DO WE NEED BIOMARKERS IN EPILEPSY?

Konrad Rejdak
Department of Neurology, Medical University of Lublin, Poland
Medical Research Center, Polish Academy of Sciences, Warsaw, Poland

Despite considerable progress in the management and treatment of epilepsy patients, there are still many problems remaining unsolved. The most important include pharmacoresistance in around one third of patients, unknown mechanisms of epileptogenesis and heterogeneity of clinical outcomes in patients with chronic epilepsy. Reliable biomarkers are essential for identifying specific problems and quantitatively measuring our success in resolving them, not only for research purposes, but also for individual patient care. Surprisingly, the field of epilepsy has no reliable biomarkers, as yet (Engel, 2008).

In parallel to structural neuroimaging or electrophysiological studies, there is an increasing interest in biochemical brain-specific surrogate markers. There is a need for sensitive in vivo assessment methods that are quantitative, reliable, reproducible, and safe. For repeated use over a period of years, they must be acceptable to patients and to a healthy control group. If large numbers of patients are to be evaluated, it is beneficial if the methods can be reliably applied in multiple sites. Biochemical biomarkers specific for the CNS pathology and disease fulfill the above criteria. This paves the way for potential applications of biochemical biomarkers such as monitoring seizure related pathological processes, following the process of epileptogenesis after brain insult, and indentifying patients at risk of pharmacoresistance. At current stage the first issue has received much attention and there are number of studies analyzing the potential biomarkers representative for different aspects of seizure related phenomena, which might facilitate solving the major controversy in that area.

There is general consensus that status epilepticus has deleterious effects on brain tissue, but whether brief recurrent seizures are also destructive to neurons is discussed controversial. The epilepsies form a heterogeneous group of conditions in which overt seizures are only one manifestation. Apparently, similar seizure may cause cerebral damage in the context of one form of epilepsy but not in another. Subclinical seizures and interictal epileptiform activity might also cause cerebral damage. Currently available methods to assess the degree of progression of neurodegeneration in epilepsy patients include neuropsychological assessment, neuroimaging or pathological studies of resected in vivo or postmortem brain tissue. However, they have many limitations and published data gave many contradicting results, as they were influenced by different confounding factors. Serial EEG studies have not been shown to be a sensitive indicator in this regard. Besides, there are examples of postmortem studies that demonstrated the poorly controlled generalized seizures including episodes of status epilepticus were not inevitably associated with neuronal damage and hippocampal sclerosis. This clearly indicates that other factors may play a role in modulation of the cascade of pathological events leading to cell death. In addition, genetic factors may predispose some individuals to be at greater risk than others. Neuron-specific enolase (NSE) and S100B protein demonstrated to be raised in CSF and serum of patients recovering from status epilepticus or recurrent seizures, although the results differed from study to study depending on the population characteristics and especially seizure type (DeGiorgio et al., 1995; Leutmezer et al., 2002; Shirasaka et al., 2002; Palmio et al., 2008). This may at least in part be related to the fact that NSE and S100B are of limited cellular specificity (Petzold, 2007).

Thus, there is still need for searching more highly specific and sensitive biomarkers for detecting *in vivo* damage to neurons following seizures.

Epileptogenesis is defined as the process of developing epilepsy—a disorder characterized by recurrent seizures—following an initial insult. Seizure incidence during the human lifespan is at its highest in infancy and childhood. Animal models of epilepsy and human tissue studies suggest that epileptogenesis involves a cascade of molecular, cellular and neuronal network alterations. Within minutes to days following the initial insult, there are acute early changes in neuronal networks, which include rapid alterations to ion channel kinetics as a result of membrane depolarization, posttranslational modifications to existing functional proteins, and activation of immediate early genes. Subacute changes occur over hours to weeks, and include transcriptional events, neuronal death and activation of inflammatory cascades. The chronic changes that follow over weeks to months include anatomical changes, such as neurogenesis, mossy fiber sprouting, network reorganization, and gliosis. At present there are only few studies identifying biochemical biomarkers specific for above processes.

Similarly, our knowledge on the mechanisms of the pharmacoresistance is very limited, what hampers biomarker research. One hypothesis assumes that refractory epilepsy is associated with a localized over-expression of drug transporter proteins such as P-glycoprotein (Pgp) in the region of the epileptic focus, which actively extrudes antiepileptic drugs (AEDs) from their intended site of action. However, although this hypothesis has biological plausibility, there is no clinical evidence to support the assertion that AEDs are sufficiently strong substrates for transporter-mediated extrusion from the brain. The quantitative assessment of the expression of Pgp under in vivo conditions might provide evidence whether Pgp or other efflux transporters are involved in AED resistance.

In conclusion, further extensive studies are needed in this new research area in epileptology. A reliable epilepsy biomarker could revolutionize the diagnosis and treatment, as well as prevention, and eventual cure, of epilepsy.