Potential Biochemical Markers of Epilepsy

Marina Yu. Maksimova, Ekaterina M. Abbasova, Anna D. Shitova

Research Center of Neurology, Moscow, Russia

Abstract

The diagnosis of epilepsy and assessment of the frequency and severity of seizures are essential for the treatment of patients. Epileptogenesis monitoring at different stages can be beneficial in assessing the efficacy of antiepileptic therapy. This approach relies on the concept of biomarkers. A subset of these biomarkers may possess not only diagnostic value but also prognostic value, which is defined as the ability to predict the nature of the epilepsy course and the probability of recurrent seizures.

Keywords: *epileptogenesis; biomarkers; epilepsy*

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For correspondence: 80 Volokolamskoye shosse, Moscow, Russia, 125367. Research Center of Neurology.
E-mail: ncnmaximova@mail.ru. Marina Yu. Maksimova

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Потенциальные биохимические маркеры эпилепсии

М.Ю. Максимова, Е.М. Аббасова, А.Д. Шитова

Научный центр неврологии, Москва, Россия

Аннотация

Диагностика эпилепсии, оценка частоты и тяжести эпилептических приступов являются неотъемлемыми условиями лечения больных. Мониторинг эпилептогенеза на разных стадиях обеспечивает контроль эффективности противоэпилептической терапии. Базовым понятием такого подхода является категория биомаркеров, некоторые из них могут иметь, помимо диагностического, и прогностическое значение, которое заключается в возможности предсказать характер течения эпилепсии и вероятность возникновения повторных эпилептических приступов.

Ключевые слова: *эпилептогенез; биомаркеры; эпилепсия*

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Адрес для корреспонденции: 125367, Россия, Москва, Волоколамское ш., д. 80. Научный центр неврологии.
E-mail: ncnmaximova@mail.ru. Максимова М.Ю.

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Introduction

In a mechanistic context, epileptogenesis is defined as the process by which the brain's neural network undergoes reorganization, accompanied by increased susceptibility to seizures and the probability of spontaneous recurrent seizures [1].

Previously, epileptogenesis was considered to be represented by the latent period, the time between the epileptogenic insult (epileptogenesis had been studied mainly in models of post-traumatic or post-stroke epilepsy) and the appearance of the first unprovoked seizure [2].

Subsequent studies have shown that epileptogenesis is progressive process. The phenomenon of "kindling," defined as an escalation in neuronal activity triggered by repetitive electrical or chemical stimuli, underscores the notion that recurrent seizures may amplify the probability of subsequent seizures. This view is consistent with the theory that "seizures beget seizures" and further neuronal death proposed by W. Gower in 1885 [3]. Concurrently, some authors have critically reviewed existing data on the effects of recurrent seizures on brain neural networks. On the one hand, epileptic activity causes molecular, structural, and functional changes, including neuronal loss, circuitry reorganization, and metabolic changes that may contribute to disease progression. On the other hand, seizure remission in two thirds of epilepsy cases and various chronic epilepsy animal models oppose the theory. Experimental studies showed that seizures could induce neural changes that increase the seizure threshold and decrease the risk of a subsequent seizure [2].

At the cellular level, epileptogenesis includes:
- dramatic decrease in the number of neurons and synapses;
- astrogliosis;
- microglial activation;
- agiogenesis [4].

Recent decades have brought dramatic changes in the understanding of the molecular dysfunction cascade in epilepsy, to which various dynamic processes contribute: formation of excitatory synapses; ion homeostasis imbalance; compromised blood-brain barrier (BBB) integrity; glymphatic dysfunction; and accumulation of proinflammatory cytokines along with amyloid and phosphorylated tau proteins [4].

Epileptogenic factors are believed to initially lead to selective neuronal vulnerability. However, this theory can be refuted by a study in which hyperthermia-induced epilepsy is not associated with neuronal loss [2]. A key mechanism underlying epileptogenesis is the loss of inhibitory interneurons [5].

Activated astrocytes play a pivotal role in the dysfunction of the BBB and glymphatic system, mediated through the release of proinflammatory cytokines, and facilitate the abnormal neuronal excitability. Astrocytes release gliotransmitters, such as glutamate, which alter synaptic activity and further contribute to the neuronal imbalance between excitation and inhibition characteristic of epileptic circuits [6].

