TREATMENT-RESPONSIVE SUBACUTE LIMBIC ENCEPHALITIS AND NMDA RECEPTOR ANTIBODIES IN A MAN

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Clinical/Scientific Notes

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Disturbances of memory, behavior, cognition, and seizures can result from immune-mediated encephalitides. These disorders can be paraneoplastic or not and may associate with several antibodies.[1] Recently, a treatment-responsive paraneoplastic encephalitis that associates with antibodies to NR1/NR2 heteromers of the *NMDA* receptor (NMDAR) was reported.[2] Patients were young women with teratomas, usually of the ovary, who presented with prominent psychiatric symptoms, and less frequently with features of limbic encephalitis. We report a man with treatment-responsive limbic encephalitis and antibodies to NR1/NR2 heteromers.

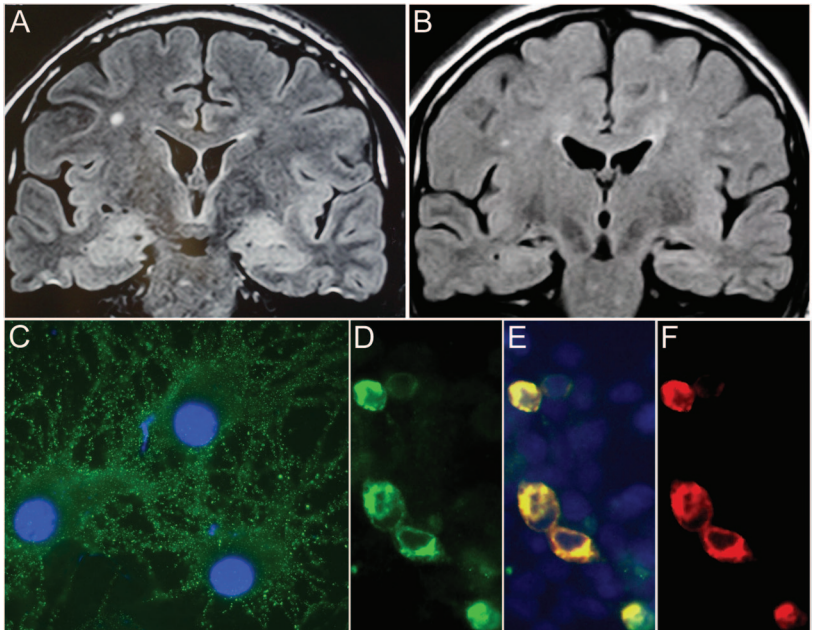
Case report. For 3 months this 53-year-old man had progressive short-term memory deficits and disorientation that forced him to leave his job. During the month before hospital admission he had multiple episodes compatible with partial complex seizures. He had no past medical history of interest. The neurologic examination only revealed short-term memory deficits and impairment of temporal orientation. Blood cell count, general chemistry, B12, folic acid, thyroid function test, thyroglobulin antibodies, RPR, Lyme serology, antibodies to double stranded DNA, and SSA/Ro and SSB/La were unrevealing. CSF analysis showed 5 WBC/μL (100% lymphocytes) and normal glucose and protein concentration. Serum and CSF disclosed the same oligoclonal IgG bands. Paraneoplastic antineuronal and VGKC antibodies were negative. EEG demonstrated bilateral temporal lobe epileptic activity. MRI of the brain revealed noncontrast enhancing T2 and FLAIR hyperintensities involving the medial aspect of the temporal lobes and nonspecific hyperintensities in the frontal lobes (figure, A). Ultrasound of the testis, CT of the chest, abdomen and pelvis, and body [^{18}F] fluorodeoxyglucose were normal. A transient elevation of the prostate-specific antigen led to a biopsy of the prostate that revealed no malignant cells. The patient was diagnosed with limbic encephalitis and treated with carbamazepine 200 mg/8 hours, methylprednisolone (1 g/day for 5 days and 60 mg/day for the next 2 weeks followed by progressive tapering), and IV immunoglobulins (0.4 g/kg for 5 days). The seizures resolved after carbamazepine was started, and the memory deficits and disorientation progressively improved during the 4 weeks of hospitalization. Follow-up 4 months after discharge demonstrated improvement of the MRI (figure, B), a normal neurologic examination, and the patient was planning to return to work.

