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Current Understanding of the Etiopathogenesis and Directions of Therapy for Postoperative Cognitive Dysfunction

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Abstract

The phenomenon of postoperative cognitive dysfunction is understood as a symptom complex of cognitive spectrum disorders often observed in patients after various surgical procedures. Despite the rising incidence and potential high probability of negative outcomes, including both long-term effects on the nervous system and longer periods of hospitalization along with the need to consult generalists, today's disease classifications, such as DSM-V, do not distinguish this pathology as a separate one. The present review attempts to highlight the contemporary aspects of postoperative cognitive dysfunction etiopathogenesis, key theories on it, its known mechanisms, and up-to-date therapeutic strategies that could be of interest to both scholars and medical practitioners.

Keywords: Postoperative cognitive dysfunction, cognitive dysfunction, neuroinflammation, neurotoxicity

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1. Introduction

Postoperative cognitive dysfunction (POCD) is an umbrella term that denotes one of the most common neuropsychological disorders developing in the postoperative period, predominantly in older and elderly patients [1-3]. This pathology is marked by a range of neurocognitive changes that can be observed throughout several weeks after an operative procedure and can to varying degrees diminish the patient's quality of life. The primary manifestations of POCD include reduced attention span, amnestic disorders, impaired perception and processing of information, and other neuropsychological disorders, often accompanied by changes in personality and emotions [2, 4, 5]. The duration of the condition varies from a few days to several months (there are reports of symptoms persisting for a year or more). Further progression of cognitive deficits is also possible and may lead to early retirement, reduced quality of life, and negative social implications [1, 6, 7]. POCD is associated not only with lower quality of life but also with exacerbations of the underlying disease and an almost twofold increase in one-year postoperative mortality rates. Several studies, including meta-analyses and thematic reviews, suggest that the estimated risk of POCD in the first week after an operation ranges from 10 to 75%. After three months, this probability ranges from 12 to 45% and considerably lowers during the first year to as little as 3% [1, 6-8]. Preoperative risk factors include old age, the initial level of education, the so-called cognitive reserve, and comorbidities (predominantly cardiovascular and/or psychiatric) [3, 9, 10]. Some researchers assert that the incidence of POCD does not differ significantly in patients who underwent cardiac and non-cardiac surgeries. However, this statement finds contrary evidence of varying strengths, which makes it impossible to interpret this risk factor unambiguously [9, 11-13]. Considering that the duration and type of operation along with the chosen type of anesthesia are among the standard intraoperative risk factors, it is probable that cardiac surgery, due to its specifics, also acts as a factor in the development of POCD [2, 6, 9, 14, 15]. Furthermore, open World Health Organization data and numerous publications indicate that the number of surgical interventions performed annually is increasing worldwide, which naturally also applies to older patients [16-18]. This factor determines the urgency of the study of POCD, especially from an interdisciplinary standpoint.

2. Etiopathogenic aspects

Despite the rising interest of the scientific community and decades of research, the methods of diagnostics and treatment are still fraught with imperfections, and the mechanisms of POCD pathogenesis remain not understood in full. In a broad sense, any disturbance of homeostasis and metabolic processes in the nervous system induced by surgical interventions is considered the mechanism of development of this pathology [2, 19]. Among such disturbances are neuroinflammation, oxidative stress,

mitochondrial dysfunction, impaired blood-brain barrier (BBB) permeability, impaired synaptic transmission, and impaired neurotrophic support [1, 3, 9]. The etiopathogenic mechanisms of POCD are similar to other neuropsychological disorders. For instance, POCD involves extracellular deposition of beta-amyloid and intracellular accumulation of intracellular phosphorylated tau protein, much like Alzheimer's disease [20]. Importantly, however, the described processes are largely conditioned by the type of anesthetic (general anesthesia is named as the leading risk factor in a number of studies) and the medications administered [11, 21, 22]. Other prerequisites include preoperative cortisol levels, glycemic profile, hyperventilation, hypotension, and several other criteria that make up the overall picture of the systemic inflammatory response [8, 23, 24]. A peculiar perspective on the issue is voiced by Western researchers, who point out the role of non-coding (nc) RNAs in the pathogenesis of POCD [25]. Activation of inflammation-associated cells, as well as changes in cytokine levels induced by tissue damage, are closely associated with abnormal levels of ncRNA expression. The latter can either limit or facilitate neuroinflammation by interfering with underlying pathologic processes like BBB disruption and microglia activation, thereby contributing to the outcome of excessive inflammatory responses [26-28]. Researchers indicate certain patterns of ncRNA expression patterns and biological functions that differ depending on individual differences and the type of anesthesia. Abnormal activation of signaling pathways (NF-kB transcription factor, PI3K pathway, etc.) also plays an important part in the development of cognitive impairment in POCD, which could potentially be used as part of preventive measures [25, 28, 29].

