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NEURONAL BIOMARKERS OF BRAIN DAMAGE IN PREECLAMPSIA (LITERATURE REVIEW)

Rakhmatulaeva G. K, Khudayarova S. M.
Department of Neurology and Medical Psychology Tashkent State Medical University

Abstract: Preeclampsia (PE) is a multi-organ pregnancy complication accompanied by significant changes in the central nervous system. Neurological disorders in PE include headache, seizures, cognitive impairment, stroke, and posterior reversible encephalopathy syndrome (PRES). In recent years, increasing attention has been paid to the search for objective laboratory biomarkers reflecting the degree of neuronal and glial damage. Among these, neuronal proteins - GFAP, NfL, S100B, and NSE - have gained particular importance, reflecting different types of brain tissue damage. This review summarizes current literature data on the role of these markers in preeclampsia and their potential in diagnosis and prediction of neurological complications.

Keywords: preeclampsia, GFAP, NfL, S100B, NSE, neuronal markers, brain damage, biomarkers.

Introduction. Preeclampsia (PE) remains one of the leading causes of maternal mortality and perinatal complications worldwide [1]. According to the Global Burden of Disease 2019 study, the total number of hypertensive disorders of pregnancy (HDP) cases increased from ~16.30 million in 1990 to ~18.08 million in 2019, representing a growth of ~10.92% [4]. Despite progress in obstetrics and intensive care, this pathology continues to pose a serious healthcare problem, especially in developing countries. PE is characterized by systemic endothelial dysfunction, which leads to vasoconstriction, organ hypoperfusion, and activation of inflammatory cascades [2].

Key pathophysiological mechanisms of PE include: imbalance between proangiogenic (VEGF, PlGF) and antiangiogenic (sFlt-1, endoglin) factors; placental ischemia and oxidative stress; systemic inflammation and endothelial activation; vascular wall damage and microcirculatory disturbances [3].

One target of these systemic changes is the central nervous system. Patients with PE often develop cerebrovascular complications, including headache, visual disturbances, seizures, ischemic or hemorrhagic stroke, as well as posterior reversible encephalopathy syndrome (PRES) [4]. Brain damage in PE is caused by the combined effects of hypertension, vasospasm, hypoperfusion, and blood-brain barrier disruption [5]. This results in brain edema, white matter ischemia, and damage to neuronal and glial structures [6].

In complicated preeclampsia, the risk of acute cerebrovascular complications can reach 1 case per 500 deliveries when considering severe ischemic or hemorrhagic events [1]. Among deaths related to preeclampsia and eclampsia, 60-70% are due to cerebral complications, including seizures, brain edema, and stroke (hemorrhagic or ischemic) [2].

Traditionally, assessment of cerebral complications in PE has been based on clinical manifestations - headache, seizures, photopsias, cognitive disorders, which, however, reflect late stages of nervous tissue damage [7]. Routine neuroimaging methods (MRI, CT) have high diagnostic value, but their use in obstetric practice is limited.

Therefore, in recent years, there has been growing interest in studying molecular markers of nervous system damage that allow detection of subclinical brain injury before the appearance of pronounced symptoms [8]. Such promising markers include neuronal and glial proteins circulating in blood during nervous tissue cell destruction. The following molecules have attracted the most attention from researchers: glial fibrillary acidic protein (GFAP) - a marker of astrocytic damage; neurofilament light

chain (NfL) - an indicator of axonal destruction; S100B protein - reflects blood-brain barrier integrity disruption; neuron-specific enolase (NSE) - an indicator of neuronal damage during hypoxia and metabolic stress.

Glial Fibrillary Acidic Protein (GFAP)

This is a structural protein of intermediate filaments, predominantly expressed by astrocytes, providing cytoskeletal maintenance and participating in blood-brain barrier regulation [4]. When the central nervous system is damaged, especially under conditions of hypoxia, ischemia, or inflammation, astrocytic membrane destruction occurs with GFAP release into cerebrospinal fluid and systemic circulation [5]. Several studies have demonstrated that elevated GFAP concentrations are found in women with severe preeclampsia and eclampsia, reflecting glial damage and astrocyte activation in response to cerebrovascular disorders [6].

