Neurexin-3α

A new antibody target in autoimmune encephalitis

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Acute encephalitis is an inflammatory brain disease with a complex differential diagnosis associated with appreciable morbidity, mortality, and costs. Infectious agents, particularly viruses, were traditionally considered the predominant causes. The discovery of neuronal cell-surface autoantibodies (NSAbs) has helped identify a subgroup of patients with encephalitis who often respond well to immunotherapy. Autoantibodies were not mentioned in a 2007 retrospective study on the causes of acute encephalitis, but 3 years later the same authors reported that 8% of cases were associated with autoantibodies against the voltage-gated potassium channel complex and the NMDA receptor (NMDAR).[1,2] In subsequent years, several new targets have been reported in patients with encephalitis. In approximate order of decreasing frequency, these include the NMDAR, leucine-rich, glioma inactivated 1 (LGI1), gamma aminobutyric acid receptor B ($GABA_BR$), contactin-associated protein-like 2 (CASPR2), gamma aminobutyric acid receptor A ($GABA_AR$), dipeptidyl aminopeptidase-like protein 6 (DPPX), metabotropic glutamate receptor 5 (mGluR5), and the dopamine 2 receptor (D2R).[3,4]

In this issue of *Neurology*®, Gresa-Arribas et al.[5] add neurexin-3α to this growing list of autoantibody targets in encephalitis. They identified 5 patients over 10 years whose serum and CSF demonstrated distinctive immunoreactivity to rat neuropil. Neurexin-3α was the antibody target by immunoprecipitation and mass spectrometry, and this was confirmed by cell-based assay.

The patients with neurexin-3α antibodies showed a phenotype reminiscent of those with NMDAR antibodies, with an infectious prodrome followed by cognitive dysfunction, seizures, reduced consciousness, and orofacial dyskinesias sometimes following a severe clinical course; patients often have a lymphocytic pleocytosis and normal brain MRI. Despite the absence of prominent psychiatric features, a more diffuse movement disorder, and dysautonomia, these patients meet newly published criteria for probable NMDAR-antibody encephalitis[6] and may constitute a proportion of patients with seronegative mimics of NMDAR-antibody encephalitis. Indeed, this is a recognized clinical cohort, and although 179 patients with well-characterized or suspected autoimmune encephalitis did not have neurexin-3α antibodies, the authors do not state whether these patients had an NMDAR-antibody encephalitis-like phenotype.

Neurexins are a family of predominantly presynaptic cell-surface glycoproteins encoded by 3 large genes.[7,8] Each gene encodes an α or a β transcript, giving rise to 6 transcripts that can produce nearly 4,000 proteins by differential splicing. Neurexin-3α, the largest and most polymorphic member of the family, covers almost 2% of chromosome 14 and accounts for 74% of all possible splice variants. These large proteins interact across the synaptic cleft with postsynaptic adhesion proteins via their polymorphic extracellular N-terminal domains. This adds to the growing repertoire of cell adhesion molecules, including CASPR2, contactin-2, and neurofascins, which are known autoantibody targets. In addition to this function, neurexins modulate presynaptic Ca^{2+} channel function and neurotransmitter release via their conserved C-terminus. The authors showed a direct effect of neurexin-3α antibodies on cultured neurons, with a reduction in surface-expressed neurexin-3α in both developing and mature neurons. The finding of reduced synapse number in developing neurons may not have clinical relevance given the adult phenotype of the condition. However, in vivo investigations may help explain how loss of neurexin-3α alters neuronal function and consequently may inform the molecular basis of the clinical phenotype.

The identification of these antibodies is potentially important to the clinical workup of patients with encephalitis because it is likely that they define another NSAb-mediated nonparaneoplastic disorder with direct implications for the use of immunotherapies.[3,6,9] However, the detection of only 5 patients in 10 years in a specialist center suggests that this disorder is uncommon. Perhaps common autoantibody discovery in encephalitis is reaching its nadir rather than being an expanding future entity. A resultant broader question in the field is whether this type of incremental approach to antibody discovery will

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substantially benefit patients or whether time and money is better utilized in systematically investigating the effects of therapies and clinical outcomes of established autoimmune diseases.

Many diagnostic centers have developed autoantibody assays, but multicenter evaluation of the reproducibility or consistency of different antibody assays has been performed only for neuromyelitis optica.[10] Debates continue as to whether live or fixed mammalian cells expressing the target or brain tissue sections are preferred as the substrate, and whether microscopy or quantitative flow cytometry is the optimal detection method. Primary neuronal culture immunofluorescence is used in specialist centers to increase the confidence in a positive conventional assay result, but multiple testing may reduce overall sensitivity and select for patients with higher antibody titers. On the other hand, use of single assays alone has an increased risk of generating positive results in patients without autoimmune syndromes. Future studies will be needed to determine assay relevance in nonautoimmune diseases.[11]

Gresa-Arribas et al. have identified a likely pathogenic antibody target in autoimmune encephalitis and an assay that will allow future definition of the neurexin-3α antibody-associated disease spectrum, including mimics of NMDAR-antibody encephalitis. Future research efforts should aim to develop high-throughput screening methods for NSAb detection to ensure we capture the full variety of antigenic synaptic, axonal, and glial proteins. With such developments comes the need for rigorous multicenter studies examining the relative merits of antibody detection methodologies and their ongoing consistency.

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