Invited Review

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Inflammatory biomarkers in epilepsy

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Abstract

Epilepsy affects millions of people worldwide and has a great burden on world health. Improvement of seizure outcomes mostly relies on establishment of individualized risk factors for epileptogenesis and drug resistance. Several circulating molecules could serve as diagnostic and prognostic biomarkers at different stages of the disease. Inflammatory markers, blood-brain barrier markers, oxidative stress markers, microRNAs, autoantibodies, hormones and growth factors are promising fields of research for biomarkers in epilepsy. Several experimental studies and only a few clinical studies have revealed associations between inflammatory biomarkers and clinical outcomes of epilepsy. Herein, we detail the clinical and immunological significance of several factors of inflammation that may in due time serve as biomarkers of epilepsy in an effort to potentially inspire the researchers towards the development of reliable prognostic biomarkers for epilepsy.

Keywords: Biomarker, epilepsy, inflammation, microRNA, oxidative stress

INTRODUCTION

Epilepsy is a chronic neurological disease that affects millions of people worldwide and leads to decline in quality of life. Approximately 30% of the patients cannot remain seizure-free despite the use of multiple antiepileptic drugs (AEDs). Currently, AEDs cannot prevent epileptogenesis, but only provide symptomatic benefits. Differences in pharmacokinetics of the drugs among individuals is believed to be an important factor in the inability to obtain the desired response to the drugs (1). Biomarkers could be useful to determine which patients are likely to develop epilepsy after a neurological insult, to predict the development of epilepsy after the first seizure, to establish the individual risk factors and to ensure that the individualized treatment options are applied at the right time to the right person. Furthermore, classifying patients according to drug resistance through biomarkers would provide more effective selection of appropriate patients for drug treatments, thus lowering the cost of trials (2). Imaging, electrophysiological measurements, circulating metabolites and gene expression studies can act as biomarkers for epilepsy and epileptogenesis at different stages. In this paper we will focus on inflammatory markers, oxidative metabolites, epigenetic studies, autoantibodies and clinical studies associated with potential biomarkers that are produced by different cell types of the central nervous system (Table 1, Figure 1).

Inflammatory Markers

Neuroinflammation is a biological process primarily mediated by activated microglia, astrocytes, neurons and endothelial cells and developed in response to various triggers like toxins, infectious agents and autoimmune etiology. Right along with these 'classical' triggers, enhanced neuronal activity as seen in epileptic seizures could cause an inflammatory response that was recently named 'neurogenic neuroinflammation' (3). As shown in experimental models, inflammatory molecules may modulate neuronal excitability and have a role in epileptogenesis and drug resistance mechanisms (4, 5). In addition, it is thought that an inflammatory response develops following brain injuries that can trigger epileptogenesis, and this response is considered to be the decisive factor for epileptogenesis in susceptible areas (6).

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Interleukin 1 receptor (IL-1R) / Toll like receptor (TLR) pathway is an important signal for activation of innate immune system. In experimental studies, increased expression of interleukin 1-beta (IL-1β) (the endogenous ligand of TLRs) was detected during epileptogenesis in perivascular astrocytes and blood-brain-barrier (BBB) endothelial cells (7). The pro-inflammatory effects of IL-1β are reversed by IL-1 receptor antagonist. It has been shown that the balance of these two molecules shifts towards the pro-inflammatory IL-1β in individuals with drug-resistant epilepsy (8). High levels of IL-1β in cerebrospinal fluid (CSF) and serum of patients with post-traumatic epilepsy suggested that this cytokine could be used as a prognostic marker (9).

Administration of tumor necrosis factor alfa (TNF-α) into the mouse hippocampus reduces seizure frequency through TNF-α receptor type 2 and promotes seizures via TNF-α receptor type 1. In light of this information, it can be concluded that not only the level of cytokines, but also receptor interactions are related to epileptogenesis (10).

