no signs of tumor tissue were observed in the lateral walls of the third ventricle. A small fragment of the tumor was sampled for biopsy. According to the results of an urgent biopsy — lymphoma.

On SCT scan of the brain after the surgery (see Fig. 1B), foci of pathological density in the substance of the brain were not detected. The lateral ventricles are moderately asymmetrically dilated in the projection of the bodies. The median structures

of the brain are not biased. Basal cisterns are traceable, not narrowed. Subarachnoid space is symmetrical, not expanded. Cerebellar sulci are underlined.

On the first day after the surgery the patient experienced steady motor anxiety, with a variety of unfocused movements secondary to depressed consciousness. The management of this condition was carried out without the administration of antipsychotics because of fears of a further decrease in the level of consciousness, but using soft fixation of the limbs to the bed, with inspection every two hours.

On the third day after the surgery, the patient's condition deteriorated sharply: a series of focal seizures occurred, the last one — with secondary generalization. After the first attack, anticonvulsant therapy was prescribed: Relanium 10 mg i.m., Convulex 1,000 mg by i.v. drop infusion, Keppra 2,000 mg i.v. After the third attack, depression of wakefulness level to stupor was noted, tracheal intubation was performed, the patient was placed on mechanical ventilation (MV). During the examination, myoclonic contractions of the facial muscles were observed. Due to MV, the patient did not respond to addressed speech.

In the next two days, the condition did not change: she lay in a given pose with her eyes closed, did not respond to addressed speech, a mimic reaction to pain stimuli appeared. Due to the absence of epileptic seizures and depression of consciousness, anticonvulsant therapy was canceled.

On the 5th day after the surgery the patient experienced an episode of ventricular fibrillation with ineffective blood circulation. Resuscitation (indirect cardiac massage, defibrillation, the introduction of antiarrhythmic drugs) led to the restoration of heart rhythm.

