EDITORIAL OPEN ACCESS

The Calm Between Storms

Serum Biomarkers in Assessing Interattack Astrocytopathy in Neuromyelitis Optica Spectrum Disorder

Carolyn Goldschmidt, DO, and Robert A. Bermel, MD

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Correspondence
Dr. Bermel
bermelr@ccf.org

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Cytoskeletal structural proteins, released when cellular damage occurs, are biomarker candidates under investigation for many neurologic diseases. Among the potential markers, neurofilament light chain (NfL), expressed in neurons, and glial fibrillary acidic protein (GFAP), expressed in astrocytes, can now be measured in the serum (sNfL and sGFAP) thanks to advances in highly sensitive analytic methodologies, with strong correlation to CSF levels. Early studies of sNfL and sGFAP in MS and neuromyelitis optica spectrum disorder (NMOSD) focus on potential roles as biomarkers of treatment response, risk for relapse, and risk for disability progression.[1-4] Not surprisingly, levels of sGFAP increase during NMOSD relapses, as the disease process is primarily an astrocytopathy mediated by AQP4-IgG.[4,5] More complex questions include how these levels change in between relapses, during disease stability, and if this could be useful in determining treatment response, predicting disability progression, or guiding therapy.

In this issue of *Neurology: Neuroimmunology and Neuroinflammation*, Hyun et al describe their study measuring sGFAP and sNfL in both participants with active and stable NMOSD and healthy controls. They found that sGFAP and sNfL levels were significantly elevated during clinical attacks, but quickly decreased to interattack levels that were below the cutoff value, which was determined during the study using the healthy controls.[6] This trend was steeper for sGFAP levels compared with sNfL. An important feature of the Hyun study is that all 20 participants with NMOSD were treated with rituximab using a standard protocol for the duration of follow-up. The authors conclude that subclinical astrocyte damage, as measured by sGFAP, rarely occurs during interattack periods in individuals with treated NMOSD.

This result is somewhat in contrast to results of a recent study by Wantanabe et al, which found that both sNfL and sGFAP levels were higher in participants with NMOSD than healthy controls, even during disease remission; however, in a more heterogeneous study group, some of whom were not on any treatment.[4] Additional challenges of comparing across studies relate to the technical features of assays, which are pushing the limits of detection to achieve sufficient sensitivity to reliably measure these proteins in the peripheral blood.

Important limitations of the Hyun study are that we cannot tell if sampling more frequently than every 3 months would detect interattack subclinical elevations in sGFAP or more accurately characterize the beginning of an attack. The study used retrospectively assigned Expanded Disability Status Scale scores via chart review, which is not likely the most accurate or sensitive measure of clinical status. The results should only be generalized to patients on treatment with rituximab. The population studied is exclusively Korean, and conceivably phylogenetic differences could lead to different disease behavior in different populations.

The clinical course of NMOSD would suggest that there is not strong evidence for a progressive, degenerative phase of the disease independent of relapses, like is seen in MS, although

From the Mellen Center for MS Treatment and Research, Neurological Institute, Cleveland Clinic, Cleveland, Ohio.

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data are mixed.[7-9] It would be reasonable to surmise therefore that large amounts of subclinical damage do not occur between attacks. However, as our imaging and laboratory measurement capabilities advance and our range of therapeutic options expand, there may be value in detecting and controlling interattack disease activity if it can be appreciated at a cellular level and its consequences defined. For now, it is useful to be able to visualize the stability of these biomarkers in between relapses and their significant increase during relapses.

Studies such as this represent important milestones in the search for accessible serum biomarkers of disease activity or response to therapy in NMOSD. The promise of using serum biomarkers to potentially predict NMOSD relapses before clinical manifestations certainly has appeal. Previous studies have shown that sNfL levels increase just before clinical events in MS, and it is known that sNFL and sGFAP are greatly elevated during acute NMOSD attacks.[5,10] In NMOSD, the utility of predictive biomarkers is particularly appealing. Even with early accurate diagnosis and effective preventive therapy, disabling relapses remain all too common in NMOSD. MRI surveillance does not effectively identify subclinical disease activity; therefore, imaging monitoring for disease activity outside of clinical attacks is challenging. The ability to predict and preempt a relapse, with an even lower threshold to escalate treatment if needed, could change the NMOSD disease course and potential disability accrual. For this task, measurement of cytoskeletal elements alone may be insufficient, and discovery of such biomarkers may require looking at other immunologic or cellular modulators of disease activity. Because of the devastating and permanent disability that can accompany NMOSD attacks, the potential benefit of overtreatment outweighs the risk of undertreating this disease. One blood draw per month to potentially preserve vision or mobility could be a game changer.

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