Levels of soluble intercellular adhesion molecule 5 (sICAM5), which is expressed by glutamatergic neurons and shows anti-inflammatory activity by binding to target receptors on microglia and lymphocytes, are found to be decreased in drug resistant epilepsy cases compared to controls, despite the increase in the levels of IL-1β (11). In another study it has been

Figure 1. HGMB1 is a nuclear protein that is released to cytoplasm and extracellular matrix subsequently by neurons and glial cells under pathological contidions like inflammasome activation and contributes to epileptogenesis. Mitochondrial activation due to increased metabolic demand could cause enhanced production of NADPH and ROS and eventually leads to neuronal hyperexcitability. Inflammatory cytokines like IL-1β, TNF-α and IL-6 have been found to be related to epileptogenesis and drug resistance in several studies, also expression of IL-1β was found to be increased in astrocytes and endothelial cells that maintain BBB, during epileptogenesis. S100B, GFAP and NSE are molecules synthesized by neurovascular unit components and in the case of disruption of BBB they are released to vascular lumen. Detection of these molecules in peripheral blood might be useful to predict development and prognosis of epilepsy

IL-1 β: Interleukin 1 beta; IL-6: Interleukin 6; TNF-α: Tumor necrosis factor alfa; HMGB1: High mobility group box 1; NADPH: Nicotinamide adenine dinucleotide phosphate; ROS: Reactive oxygen species; BBB: Blood-brain-barrier; TBI: Traumatic brain injury, S100B: S100 calcium-binding protein B; GFAP: Glial fibrillary acidic protein; NSE: Neuron-specific enolase; P: Pericyte; A: Astrocyte; EC: Endothelial cell