Incubation of live rat hippocampal neuronal cultures with the patient's serum and CSF revealed antibodies that labeled the cell surface and neuronal processes (figure, C). Using previously reported techniques,[2] the target autoantigens were identified as the NR1/NR2 heteromers of the NMDAR (figure, D through F). Immunoblots of these proteins were recognized by commercial NR1 or NR2 antibodies but not the patient's antibodies (not shown). Limited amount of CSF prevented analysis of intrathecal synthesis of antibodies. Serum antibody titers (using serial dilutions on rat hippocampal immunohistochemistry) showed a tenfold decrease at the 4-month follow-up (from 1:4,000 to 1:400).

Discussion. Experience suggests that up to 40% of patients with limbic encephalitis do not have classic antineuronal or VGKC antibodies.[1,3] Recent studies show that many of these "seronegative patients" actually have antibodies against neuronal cell surface antigens mainly concentrated in the hippocampus.[4] One of these antigens corresponds to extracellular epitopes of NR1/NR2 heteromers of the NMDAR. All patients previously reported with these antibodies were young women with teratoma, and the antibodies reacted with cells expressing interacting NR1/NR2 subunits (functional channel), but not with immunoblots of these cells or NR1/NR2 proteins.[2] The associated syndrome usually presents with psychiatric manifestations (less frequently with short-term memory deficits) and may evolve

Supplemental data at www.neurology.org

Figure MRI and patient's antibodies



(A) MRI FLAIR at symptom presentation shows predominant hyperintensities in the medial temporal lobes and insular region, and smaller areas of abnormal signal in the frontal lobes. (B) MRI FLAIR at follow-up shows significant improvement of the temporal and insular region abnormalities. (C) Reactivity of the patient's CSF with the cell surface of cultures of rat hippocampal neurons. Nuclei are demonstrated with 4′,6-diamidino-2-phenylindole (DAPI, blue staining). (D–F) Confirmation that the patient's antibodies selectively react with NMDAR is shown using HEK293 cells expressing NR1/NR2A heteromers of the NMDAR. The reactivity of the patient's CSF (green, D) co-localizes (yellow, E) with the reactivity of a commercially available NR2A antibody (red, F). In addition, panel E shows a background of non-transfected cells (blue nuclei stained with DAPI) that are not reactive with the patient's antibodies or NR2A antibodies. Similar studies using HEK293 cells expressing NR1/NR2B demonstrated that the patient also had antibodies against these heteromers (see figure e-1 on the *Neurology*® Web site at www.neurology.org). C–F, Immunofluorescent technique, C (oil lens ×800), D–F (×400). The commercial NR2A antibody was used at 1:50 dilution (Upstate Biotechnology, Lake Placid, NY), patient's CSF at 1:10, and Alexa Fluor secondary antibodies at 1:2,000 (Molecular Probes, OR), as reported.[2]

to life-threatening complications including seizures, hypoventilation, and autonomic instability. Patients usually recover after removing the teratoma and immunotherapy.

Several notable findings of our patient are that he is a man, with classic features of limbic encephalitis, and all studies for cancer have been negative to date. Furthermore, he had dramatic clinical and radiologic improvement that associated with a decrease of NMDAR antibody titers.

Antibodies predominantly reacting with intracellular (C-terminal) and less frequently N-terminal linear epitopes of NR2 subunits (without requirement of NR1) have been reported in several disorders, including epilepsia partialis continua, Rasmussen encephalitis,[5] and some cases of non-herpetic limbic encephalitis identified in Japan.[6] Furthermore, some patients with neuropsychiatric lupus have anti-double stranded DNA antibodies that crossreact with an epitope present in both NR2A and NR2B subunits.[7] In all these disorders, the antibodies are detectable by immunoblot of single NR2 subunits and therefore differ from those of our patient, suggesting different syndrome-epitope associations.

The present case brings into consideration the NR1/NR2 heteromers of NMDAR as autoantigens of limbic encephalitis, paraneoplastic or not. Recognition of encephalitides associated with these antibodies is important because despite their severity, they often respond to treatment.

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