BBB disruption triggers albumin accumulation in the extracellular space. By activating transforming growth factor beta (TGF-β) receptors on astrocytes, albumin activates TGF-β signaling pathways, TGF-β formation, and increased astrocyte activity, which causes dysregulation of potassium and glutamate content in the cells and further enhancement of proinflammatory cytokines (interleukin-1β and -6) secretion. The expression of astrocytic inwardly rectifier potassium channels (mainly Kir4.1 subunits, which regulate inward passage of potassium ions) has been shown to decrease in epileptogenic regions during epileptogenesis, which causes neuronal hyperexcitability [7]. This condition is exacerbated by decreased levels of amino acid transporters. Matrix metalloproteinases that degrade tight junctions of the BBB (due to destruction of dystroglycan, a protein that anchors astrocyte endfeet to the vascular basement membrane, accompanied by leukocyte infiltration of brain tissue) and increase the release of proinflammatory cytokines also play a certain role in the BBB destruction [8, 9]. During epileptogenesis, the clearance of cytokines regulated by the glymphatic system is impaired due to dysfunction of perivascular spaces [4].

The vicious circle of epileptogenesis includes astrogliosis, which contributes to aquaporin-4 (AQP4) dysregulation. The fundamental role of AQP-4 is maintaining water homeostasis and contributing to potassium buffering in the brain, i.e. prevention of excitotoxicity. Dysregulated AQP-4 expression can lead to ion imbalances in the extracellular environment, promoting neuronal hyperexcitability and increasing the risk of recurrent seizures [10].

The mechanistic target of rapamycin (mTOR) signaling pathway is one of the potential metabolic pathways of epileptogenesis. Studies have shown that the mTOR pathway is involved in epileptogenesis in genetic epilepsies and tuberous sclerosis. The mTOR pathway regulates synaptic plasticity, ion channel expression, and programmed cell death. The mTOR dysfunction (impaired cell proliferation, synaptic plasticity, ion channel expression) that occurs during pathologic processes in brain tissue leads to epilepsy. Hyperactivation of the mTOR signaling pathway has been observed in genetic animal models of epilepsy [11].

According to the basic definition, a biomarker is a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention [4].
According to the purpose, all epilepsy biomarkers are subdivided into:
1) Biomarkers that define a group of patients at high risk of disease development (high predisposition to epilepsy).
2) Diagnostic biomarkers.
3) Monitoring biomarkers that characterize the disease severity and enable prediction of the progression probability and prognosis.
4) Biomarkers whose function is to evaluate the efficacy and safety of antiepileptic therapies and methods in animal experimental models.
5) Biomarkers used to optimize the selection of homogeneous groups of patients for clinical trials.

The study of biomarkers in epilepsy encompasses several domains, including risk stratification, the diagnostic process, the assessment of severity, and prognosis determination. It also covers clinical trials of new agents and medical technologies. Evaluation criteria for diagnostic tests include rapidity of performance, reliability of the results obtained, the ability to use diagnostic information to optimize treatment programs, ease of use, high sensitivity and specificity. To date, no epilepsy marker that satisfies all of the aforementioned criteria has been identified. Consequently, the prevailing approach involves the study of potential candidates using a multiparametric detection method [4].

Biochemical Markers in Epilepsy

Amphoterin

Amphoterin (high mobility group box-1, HMGB1) participates in the immune response through binding to Toll-like receptor 4 (TL4) and releases tumor necrosis factor-α (TNF-α), interleukins (IL)-1 and -6 by activating macrophages and endothelial cells. In addition, by stimulating TL4 and neutrophils HMGB1 induces oxidative stress. In the central nervous system (CNS), HMGB1 mediates microglial activation. HMGB1 serum levels increase within 3–4 h post-seizure [12]. Overexpression of P-glycoprotein under the influence of HMGB1 is associated with the development of pharmacoresistance [13].

