Response to Letter by Urra et al Regarding Article, “Autoimmune Responses to the Brain After Stroke Are Associated With Worse Outcome”

Response:

We appreciate the interest in our work and concede that we have generated more questions than we have answered. We are, however, able to address some of the questions raised by Urra and colleagues.1 In our study cohort, we did find that infection was an independent predictor of poor outcome at 90 days; this finding was published in an earlier article focusing on the potential role of interleukin-1 receptor antagonist in predisposing patients to poststroke infection.2

The issue regarding the relative importance of infection versus stroke severity for determining the likelihood for developing TH1 responses to brain antigens after stroke is an important one deserving of further discussion. In our study cohort, all patients who developed pneumonia had a National Institutes of Health Stroke Scale score of at least 20. Outcome data at 90 days were available for 18 patients with an initial National Institutes of Health Stroke Scale score ≥20, and of these 18 patients, 6 of 10 (60%) with pneumonia and 4 of 8 (50%) without pneumonia developed a TH1 response to myelin basic protein (MBP). The power to detect an effect of infection on the propensity to develop a TH1 response to MBP above and beyond that of stroke severity alone is obviously limited by these small numbers.

Our hypothesis is that infection increases the risk of developing a TH1 response to brain antigens by virtue of pathogen-associated molecular patterns associated with the infectious agent activating Toll-like receptors and the innate immune system to provide the inflammatory stimuli necessary for an adaptive immune response to occur. Clearly, infection is not the only determinat for developing TH1 responses to brain antigens given that patients who remained infection-free also developed such responses. It is certainly possible that endogenous danger signals (alarmins) released by necrotic brain tissue after stroke could also activate the innate immune response through Toll-like receptors and predispose to a TH1 response to brain antigens. We did assess the systemic concentrations of high mobility box group-1 protein, a well-characterized alarmin, and did not find a relationship between higher plasma high mobility box group-land the likelihood of developing a TH1 immune response to MBP or any of the other brain antigens after stroke (unpublished data).

We focused on the role of the immune response at 90 days in predicting outcome because it takes time for an adaptive immune response to occur and amplify in the presence of antigen to the point where it could reasonably be detected. In data not shown, the TH1 response to MBP at 90 days was similarly predictive of outcome at 180 and 365 days. Of import, there was a statistically significant decrease in the TH1 response to MBP over time in patients who had a TH1(+) response at 90 days but no change in those without a TH1(+) response. It therefore seems likely that endogenous immunomodiulatory mechanisms are at play to limit this autoimmune response as has been seen in animal models of experimental autoimmune encephalomyelitis.3,4

We agree with Drs Urra, Planas, and Chamorro that further studies are needed to understand the risk factors for developing a TH1 response to MBP. One must consider the very real possibility that the immune response to MBP is only a marker for an immune response to some other antigen that may be more important in influencing stroke outcome, a possibility that will need to be addressed in additional studies. Furthermore, the kinetics of the immune response to brain antigens after stroke and the endogenous mechanisms that regulate it need to be better understood. Such additional data may help to identify therapeutic interventions that could affect the long-term outcome from stroke.

Disclosures

None.

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