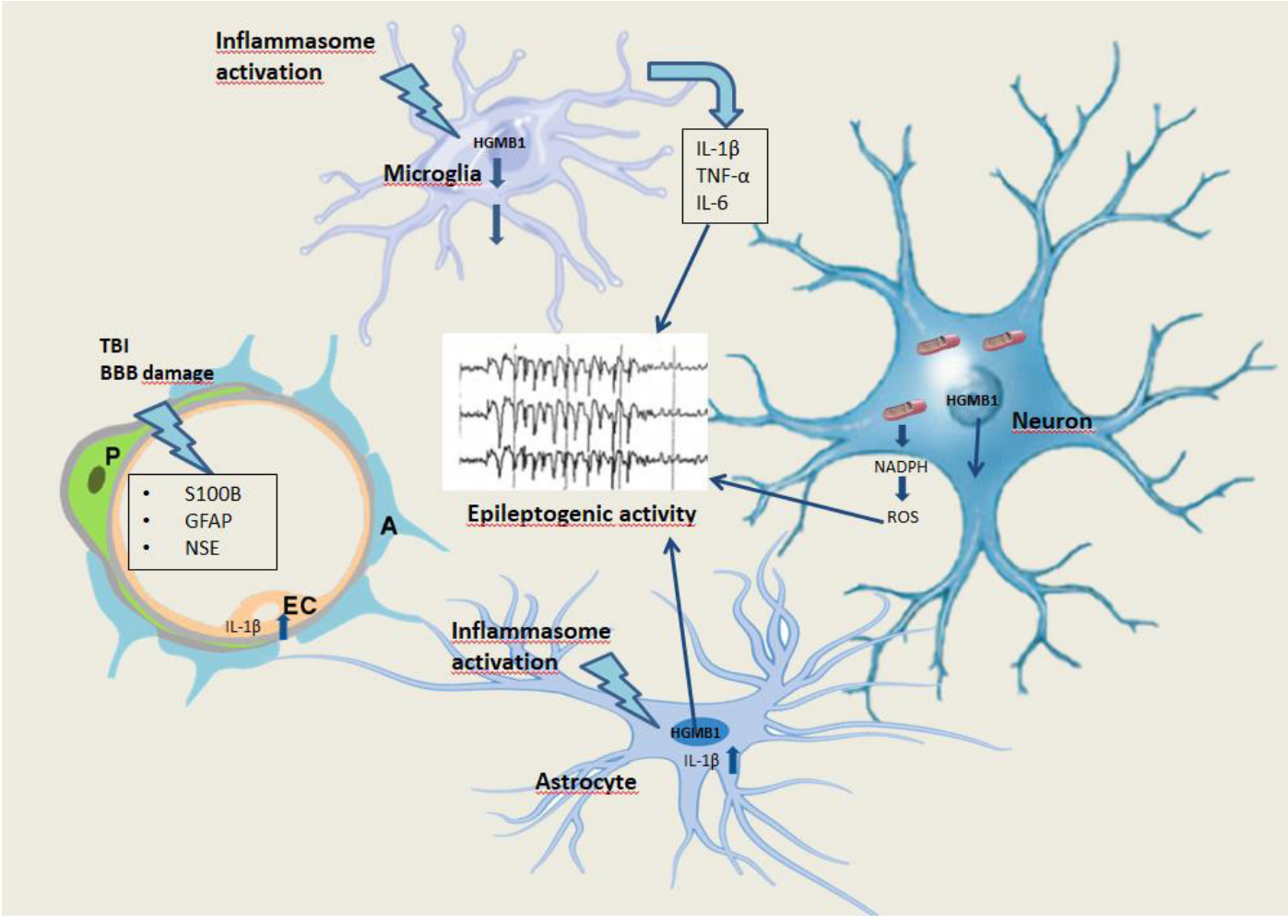

Table 1. Cellular basis of candidate biomarkers in epilepsy

Microglia	
	IL-1 β
	IL-6
	TNF-α
	HMGB1
Astrocyte	
	S100B
	HMGB1
	GFAP
Neuron	
	NSE
	BDNF
	IGF-1
	sICAM5

IL-1 β: Interleukin 1 beta; IL-6: Interleukin 6; TNF-α: Tumor necrosis factor alfa; HMGB1: High mobility group box 1; S100B: S100 calcium-binding protein B; GFAP: Glial fibrillary acidic protein; NSE: Neuron-specific enolase; BDNF: Brain derived growth factor; IGF-1: Insulin-like growth factor 1; sICAM5: Soluble intercellular adhesion molecule 5

suggested that plasma ratio of chemokine CCL17 and sICAM5 might be useful to predict seizure activity (12).

The complement system, which is an important part of the innate immune system, has also been studied as a potential biomarker in epilepsy, and C3 levels have been shown to be higher in epilepsy patients than in controls (13).

Chemokines are chemoattractant molecules that regulate leukocyte migration through BBB. The chemokine CCL2 has been shown to be elevated in drug resistant epilepsy patients. Administration of CCL2 receptor antagonist in experimental models of lipopolysaccharide-induced seizures results in suppression of seizure activity (14).

The short life of cytokines and different methods used to detect their levels could be the reason of conflicting results obtained from the studies and consequently inflammatory molecules might prove to be difficult to be utilized as biomarkers (11).

Blood-Brain-Barrier Markers

Disruption of the blood brain barrier also contributes to epileptogenesis by facilitating the exposure of neurons to pro-inflammatory cytokines (15). It is also thought to play a role in drug resistance by synthesis of various transporters and enzymes (16). As a result of increased permeability in the BBB, the molecules that are normally expected to be found only in the CNS may find a chance to diffuse into peripheral blood. Some of these molecules are S100 calcium-binding protein B (S100B), neuron-specific enolase, and glial fibrillary acidic protein (GFAP) (5).

S100B is a protein released from activated astrocytes and is a promising biomarker candidate for post-traumatic epilepsy. After traumatic brain injury (TBI), acute impairment of BBB causes elevated serum levels of S100B (17). More importantly, S100B is a strong negative predictor of BBB disruption and could be useful to determine patients at low risk to develop epilepsy after TBI (5, 18).

