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REVIEW ARTICLE

Blood biomarkers in epilepsy

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Robust and accessible biomarkers are greatly needed in epilepsy. Diagnostic and prognostic precision in the clinic needs to improve, and there is a need for objective quantification of seizure burden. In recent years, there have been advances in the development of accessible and cost-effective blood-based biomarkers in neurology, and these are increasingly studied in epilepsy. However, the field is in its infancy and specificity and sensitivity for most biomarkers in most clinical situations are not known. This review describes advancements regarding human blood biomarkers in epilepsy. Examples of biochemical markers that have been shown to have higher blood concentrations in study subjects with epilepsy include brain proteins like S100B or neuronal specific enolase, and neuroinflammatory proteins like interleukins, and tumor necrosis factor-alpha. Some of the blood biomarkers also seem to reflect seizure duration or frequency, and levels decrease in response to treatment with antiseizure medication. For most biomarkers, the literature contains seemingly conflicting results. This is to be expected in an emerging field and could reflect different study populations, sampling or analysis techniques, and epilepsy classification. More studies are needed with emphasis put on the classification of epilepsy and seizure types. More standardized reporting could perhaps decrease result heterogeneity and increase the potential for data sharing and subgroup analyses.

KEYWORDS
biomarker, blood, diagnostic study, epilepsy, seizure

1 | INTRODUCTION

Epilepsy signifies an enduring predisposition for seizures. The diagnosis is clinical and most often based on symptom descriptions by the patient and/or witnesses. Even if one or several seizures have occurred, it can be difficult to determine whether these reflect an actual enduring predisposition for seizures or transient factors like acute brain disease or substance abuse. Unsurprisingly, misdiagnosis is common. An erroneous epilepsy diagnosis carries substantial costs—human and financial—by imposing stigma, life style limitations, antiseizures medication (ASM) side effects, and terminated search for alternative explanations of the symptoms.[1]

The lack of reliable biomarkers hampers the field also in patients who undoubtedly have epilepsy. The current measure of disease burden is patient or caregiver recollection of seizures, sometimes assisted by seizure diaries, a very unreliable method. Nonetheless, seizure diary is the method used also in registration-purpose clinical trials of new ASMs. Needless to say, the method only captures seizures that the person is aware of, and excludes many persons with epilepsy who are unable to communicate their seizure burden.

2 | EXISTING METHODS FOR EPILEPSY DIAGNOSIS

A thorough history is the only basis for most epilepsy diagnoses today. The physician will ask about symptoms, collect witness accounts, and thereafter rely heavily on pattern recognition to diagnose whether the symptoms presented are likely to have been caused by a seizure. Stereotypic features, a seizure-typical duration, and typical semiology are some clinical clues.

Statistically, a single seizure is a one-time occurrence in approximately 20%–50%.[2] In most instances, epilepsy cannot, therefore, be diagnosed after a first seizure. A work-up with electroencephalography (EEG) and imaging usually follows. Epileptiform activity on EEG or imaging abnormalities increase the likelihood of further seizures approximately twofold, but the investigations do not in themselves allow a diagnosis of epilepsy after just one seizure.[2] After recurrence of another unprovoked seizure, the risk of further seizures is high. Epilepsy is usually diagnosed and ASM started. If symptoms nonetheless continue, video-EEG—an in-hospital usually week-long recording of EEG and video—can allow a more accurate diagnosis and quantification of seizure burden.

In 2014, the International League Against Epilepsy revised its clinical definition of epilepsy and allows a diagnosis to be made already after one seizure if there is clear indication of a high recurrence risk (reflecting an enduring predisposition).[3] In the absence of biomarkers, the epilepsy field has turned to statistics and clinical risk factors to use this possibility. Elaborate clinical scales now allow very good identification of patients at high risk of epilepsy after a first seizure, mostly after stroke.[4] The underlying issue is, however, not solved; statistical risk factors can only indicate that it is very likely that a person will have more seizures, not that an enduring predisposition for seizures is actually present.

3 | APPLICATIONS OF BLOOD BIOMARKERS IN EPILEPSY

The advances in our understanding of how biochemical markers can reflect brain pathology has given rise to optimism in the epilepsy field. Although there is much exciting research using connectivity/resting state imaging to detect epilepsy and devices ranging from smart watches to implantable EEG to assess seizure burden, cost, and impracticality limit the usefulness of such techniques for larger patient groups. Blood tests capable of identifying epilepsy and seizure burden would be a more scalable option.