3. Neuroanatomy

Latest thematic sources suggest that at the core of POCD lie dysfunctions of the hippocampus, thalamus, islet, cerebellum, and other parts of the brain. In animal experiments modeling the effects of surgery and patient age on cognitive function, cognitive impairment was found to be associated with changes in the functioning of specific areas of the brain. Despite the diversity of cerebral abnormalities in POCD, the research mostly focused on postoperative dysfunction of the hippocampus, which plays a pivotal role in learning and memory processes [27]. Surgical intervention can cause loss of dendritic spines in aged rat neurons in the CA1 region of the hippocampus and the dentate gyrus, accompanied by neurotoxicity and neuroinflammation [14, 30-32]. There is an active investigation of the role played in the pathogenesis of POCD by the prefrontal cortex and temporal lobes, associative areas of the brain responsible for behavioral control, integrative information processing, and many other functions [33, 34]. Several studies have revealed a correlation between the development of POCD and abnormalities in the prefrontal cortex and medial temporal cortex, which are particularly vulnerable to age-related changes that result in the loss of dendritic spicules [16, 30]. The thalamus participates in the transmission and processing of signals from various brain regions. In several clinical cases, MRI imaging has shown decreased thalamic and hippocampal volume in patients with POCD, suggesting a connection between them [31, 35].

The cingulate gyrus, which is part of the limbic system and is involved in memory and information storage, also plays a prominent role in the pathogenesis of POCD [18]. Its dysfunction can result in impaired working memory in patients with POCD [11, 22].

4. POCD diagnosis

POCD diagnosis is based on neuropsychological testing, identification of biomarkers, neuroelectrophysiological testing, and, to a lesser extent, neuroimaging. In the current version of the DSM-V, as well as in the ICD-10/11 register, this diagnosis, along with the generally accepted diagnostic criteria, is absent. In literature and clinical practice, this pathology is considered through the prism of neurocognitive diseases (NCD), where it is referred to as a subgroup of perioperative disorders [2, 12]. Detection of POCD involves neuropsychometric testing: the Mini Mental State Examination (MMSE), the Frontal Assessment Battery (FAB), the Montreal Cognitive Assessment test (MoCA test), and the Wechsler Intelligence Scale (WIS) [36, 37]. Nevertheless, a single test is insufficient to detect POCD because the diagnosis requires preoperative baseline data and analysis of postoperative changes to quantify cognitive decline [17]. Several authors caution clinicians against premature diagnosis, drawing attention to the minimal time from surgical intervention (<7 days) due to the need to analyze and assess the likely consequences in the short term [2]. Thus, the first week can be a tool for differential diagnosis between POCD and postoperative delirium [19, 29]. However, there is currently no necessary and generally accepted approach to this issue, which significantly complicates routine diagnosis and factor stratification despite numerous publications.

5. Current therapy for POCD

Current therapy for POCD is comprised of two directions: preventive measures along with ruling out another disease that may cause similar changes and post-syndromic treatment [15, 36]. In recent years, there has been considerable interest in developing and identifying effective therapeutic strategies to minimize the potential pathogenetic mechanisms of POCD: preference for anesthetics with lower potential for toxicity to the central nervous system and neuroprotection. There has been widespread discussion of the use of sevoflurane and its possible mechanism of induction of neuronal apoptosis against the background of cross-dysregulation of iron and glucose metabolism, which disrupts energy processes in the brain [38]. This claim has been evidenced in animal models with subsequent neuroimaging and morphological analysis [39, 40]. Similar results have been seen in studies of this pathology at the cellular level. Analysis of sevoflurane-induced POCD-associated exosomes isolated from patient plasma has confirmed a possible mechanism of stimulation of microglia cell apoptosis (HMC3), which can also be viewed as an additional harmful effect of sevoflurane on the central nervous system [41-43]. Possibly, as a preventive measure during preoperative preparation and in the presence of risk factors, anesthetics should be selected more carefully, avoiding sevoflurane in elderly patients if possible. An equally common drug, ketamine, has shown no special advantages in the

neuroprotective aspect in patients with POCD in one of the meta-analyses [44]. The use of esketamine is associated with a lower incidence of POCD and a positive effect on neuroinflammatory processes, which has been noted by researchers in recent years [45, 46]. Another notable drug is dexmedetomidine, a central agonist of alpha-2 adrenoreceptors, the use of which is associated with a high level of neuroprotective properties. Thus, a meta-analysis of seven case studies indicates that the incidence of POCD one week after surgery was significantly lower in the group of patients treated with dexmedetomidine [47]. These results are also supported from the point of ncRNA involvement – apparently, the molecules contribute to the protective effect of dexmedetomidine on postoperative cognitive function [48]. According to another point of view, based on the correlation between high concentrations of inflammatory markers (C-reactive protein, interleukin-6) and the development of POCD, the use of glucocorticosteroids (e.g., dexamethasone) may be justified as a preventive measure. However, recent studies have not found significant correlations [13, 49].

6. Conclusions

In recent years, scientific literature has been rich in heterogeneous information on the topic of POCD, where each work expands and complements the knowledge of the pathology at all levels. The urgency of studying POCD is increasingly recognized due to its prevalence and the increasing number of surgeries involving the elderly patient population. The lack of a universal approach and generally accepted criteria creates additional difficulties for both academic study and clinical practice, which undoubtedly calls for a multidisciplinary approach and a broad awareness among specialists from different disciplines.

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