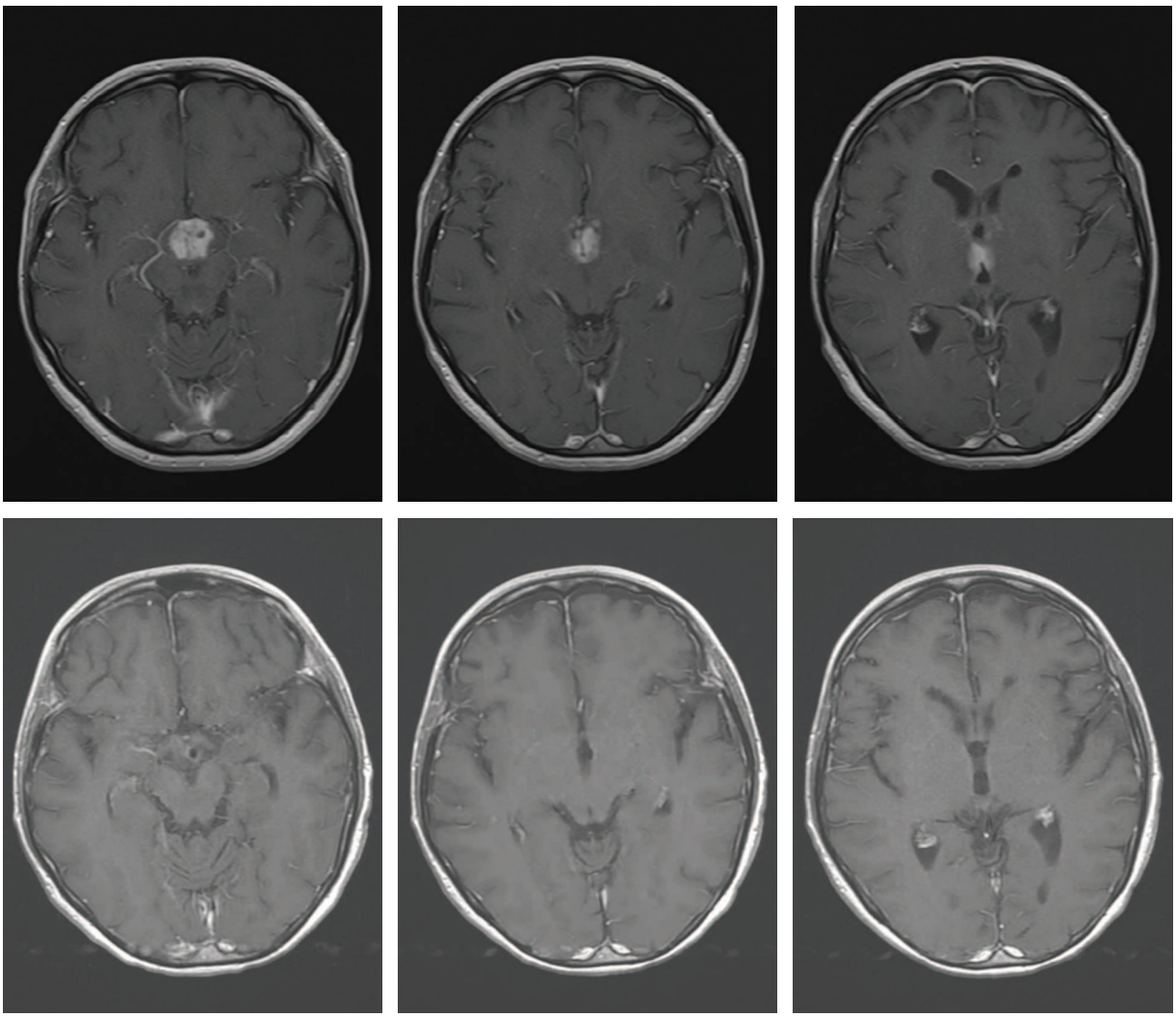

Figure 1. *SCT with contrast enhancement: A – before surgery. Hyperintense tumor in the projection of the third ventricle is visualized; B – after surgery*

Four days later, there was a short episode of atrial fibrillation with tachycardia, severe arterial hypotension up to 40/20.

All this time, the patient's level of activity remained the same (passive posture, periodic flexion in the elbow joints, lack of answers to questions, the presence of only intermittent half-opening of eyes in response to external stimuli).

A day later, pneumothorax was revealed in the patient, and therefore drainage was inserted.

The next day (on the 11th day after the surgery), eyes could spontaneously open.

On the 12th day, she responded, she brought her tongue out of the line of teeth when asked. Two weeks after the surgery, gaze fixation appeared.

Three days later, the recovery process was complicated by purulent tracheobronchitis, which required antibiotic therapy.

Despite the extremely rapid exhaustion associated with severe somatic complications, spontaneous recovery continued: 26 days after the surgery, the patient was awake during the day, watching what was happening, and spontaneous motor activity appeared. She still lay in a given position, but fixed her gaze on the addressed speech, carried out simple instructions, and the range of purposeful movements in the limbs widened. When using the cannula, it turned out that the speech function was preserved. This allowed us to identify fluctuations in the level of consciousness, manifested by episodes of psychomotor anxiety.

On the 31st day of hospitalization, taking into account the histological diagnosis, as well as the patient's condition, a chemotherapy course was started in monotherapy mode: Temozolomide 150 mg/m² — 250 mg orally daily from 1 to 5 days of the 28-day cycle. After the first week of therapy, taking into account the relative aggravation of the patient's condition, deterioration of hematological parameters (decrease in WBC count to 1.45 thousand per ml, neutrophils — to 0.43 thousand in ml, platelets — up to 22 thousand per ml), chemotherapy was interrupted.

The patient was transferred from the intensive care unit to the neurosurgical department 35 days after the surgery. On the same day, she was re-examined by a psychiatrist in connection with excitation: at the time of the examination she did not show complaints, contact was difficult due to the presence of a tracheostomy tube. During the examination, motor anxiety was noted, she tried to pull out the catheter, continued to do so, despite persuasion to stop.

A week later, on the 39th day after the surgery, the psychiatrist noted depleted facial expressions, indifferent facial expression. The patient was lying in bed, not trying to change her posture during the examination. Eye contact was maintained. By this time, steady contact with the patient was established, she turned out to be self-oriented, disoriented in time (she said that "it is now lunch", although the examination was carried out at 11.00 am), was not exactly oriented in the place ("in the Burdenko rehabilitation center"). She correctly listed the food eaten for breakfast. She could not explain the reason for being in the hospital. She stated that she wanted to "get out of this tale." She complained of weakness, expressed a desire to "remove the catheter." She answered questions, after a short pause, generally to the point. She followed simple and complex instructions. She assumed that her grandchildren and children were somewhere here: "They're walking somewhere." According to her husband, earlier relatives actually came to visit her one by one. She said, "The head doctor of the hospital specifically gives sedative medications in order to prevent meeting with relatives, so that there is no desire to communicate with them."

