LETTERS

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

To the Editors:

We have read with great interest the recent article in *Epilepsia* from Diamond et al.[1] Although the role of interleukin (IL)-1β in epileptogenesis is a topic of importance, the article fails to address several key issues. First, although the authors mention the importance of the blood–brain barrier (BBB) and the potential role of type II IL-1 transporters in moving IL-1β across the endothelial barrier, they fail to investigate any markers of BBB integrity in their study. A simple analysis of the cerebrospinal fluid (CSF)/serum albumin ratio may have clarified the role of BBB dysfunction versus intrinsic central nervous system (CNS) IL-1β production in determining the CSF/serum IL-1β ratio. Furthermore, the authors primary variable of interest was time to first seizure, whereas seizure recurrence was not investigated. Although late posttraumatic seizures are an important risk factor for developing epilepsy, it is incorrect to assume these patients truly developed epilepsy without any data concerning further seizure activity over time. Although this study provides some evidence of a genetic component to risk of posttraumatic epilepsy (PTE), controversy remains over the functional difference of the rs1143634 single nucleotide polymorphism (SNP) and the unclear role of peripheral production of IL-1β and their role in epileptogenesis following traumatic brain injury (TBI). It is important to realize that a much more nuanced understanding of the role of IL-1β and its genetic variants in PTE is necessary before any firm conclusions regarding genetic susceptibility to PTE can be made.

DISCLOSURES

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCE

1. Diamond ML, Ritter AC, Failla MD, et al. IL-1β associations with posttraumatic epilepsy development: A genetics and biomarker cohort study. *Epilepsia* 2014;55:1109–1119.

In response to comments on IL-1β associations with posttraumatic epilepsy development: A genetics and biomarker cohort study

To the Editors:

Thank you for the opportunity to respond to comments from Janigro and Wathen about our study. The points raised allow us to emphasize key study concepts and to integrate further the literature on inflammatory mechanisms and blood–brain barrier (BBB) dysfunction associated with posttraumatic epilepsy (PTE). Janigro and colleagues have reported that (1) seizure activity triggers complex bidirectional communication between the central nervous system (CNS) and peripheral immune organs[1]: (2) IL-1β is an etiologic trigger for BBB breakdown associated with seizure activity[2]; and (3) BBB damage can be modified experimentally in epilepsy models by targeting IL-1β pathways.[2] Traumatic brain injury (TBI) of course, represents another accepted mechanism by which BBB disruption occurs, with peripheral and CNS contributions to the accompanying inflammatory response.

We agree that cerebral spinal fluid (CSF)/serum albumin ratios, one of many markers of BBB dysfunction, would confirm BBB compromise in our population. However, because of known IL-1β synthesis in both the periphery and CNS, extracerebral injury effects on CSF and serum cytokine levels post-TBI,[3] and TBI-induced temporal and regional changes in BBB integrity, we speculate that these factors would confound precise quantification of BBB compromise and complicate group-based analyses involving time-averaged IL-1β levels when linking this analysis to ratios of albumin, a protein that is ~4 times larger than IL-1β and a marker for which only peripheral synthesis occurs and active BBB transport does not exist. It is notable that our work shows the CSF/serum ratio, but neither CSF nor serum IL-1β levels alone, was associated with PTE risk, suggesting the importance of *IL-1β transit* on epileptogenesis and with PTE risk. Although we suggest these acute IL-1β ratios carry some prognostic value for PTE, we acknowledge limitations by speculating how these ratios may result from BBB dysfunction, IL-1 transporters, or other mechanisms. Additional studies need to elucidate the degree to which various transit mechanisms contribute to IL-1β ratios. Janigros work also suggests that