Identifying epilepsy through blood tests is a profound challenge, but not unrealistic. Patients with a first seizure represent an enriched high-risk population that usually come in contact with health services—which allows blood sample collection that can be analyzed with high-throughput screening methods. Pilot studies have demonstrated feasiblitiy.[5–7] Another approach is to study patients with an acute brain disease that entails a high risk of symptomatic epilepsy. This approach has the advantage of a known starting date of potential epileptogenesis. Example of this approach include test of biomarkers panels in acute stroke and the EpiBios4Rx project of posttraumatic epilepsy.[8,9]

Another important application of blood biomarkers in epilepsy would be to quantify seizure burden. Currently, ASMs are titrated based on clinical response—the absence of overt seizures. Biomarkers of disease activity, like NT-proBNP for heart failure or HBA1c for diabetes, would greatly facilitate management. Ideally, the marker or markers should be responsive to small amounts of subclinical seizure activity, allowing intervention like sleep of revision of ASM therapy before a clinical seizure occurs. Conceptually, seizures do leave metabolic traces—for instance transiently increased lactate levels.[10,11]

Here, we summarize current research on promising candidate plasma and serum biomarkers in epilepsy. The review discusses only human studies.

4 | BLOOD BIOMARKERS OF EPILEPSY

4.1 | Neuronal/brain biomarkers

Biomarkers that originate in the brain are a natural starting point for detecting pathophysiological changes associated with epilepsy. Identified candidates include S100 calcium-binding protein B (S100B), neuronal specific enolase (NSE), glial fibrillary acidic protein (GFAP), neurofilament light protein (NfL), microtubule-associated protein tau (Tau), ubiquitin C-terminal hydrolase 1 (UCHL-1) and metalloproteinase 9 (MMP-9), all of which are abundantly present in neural tissues.

4.1.1 | S100 calcium-binding protein B (S100B)

S100B is primarily expressed in astrocytes.[12] The expression of S100B is stimulated by CNS damage and the inflammatory response caused by a stroke, and the protein has been investigated as a biomarker of subsequent poststroke epilepsy. Levels of S100B are higher in patients with epilepsy after stroke than age-matched patients with single seizures.[5] However, in the acute phase of stroke low levels of S100B have been associated with an increased risk of later poststroke epilepsy.[8] Elevated S100B-levels have been demonstrated in adults and children with temporal lobe epilepsy (TLE).[13–15] In one study, S100B was higher in female TLE patients than males, hinting at possible interactions between S100B and sex hormones.[16] Some findings have been inconsistent, reporting no significant differences between epilepsy and control groups[17,18] or even a decrease in serum S100B levels in epilepsy.[19,20] Moreover, the short half-life of S100B (25–113 min) could pose as a challenge for its reliable measurement.[13] Currently, positive studies seem to dominate, and two recent meta-analysis support elevation of S100B protein level in persons with epilepsy.[7,21]

4.1.2 | Glial fibrillary acidic protein (GFAP)

Glial fibrillary acidic protein is predominantly expressed by astrocytes in CNS. Higher-than-control levels of GFAP in the blood has been reported in both children and adults with epilepsy.[22–24] We also detected higher GFAP levels in patients with poststroke epilepsy compared to patients with single seizures that did not develop epilepsy.[5] In addition, we observed that serum GFAP remained at elevated levels long after a patient experienced a stroke, which could indicate severe brain injury or prolonged response.[5] A benefit of GFAP over other biomarkers as a serum marker is its relatively long half-life.[22]

4.1.3 | Neuronal specific enolase (NSE)

Neuronal specific enolase is a glycolytic enzyme unique to neurons and neuroendocrine cells. A range of studies have implicated increased levels of NSE in epilepsy. A marked increase in serum NSE was reported in TLE, but not in extratemporal lobe epilepsies (XTLE).[25] The authors concluded that the risk of seizure-related damage could differ between TLE and XTLE, implying that NSE may prove useful in distinguishing between certain epileptic conditions. High NSE levels decreased after treatment with carbamazepine and oxcarbazepine in patients with focal seizures.[26] Furthermore, a recent meta-analysis by Mu et al.[27] reported that levels of NSE in serum are elevated in childhood epilepsy.

There are also conflicting results. Hamed et al. found lower levels of NSE in children's with epilepsy.[20] A comparison study between epilepsy and PNES did not find significant differences in either patient group in relation to controls.[28] We did not find a difference in NSE levels between patients that developed epilepsy and those who only had a first seizure,[5] and Chang et al. did not observe substantial differences between TLE and control patients.[14] The clinical usefulness and role for NSE in epilepsy remains to be determined.