Oxidative Stress Markers

Increased metabolic need during epileptic seizures causes changes in mitochondrial functions, enhances nicotinamide adenine dinucleotide phosphate production and consequently increases reactive oxygen species (ROS) synthesis. ROS may contribute to epileptogenesis by increasing neuronal hyperexcitability or by altering the structure of molecules such as lipids, proteins and deoxyribonucleic acid (19, 20). The change in the redox state of the brain also causes an increase in disulfide high mobility group box 1 (HMGB1) synthesis. HMGB1 is a chromatin binding protein found in the nucleus under physiological conditions that regulates transcription. Activation by the inflammasome complex causes translocation of this protein from the nucleus to the cytoplasm and then to the extracellular space. Redox modifications lead to synthesis of the disulfide HMGB1 form that contributes to seizure pathogenesis thereby leading to cell death by increasing calcium permeability of the N-methyl-D-aspartate receptor (NMDAR) (21). It also acts by binding the TLR4 and receptor for advanced and glycation end products on immune system cells and thus regulating the release of pro-inflammatory cytokines through nuclear factor kappa B activation (22). Relationship between brain injury-induced neuroinflammation and HMGB1 has been known for a long time (23). Increased expression of HMGB1 and TLR4 receptor has been reported in hippocampus of mesial temporal lobe epilepsy (MTLE) mouse models (24) as well as in the brain tissues of post-surgical drug resistant epilepsy patients (25). In another study, HMGB1 and IL-1β were speculated to predict the frequency of seizures (26). Anti-HMGB1 monoclonal antibodies which act by inhibiting translocation of HMGB1 from the nucleus, have been shown to reduce seizure frequency and provide cognitive improvement in experimental status epilepticus (SE) models (27). HMGB1 is a strong biomarker candidate for epilepsy due to its relation with epileptogenesis and drug resistance and its peripheral blood levels strongly correlate with the CNS levels. On the other hand, it is not specific for epilepsy and further clinical studies are needed to evaluate its role as a biomarker and therapeutic target (28).

MicroRNA (miRNA)

MicroRNAs are short-coding RNAs that regulate gene expression through mRNA. The expression levels of miRNAs could change under pathological conditions and thus they may serve as candidate diagnostic and prognostic biomarkers as well as therapeutic targets.

Expression of miR-146a, a miRNA related to inflammatory pathways, was found to increase in reactive hippocampal astrocytes of TLE cases. It was noted that this increase was especially in the regions where neuronal death and gliosis occurred (29). In a study of miRNA expression in hippocampal samples of patients who had refractory TLE and underwent surgical intervention, hsa-miR-487a was found to be related to prognosis during the post-surgical period (30). Wang et al. suggested that hsa-miR-106b-5p has high specificity and sensitivity for epilepsy diagnosis and hsa-miR-301a-3p could be a prognostic marker to predict the drug resistance (31, 32).

Depletion of miR-128, which regulates motor activity and neuronal hyperexcitability by interacting with ERK2 pathway and ion channel expression, results in fatal epilepsy in a mouse model (33). Expression of miR-134 levels has been shown to decrease in epileptic rat brains and peripheral blood compared to controls (34). In another study, inhibition of miR-134 was shown to provide a reduction in spontaneous seizures following SE in the mouse model (35).

Blockage of miR-22, which has been shown to target the cytoplasmic polyadenylation binding protein, resulted in enhanced neuroinflammation and increased frequency of seizures in an epileptic mouse model (36). miR-22 possibly regulates inflammation via P2X7 receptor, which regulates production of active forms of IL-1β and IL-18 through inflammasome complex activation (37). miR-124 levels are associated with microglia activation and have been shown to decrease in experimental epilepsy models and epileptic patients. However, serum levels of miR-124 do not correlate with the frequency of spontaneous seizures (38). Suppression of miR-155 provides improvement in post-ictal behavior in experimental animals (39).

In children with drug-resistant TLE miR-181 that targets AMPA receptors has been found to be elevated in temporal lobe tissue and silencing of miR-181 has resulted in protection against neuronal death (40). miR-203 targets inhibitor glycine receptor-β and increased levels of this miRNA have been shown in the hippocampus of epileptic patients and experimental models. Furthermore, administration of intranasal miR-203 antagomir provides a reduction in seizure frequency (41). miR-219, which negatively regulates NMDAR functions, has a seizure suppressing role in experimental models (42).

Chen et al. have detected increased miR-210 and decreased γ-aminobutyric acid (GABA) levels in hippocampal tissue of pilocarpine-induced SE models and shown that inhibition of miR-210 results in decreased hippocampal apoptosis and increased GABA levels (43).

miR-199 targeting mTOR pathway inhibitors has been found to be highly expressed in hippocampus of pilocarpine-induced SE models and may be considered as a therapeutic target (44). miR-221 and miR-222 were observed to control ICAM1 expression and are selectively co-expressed in astrocytes of TLE patients (45).