On the 42th after the surgery, according to her husband, she quickly forgot the current information. During the entire examination she was sitting in a chair. She was correctly oriented in time; however, she said she was in the "Semashko hospital." She complained that she had been under treatment for a long time, she was tired, her legs hurt from compression underwear, and she demanded to "let her out". She slept at night. She followed simple instructions. Aminophenylbutyric acid 500 mg/day, quetiapine 12.5 mg were prescribed upon excitation.

By the 46th day after the surgery, the patient was correctly oriented in her own situation and time, but was not always oriented in place. She complained about taking medication, stating that she did not need it, she said "they do it on purpose" in response to the question "why?" "I do not know, my relatives need it." She did not acknowledge that she was ill, she believed that it was invented despite the fact that she was repeatedly told about the disease and the course of treatment. Risperidone 0.5 mg x 2 times a day was prescribed.

An increase in the rehabilitation load (verticalization) led to the collapse of the patient (BP 80/50), after which she was in a state of drowsiness for several hours. After 2 hours, the condition stabilized, an episode of impaired consciousness was completely amnesized.

On the 49th day after the surgery, during examination she was lying in bed, practically without changing her posture, complained that "they inject drugs that are harmful, that are unnecessary," she asked for a break for one day, refused to eat curd, because "it is not crumbly". The daily dose of risperidone was increased to 2 mg.

On the 53rd day after the surgery, according to the daughter and the treating doctor, during the day the patient refused to take food, medicine, threw pills at the staff, relatives, and she could not be persuaded. On examination, she was lying in bed, turned to her interlocutor with a speech addressed to her. She engaged in the conversation calmly. She agreed to talk only in private with the doctor. She asked her relatives to leave the ward. She stated that she refuses pills and injections, as the drugs "harm her". She was not sure that she was being given the drugs that were actually prescribed. She demanded to show her the "doctor's prescription." She correctly named the current year, month, and day. She remembered the name of the hospital with a clue. It was difficult for her to say how many days she had been in the hospital. She was not sure if surgery had been performed. During the examination, her movements were calm. After lengthy persuasion, she agreed to take risperidone. She slept at night.

By the day of discharge (56 days after the surgery), there was a positive trend in the form of normalization of sleep, appetite, restoration of orientation in place and time. She was calm in the bed. She took drugs without persuasion, she did not express ideas of reference.

Follow-up data was obtained at a distance, according to the daughter.

After discharge from the institute, the patient underwent 6 courses of chemotherapy in an altered mode, taking into account the hematotoxicity of the initial regimen: 1) temozolomide 250 mg per day, from 1 to 4 days, and 2) rituximab — 375 mg/m^2 — once every 3 weeks intravenously by drop infusion (slowly). Rehabilitation treatment was carried out twice in a rehabilitation hospital.

After the first course of chemotherapy, motor deficiency significantly regressed: began to walk independently, go out to the street, fully maintain herself, it became possible to leave her at home alone. In the summer, on her own initiative, she worked in the garden near the house. Once, with the help of relatives, she went to work, where she spent several hours surrounded by employees, but she did not show signs of fatigue. In the first months in the evenings there were episodes of confusion, when she did not understand where she was, in the future said episodes stopped. Extreme passivity was noted in relation to measures for further recovery, as well as irritation in response to the offer of various available preoccupations. She spends a lot of time on the computer, makes meaningless purchases on the Internet. She is not interested in the life of loved ones, at the same time requires special attention. She says that she would like to go to work, although she formally understands that she is not able to do it.

Discussion

The observation described in this report is a complex case of the emergence and development of psychopathological symptoms in a patient with small lymphoma, localized in the projection of the third ventricle of the brain. Mental disorders in the form of impaired memory and disorientation debuted sharply, after chills, accompanied by cerebral symptoms (headache, vomiting, lethargy).

