Biological Psychiatry

Clinical and Electrophysiological Effects of D-Serine in a Schizophrenia Patient Positive for Anti-*N*-Methyl-D-Aspartate Receptor Antibodies

To the Editor:

The term anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis refers to an autoimmune disorder in which immunoglobulin G antibodies (ABs) against the NR1 subunit of NMDAR cause receptor internalization and decreased NMDAR-mediated neurotransmission. NMDAR encephalitis predominantly affects women, children, and young adults; occurs with or without tumor association; and is characterized by a predictable set of symptoms including psychosis as a common early feature, disorganized behavior, motor (e.g., catatonia and dyskinesia) manifestations, and seizures. NMDAR encephalitis is responsive to immunotherapy but refractory to antipsychotic medication and is associated with the long-term persistence of behavioral and cognitive deficits. Patients' ABs decrease the surface density of NMDAR clusters via antibody-mediated capping and internalization resulting in decreased NMDAR-mediated synaptic currents (1,2). This relative NMDAR function loss may underlie the deficits in behavior and cognition that are hallmarks of NMDAR encephalitis.

A proportion of clinically diagnosed schizophrenia patients may be seropositive for anti-NMDAR ABs. The seropositivity prevalence rates seem to be 1 in 10 to 20 patients but may differ among patient types (3). Furthermore, similar seropositivity rates were reported among healthy individuals (4), rendering the significance of anti-NMDAR ABs presence less clear. We hypothesized that: 1) seropositive patients can be identified among chronic schizophrenia patients having illness features that are also characteristic manifestations of anti-NMDAR encephalitis (3); and 2) NMDAR AB positive patients will respond to treatment with D-serine (DSR), which acts in vivo as NMDAR co-agonist.

Anti-NMDAR AB levels were assessed in 17 DSM-IV diagnosed schizophrenia patients who fulfilled the following inclusion criteria: 1) treatment resistance to antipsychotic pharmacotherapy; and 2) at least one of the following: an abrupt start of disease, lack of previous or family psychiatric history, and atypical disease course; or presence of hebephrenic, catatonic, dyskinesia features or seizures unaccounted by a neurological or other disorder.

Detection of ABs against extracellular epitopes of NMDAR was performed using a previously described cell-based assay (5). One of the 17 patients was strongly seropositive, at both X200 and X10 dilutions, for both immunoglobulin G and immunoglobulin M anti-NR1 AB isotypes. This was a 67-year-old female who, at age 27 after a period of continuous headaches for which no organic basis had been found, had abruptly developed an acute psychosis characterized by grandiose and paranoid delusions, mystical thinking, elated affect, and agitation. Following diagnosis, she never returned to her previous functional level and except for short attempts at living in the community has been hospitalized ever since. She has been generally refractory to treatment with antipsychotic drugs but has not been diagnosed with any medical or neurological disorder. At present, she is maintained on sulpiride 50 mg/day, citalopram 40 mg/day, lorazepam 1 mg/day, and promethazine 50 mg/day. Medical and neurological examinations and clinical laboratory parameters have been consistently unremarkable. Abdominal ultrasound examination performed post NMDAR ABs assessment showed no ovarian teratoma or other abnormalities.

Following detection of seropositivity, we conducted magnetic resonance imaging and continuous electroencephalography (cEEG) studies to determine presence or absence of findings characteristic of anti-NMDAR encephalitis and as a baseline for pharmacologic NMDAR-based intervention. Nonspecific fluid-attenuated inversion recovery and T2 signal hyperintensities were present in the periventricular white matter, subcortically, and deep bifrontally and biparietally in the cortex (Figure 1A). cEEG showed a normal background activity with superimposed semirythmic diffuse extreme delta brush events that were present frontotemporally with right side predominance (Figure 1B, left). Both types of abnormalities are consistent with those observed more generally in anti-NMDAR encephalitis (1,6).

After a thorough discussion of risks and benefits, the patient and her family signed informed consent to receive adjuvant DSR in an open-label 6-week clinical trial in which DSR dose was increased gradually from 1.5 to 4 g/day without any change in ongoing medication. Symptoms and side effects were assessed biweekly. DSR was well tolerated and no side effects were registered. At week 6, all Positive and Negative Syndrome Scale symptom clusters improved and Positive and Negative Syndrome Scale total score decreased from 97 to 80, corresponding to a 34% decrease within the framework of the 1 to 7 scoring. The average item score decreased from 3.2 (mild-moderate) to 2.7 (minimal-mild). Simpson Angus Scale for Extrapyramidal Symptoms total score decreased from 5 to 3. The quality of life of the patient, as assessed by Schizophrenia Quality of Life Scale (7), improved considerably, resulting in a 37% total score reduction (147.06 vs. 93.37).

cEEG was repeated at the end of the 6-week period and showed an apparent reduction of extreme delta brush-type activity (Figure 1B, right). To assess this quantitatively for both baseline and posttreatment recordings, approximately 2 minutes of randomly selected artifact-free EEG activity were divided into 2-second epochs. Fast fourier transforms were computed for 15 randomly selected epochs and were averaged to obtain spectral density power (μV2/Hz) of delta (.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), and beta (12.5–30.0 Hz) bands. In support of visual impression, the comparison of baseline versus 6-week data indicated significant decreases in both delta (45.9 ± 24.3 vs. 9.1 ± 3.1; $F_{1,30} = 36.5$, $p = .001$) and beta (4.87 ± 1.73 vs. $1.13 \pm .91$; $F_{1,30} = 58.7$, $p = .001$) spectral power in the right frontotemporal region (F8 electrode).