Hormones and Growth Factors

Recent studies have shown that some hormones and growth factors are associated with epileptogenesis and drug resistance. In animal models with lower serum brain derived growth factor (BDNF) threshold for SE was decreased after TBI compared to animals with normal BDNF levels and it is suggested that BDNF might be useful to predict vulnerability to seizures (46). In a study with 135 epilepsy patients serum BDNF levels were found to be negatively correlated with severity of disease and seizure frequency (47). BDNF also could be useful to differentiate psychogenic non-epileptic seizures (PNES) from epilepsy patients since serum BDNF levels are decreased in epilepsy patients compared to PNES cases (48).

Insulin-like growth factor-1 (IGF-1) is an essential growth factor for brain development and reduces neuroinflammation (49). In infantile spasm patients, low IGF-1 levels were found to be correlated with severity of disease, poor response to treatment and mental retardation (50).

Auto-Antibodies

In recent years auto-antibodies that target neuronal surface antigens and intraneuronal cytoplasmic or nuclear antigens have been related with epilepsy associated with autoimmune encephalitis. Neuronal antibodies (NAAs) against NMDAR, the voltage-gated potassium channel complex proteins LGI1 and CASPR2 and glutamic acid decarboxylase received particular attention. Dubey et al. reported NAA seropositivity in 34.8% of 112 patients (51). Similarly in a study with 111 MTLE-HS patients, a seropositivity ratio of 22.5% was obtained (52). Some of the NAA positive patients gave a positive response to immunotherapy implying that these antibodies might serve as therapeutic biomarkers (52, 53).

Neuronal antibodies have been also reported in SE patients with unknown etiology but it has not been established as yet whether these antibodies are pathogenic or emerge as a bystander effect in SE pathogenesis (54). Clinical studies suggest that epilepsy with autoimmune etiology is more likely to have better seizure outcomes especially after immunotherapy. Dubey et al. developed a scoring system based on previous studies to help the diagnosis of autoimmune epilepsy. New onset and rapidly progressive mental status change, autonomic dysfunction, neuropsychiatric findings, signs of a viral prodrome, faciobrachial dystonia, drug resistance, inflammatory findings in CSF, MRI findings suggestive of limbic encephalitis and underlying malignancies suggest evaluation of NAAs and immunotherapy (51).

Clinical Trials

Most of the data for biomarkers in epilepsy are based on experimental studies and there is a limited number of clinical

studies. In The Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) study, investigators searched for a relationship between febrile seizures and cytokines and found low IL-1ra / IL-1β ratio, which suggested insufficient suppression of IL-1β by its antagonist IL-1ra, could contribute to seizure induction (55).

In a study examining the relationship between iron metabolism and cytokine levels, increased levels of IL-6 and decreased levels of TNF-α were detected in sera of patients with focal epilepsy. The decrease in transferrin values in the same patient group was thought to be due to the effect of this change in cytokines on iron metabolism (56).

EPISTOP study, which was conducted in patients with tuberous sclerosis, a neurocutaneous disease characterized by severe focal seizures, has shown increased expression of IL-1β and oxidative stress markers such as heat-shock protein 70 and glutamate-cysteine ligase catalytic subunit by cortical tubers (57, 58).

Evaluation of 11 electrical SE in sleep patients versus 20 controls revealed that IL-6 levels were higher in the patient group and immunomodulating treatment caused a decline in cytokine levels in parallel to amelioration of electroencephalogram findings (59).

Conclusive Remarks

In the journey of search for candidate biomarkers of epilepsy, heterogeneity of epileptic disorders and diversity of factors related with epileptogenesis and drug resistance are challenging factors. Studies designed for innovation of prognostic biomarkers mostly suffer from paucity of recruited epilepsy patients, absence of sensitivity and specificity measurements and standardization of kits and materials used for measurement of specific biomarkers. However, prediction of whom to has and when to has epilepsy of a patient would gain a significant advantage in the fight against the disease, therefore further research in the field of biomarkers for epilepsy with larger patient cohorts and epilepsy subgroups is crucial.

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