Epidemiology, Etiology, Clinical Description, and Prevention of Postoperative Cognitive Dysfunction

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ABSTRACT

General anesthesia can cause damage to the central nervous system (CNS) that occurs in the postoperative period, among such injuries, postoperative cognitive impairment (POCD) takes the main place, and it can develop in patients of any age, without a history of psychoneurological diseases. Postoperative cognitive disorders worsen the quality of life of patients, make it difficult for them to perform their professional work and social tasks, which has become an urgent problem of modern anesthesiology in recent years1. When the prevalence of POCD was determined, it ranged from 7% for minor surgery at 1 week and 3 months postoperatively to 17% and 41% for major surgery at 3 months.

Keywords: postoperative cognitive dysfunction, central nervous system, general anesthesia.

Introduction. The central nervous system (CNS) can be affected in many ways after general anesthesia, including postoperative cognitive dysfunction (POCD), which can develop in patients of various ages and in uncomplicated, neuropsychiatric cases. POCD worsens the quality of life of patients, which makes it difficult to perform their professional and social functions, which has recently been one of the urgent problems of modern anesthesiology [1]. POCD (Postoperative Cognitive Dysfunction) is a cognitive impairment that develops early and persists late postoperatively, clinically manifesting as memory impairment, difficulty concentrating, and disturbances [2]. Other higher cortical functions (thinking, speech, etc.) confirmed by neuropsychological test data. At the same time, POCD occurs in patients with uncomplicated neuropsychiatric anamnesis. In 1955, Dr. D. Bedford reported cases of memory impairment in elderly patients undergoing surgery and general anesthesia. More than 65 years have passed since then, but the problem of cognitive impairment after general anesthesia has not been solved [3].

The prevalence of POCD is from 7% when it is detected, after one week and 3 months for minor surgery, to 17% and 41% after 3 months for major interventions, respectively [4]. Epidemiological data on the incidence of POCD are conflicting. In general surgery, the frequency of early POCD reaches 30%, and persistent POCD lasting more than 3 months is observed in 10% of patients on average. A recent review of the literature, including 80 independent studies, shows the frequency of POCD according to different authors, which is - 36.8% on average; after cardiac surgery - from 3 to 47%, and 3-5 years after the operation in 42%; after non-cardiac surgery - from 7% to 26%, 9.9% after 3 months or more, 1% of patients - more than 2 years. Occurs in 30-65% of POCD patients. leaving the hospital or 20-40%, 2-3 months after surgery [5]. An international multicenter prospective randomized study (1998) showed that neither perioperative hypotension (less than 60%

decrease in SBP in 30 minutes) nor hypoxia (SpO2 80 for more than two minutes) causes POCD, while it plays a leading etiological role. General anesthesia (GA) has been reliably proven in the development of persistent POCD. In the last 10-15 years, there has been an interest in studying the functional state of the CNS after 8 operations under general anesthesia [6].

Among the risk factors for the development of POCD, in addition to the type of general anesthesia, there are patients' age, low educational (intellectual) level and depressive disorders in the preoperative period, as well as aggravated neurological and somatic anamnesis. The importance of age as a risk factor for POCD is related to significant age-related differences in physiology and pharmacokinetics [7].

Neurological complications of general anesthesia. The problem of neurological complications of general anesthesia is one of the most urgent problems in neurology and anesthesiology. Such close attention to it is connected with the high frequency of anesthetic complications, and the issue of their prevention remains controversial. Effects of anesthesia on the functional state of the central nervous system, increasing the number and volume of claims for anesthetic errors (in Western countries). Neurological diseases, until death, occupy one of the leading places in the statistics of anesthetic complications [8]. General anesthesia can cause various damage to the central nervous system in the postoperative period: psychopathological and psychotic reactions, convulsive syndrome, postoperative cognitive dysfunction, tremors, coordination disorders, choreoathetosis. Acute sensorineural hearing loss, stroke, spastic paraplegia, partial degeneration of the spinal cord (in vegetarians), opisthotonus, hyperthermia.

