


Caught in the Act: Cerebrospinal Fluid Markers of Concurrent Mechanisms of Antibody-Mediated Encephalitis

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Prospective Quantification of CSF Biomarkers in Antibody-Mediated Encephalitis

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Objective. To determine whether neuronal and neuroaxonal injury, neuroinflammation, and synaptic dysfunction associate with clinical course and outcomes in antibody-mediated encephalitis (AME), we measured biomarkers of these processes in CSF from patients presenting with AME and cognitively normal individuals. **Methods.** Biomarkers of neuronal (total tau, VILIP-1) and neuroaxonal damage (neurofilament light chain [NFL]), inflammation (YKL-40), and synaptic function (neurogranin, SNAP-25) were measured in CSF obtained from 45 patients at the time of diagnosis of NMDA receptor ($n = 34$) or LGII/CASPR2 ($n = 11$) AME and 39 age- and sex-similar cognitively normal individuals. The association between biomarkers and modified Rankin Scale (mRS) scores were evaluated in a subset ($n = 20$) of longitudinally followed patients. **Results.** Biomarkers of neuroaxonal injury (NFL) and neuroinflammation (YKL-40) were elevated in AME cases at presentation, whereas markers of neuronal injury and synaptic function were stable (total tau) or decreased (VILIP-1, SNAP-25, neurogranin). The log-transformed ratio of YKL-40/SNAP-25 optimally discriminated patients from cognitively normal individuals (area under the receiver operating characteristic curve .99; 95% confidence interval .97, >.99). Younger age ($\rho = -.56$; $P = .01$), lower VILIP-1 ($\rho = -.60$; $P < .01$) and SNAP-25 ($\rho = -.54$; $P = .01$), and higher $\log_{10}(\text{YKL-40/SNAP-25})$ ($\rho = .48$; $P = .04$) associated with greater disease severity (higher mRS score) in prospectively followed patients. Higher YKL-40 ($\rho = .60$; $P = .02$) and neurogranin ($\rho = .55$; $P = .03$) at presentation were associated with higher mRS scores 12 months following hospital discharge. **Conclusions.** CSF biomarkers suggest that neuronal integrity is acutely maintained in AME, despite neuroaxonal compromise. Low levels of biomarkers of synaptic function may reflect antibody-mediated internalization of cell surface receptors and may represent an acute correlate of antibody-mediated synaptic dysfunction, with the potential to inform disease severity and outcomes.

Commentary

Autoimmune encephalitis with antibody to neuronal surface antigens has emerged as an important class of neurological disorders.¹ How the immune reaction and the antibody itself contribute to the signs and symptoms of the disease and to the long-term neurological damage and functional disability is still being unraveled.

In vitro models indicate that most of these antibodies exert a functional, and thus potentially reversible, effect on receptors and ion channels trafficking, leading to internalization of molecules that are important for axonal and synaptic transmission.² This likely explains the sometimes spectacular response and frequently complete clinical recovery after immune therapies are given. However, the few available pathological studies of biopsy and autopsy samples have also revealed inflammatory reaction in the brain tissue. Patients with N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis mostly show antibody-producing cells, while patients with voltage-gated potassium channel (VGKC)-complex antibody encephalitis, including leucine-rich, glioma inactivated-1 (LGII) also present signs of an antibody- and complement-mediated neuronal injury and cerebral atrophy.^{3,4}

These findings are line with the known risk of developing hippocampal sclerosis, epilepsy, and irreversible long-term memory deficits after LGII antibody encephalitis, especially if treatment is delayed, while acute and long-term brain injury is less frequently reported in NMDAR antibody encephalitis. These data suggest that the pathophysiology of antibody-mediated encephalitis is a complex interplay of axonal and synaptic dysfunction, inflammation, and neuronal injury, not to mention the additional effect of seizures and status epilepticus (SE) which are frequent in this setting.