MicroRNA

MicroRNAs (miRNA) are a group of non-coding, single-strand, endogenous molecules. miRNAs are involved in both physiological (cell division, cell cycle control, cell differentiation, apoptosis, angiogenesis) and pathological processes through regulation of homeostasis [14].

There is evidence that miRNAs are modulators of the immune response [15], are involved in the destruction of the BBB [16], and activate oxidative stress by enhancing the expression of enzymes that induce the formation of reactive oxygen species (ROS) [17].

Elevated levels of miRNA-23a, -34a, -132, and -146a have been found in epilepsy [18]. miRNA-4521 and -301a-3p have been reported as potential markers of pharmacoresistant epilepsy [19].

Aquaporins

Aquaporins are a group of membrane proteins involved in the transport of water and ions across the cell membrane. Through their function, aquaporins regulate water homeostasis, cell migration, and inflammation.

M.M. Salman et al. discovered high levels of AQP4 in brain tissue samples obtained during amygdalohippocampectomy [20].

Elevated AQP4 levels were found in resection samples of epileptic temporal cortex [21]. G.T. Manley et al. hypothesized a relationship between AQP4 and drug-resistant epilepsy. The water-electrolyte (especially potassium ion) imbalance in astrocytes leads to the release of potassium ions from the neuropils into the intercellular space, where they are uptaken and deposited by astrocytes. Osmotic swelling of astrocytes, which reduces the extracellular space volume, increases epileptiform activity.

Glial fibrillary acidic protein

Glial fibrillary acidic protein (GFAP) is a type III intermediate filament protein that is expressed by numerous cell types of the CNS, including astrocytes. GFAP is a marker of astrogliosis that develops in hippocampal sclerosis [22–24].

Matrix metalloproteinase

Matrix metalloproteinase-9 (MMP9) is a zinc-dependent endoprotease that is actively involved in extracellular matrix degradation, neuroinflammation, BBB function, and synaptic plasticity. During a seizure, high cytokine expression stimulates MMP9 activation, which is accompanied by the degradation of the extracellular matrix and the BBB disruption [25–27].

Cytokines

Cytokines are specific proteins produced by glial cells and neurons during neuroinflammation. Pro-inflammatory cytokines (IL-1β, -2, -6) have been found in negligible amounts in the CNS. In clinical studies, IL-1β, IL-6 and TNF-α levels have been shown to be significantly elevated in febrile convulsions [28]. Overexpression of IL-1β by microglia and astrocytes is believed to enhance glutamate accumulation and neuronal excitability.

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is the most sensitive indicator of neuroplasticity. BDNF synthesis, processing, or transport disorders can lead to a variety of neurological diseases, including Alzheimer's disease, Huntington's disease, and epilepsy. BDNF circulates in the blood, does not cross the BBB, and is deposited in platelets and leukocytes. Increased expression of BDNF and its receptor TrkB has been reported in temporal lobe epilepsy and hippocampal sclerosis [29].

Glial cell-derived neurotrophic factor

Glial cell-derived neurotrophic factor (GDNF) is involved in the development and maintenance of neurons and gliocytes. It is expressed in neurons and binds to GDNFα-1 receptors. GDNF/GDNFα-1 complex conducts signals to nigrostriatal dopaminergic neurons, motor and sensory neurons, supporting their survival. In epilepsy, GDNF is believed to be initially synthesized in activated astrocytes and microglia and subsequently detected in cerebrospinal fluid [30].

Biomarkers of neurodegeneration

The frequent hippocampus involvement in the epilepsy pathogenesis has prompted a substantial number of studies investigating the relationship between epilepsy and dementia [31, 32].

There is evidence that tau protein and beta-amyloid are not only products of neurodegeneration but are also involved in epileptogenesis [33]. The potential relationship between these diseases may be attributable to the glutamate neurotoxicity. Beta-amyloid promotes secretion and accumulation of glutamate in the synaptic cleft, leading to activation of intracellular calcium and phosphorylated tau protein production [34]. The dysregulation of calcium-mediated pathways has been demonstrated to increase neuronal excitability and accelerate neurodegeneration.

