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Immunoglobulin G Antibodies to the N-Methyl-D-Aspartate Receptor Are Distinct from Immunoglobulin A and Immunoglobulin M Responses

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Dahm and colleagues recently reported that approximately 10% of patients and healthy individuals may have IgA, IgG or IgM autoantibodies to the NR1 subunit of the NMDA receptor in their serum ("Seroprevalence of autoantibodies against brain antigens in health and disease").[1] They specifically conclude that "the obtained data may serve as a reference for clinicians advising caution with respect to any conclusions on a causal association of serum antibody with brain disease."

In respect to NMDAR encephalitis their interpretation of this data is misleading and may cause confusion for readers. The prevalent responses measured in the current paper were mostly IgM and IgA antibodies, all measured only in serum, and often at lower serum titer (1:10) than reported as cut-off for anti-NMDAR encephalitis (1:40).[2] There are no data to suggest an association between IgA or IgM antibodies with NMDAR encephalitis and their detection has no utility for diagnosing this disease. Age-related seroprevalence of control cohorts was previously shown to be around 10%. Whether the presence of high titers of these IgA or IgM antibodies in CSF associates with disease (e.g. slow cognitive decline)[3] remains to be elucidated.

As the authors noted, IgG antibodies to surface epitopes of the receptor are associated with anti-NMDA receptor encephalitis. Indeed, IgG NMDAR antibodies were only detected in this study in 34/2533 (1.3%) and 20/1703 (1.2%) of the "disease group" or "healthy control group", respectively. This is within the known rate of false positive results if testing is done

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in serum samples only without comprehensive assessment of CSF samples.[2, 4] IgG NMDAR antibodies to surface epitopes of the receptor measured in CSF are highly specific for a characteristic autoimmune neurological syndrome that has specific tumor associations (ovarian teratoma), evidence of brain inflammation in many patients (based on MRI and/or CSF analysis), characteristic EEG findings in some patients (extreme delta brush) and an established response to immunotherapy. These antibodies are also present in most patients' serum but are more specifically measured in CSF and many patients show evidence of intrathecal synthesis of the antibodies.[2] They cause cross-linking and internalization of the NMDA receptor on cultured neurons.[5]

Therefore grouping these three antibody classes together and making general conclusions is not accurate or appropriate. We hope that clarification and emphasis of these important differences can alert clinicians and prevent misinterpretation of test results and potential over- or under-treatment of patients.

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