

NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Antibody-Mediated Encephalitis Mechanisms

Encephalitis associated with N-methyl-D-aspartate receptor antibodies can have a devastating impact on patients' cognitive and psychiatric function. Researchers at the University of Pennsylvania, Philadelphia, obtained cerebrospinal fluid (CSF) and sera at random from a series of 320 patients with clinical manifestations of the disease to explore the cellular mechanisms by which antibodies cause the loss of NMDA receptors.

Anti-NMDA receptor antibodies trigger symptoms of memory loss, deficits in learning and cognition, and psychosis in patients with anti-NMDA receptor encephalitis by crosslinking and internalizing synaptic NMDA receptor clusters, according to findings reported by Ethan G. Hughes, Ph.D., and his colleagues. (Dr. Hughes is now a postdoctoral fellow at Johns Hopkins University, Baltimore.)

Among patients with clinical manifestations of the disease, they found that purified anti-NR1 antibodies reduced the surface and total cluster density of NMDA receptors on cultured hippocampal neurons in a titer-dependent fashion. (The NR1 epitope is one of two protein subunits that form the NMDA receptor.) The researchers cultured the neurons with CSF samples that had been obtained at two different time points of the disease in two patients. In one of the patients, they found that CSF taken from the patient at symptom presentation had a higher titer of anti-NR1 antibodies than was present during symptom improvement; whereas in the second patient, they found that the CSF obtained during symptom worsening had a higher antibody titer than at symptom presentation. Periods in which anti-NR1 antibody titers were higher also had greater declines in NMDA receptor surface and total cluster density (*J. Neurosci.* 2010;30:5866-75).

Further experiments with hippocampal neurons cultured with CSF or purified anti-NR1 antibodies demonstrated that the patients' antibodies "dramatically reduced" the synaptic localization of NMDA receptor clusters in a titer-dependent fashion without affecting the overall structural integrity of excitatory neurons, synapses, or other synaptic proteins or receptors. The

density of the NMDA receptor clusters returned to baseline levels 4 days after the antibodies were removed, demonstrating the reversibility of the antibodies' effects. Whole-cell patch recordings found that the antibodies decreased only NMDA receptor-mediated currents and not those mediated by other receptors. The patients' antibodies promoted the internalization of the receptors by binding to, capping, and crosslinking them.

In addition to the study of patients with the disease, the researchers directly infused human anti-NR1 antibodies into the hippocampus of adult rats for 2 weeks. They found that the antibodies had bound to the rat hippocampus in a predictable pattern that was dependent on NMDA receptor density and similar to the pattern seen in patients with anti-NMDA receptor encephalitis. The density of

NMDA receptor clusters had declined significantly in regions where the antibodies had been deposited, similar to what was observed in sections of the hippocampus in two patients who died from anti-NMDA receptor encephalitis.

The fact that many patients who develop anti-NMDA receptor encephalitis are first admitted to psychiatric institutions with schizophrenia-like symptoms suggests that NMDA receptor hypofunction underlies the symptoms of anti-NMDA receptor encephalitis and many manifestations of schizophrenia, Dr. Hughes and his colleagues wrote.

The research was funded by grants from the National Institutes of Health.

Dr. Carter's comment: Anti-NMDA receptor encephalitis is the first of several "autoimmune synaptic encephalopathies" that have been described within the last 5 years. Other similar disorders with different receptor targets include anti-AMPA receptor encephalitis and anti-GABA receptor encephalitis. These disorders share

certain clinical features such as female predominance, frequent association with neoplasm, and presentation with psychosis, behavioral changes, or intractable seizures. Importantly, these disorders are treatable and reversible if recognized early and treated aggressively with immunosuppressive therapies and removal of the neoplasm if present.

The experiments of Dr. Hughes and his associates elegantly clarify the cellular and synaptic mechanisms of anti-NMDA receptor encephalitis using both in vitro and in vivo models. They demonstrate that antibodies from patient sera or CSF reversibly reduce synaptic NMDA receptor clusters by binding, crosslinking, and internalizing NMDA receptors without damaging synaptic connections or the number or structural integrity of these synapses. Furthermore, this reduction in synaptic NMDA receptors shows a linear correlation with the titer of anti-NMDA receptor antibodies. Patient anti-

bodies also reduce synaptic NMDA receptor currents, and reduce NMDA receptor cluster density in rodent and human hippocampus slices in vivo.