The frequency and severity of neurological complications vary depending on the type of general anaesthesia, the patient's somatic and neurological condition. As a result of the patient's sleep and many other factors in the preoperative period, it is impossible to conclude that general anesthesia causes certain damage to the central nervous system. However, many studies devoted to this problem have noted depression of some cognitive and psychomotor functions of the functional state of the central nervous system in the postoperative period [9]. Adverse effects of almost all known anesthetics are observed on the central nervous system. Moderate therapeutic doses of anesthetics and narcotic analgesics such as morphine, lidocaine, fentanyl, amphetamine, halothane, sodium oxybutyrate, hexenal, ketamine, nembutal have also been shown in the literature to have a negative effect on the central nervous system. Therefore, in recent years, the harmful effects of general anesthesia on the brain have been studied [10].

According to many authors, clinical manifestations of brain dysfunction after the effect of general anesthesia last for a certain period of time (from several days to several months of the postoperative period). At the same time, it was noted that an increase in the duration of general anesthesia leads to an increase in the duration and strength of brain dysfunction in the postoperative period. Even low and moderate concentrations of anesthetics have a negative effect on the functioning of the most complex complexes and associations of neurons in the central nervous system. However, it is very difficult to evaluate and measure the highly organized higher cortical functions of the brain, so we can assume that their disruption can be caused by low and moderate concentrations of general anesthetics. In this regard, postoperative cognitive dysfunction is considered by neurologists and anesthesiologists not as a complication, but as an "effect of general anesthesia" [11]. The presence of more serious neurological complications of general anesthesia, such as psychomotor agitation, hallucinations, and convulsive syndromes, often distracts the attention of clinicians.

Epidemiology. The incidence of neurological complications of general anesthesia is highly variable, from 2 to 15.4%. According to most authors, neurological complications of general anesthesia in the postoperative period, except for neurosurgical and cardiac surgery, are the

norm with a frequency of up to 0.04%. Elderly people and patients with peripheral vascular insufficiency with a history of cerebrovascular diseases have a much higher risk of developing neurological complications of general anesthesia.

Etiology and pathogenesis. The frequency and strength of the effect of general anesthesia on the central nervous system depends on the dose of the anesthetic agent and the duration of general anesthesia. An increase in the risk of damage to the central nervous system is noted when the duration of general anesthesia is prolonged for more than 3,5-4 hours. With long-term general anesthesia, changes in the hemodynamic profile are observed after 3 hours of anesthesia and reach maximum values at 5-6 hours of general anesthesia [12]. Many factors of general anesthesia are involved in the pathogenesis of neurological complications, including metabolic, hemorheological, hypoxic, toxic, damage to the walls of cerebral vessels at the microcircular level, disruption of intracellular calcium metabolism, disruption of associative and interneuronal connections. The mechanisms of occurrence and development of postoperative cognitive impairment remain unclear. The main target of the drugs used in anesthesia practice is the brain [13].

At the same time, the nature and extent of the effect of anesthetics on the central nervous system is traditionally related to the depth and duration of anesthesia. Many factors are involved in the pathogenesis of POCD, including metabolic, hemorheological, hypoxic, toxic, which causes damage to the walls of cerebral vessels at the level of the microcirculation bed, disruption of intracellular calcium metabolism, disruption of associative and interneuron connections. The level of different brain structures. It is believed that the mechanism of action of GA is carried out in central structures, mainly in the reticular formation, the inhibition of which leads to a decrease in the activating effect raised in the cerebral cortex, the latter is enhanced by deep drug depression [14]. CNS during long-term general anesthesia According to modern concepts, anesthetics accumulate mainly in the brain, and the rate of their release and metabolism in the body is inversely related to the duration of GA.

Kline R.P. et al., using quantitative nuclear magnetic resonance, have shown an increase in the rate of atrophy of the gray matter of the cerebral cortex, hippocampal atrophy, and atrophy of the hippocampus in elderly patients for about six months after surgery. The authors aimed to study the structure of the brain in relation to cognitive functions in elderly patients in the perioperative period in order to improve the understanding of the risk of developing cognitive dysfunctions after surgery and concluded that in elderly patients (55-90 years old). Surgery leads to acceleration of brain atrophy for 5-9 months after surgery, which corresponds to the time period for the formation of postoperative brain dysfunctions. Mini-Mental State Examination (MMSE), tests for memorization and reproduction of semantic chunks, tests for visual memory, "5-word" memorization test, batteries of neuropsychological tests, including attention, short-term and long-term memory (hearing and vision), visual-spatial orientation, language (learning syntax, word meanings, oral and written speech speed, etc.) [15].

