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Response by Sperber et al to letter regarding article, "Serum Anti-NMDA (N-Methyl-D-Aspartate)-Receptor Antibodies and Long-Term Clinical Outcome After Stroke (PROSCIS-B)"

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Citation

Sperber, P. S., Pruss, H., Siegerink, B., & Liman, T. G. (2020). Response by Sperber et al to letter regarding article, "Serum Anti-NMDA (N-Methyl-D-Aspartate)-Receptor Antibodies and Long-Term Clinical Outcome After Stroke (PROSCIS-B)", *51*(2), E29-E29.
doi:10.1161/STROKEAHA.119.028095

Version: Publisher's Version
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Note: To cite this publication please use the final published version (if applicable).

Letter to the Editor

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Response by Sperber et al to Letter Regarding Article, “Serum Anti-NMDA (N-Methyl-D-Aspartate)-Receptor Antibodies and Long-Term Clinical Outcome After Stroke (PROSCIS-B)”

In Response:

Herewith we respond to the letter to the editor regarding our recent publication “Serum anti-NMDA (N-methyl-D-aspartate)-receptor antibodies and long-term clinical outcome after stroke (PROSCIS-B).” In his letter, Dr Dalmau points out the relevance of distinguishing the different anti-NMDAR-abs (N-methyl-D-aspartate-Receptor GluN1-antibody) immunoglobulin isotypes in different diseases.

We have measured serum NMDAR1-abs of the IgM, IgA, and IgG isotype in a large cohort of patients with stroke, and data from our study point towards a relevant role of NMDAR1-abs seropositivity, primarily of the IgA and IgM isotype, as biomarkers for poor outcomes after ischemic stroke. It should be clear, that with our study, we are able to show independent associations, however, as for any data from observational studies, one should not draw strong conclusions on the underlying biological mechanism from these data alone.

To put our findings in perspective, in the study by Hara et al,¹ IgA and IgM NMDAR1-abs were not reacting with cultured live neurons, as pointed out by our colleague. However, this finding is in contrast with other studies^{2,3} and does not exclude interactions of IgA and IgM with NMDA-receptors on other cell-types. Furthermore, the observation that IgA and IgM NMDAR1-abs were also associated with cognitive impairment in other cohort studies than ours,^{2,4} supports a relevant role of these circulating antibodies.

As stated earlier, we have also measured IgG antibodies, which are primarily known for their implications in anti-NMDAR encephalitis. We found that only 2 subjects of the PROSCIS-B study (Prospective Cohort With Incident Stroke - Berlin) were IgG seropositive, both with low titers (1:100). Not surprisingly, when we repeated our analyses after excluding these patients the results remained materially unchanged. As additional information of interest, medical records from these IgG seropositive patients, which were obtained for this study, revealed no indication for a neuropsychiatric disease of these patients.

We have also estimated independent effect sizes for the other isotypes (ie, IgA and IgM separately), which—irrespective of the limited power—were not substantially different between IgA and IgM. This finding, which we provide in the supplement of our article, suggests that the observed associations in our study are not attributable to only one of the 2 immunoglobulin isotypes. To conclude, we fully agree that the different isotypes of NMDAR1-abs should not be simply lumped together.

To understand the pathogenicity of NMDAR1-abs of the IgA and IgM isotypes, it would be interesting to clarify whether antibodies were preexisting before the stroke or whether they developed in the acute stroke phase. This is especially important

because it was repeatedly shown that a significant proportion of the elderly harbor serum NMDAR1-abs of the IgA and IgM isotype. Future laboratory and clinical studies will help elucidating the clinical relevance of this observation for stroke, cognitive impairment, and other diseases further, as this insight could provide new therapeutic or surveillance strategies.

Sources of Funding

P.S. Sperber reports funding from FAZIT-STIFTUNG Gemeinnützige Verlagsgesellschaft mbH.

Disclosures

None.

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