This report solidly establishes the role of anti-NMDA receptor antibodies in the pathogenesis of this disorder, creating a new paradigm of central nervous system synaptic

autoimmunity. The reversibility of this process is also encouraging for clinicians who may see and treat patients with these disorders, which are likely highly underrecognized at present. The challenge for the future will be to translate these basic science advances into effective treatments for these disorders, and to recognize new forms and presentations of this widening family of autoimmune synaptic encephalopathies. ■

Clinical perspective by DR. CARTER, an associate professor of neurology at the Mayo Clinic College of Medicine and a consultant in the department of neurology at the Mayo Clinic Arizona.

Research report by Jeff Evans, Managing Editor.



BY JONATHAN CARTER, M.D.

The periods during which the patients' anti-NR1 antibody titers were higher also had greater declines in NMDA receptor surface as well as in total cluster density.

TCD May Help Identify Stroke Risk in Asymptomatic Patients

BY DOUG BRUNK

FROM THE LANCET NEUROLOGY

Transcranial Doppler helped clinicians identify groups of patients with asymptomatic carotid stenosis who were at low or high risk of future stroke in a large, multicenter study.

"This technique might be a useful risk predictor for identifying those patients who might benefit from intervention with carotid endarterectomy," researchers led by Dr. Hugh S. Markus of the department of clinical neuroscience at St. George's University of London, reported (*Lancet Neurol.* 2010 May 28 [doi:10.1016/S1474-4422(10)70120-4]).

The findings come from the Asymptomatic Carotid Emboli Study (ACES), a first-of-its-kind prospective observational study of 467 patients with asymptomatic carotid stenosis of at least 70%. The patients underwent two 1-hour transcranial Doppler (TCD) recordings from the ipsilateral middle cerebral artery at baseline

and one 1-hour recording at 6, 12, and 18 months. They were followed up for 2 years for the study's primary end point of ipsilateral stroke and transient ischemic attack (TIA).

The mean age of the patients was 72 years, and 26% were women. The majority (90%) had hypertension, 46% were previous smokers, and 15% were current smokers.

Dr. Markus and his associates found that embolic signals on TCD were present in 77 (16%) of the patients at baseline. Compared with their counterparts who did not have embolic signals at baseline, the 77 patients who did were 2.54 times more likely to have an ipsilateral stroke or TIA at 2 years, and 5.57 times more likely to have an ipsilateral stroke alone.

Between baseline and 2 years, the absolute annual risk of ipsilateral stroke or TIA in patients who had embolic signals

VITALS

Major Finding: Patients with asymptomatic carotid stenosis of at least 70% were 2.54 times more likely to have an ipsilateral stroke or TIA at 2 years if they had embolic signals on transcranial Doppler at baseline, compared with those who did not.

Data Source: A study of 467 patients evaluated at 26 centers worldwide.

Disclosures: Funded by a British Heart Foundation Program Grant. The investigators reported having no conflicts of interest.

at baseline was 7.13%, compared with 3.04% in those who did not; whereas the absolute risk of ipsilateral stroke alone was 3.62% in patients who had embolic signals at baseline, compared with 0.70% in those who did not.

The presence of embolic signals on the TCD recording at each visit was used to predict greater risk for ipsilateral stroke or TIA during the subsequent 6-month period. Embolic signals during the previous visit increased the risk for ipsilateral stroke

or TIA by a factor of 2.63 and for ipsilateral stroke alone, by a factor of 6.37.

Although the researchers called the study results "widely applicable," they acknowledged that bias "could have occurred in those cases of asymptomatic carotid stenosis where the surgeon was unwilling to enroll the patient, which could have led to exclusion of a higher risk group of patients." They also emphasized that better ways to automatically detect embolic signals are needed before TCD is widely used for risk stratification in this patient population.

"TCD recording itself is simple, noninvasive, and widely used in clinical practice worldwide," they wrote. "However, review of data for the presence of embolic signals is time consuming and relies on trained observers. Inter-observer reproducibility studies have reported that there is a high reproducibility among trained observers in detection of embolic signals, but that without adequate training some centers interpret the criteria incorrectly." ■