Instrumental methods such as computerized, magnetic resonance and positron emission tomography allow to detect organic changes in brain structures. Thus, Israeli scientists demonstrated the effectiveness of contrast-enhanced MRT to detect blood-brain barrier permeability disorders, which are accompanied by an increase in the permeability constant associated with postoperative cognitive dysfunction. Compared with microembolization, the superiority of the negative effects of increasing the permeability of the blood-brain barrier has also been shown. Chinese scientists show the predominance of postoperative hypoperfusion and postoperative hyperperfusion factors and reject the leading role in the development of POCD by microembolization [16].

To exclude the influence of other factors on cognitive functions, D. J. Culley et al. (2003) investigated the long-term effects of non-operative two-hour GA (1.2% isoflurane/70%

nitrous oxide/30% oxygen) and found adverse effects of OA on spatial learning and memory in young and old rats. After GA, the rats rested for 24 h, and then their cognitive function was tested daily in the maze for 4–8 weeks. The study showed severe damage to brain cells in all rats. Rats exposed to GA performed significantly worse in intelligence and memory tests (using a maze). In all other aspects, the "treated" rats did not differ from the normal ones. Since the drugs have already been eliminated from the subjects' brains during this period of cognitive function studies, the authors concluded that GA directly damages the central nervous system, alters the neurochemical cascades of memory mediators, and this negative pharmacological trace lasts longer. thought before. Thus, the authors concluded that GA is one of the leading etiological factors of the development of POCD [17].

Many authors consider the neurotoxic effect of general anesthesia to be one of the main causes of cognitive impairment after surgery, and 3 groups of factors are distinguished in the etiology of POCD: - residual effects of general anesthesia components and their degradation products, effects of long-term sedatives active against the central nervous system, postoperative analgesia insufficient; - the level of antinociceptive protection of brain structures achieved during the operation, its failure leads to overexcitation and depletion of the energy balance of neurons in the cerebral cortex and subcortical formations that provide sufficient consciousness; - general (hypoxemia, acute anemia, hypocirculation) and local (changes in cerebral perfusion, ICP) harmful effects of hypoxia [18]. Patients with postoperative cognitive dysfunction complain of a sleep-wake cycle disturbance, fatigue during mental stress, and a decrease in the quality and speed of the normal rhythm of mental and physical activity. There are reports of more serious disorders of higher cortical functions, including in young patients: impaired consciousness, amnestic aphasia, agraphia, acalculia, prosopagnosia. Cognitive disorders are divided into mild, moderate and severe. Mild cognitive impairment refers to unexpressed difficulties in daily activities, mainly associated with impaired memorization of new material. Moderate cognitive impairment is characterized by significant difficulty in daily activities with memory retention only for well-remembered or personal information. Severe cognitive impairment is manifested by the inability to remember new information, as well as to repeat existing ones [19].

It should be noted that after general surgical interventions performed under general anesthesia, cognitive dysfunctions were observed in all age groups of patients. There are publications that show that the frequency and severity of side effects of anesthesia on the central nervous system are influenced by the dose of anesthetic and the duration of general anesthesia. It is worth noting that all known anesthetics and narcotic analgesics have a negative effect on the cognitive and psychomotor functions of the central nervous system, even in moderate therapeutic doses, including morphine, fentanyl, amphetamine, halothane, hydroxybutyrate, hexenal, ketamine, propofol (diprivan). The brain (its subarachnoid space), as well as other important organs (lungs and bronchi, liver, kidneys, intestines) is the main place for immune cells involved in the regulation of cognitive functions, homeostasis and neurogenesis. At the same time, moderate stress stimulates the production of anti-inflammatory cytokines. At the same time, high levels of IL 1β, 6 and TNFα can be detected not only in the bloodstream, but also in various organs and tissues. The neuroinflammatory response is an integral part of normal cognitive processing. The brain is different from other organs and tissues. immunoprivileging, which is provided by the presence of the blood-brain barrier. It acts as a highly selective filter that protects the nervous tissue from microorganisms circulating in the blood, toxins, cellular and humoral factors of the immune system [20].