4.1.4 | Neurofilament light protein (NfL)

Neurofilaments are axonal proteins that maintain the structure of neurons and are subsequently released into the CSF and blood stream upon neuroaxonal damage. NfL is an established clinical marker of neurodegenerative diseases, including Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis.[29] There are limited studies that discuss its usage as a serum or plasma marker in epilepsy; however, elevated serum levels have been reported in autoimmune epilepsy.[30] A study on patients with Down syndrome also reported near-significantly higher levels in those with epilepsy.[31] Elevated serum concentrations were detected in adults with poststroke epilepsy (PSE) when compared to single seizure patients, but not in patients with non-stroke related epilepsy.[5]

4.1.5 | Ubiquitin carboxy-terminal hydrolase L1 (UCHL-1)

Ubiquitin carboxy-terminal hydrolase L1 is a brain-specific enzyme found in high concentrations in neurons. UCHL-1 has been linked to neuronal death and BBB permeability and is identified in the bloodstream soon after injury, meaning it could aid in early intervention of neuroprotective therapies. It has, therefore, been implicated as a prospective biomarker of BBB permeability and neuronal damage.[32] Elevated serum concentrations have been reported in epilepsy,[33,34] with significant concentrations detected in the plasma of patients with recurrent seizures.[32] Further research regarding serum UCHL-1 is worthwhile as its most promising characteristics are its early detection and relatively long half-life of up to 9 h in serum.[32]

4.2 | Neuroinflammatory biomarkers

Inflammation is believed to be an important process in epileptogenesis,[35] so neuroinflammatory markers are other possible epilepsy biomarker candidates. Several of these can be measured in blood.

4.2.1 | Cytokines

An increased production of cytokines has been implicated in prolonged epileptic seizures, and suggested to contribute to further inflammation and seizure generation.[36,37] Study results are still divergent with regards to which cytokines are upregulated when and for how long, which could to some extent reflect differences in methodology or study populations.

Interleukins (IL)

IL-1β is one of the most extensively studied interleukins in epilepsy, and upregulated in tonic–clonic seizures[38] and TLE.[39] IL-1β levels were also predictive of seizure recurrence in a study of ischemic stroke patients after a first epileptic seizure.[40] Plasma IL-1Ra, the antagonist to the IL-1 receptor, was also found elevated in febrile seizures, while IL-1β remained unchanged.[41,42]

Serum IL-2 and IL-4 are lesser studied interleukins in epilepsy but have been observed to increase in some epilepsy syndromes and febrile seizures.[43,44] One study did not find altered levels in children with acute encephalopathy and/or prolonged febrile seizures (PFS),[45] while another study even observed a decrease in serum IL-2 and IL-4 in epilepsies of different etiologies.[46]

High levels of plasma IL-6 have been reported in studies on febrile seizures,[42,43,47] while serum IL-6 was also observed at elevated levels in several epilepsy studies, particularly in TLE.[39,43,48,49]

Increased serum IL-8 and IL-10 levels have been demonstrated in neonatal and febrile seizures.[47,50] IL-8 was also significantly upregulated in adults with partial onset seizures and linked to seizure

severity in TLE and idiopathic generalized epilepsy (IGE).[51,52] Basnyat et al.[53] observed a reduction in plasma IL-10 in individuals with TLE and hippocampal sclerosis (HS) in contrast to TLE without HS.

Interferon gamma (IFNγ)

Postictal and interictal levels of IFNγ have been significantly elevated in individuals with epilepsy compared with controls in several studies.[43,54,55]

Tumor necrosis factor-alpha (TNF-α)

Significant upregulation of serum TNF-α has been demonstrated in patients with epilepsy, but so has unchanged TNF-α levels.[43,54,56,57] Soluble TNF receptor 2 (sTNFr2), an isoform of the TNF-α receptors, had good discriminative capacity with regard to separating patients from controls in one study, compared with TNF-α and sTNFr1.[46]

Chemokines

Increased CCL17—also known as thymus and activation regulated chemokine (TARC)—was observed in the plasma of focal epilepsy patients.[51]

4.2.2 | Neurotrophic factors (NTFs)

A recent exploratory study showed higher BDNF plasma levels in persons with epilepsy than controls,[46] but a previous serum-based study was negative.[58] Lower BDNF levels in serum have been reported in epilepsy or PNES[59] and in patients with TLE.[60] Plasma NT3, CTNF, and NGF levels were higher in persons with epilepsy than controls in another study, which round no change in NT4/5.[46]

4.2.3 | Other neuroinflammatory mediators

High Mobility Group Box-1 (HMGB1) is a nonhistone nuclear protein. With a high sensitivity and specificity, HMGB1 levels differentiated between persons with drug-resistant focal epilepsy, persons with drug-sensitive epilepsy and healthy controls.[61]

Soluble intercellular adhesion molecule 5 (sICAM5) is a CNS-specific anti-inflammatory adhesion protein. Persons with drug-resistant focal epilepsy had low sICAM5 levels compared with healthy controls in one study.[51]

5 | BLOOD BIOMARKERS OF SEIZURE BURDEN

Several studies suggest that seizures could alter levels of proteins in the plasma or serum, which could then be useful for quantification of seizure burden.

