Characterizing Biomarkers and Associations of Clinical Outcomes in Anti-LGI1 Autoimmune Encephalitis

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Background: Anti-leucine-rich glioma-inactivated 1 autoimmune encephalitis (LGI1-AE) is an autoimmune neurological disease that is characterized clinically by faciobrachial dystonic seizures (FBDS), epileptic seizures, cognitive impairment often with visual spatial and short-term memory dysfunction. This clinical syndrome is often highly responsive to immunotherapy, particularly corticosteroids, plasma exchange (PLEX), IVIG, and rituximab. Nevertheless, there have been no randomized controlled clinical trials to confirm treatment benefit. Identifying biomarkers of disease activity and injury in LGI1-AE will provide crucial knowledge for the design and conduct of future treatment trials and provide a template for future investigations of rare AEs.

Objective: To characterize biomarkers of inflammation and neuronal and glial injury associated with disease activity in LGI1-AE.

Methods: We screened 21 patients with a diagnosis of autoimmune encephalitis from the autoimmune, paraneoplastic, and inflammatory neurological disease (APIND) registry and identified eight patients with a positive LGI1 antibody. We tested a battery of biomarkers including neurofilament light chain protein (NfL), glial fibrillary acidic protein (GFAP), tau, ubiquitin C-terminal hydrolase L1 (UCH-L1, and C-X-C Motif Chemokine 13 (CXCL13) using the Quanterix by Simoa ® platform. Clinical information was reviewed from the electronic record including brain MRI, cognitive testing, seizure frequency and immunotherapies were recorded. Biomarker levels were correlated with disease severity and activity.

Results: Twenty-one LGI1 AE patients were prospectively enrolled from October 2018 to April 2024 and 16 migraine headache patients (56.3% male, average age 58.0 years old) served as non-inflammatory controls for our biomarker testing. One patient in our cohort had a clinical relapse in one LGI1 AE patient. Overall, both mRS and MoCA improved over time. The mRS at symptom onset was 3.34 and dropped to 0.56 at 5-year follow up. Mean MoCA scores were 18.45 at the onset and increased to 29.40 at 6-year follow up. This cohort remained seizure-free for up to 6 years post symptom onset. When associating initial NfL levels with MoCA scores over time, there was a trend of improvement in the MoCA score earlier in the disease duration with lower NfL levels at symptom onset. Plasma levels of IL1b, IL6, and IL10 cytokines in LGI1 AE patients at the time of study enrollment compared to controls showed differences, with only IL10 being significant.

Conclusions: We show that NfL and GFAP may be useful measures to understand disease progression in patients with LGI1 AE. These biomarkers correlate with improvement following initial symptoms of anti-LGI1 autoimmune encephalitis and increase with clinical relapse. Additional systematic studies are needed to better define correlation with disease activity and effects of immunotherapy. It may be helpful to include these blood-based biomarkers as exploratory measures in future randomized controlled trials.