Nonspecific immune protection of the brain is provided by a dense network of microglial cells (phagocytes of bone marrow origin), which constantly "scan" their microenvironment and are always ready to signal when potentially dangerous factors are detected. In addition, both neurons and glial

cells can synthesize pro-inflammatory and anti-inflammatory cytokines and their receptors for their internal needs without the involvement of immune system cells. Stress of any origin is accompanied by an increase in the concentration and permeability of cytokines in the blood serum. As a result, cytokines circulating in the blood enter the brain, where they begin to perform other non-immunological functions. In addition, the weakening of the barrier function of the BBB and the developing neuroinflammatory response contribute to the mass migration of dendritic cells and lymphocytes from the perivascular space to the brain parenchyma. Repeated episodes of stress promote the accumulation of immune cells in the brain, cause irreversible changes in BBB permeability, and impair adult neurogenesis in the dentate gyrus of the hippocampus [21].

The immune system and the central nervous system have a two-way interaction. Protecting the body from infections and recovering from tissue damage means not only the activation of the immune system, but also a complex neuroendocrine response that coordinates the central nervous system, and several anti-inflammatory cytokines act as signaling molecules in the interaction between the immune system and the brain.

Interleukin-6 (IL-6) is a cytokine with pro-inflammatory and anti-inflammatory properties. It regulates the immune system and is also involved in cognitive function. Currently, there are many facts confirming the important role of IL-6 and C-reactive protein in the pathogenesis of POCD, determined by the high-sensitivity method (hs-CRP). Evidence that IL-6 gene polymorphisms contribute to the development of POCD suggests that mechanisms of activation of the inflammatory response may be important factors contributing to the development of cognitive impairment after surgery. This view is consistent with existing knowledge about IL-6 as a marker that promotes and mediates an active inflammatory response [22].

A single nucleotide substitution in the promoter region of the IL-6 gene (174G/C) regulates its expression and, as a result, mediates increased production of IL-6 and triggers an active inflammatory response. After surgery, IL-6 gene polymorphism affects plasma levels and functional activity of IL-6 and is believed to be associated with other perioperative inflammatory complications. However, the relationship between IL-6 polymorphisms and perioperative neurological outcomes has not been previously described.

There is evidence that the subclinical inflammatory process is one of the factors of unfavorable prognosis that can initiate the instability of existing hemodynamically insignificant disorders of cerebral circulation. Thus, appropriate preoperative screening may lead to the development of additional perioperative measures to reduce the risk of developing cognitive impairment [23]. Determining the specific mechanisms of the effect of immunogenetic genotype polymorphism will be important to identify targets to modulate the perioperative inflammatory response and improve the prognosis and prevention of postoperative cognitive disorders. Due to the multifactorial nature of POCD, in recent years there has been a trend towards a multidisciplinary approach to solving this problem by involving specialists of various specialties, including not only anesthesiologists, but also neurologists, clinical neurophysiologists, pathophysiologists, immunologists, medical psychologists.

A new study from the University of California, San Francisco suggests that brain inflammation and cognitive decline after surgery is initiated by brain immune cells called microglia. Before surgery, an oral drug that temporarily destroys microglia interfered with memory test results. The discovery suggests a new approach to preventing the disease in humans. Based on new research, scientists believe that brain microglia initiate and orchestrate this response, including infiltration of peripheral immune cells and memory loss [24]. However, neurologists do not take into account the negative effects of central anesthetics on the central nervous system in young patients after long-term surgical interventions in general surgery.

As a result, patients discharged from the hospital, as a rule, are observed by surgeons,

and the dynamic dispensary goes beyond the scope of neurological observation, but cognitive disorders may remain in postoperative patients, labor and social adaptation processes are disturbed and the risk of developing dementia increases. Optimizing neurological support in the postoperative period allows to implement a set of measures for the prevention, early diagnosis and treatment of POCD in young patients, to reduce the risk of developing permanent POCD and social adaptation among the working population [25].

Of particular interest are the possibilities of using nootropics under general anesthesia (GA), which can cause various damage to the central nervous system (CNS) in patients undergoing surgery. Interest in the issue of neuroprotection is not accidental. In a number of studies conducted by researchers, the need for the use of neurometabolic drugs has been proven to prevent the development of brain complications in the postoperative and postoperative period. Despite the fact that the presence of persistent POCD has been reliably confirmed by psychometric tests in all age groups of patients, the social and economic consequences of POCD have not been sufficiently studied. At the same time, analyzing the literature data, it should be recognized that persistent POCD after GA surgery is real and much more common than previously thought [26].