Being able to tease out and quantify the extent of these different mechanisms at the individual level might be of diagnostic, therapeutic and prognostic value. In this study, the authors investigated the level of cerebrospinal fluid (CSF) biomarkers of neuronal (tau, visinin-like protein-1 [VILIP-1]), axonal (neurofilament light chain [NFL]), and synaptic (synaptosomal-associated protein-25 [SNAP-25] and neurogranin) integrity and of glial activation and neuroinflammation (chitinase-3-like protein [YKL-40]) in patients with antibody-mediated encephalitis.⁵ Several of these markers might be familiar to some neurologists, but perhaps less to epilepsy specialists, as they have been studied in other neurological diseases,





such as degenerative disorders, stroke, traumatic or anoxic brain injury, and multiple sclerosis, usually with promising results. Some, such as tau and VILIP-1, have also been linked to neuronal injury secondary to seizures and SE.^{6,7}

The authors included 45 patients (34 with NMDAR, 7 with LGI1, and 4 with contactin-associated protein-like 2 [Caspr2] antibody) and 39 controls matched for age and sex. Compared to controls, patients had an increased level of inflammatory and axonal injury markers and a decreased level of synaptic integrity markers compared to controls, and independently of age and time from onset to the lumbar puncture. There was, overall, little evidence of neuronal injury. These results might have been mostly driven by the larger subgroup of patients with NMDAR antibodies. The authors thus performed a post-hoc analysis that revealed differences between the NMDAR and LGI1/Caspr2 subgroups, with the latter showing higher levels of markers of neuronal injury. Altogether, this set of findings remarkably confirms, in human patients at the acute phase of the disorder, what we know thus far from in vitro and pathological studies in terms of pathophysiological similarities and differences between NMDAR and LGI1/Caspr2 antibody encephalitis.

It is not sure yet whether these markers will prove useful for the differential diagnosis of autoimmune encephalitis from other diseases with similar clinical manifestations, as controls were all healthy subjects. It would now be important to see if they can also discriminate encephalitis with antibodies to neuronal surface antigen, including other antibodies than NMDAR and LGI/Caspr2, from clinically related conditions, such as paraneoplastic encephalitis with antibodies to intracellular antigens (Hu, etc.) and infectious encephalitis. Also, simultaneously exploring the complementary value of additional markers that have been identified in recent studies, such as cytokines and chemokines,⁸⁻¹⁰ would be of interest, with the aim to provide a broader set of diagnostic and prognostic markers.

Another question that remains, given the known association between some of these biomarkers (tau, VILIP-1) and epilepsy and seizures, is how much of the observed differences with controls might be due to seizures and SE-related brain dysfunction and injury. It would have been interesting, for example, to compare the levels of biomarkers between patients with different seizure burdens.

The relationship between CSF biomarkers and outcome was less convincing, largely because the subgroup of patients who were followed until 12 months was small (N = 20; 10 NMDAR and 10 LGI1/Caspr2). Also, there were differences in severity and outcome between the NMDAR and LGI1/Caspr2 groups. As expected, patients with NMDAR encephalitis had a more severe course, requiring ICU admission, multiple immune therapies, and more time in the hospital. They reached a worse clinical status during the acute phase and tended to have less favorable outcome at discharge and at 12 months. So, while a few associations between biomarkers and outcome were noted, they should be interpreted with caution, as they might reflect differences between the types of encephalitis rather than real prognostic information. Further studies with larger samples should now aim to confirm these associations within “pure” populations of antibody-specific subtypes of antibody-mediated

encephalitis. That being said, 1 finding deserves to be mentioned. Markers of synaptic integrity were interestingly lower in patients with the most severe clinical presentation in the acute stage but were higher in patients with worse functional outcome. This could suggest that antibody-mediated internalization of synaptic proteins plays a key role in the acute clinical manifestations of the disorder but not in the long-term sequelae, which might rather be attributed to the other mechanisms: inflammation and neuronal injury.

Altogether, this study expands our understanding of this important but still poorly understood group of disorders and opens new doors for diagnosis and treatment.

By Nicolas Gaspard

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