COMMENTARY

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Commentary on IL-1β associations with posttraumatic epilepsy development: A genetics and biomarker cohort study

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Human posttraumatic epilepsy (PTE), the most common acquired epilepsy in teenagers and young adults,[1] is an unfortunate natural experiment that may provide insight into epileptogenesis and antiepileptogenic interventions. In PTE, epilepsy develops weeks to months after traumatic brain injury (TBI), and often in a previously nonepileptic and otherwise healthy brain. Particularly in severe TBI, the injury timing is well-documented, and by necessity for critical care, the patients are closely monitored with access to imaging, electrophysiologic, blood, and cerebrospinal fluid (CSF) biomarkers. Yet, the neurobiology of events that take place in the time between TBI and the first seizure of PTE, remains incompletely understood. This gap in knowledge about the mechanisms of posttraumatic epileptogenesis limits our capacity to develop successful antiepileptogenic interventions. As intriguing as the fundamental question of why PTE follows TBI after a seizure-free latent period, are the questions of why only a minority of patients with severe TBI, approximately 20%, develop PTE, and whether a biomarker measure may predict individual PTE likelihood. The selection for the 2015 *Epilepsia* Prize from Diamond et al., "*IL-1β associations with posttraumatic epilepsy development: A genetics and biomarker cohort study,*[2]" addresses these important questions.

The authors studied a sizeable (n = 256) and relatively homogenous cohort of patients with moderate-to-severe TBI who were part of an otherwise larger group enrolled in a study aimed to evaluate the contributions of genetics and related biomarkers to post-TBI outcomes. PTE developed in 16.4% of this group. Based on a growing literature that implicates autoimmune and inflammatory mechanisms in post-TBI pathophysiology, including in posttraumatic epileptogenesis, they formulated and tested a hypothesis that IL-1β concentrations in the CSF and in serum are predictive of

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PTE. IL-1β, a proinflammatory cytokine produced by activated microglia and astrocytes, is increased in the CNS after TBI, and may mark a sustained proinflammatory state that contributes to PTE. Furthermore, to study genetic susceptibility to IL-1β-mediated posttraumatic epileptogenesis, the investigators tested whether individual genotypes at selected small nuclear polymorphism (SNPs) of the gene coding for IL-1β (IL-1β) also predicted PTE likelihood. With this approach of studying both the gene and gene product in PTE the authors demonstrate that both a high CSF-to-serum IL-1β concentration ratio and the specific heterozygous CT genotype in one SNP in the IL-1B gene promoter region, rs1143634, are associated with increased PTE risk.

This was the first study to investigate the contributions of both IL-1β levels and IL-1B genetics in a single large TBI patient cohort. Although IL-1β has been implicated previously in nontraumatic epilepsy and epileptogenesis, neither its role nor the role of a specific IL-1β polymorphism as PTE biomarkers has been measured.

Of interest, CSF IL-1β was elevated in all TBI subjects relative to an uninjured control population and did not by itself mark a PTE risk. Thus rather than high CSF IL-1β, a low serum IL-1β concentration in the PTE versus non-PTE patients with TBI accounted for the increased CSF-to-serum ratio. This finding underscores the complexity of TBI and PTE biomarker biology where one-dimensional metrics, individual measures that predict the likelihood of PTE with adequate specificity and sensitivity have been elusive. An appropriately cautious discussion in this article suggests an intriguing blood-to-brain IL-1β transport that may account for proinflammatory accumulation of peripheral IL-1β in the CNS. If validated, this would be in contrast to other cytokines and reactive proteins that follow a brain-to-blood transport and concentration gradient. These data thereby suggest that peripheral IL-1β production and transport may present novel therapeutic targets.

IL-1β is representative of the larger class of signaling molecules that likely contribute to immune-mediated posttraumatic neuronal dysfunction, and this article expands on its contribution to PTE. The authors also add to their group's prior preclinical research, which indicates that levetiracetam, a common first-line antiepileptic drug, suppresses regional posttraumatic IL-1β production and by this mechanism may suppress posttraumatic seizures.[3] These new data support future design and testing of antiepileptic and antiepileptogenic strategies that target IL-1β-related immune signaling pathways.

The authors do not speculate as to the mechanistic contributions to PTE of the rs1143634 SNP CT heterozygous state, and indeed the experiment was not designed to address this question. However, the targeted approach to look simultaneously at the prognostic values IL-1β levels and IL-1B genetics suggests future work that will also incorporate measures of both the gene and the gene product in TBI research.

The clinical TBI field and growing body of science dedicated to PTE and posttraumatic epileptogenesis will benefit from this report, which is a step toward practical gene and protein biomarkers that predict post-TBI outcomes. These results implicating IL-1β protein and gene in PTE are particularly versatile as they can be incorporated either into future basic preclinical research aimed to elucidate PTE mechanisms and test novel therapies, or into the design of prospective clinical trials.

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Disclosure

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