This case suggests that NMDAR AB seropositive individuals can be identified among chronic treatment-resistant

http://dx.doi.org/10.1016/j.biopsych.2014.08.023
ISSN: 0006-3223

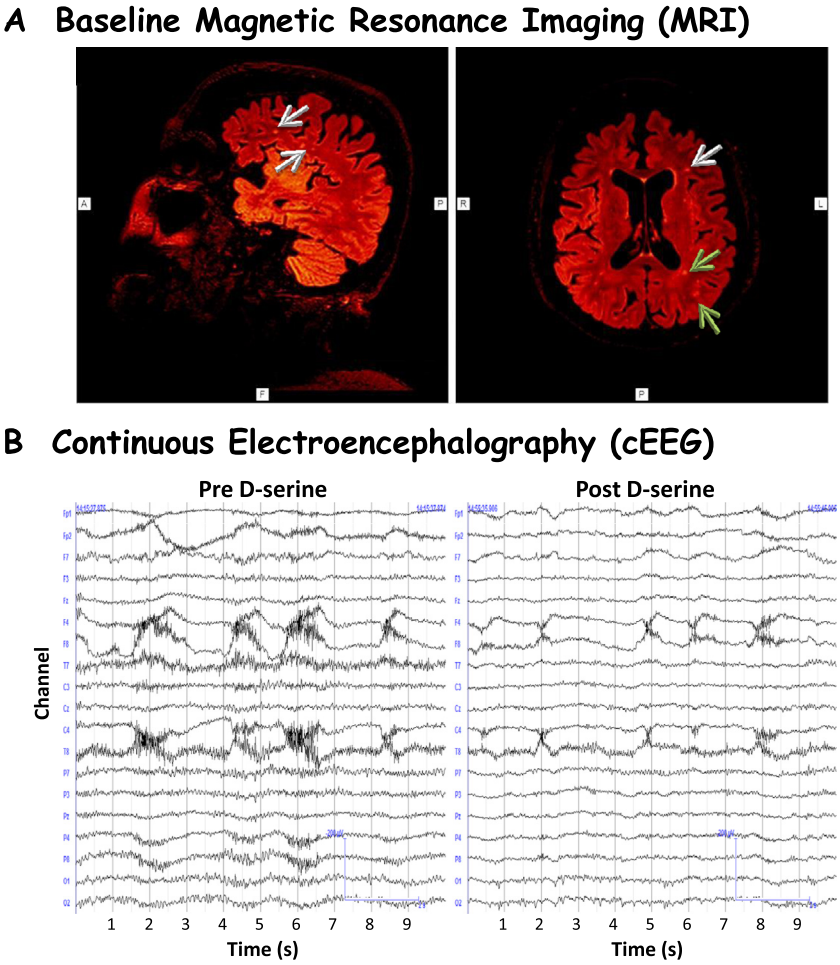

Figure 1. MRI and cEEG findings pre and post 6-week D-serine administration. **(A)** Sagittal and axial fluid attenuated inversion recovery MRI of the brain, showing asymmetrical increased foci of high-signal intensity in the cortex and subcortical white matter of both left frontal lobe (white arrows) and parietal-occipital lobes (green arrows). **(B)** cEEG (average reference) demonstrates reduced extreme delta brush electrographic pattern following D-serine administration.

schizophrenia patients. The naturally occurring amino acid DSR may be beneficial for this patient subgroup. DSR has been shown to ameliorate negative, cognitive, and anti-psychotics-induced motor symptoms predominantly in samples of treatment-resistant schizophrenia patients (8). No significant adverse events have been observed with ≤4 g/day DSR doses and both acute and chronic administration of 1 g to 2 g DSR in humans result in ≥100 times increase in DSR serum levels (8). DSR binds at the glycine modulatory site on the NR1 subunit, resulting in increased frequency of NMDAR channel opening and may alleviate the AB-induced reduction in NMDAR function by enhancing the activity of remaining cell-surface receptors or by obstructing AB-generated receptor internalization. However, this preliminary study is limited by the use of serum rather than cerebrospinal fluid samples and exclusive focus on NMDAR ABs. Future studies including cerebrospinal fluid as well as serum samples and assessment of more extensive brain AB panels appear warranted.

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Acknowledgments and Disclosures

This work was supported by the Crown Foundation, Chicago, Illinois.

We thank Drs. Kenji Hashimoto and Yakir Kaufman for their assistance in the implementation of the study.

Uriel Heresco-Levy is an inventor in patent applications for the use of *N*-methyl-D-aspartate receptor modulators in autoimmune-induced glutamatergic receptor dysfunctions. Daniel Javitt holds intellectual property rights in glycine, D-serine, and glycine transport inhibitors for schizophrenia and related conditions. Marina Ermilov, Andrea R. Durrant, Kazushi Miya, and Hisashi Mori report no biomedical financial interests or potential conflicts of interest.

Article Information

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