5.1 | Brain proteins

Neuronal specific enolase has been shown to increase even after a single seizure,[62] and to reflect seizure frequency in TLE.[14] NSE was also associated with seizure duration in children; children with convulsive SE presented significantly higher serum levels of NSE than controls and those with idiopathic epilepsy.[63,64] High levels of NSE or S100B decrease in response to antiseizure medication.[15,26] Correlations to seizure severity and frequency have been reported with serum metalloproteinase 9 (MMP-9).[65,66] Increased levels have been reported in both prolonged febrile seizures[65] and tonic–clonic seizures.[67] After generalized tonic–clonic seizures, serum MMP-9 remained detectable up to 24 h post-seizure.[67]

5.2 | Cytokines

Serum IL-6 has been associated with seizure severity across various studies and proposed as a marker of severe epilepsy.[52,57,68,69] Similarly, IL-8 has also been implicated in seizure severity in TLE, XLE, and IGE.[36,52] Two studies have reported serum levels of IL-17a to correlate with seizure severity.[52,55] Other cytokines related to seizure burden include IL-1b, IL-1Ra, IL-10, IL-17a, TNF-α, and sTNFr2.[46-48,50,56]

5.3 | Other proteins or lactate

Biochemical changes believed to reflect the metabolic demands and muscular damage caused by a tonic–clonic seizure are well described in epilepsy—most well-known are the muscle enzyme creatine kinase (CK) and lactate.[11] These changes are, however, transient, making them not very useful as indicators of response to therapy. Another example is prolactin. Several studies have found HMGB1 levels to increase immediately after convulsive seizures and remain elevated for hours.[24,70,71]

6 | CHALLENGES IN BLOOD-BIOMARKER DEVELOPMENT

Even though blood biomarkers offer many advantages such as blood samples being easily accessible and cost-effective, there are many challenges in the development of blood-based biomarkers. For instance, the very large dynamic range of different protein concentrations from high abundance to very low levels create methodological challenges in protein identification and quantification in blood.[72] There could be very low amounts of proteins of the CNS entering into peripheral bloodstream and biomarkers that are not secreted from the CNS to blood might remain undetected. In addition, it cannot be ignored that blood levels of many inflammatory cytokines are unstable or

are difficult to measure owing to the lack of sensitive assays.[73] These methodological difficulties could explain some of the heterogeneity of the literature, and the conflicting results for several biomarkers.

Another challenge in the field is understanding the sensitivity and specificity of potential biomarkers. Ideally, biomarkers of epilepsy should reflect some specific process that is not influenced by other brain pathology. Markers assessing seizure burden should be similarly specific. The field is not yet there. Currently, studies are trying to identify candidate biomarkers, the diagnostic performance of these will be a subsequent question. It is also very possible that one or two biomarkers will not suffice for this purpose. Instead, advanced analytics or machine-learning may allow more complex analysis of panels of biomarkers—interpreting complex patterns of brain injury or inflammatory markers.

7 | CONCLUSIONS AND FUTURE PROSPECTS

In this review, we have provided a narrative overview of promising blood-based biomarkers in epilepsy. Future research is needed in order to expedite the use of these biomarkers in clinical practice. Progress in the field will probably require large and well-characterized sample collections from longitudinal studies of well-defined patient cohorts. Particular effort should probably be put into more meticulous classification of epilepsy and seizure type. Epilepsy is a very heterogenous disease, and a biomarker of epileptogenesis in one context or a particular seizure type may not be identified in studies on too heterogenous study populations. Collaborative efforts to create common data elements to include in epilepsy blood biomarker studies could perhaps enhance possibilities for data sharing and subgroup analyses. Candidate markers need to be compared between different patient groups (with vs. without epilepsy, with recent seizures vs seizure-free, etc). After that, sensitivity and specificity need to be determined for each clinical use. Diagnostic blood biomarkers are a long way off, but the field is moving.

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This review article contains no original data.

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