S100β

S100β is a glial-derived protein, a member of the S100 family of calcium-binding proteins. At low concentrations, S100β stimulates astrocyte proliferation and modulates functional rearrangement of synapses, exerting a neurotrophic effect. At high concentrations, S100β has a toxic effect on astrocytes, induces neuroinflammation, and promotes epileptogenesis [35]. There is strong evidence that elevated S100β levels are associated with the severity and prognosis of epilepsy [36, 37]. High S100β expression in the acute phase of stroke is a marker of post-stroke epilepsy [38].

Neuron-specific enolase

Neuron-specific enolase (NSE) is a dimeric glycolytic enzyme composed of 3 subunits and 5 isoenzymes (αα, ββ, γγ, αβ, and αγ). The αα isoenzyme is known to be found in glial cells, whereas γγ enolase is neuron-specific. NSE is a marker of neuronal death in stroke and hypoxia [39].

Elevated NSE levels have been found post-seizure and in status epilepticus [40, 41]. However, there is evidence that there is no association between temporal lobe epilepsy and NSE levels [42, 43].

NSE is also found in platelets and red blood cells; therefore, evaluating NSE levels in the blood may not be accurate in hemolysis.

Ubiquitin carboxy-terminal hydrolase L1

Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) is an enzyme found in large quantities in neurons. UCH-L1 levels are associated with neuronal death and increased BBB permeability. UCH-L1 enters the bloodstream shortly after brain damage and therefore may be a potential biomarker of epilepsy. Despite the paucity of studies, there has been evidence of increased blood levels of this enzyme both in patients with a history of recurrent epileptic seizures [44] and post-seizure [45, 46].

Visinin-like protein

Visinin-like protein 1 (VILIP-1) is a neuron-specific calcium-binding protein. It was previously studied as a biomarker of stroke, Alzheimer's disease, and traumatic brain injury. In the study by M.A. Tikhonova et al. no association between VILIP-1 levels in hippocampal preparations and blood was observed; however, this study was performed on a small sample of patients [47]. On the contrary, Z. Tan et al. found that VILIP-1 levels were positively associated with severity of epilepsy [48].

Conclusion

The identification and validation of potential biochemical markers is of paramount importance for elucidating the pathogenesis of epilepsy and establishing laboratory methods for its diagnosis. Furthermore, this may also serve as a foundation for identifying targets for antiepileptic therapy.

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Information about the authors

Marina Yu. Maksimova – Dr. Sci (Med.), Prof., Head, 2nd Neurological department, Institute of Clinical and Preventive Neurology, Research Center of Neurology, Moscow, Russia, https://orcid.org/0000-0002-7682-6672
Ekaterina M. Abbasova – postgraduate student, 2nd Neurological department, Institute of Clinical and Preventive Neurology, Research Center of Neurology, Moscow, Russia, https://orcid.org/0009-0009-7105-3103
Anna D. Shitova – postgraduate student, 2nd Neurological department, Institute of Clinical and Preventive Neurology, Research Center of Neurology, Moscow, Russia, https://orcid.org/0000-0003-0787-6251

Authors' contribution: *Maksimova M.Yu.* – study conceptualization, literature analysis, writing the text of the article, scientific editing; *Abbasova E.M.* – literature review, writing the text of the article; *Shitova A.D.* – literature review.

Информация об авторах

Максимова Марина Юрьевна – д-р мед. наук, профессор, руководитель 2-го неврологического отделения Института клинической и профилактической неврологии Научного центра неврологии, Москва, Россия, https://orcid.org/0000-0002-7682-6672
Аббасова Екатерина Мурадовна – аспирант 2-го неврологического отделения Института клинической и профилактической неврологии Научного центра неврологии, Москва, Россия,
https://orcid.org/0009-0009-7105-3103
Шитова Анна Денисовна – аспирант 2-го неврологического отделения Института клинической и профилактической неврологии Научного центра неврологии, Москва, Россия, https://orcid.org/0000-0003-0787-6251

Вклад авторов: *Максимова М.Ю.* – определение концепции работы, анализ проведённых исследований, написание текста рукописи, научное редактирование; *Аббасова Е.М.* – обзор публикаций по теме работы, написание текста статьи; *Шитова А.Д.* – обзор публикаций по теме работы.