AN OUTLOOK OF BIOMARKERS OF EPILEPSY: IN-DEPTH REVIEW

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Epilepsy is the most common serious primary disease of the brain. Approximately 10% of people can expect to have at least one epileptic seizure during a normal lifespan, and one third of these will develop epilepsy. In our study, we report most of the potential biomarkers of epilepsy to date, according to their magnitude in either diagnosis of epilepsy or estimation of the efficacy of antiepileptic treatment through reviewing the significance of each of: pathologic High-Frequency Oscillations pHFOs, brain inflammation, Blood Brain Barrier BBB dysfunction, Traumatic Brain Injury TBI and microRNAs as a potential biomarker of epilepsy.

High-Frequency Oscillations as a Biomarker in Epilepsy

Pathological high-frequency oscillations (pHFOs) (HFOs, >80Hz) , identified in interictal EEG recordings seem to have the potential to line the range of epileptogenic tissue responsible for producing spontaneous seizures. interictal HFOs with spectral frequencies between 250 and 600 Hz, termed fast ripples (FR), are found in brain areas capable of generating spontaneous seizures, including dentate gyrus, hippocampus, subiculum and entorhinal cortex. Several retrospective studies that have followed up on patients after resective surgery found that removal of tissue generating interictal pathological HFOs correlated with a good outcome. Table 1.

In conclusion, several studies with microelectrodes conclude that fast ripples are most specific for the epileptogenic zone, but in clinical studies with macroelectrodes it is useful to include both ripples and fast ripples in the evaluation of the potential epileptogenic region.

Table 1. Studies Comparing Interictal Ripples and FRs to the Potential Epileptogenic Region

Study	Subjects	Site	Electrodes	Epileptogenicity Parameter	Conclusion
Bragin and colleagues (1999)	Rats (KA) and human	MT	Micro	Epileptic individuals and seizure onset side	FRs
Bragin and colleagues (2002)	Human	MT	Micro	Multiunit neuronal synchronization	FRs
Bragin and colleagues (2004)	Rats (KA)	MT	Micro	Side of KA injection, having seizures	Both
Staba and colleagues (2004/2002/2007)	Human	MT	Micro	Seizure onset side and region atrophy	FRs
Urrestarazu and colleagues (2006)	Human	MT/F	Macro	Seizure onset zone	FRs
Jacobs and colleagues (2008)	Human	MT/F	Macro	Seizure onset zone	FRs > ripples
Worrell and colleagues (2008)	Human	MT	Micro and macro	Seizure onset zone	Both
Jacobs and colleagues (2010/2009); Zijlmans and colleagues (2011)	Human	MT/F/P/O	Macro	After discharges and seizure onset zone	Both
Ogren and colleagues (2009)	Human	MT	Micro	Hippocampal atrophy	FRs
Jiruska and colleagues (2010)	Rats (TT)	MT	Micro	Side of injection	FRs > ripples
Jacobs and colleagues (2010)	Human	MT/F/O	Macro	Surgical outcome	Ripples > FRs
Luciana Andrade-Valença and colleagues (2012)	Human	MT	Both	Onset zone	both
Chatillon CE and colleagues (2013)	Human	MT	Both	SEEG segment	FRS
Matsumoto A and colleagues (2014)	Human	FC/TC	Macro	Onset zone	both
Van 't Klooster (2015)	Human	MT	both	Surgical outcome	both
Francesca Pizzo (2016)	Human	Scalp	Both	Scalp EEG	FRS
The conclusion describes whether fast ripples or ripples were more specific for the presumed epileptogenic area or whether no clear difference was found.					
F = frontal; FC= frontal cortex; SEEG= stereoelectroencephalography; TC- temporal cortex;FR = fast ripple; KA = kainic acid; MT = mesiotemporal; O = occipital; P = parietal; TT = tetanus toxin.					

Brain Inflammation as a Biomarker in Epilepsy

MicroRNA Expression Profiling Indicates Biomarkers for Epilepsy

Over the past seven years, several target studies and genome- wide miRNA expression profiling studies have identified changes to over 100 different miRNAs in epilepsy patients and animal models. In our review we focused on four studies involving 295 human participants and rats’ models have shown that miRNA 301a-3p was significantly dysregulated in Epilepsy with one study claiming that it had the best diagnostic value for Drug resistant epilepsy with 80.5% sensitivity and 81.2% specificity (Wang at el. 2015). Two studies involving 245 human participants have shown that miR-106b-5p was significantly dysregulated in Epilepsy with one study claiming that it had the best diagnostic value epilepsy with 80.3 % sensitivity and 81.2 % specificity (Wang at el. 2015).

The major inflammatory pathways studied for their possible contribution to epileptogenesis are the activation of the IL-1b system, COX-2 and mTOR. Blockade of IL-1b signaling leads to prevention of seizure generalization or delays stage 5 seizure occurrence, respectively, and increases the threshold for afterdischarge induction. Inhibition of COX-2 during the latent phase, which follows status epilepticus, and is prodromal to spontaneous seizures onset, has given variable results. Either neuroprotection and decreased spontaneous seizures, or no major effects on neuropathology and various functional outcomes have been reported, depending on the anti-COX-2 treatment schedule and the severity of chemically or electrically induced status epilepticus in each of these studies. mTOR inhibition by rapamycin has also given contrasting results since anti-epileptogenesis actions consisting of inhibition of sprouting and decreased chronic seizure frequency have been reported in kainate-treated rodents, while chronic epilepsy onset or severity was not affected in pilocarpine-treated animals.

Blood Brain Barrier BBB Dysfunction as a Biomarker of Epilepsy

Status epilepticus induced by kainate or pilocarpine in mice has been demonstrated to upregulate adhesion molecules, such as ICAM-1, VCAM-1 and E-and P-selectin, on endothelial cells of brain microvasculature. This phenomenon was also described following epileptiform activity induced by bicuculline in an in vitro guinea pig preparation. Leukocyte adhesion on inflamed brain endothelium was implicated in the vascular leakage during seizure activity in vivo, and the interference with this phenomenon after pilocarpine-induced status epilepticus reduced the frequency of spontaneous seizures in epileptic mice.

Potential Biomarkers in TBI (Traumatic Brain Injury)

Candidate biomarkers of TBI include serum or CSF levels

Molecule	Biomaterial	Remarks
S100B	Serum/CSF	Levels correlate with injury severity after trauma and have predictive value on neurological outcome
NSE	Serum	Levels correlate with neurologic outcome after trauma and reflect neuronal damage after SE
GFAP	Serum/CSF	Levels correlate with injury severity after trauma and have predictive value on neurologic outcome; increase in CSF correlates with epileptogenesis stage in the kainic acid SE model
UCHL1	CSF	Increase in CSF correlates with epileptogenesis in the kainic acid model
MBP	Serum	Released in the course of brain trauma; predictive value for epileptogenesis to be

of protein leaking from the brain, which may represent a distinct correlate of brain damage. Table 2

Table 2. Examples of Potential Biomarkers for Epileptogenesis in Cerebrospinal fluid (CSF) and Blood Serum