Letter to the Editor

Stroke *welcomes Letters to the Editor and will publish them, if suitable, as space permits. Letters must reference a* Stroke *published-ahead-of-print article or an article printed within the past 4 weeks. The maximum length is 750 words including no more than 5 references and 3 authors. Please submit letters typed double-spaced. Letters may be shortened or edited.*

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.

Pia S. Sperber
Center for Stroke Research Berlin (CSB)
Charité – Universitätsmedizin Berlin
Berlin, Germany

Harald Prüss, MD
Klinik und Hochschulambulanz für Neurologie
Charité – Universitätsmedizin Berlin
Berlin, Germany

Bob Siegerink, PhD
Center for Stroke Research Berlin (CSB)
Charité – Universitätsmedizin Berlin
Berlin, Germany
Charité – Universitätsmedizin Berlin
Berlin, Germany

Thomas G. Liman, MD, MSc
Center for Stroke Research Berlin (CSB)
Charité – Universitätsmedizin Berlin
Berlin, Germany

References

1. Hara M, Martinez-Hernandez E, Ariño H, Armangué T, Spatola M, Petit-Pedrol M, et al. Clinical and pathogenic significance of IgG, IgA, and IgM antibodies against the NMDA receptor. *Neurology*. 2018;90:E1386–E1394.
2. Doss S, Wandinger KP, Hyman BT, Panzer JA, Synofzik M, Dickerson B, et al. High prevalence of NMDA receptor IgA/IgM antibodies in different dementia types. *Ann Clin Transl Neurol.* 2014;1:822–832. doi: 10.1002/acn3.120
3. Castillo-Gómez E, Oliveira B, Tapken D, Bertrand S, Klein-Schmidt C, Pan H, et al. All naturally occurring autoantibodies against the NMDA receptor subunit NR1 have pathogenic potential irrespective of epitope and immunoglobulin class. *Mol Psychiatry.* 2017;22:1776–1784. doi: 10.1038/mp.2016.125
4. Bartels F, Strönisch T, Farmer K, Rentzsch K, Kiecker F, Finke C. Neuronal autoantibodies associated with cognitive impairment in melanoma patients. *Ann Oncol.* 2019;30:823–829. doi: 10.1093/annonc/mdz083

(*Stroke*. 2020;51:e29. DOI: 10.1161/STROKEAHA.119.028095.)