Some authors recommend timely, early correction of cognitive disorders in the postoperative period. The only way to prevent pathology of the central nervous system after surgical interventions under long-term general anesthesia is timely diagnosis and pathogenetically based therapy aimed at strengthening the neuropsychic health of the population in order to save labor resources. Shen X. and others during experimental studies in animals (mice) found that a number of factors affect the development of cognitive impairment after surgery with general anesthesia, in particular, repeated anesthesia with certain anesthetics.

However, it is unknown what the frequency of POCD is after multiple operations. To date, there are almost no indisputable data about the structure and severity of cognitive impairment, depending on the interval between operations, and the severity of POCD after several (one year or more than two operations in several years) operations using different types of general anesthesia. undefined, there is no single algorithm for the prevention and correction of postoperative cognitive deficits after multiple operations. Although the quality of perioperative treatment of patients has significantly improved in recent decades, POCD remains a common pathology that leads to persistent cognitive impairment (especially in elderly patients), deterioration of quality of life, long hospital stay, and increased risk of other postoperative complications and even death in the late postoperative period. For a long time, POCD has been the subject of intense debate in the scientific community, ranging from diagnostic issues, clinical phenomenology, to specific recommendations for professionals and patients [27]. This is due to the increasing number of publications on this topic and the unexpected results of recent studies, in particular, which show that surgical interventions can lead to improvements in cognitive function in a number of patients; the authors even proposed the term "postoperative cognitive improvement". Considering that the number of surgical interventions worldwide reaches 250 million per year, optimization of cognitive function in the postoperative period, as well as prevention and treatment of POCD are urgent multidisciplinary health problems.

Until now, the question of the possibilities of prevention of POCD remains controversial, there is no generally accepted effective strategy to reduce the frequency of its development. A number of methods proposed by experts aimed at reducing the risk of developing CI are reduced, in particular, the transition to minimally invasive interventions and the improvement of surgical and anesthetic techniques with the use of short-term general anesthesia [28].

However, taking into account the multifactorial genesis of POCD and the involvement of mechanisms such as neuroinflammation and apoptosis in its development, it also seems justified to use

agents with neuroprotective effects. Cognitive impairment in the early postoperative period and the frequency of development of postoperative cognitive dysfunction, according to different authors, from 18 to 60%, POCD is a complex problem consisting of the patient himself and many intraoperative and postoperative risk factors. Among the main reasons for the development of cognitive disorders in the postoperative period are the long-term effects of anesthetics. The duration and depth of anesthesia, as well as microembolism, impaired cerebral perfusion and systemic inflammatory response (SIR) [29].

Development and risk factors for POCD. There is no single causative factor responsible for the development of POCD. These complications are polyetiological, and current theories consider surgical factors and anesthetic and patient-related factors as causes of POD and OCD. N. In a systematic review based on the results of 296 observations and 130 randomized clinical trials, identified the following potential mechanisms for the development of POCD: general anesthesia (15 studies), systemic arterial pressure (5), cerebral autoregulation (4), systemic inflammatory reactions (26), neuroprotective agents (17), hypothermia and heating.

It should be noted that the influence of hypoxemia and hypotension on the development of OCD is not completely clear: J. In a relatively old multicenter study by Moller et al. In elderly people, cognitive disorders after surgery often develop due to hypoperfusion or hypoxia of the brain. POCD was shown during surgery. Elderly patients were observed much more often than in the studied age group without surgery. Age and duration of anesthesia, low level of education, repeated interventions, postoperative respiratory infections and breathing. complications were risk factors for early POCD and assessed 1 week after surgery; however, only age was a risk factor for late (approximately 3 months after surgery) cognitive dysfunction [30].

Pathogenesis. Currently, there is no general understanding of the pathogenesis of POCD. One of the main causes of delirium in the postoperative period is the subsequent dysfunction with acetylcholine deficiency. Pathogenetic mechanisms that can lead to the development of these complications include: peripheral inflammatory response to surgical trauma of the body, subsequent development of neuroinflammation, disruption of the integrity of the blood-brain barrier with subsequent damage to neurons, brain autoregulation is disturbed, oxygen delivery is reduced, hyperglycemia, previous neurodegenerative diseases, accumulation of metals in the brain. Let's take a closer look at some of the proposed mechanisms [31].

The following were analyzed: the number of operations in the anamnesis, the duration of general anesthesia, the state of hemodynamics, the method of general anesthesia and the type of anesthesia used, monitoring the depth of general anesthesia 22 using BIS technology.

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