Published in final edited form as:
Am J Psychiatry. 2012 October ; 169(10): 1120–1121. doi:10.1176/appi.ajp.2012.12050646.

Serum IgG Antibodies Against the NR1 Subunit of the NMDA Receptor Not Detected in Schizophrenia

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To the Editor: A consensus exists that schizophrenia is not a single disease, but the final pathway of a variety of still unknown neurobiological derangements. Recently, several treatable autoimmune brain disorders have been identified presenting with psychotic symptoms that, in some cases, resemble those found in schizophrenia (1). Antibodies target synaptic proteins, interrupting synaptic transmission in brain networks supporting cognition and emotion. Particularly relevant are auto-antibodies against the NR1 subunit of the N-acetyl methyl D-aspartate receptor (NMDAR), which result in diminished NMDAR activity, now considered a hallmark of schizophrenia (2). In patients harboring these antibodies, initial psychiatric symptoms are usually followed by dyskinetic movements or seizures and decreased respiratory drive, with a reduced level of consciousness, often requiring intensive care (1). However, it could be postulated that a limited form of the disease may result in a milder syndrome, akin to schizophrenia. We tested this hypothesis using sera from patients with their first psychotic episode referred to the regional psychiatric center of the province of Alava, Spain, and from healthy controls. All were enrolled after written informed consent according to protocols approved by the local IRB. Blood was drawn and sera were frozen for subsequent study, blinded to patient-control status. After a one-year follow up, sera of patients who then met DSM-IV-TR criteria for schizophrenia-spectrum disorders were tested for antibodies to NR1 and other cell surface antigens using three criteria (immunohistochemistry on rat brain slices and dissociated rodent hippocampal neurons, and

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Previous presentation: Presented at the 67th Annual Meeting of the Society of Biological Psychiatry, May 3-5, 2012, Philadelphia, PA

Disclosures: Dr. Dalmau has a patent on a procedure to determine anti-NMDA antibodies and receives royalties from Euroimmun, a company that provides this procedure commercially. None of the other authors has any potential conflict to disclose.

a cell-based assay in which HEK cells recombinantly express NMDAR), as previously reported (1). Patients (n=80) and healthy controls (n=40) did not differ statistically in age (29.4±9.9 and 30.7±9.4 years), or sex (28 and 38 percent women). Anti-NR1 IgG antibodies were not detected in either group. Both had four cases with sera reactive to other, still unidentified, neuronal surface antigens. Our findings and a study of seven patients with schizophrenia (3) fail to support the hypothesis that NMDAR IgG antibodies are present in the sera of patients with schizophrenia. Although another study (4) did report NMDAR antibodies in the sera of some schizophrenia patients, it was performed without a control group and test specificity was lower (only one of the above criteria was applied); differences in the clinical diagnosis could also explain the discrepant findings. It should be noted, however, that our study does not rule out that some patients could have antibodies only in cerebrospinal fluid, but not in serum (1). Additionally, antibodies could be present in patients with acute psychosis not meeting DSM-IV diagnostic criteria at one-year.

Acknowledgments

JCM and KFB were supported by the NIH Intramural Research Program; AGP, CM, SRA and AP by the University of the Basque Country and by the Department of Health of Spain through the CIBERNED program; JdL had no external support for this project; JD by NIH grants RO1NS077851, RO1MH094741, the National Cancer Institute RO1CA89054, FIS, 11/01780, Fundació la Marató de TV3, and a McKnight Neuroscience of Brain Disorders award.

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