GFAP is considered a sensitive marker of astrocytic damage, comparable in diagnostic significance to neuronal proteins such as neurofilament light chain (NfL) and neuron-specific enolase (NSE). Elevated GFAP levels correlate with the severity of neurological symptoms, including headache, seizures, visual disturbances, and signs of encephalopathy, and are associated with the risk of developing posterior reversible encephalopathy syndrome (PRES) [7]. Furthermore, studies using highly sensitive immunoassays (such as Single Molecule Array, Simoa) have shown the possibility of early detection of GFAP elevation long before clinical manifestations of eclampsia, opening prospects for using this protein as a predictor of neurological complications [8].

Neurofilament Light Chain (NfL)

This is a low-molecular-weight neuronal cytoskeletal protein that is part of neurofilaments, which provide structural stability to axons and participate in maintaining axonal transport [7]. Axonal damage or degeneration leads to NfL release into the intercellular space, then into cerebrospinal fluid (CSF) and systemic circulation, where its concentration can be quantitatively determined using ultra-sensitive immunoassays (e.g., Simoa) [8].

Previously, elevated NfL levels have been reliably demonstrated in traumatic brain injury, stroke, neurodegenerative and inflammatory CNS diseases, including multiple sclerosis and encephalopathies of various origins [9]. In recent years, there has been growing interest in studying the role of NfL as a marker of subclinical cerebral damage in preeclampsia (PE).

Studies demonstrate that NfL levels in plasma and serum of women with PE are significantly higher than in healthy pregnant women [10]. This indicates axonal neuronal damage that may occur even in the absence of pronounced clinical symptoms. Elevated NfL values correlate with disease severity, presence of neurological manifestations, elevated blood pressure, and signs of cerebral hypoperfusion [11]. Moreover, NfL elevation is observed already in preclinical stages of PE, making this biomarker potentially valuable for early detection and prediction of neurological complications, including eclampsia, stroke, and PRES syndrome [12].

Combined determination of NfL and GFAP is considered a promising approach for differentiated assessment of neuronal and astrocytic damage. Such multi-biomarker analysis can improve the accuracy of cerebral disorder diagnosis in PE and may be used for monitoring therapy effectiveness and risk stratification [13].

S100B Protein

S100B protein is synthesized by astrocytes and oligodendrocytes and performs a calcium-binding function. Its elevation in serum is associated with blood-brain barrier integrity disruption and neuroinflammation [11]. In PE, increased S100B levels correlate with arterial hypertension severity, headache intensity, and degree of brain edema [12]. The literature notes the potential of S100B as an early marker of cerebral damage and an indicator of antihypertensive therapy effectiveness [13].

Neuron-Specific Enolase (NSE)

This is a glycolytic enzyme, an enolase γγ isoform, expressed predominantly in neurons and neuroendocrine cells [14]. NSE is localized in the cytoplasm and plays an important role in neuronal energy metabolism, ensuring conversion of 2-phosphoglycerate to phosphoenolpyruvate during glycolysis. When neuronal cell membranes are damaged, during ischemia, hypoxia, or oxidative stress, NSE is released into the extracellular space and can be detected in cerebrospinal fluid and serum [15].

Therefore, NSE is considered a biochemical marker of neuronal damage, reflecting the degree of neuronal destruction or death. Elevated NSE levels have been previously described in traumatic brain injury, stroke, hypoxic-ischemic encephalopathy, epilepsy, and neonatal asphyxia [16]. In the context of preeclampsia (PE), this protein is of particular interest as a possible indicator of hypoxic-ischemic brain damage in pregnant women.

Current studies show that NSE levels in serum of patients with severe PE and eclampsia are significantly higher than in healthy pregnant women [17]. This elevation may reflect cytotoxic and ischemic neuronal damage caused by a combination of factors - vasospasm, perfusion disorders, endothelial dysfunction, and blood-brain barrier disruption [18]. Additionally, NSE concentration correlates with clinical manifestation severity, including headache, seizure episodes, cognitive impairment, and PRES syndrome signs [19].

Elevated NSE values may be observed before pronounced clinical symptoms develop, making this marker promising for early detection of subclinical neuronal damage. In combination with other biomarkers such as GFAP and NfL, NSE determination can be used for differentiated assessment of the nature and degree of cerebral damage in PE, as well as for monitoring neurological complication dynamics in the perinatal period [20].

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