Apparently, the disturbances that appeared corresponded to the disintegration of consciousness in the form of increasing confusion. Against this background, minimal neurosurgical intervention was performed (open biopsy of the tumor, microsurgical third ventriculostomy). Despite the sparing nature of the surgery in the early postoperative period, impaired consciousness increased: disintegration gave way to depression. This occurred after a series of convulsive seizures that developed on the third day after the surgery, and then, on the 5th and 7th day, the condition worsened due to episodes of severe heart rhythm disturbance (atrial fibrillation) and pneumothorax diagnosed on the 10th day. Following these somatic disorders, despite emergency resuscitation interventions, an unconscious state lasted at least a week with further transition into depressed consciousness with limited contact.

Only after regression of somatic complications, signs of reintegration of consciousness appear, accompanied at first by episodes of unfocused excitement, and then by confabulations, protest reactions, ideas of reference, fear of poisoning, which regressed only after the prescription of risperidone.

The data of the correspondence follow-up study indicate that against the background of the resumption of chemotherapy with generally restored self-care and the cessation of episodes of confusion, there is a cognitive and emotional-personal decline with a predominant deficit of managerial functions in the form of difficulty in the formation and implementation of an activity program, insufficient criticism of her state and capabilities, blunted affect, impoverishment of interpersonal interactions and behaviors

The disorder of consciousness described in this report corresponds to the classical concept of psychopathology in tumors of the third ventricle [22]. Psychiatrists of the last century in some cases revealed phenomena such as lethargy, aspontaneity, depressed mood, sometimes confusion, disorientation, Korsakov-like syndrome and drowsiness, in others — euphoria, disinhibition, drowsiness, and sometimes motor anxiety. In some patients, a dynamic mosaic of pathological conditions was noted: drowsiness, apathy gave way to euphoria or labile delirious symptoms, impaired orientation and Korsakov-like conditions, fluctuating in intensity.

Of course, the cause of mental disorders in the preoperative period could be the blocked cerebrospinal fluid flow, and in the postoperative period — a violation of connection stability between structures responsible not only for monitoring vital functions, but also for consciousness. Heart rhythm disturbances and pneumothorax could lead to cerebral hypoxia, which seems to be a very likely cause of a significant slowdown in recovery of consciousness and mental activity in general.

It can also be assumed that some of the patient's personal characteristics, including her desire to control what is happening and people from her immediate environment (at home and at work), authoritativeness, and the complex establishment of trust were accentuated as a result of brain damage, transformed into paranoid suspicion, fear of losing control over events. The reduced, but not completely lost criticism of her own condition created the need for a person whom she could trust. Such a "confidant", if one follows the patient's logic and affiliation to medicine, could only be the doctor with whom she was more frank than with relatives, and only after a conversation with whom she agreed to receive psychotropic therapy.

The successful use of risperidone in this observation confirms the advisability of recommending the use of atypical antipsychotics in post-coma psychotic states, unlike typical ones that are safer for the process of reintegration of consciousness [23].

The effect of chemotherapy on the mental state in the above observation was ambiguous: if during the first attempt to conduct it, along with hematotoxicity, there was a slight increase in psychopathological symptoms, then, when it was planned, after discharge, on the contrary, the mental state improved, episodes of confused consciousness disappeared, self-service was restored.

Conclusions

1. Primary lymphoma of the brain is a relatively rare form of cerebral pathology, requiring special attention of doctors of various specialties, including psychiatrists.

2. Localization of primary lymphoma in the deep regions of the brain involves a quick change of severe psychopathological phenomena with a disturbance of consciousness, which, probably, are not subject to standard methods of symptomatic treatment, but require individual selection of psychopharmacotherapy and psychotherapeutic effects, aimed, in particular, at agreeing to comply with medical recommendations.

3. Against the background of chemotherapy in patients with primary cerebral lymphoma, both deterioration (probably due to intoxication) and improvement (following tumor regression) of mental state and social adaptation can occur.

Contribution of Authors

Ilyaev N.P., Maksakova O.A., Zaitsev O.S. — development of the study concept and design

Ilyaev N.P., Bykanov A.E., Troitsky A.P., Poddubsky A.A., Maryashev S.A. — data collection, and analysis of primary clinical data

Ilyaev N.P., Maksakova O.A., Zaitsev O.S. — manuscript writing

Zaitsev O.S., Pitskhelauri D.I., Kobyakov G.L., Troitsky A.A., Ilyaev N.P. — interpretation and critical analysis of the results, formulation of conclusions

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