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Further reducing *terra incognita* on the map of synaptic autoimmunity

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Over the past few years, neurology has witnessed an unprecedented discovery of new clinical entities related to autoantibodies targeting natively expressed neuronal proteins, often at the synapse.[1] In this issue of *Neurology*®: Neuroimmunology and Neuroinflammation, Honorat et al.[2] report that they successfully dug for yet another disease. Starting with the observation in 6 patients of a specific, previously unknown antibody reaction with murine brain sections, the authors identified septin-5 as the underlying target of serum and CSF antibodies. The 4 patients with available clinical information had a rapidly progressive cerebellar syndrome, 2 had prominent oscillopsia at onset. Treated patients improved with immunotherapy; however, the disease was fatal in 1.

The target protein, septin-5, is an interesting filamentous molecule highly expressed in the brain. Apart from a role in dendritic branching, it is mainly present at the synapse (figure, left). It binds to syntaxin-1, a key player in the protein complex that mediates fusion of synaptic vesicles.[3] This way it appears to regulate the position of synaptic vesicles close to the presynaptic membrane, acting as a molecular "brake" by suppressing neurotransmitter release.[4]

The present study lends support for clinicians who prefer antibody panel diagnostic that includes immunofluorescence on brain sections, where septin-5 antibodies were clearly detectable. If positive, serum and CSF should still be tested specifically on cell-based assays for the exact target for 2 general reasons. First, the underlying antibody helps to predict the clinical course, progression, and relapses but also indicates first-line therapies or tumor association. Second, many clinicians feel only comfortable with starting an often "aggressive" immunotherapy if the underlying antibody was exactly defined. Conversely, the current article may be interpreted as motivation for a low threshold regarding immunotherapy in patients with yet undefined neuropil antibodies, given that tenacious work will eventually clarify the target.

For clinical routine, we nonetheless wish finding an antibody with known target and pathogenic relevance. Pathogenicity for septin-5 antibodies is not known yet. In mice, septin-5 deficiency resulted in disrupted affective behavior and cognitive functions.[5] It is, however, not clear whether septin-5 antibodies can reach their intracellular target. There are intriguing parallels to synaptic autoimmunity with amphiphysin antibodies, associated with stiff-person syndrome (SPS) and occasionally ataxia. Super-resolution microscopy confirmed that antibodies reach synaptic nerve endings and cause a murine SPS phenotype.[6,7] As suggested for amphiphysin, septin-5 may be transiently exposed to the surface of the synaptic cleft during vesicle exocytosis, allowing septin-5 autoantibodies to play up (figure, right). The early cerebellar atrophy in 1 patient suggests that further disease mechanisms could participate, e.g., activation of complement or cytotoxic T cells, again similar to SPS patients with amphiphysin antibodies.

The diagnostic and clinical findings should now be followed by extensive basic science to confirm pathogenicity and identify the exact disease mechanisms of septin-5 antibodies. One potential step could be the recombinant generation of human monoclonal septin-5 autoantibodies from affected patients, allowing in-depth characterization of monospecific binding epitopes or the

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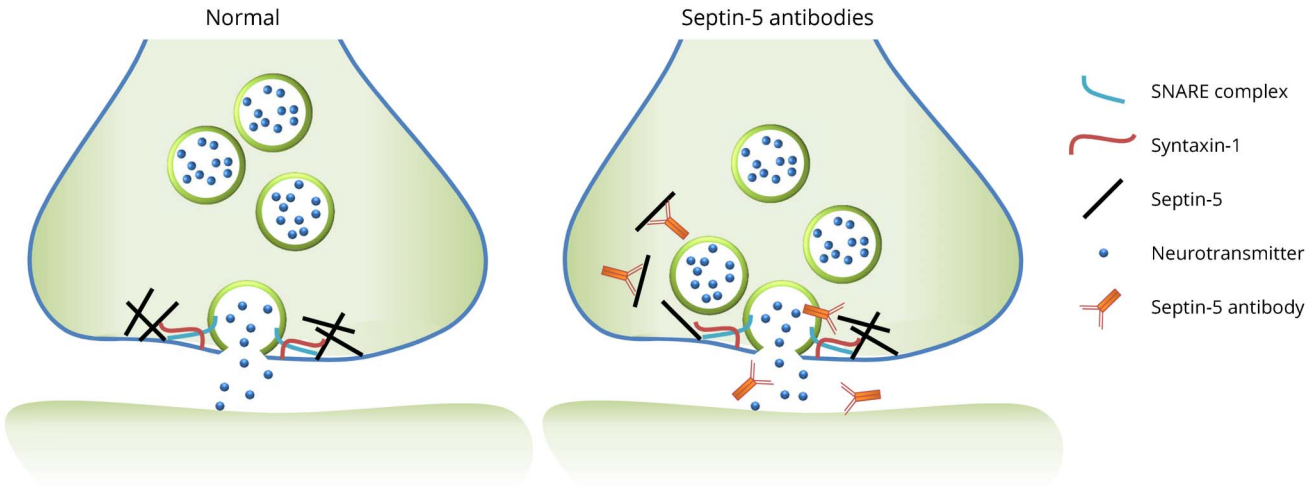
Figure Septin-5 autoantibodies target the presynapse and may interfere with neurotransmitter release



Left: fusion of synaptic vesicles and release of neurotransmitters into the synaptic cleft are tightly regulated processes involving the SNARE protein complex. The filamentous protein septin-5 acts as a molecular "brake" on this machinery through binding to syntaxin-1 and maintaining synaptic delay. Right: the possible mechanisms of septin-5 autoantibodies include internalization in the presynaptic area, interruption of septin-5 binding to vesicle-associated proteins, and dysfunction of neurotransmitter release—potentially reversible with immunotherapy.

antibody's interaction with phosphorylation partners, which is hardly possible with CSF containing polyclonal and further undetermined antibodies.[8]

This well-conducted study leaves room for further investigations. First, the number of patient samples was small, thus calling into question the generalizability of these findings. Second, 2 patients each had coexisting low-level antibodies reactive with N-type calcium channels or glutamate decarboxylase (GAD)-65, other known candidates associated with ataxia.[9] Whether this represents a broader immune attack to synaptic proteins or even a temporal evolution of humoral autoimmunity is currently unclear, as is the individual contribution to clinical symptoms. Third, the predominance of cerebellar ataxia deserves further investigations, given that septin-5 is expressed throughout the brain[10] and that human immunoglobulin G binds to most parts of the cerebellum and cerebrum.[2] It seems possible that heteromeric proteins with other septin family members might play a role here.[3]

The present study teaches for clinical practice that another synaptic protein has to be included into the growing list of relevant antibody epitopes in neurologic autoimmunity, thus further reducing "unknown land" (terra incognita) on the map of synaptic autoimmunity. Also, the search for autoantibodies has now fully arrived in the clinical workup of ataxia patients. As a next step, the field should extend clinical observations to a more molecular analysis of disease mechanisms. In my opinion, such studies will not only clarify the pathogenic role of human autoantibodies and thus legitimate immunotherapy but also will provide much broader insights into the complex functions of our brain.

Author contributions

H. Prüss: drafting/revising the manuscript.

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