Current Literature
In Clinical Science

Commentary

“The MRI was normal.” These words, which seem on their surface to bring good news, are often met with confusion and concern when expressed to family members of patients who are suffering from a debilitating form of epilepsy or other neurologic illness. The seeming discrepancy between severe clinical symptoms and signs and a normal morphologic appearance of the brain can be disconcerting to patients, relatives, caregivers, and indeed physicians.

Anti-NMDA receptor (NMDAR) encephalitis, a relatively recently described clinical entity whose features are now increasingly being investigated and understood, is an example of just such an illness (1). The disorder commonly presents with psychiatric problems after a brief prodrome of headache and nonspecific constitutional symptoms and usually progresses to involve memory difficulty, language disturbance, and epileptic seizures. Ultimately, patients can develop alterations in consciousness (including frank coma), a movement disorder such as orofacial dyskinesias, autonomic lability, and central hypoventilation; prolonged intensive care unit stays are often required. Remarkably, at least half of reported patients with anti-NMDAR encephalitis have normal conventional brain MRI findings, and even when abnormalities are seen on MRI, they are often mild, transient, and nonspecific (2). The diagnosis is generally made by measuring serum and CSF titers of anti-NMDAR antibodies, and treatment centers on removal of an associated tumor such as ovarian teratoma, if found, and immunomodulatory therapy such as intravenous immunoglobulin, corticosteroids, and plasmapheresis. Prognosis is good for about three-quarters of patients, who recover completely or nearly so (though often only after many months), but the remainder may be left quite disabled, and a small percentage of patients do not survive.

One of the persistent questions in our understanding of anti-NMDAR encephalitis has been the clinical-radiologic dissociation seen commonly in this disorder. The article by Finke et al. from Germany reports on a systematic imaging analysis of 24 patients with an established diagnosis of anti-NMDAR encephalitis (by antibody titers), and a cohort of age- and sex-matched controls, which they undertook to investigate structural and functional brain changes in this disorder. Using resting-state functional MRI (3), diffusion tensor imaging (4), and voxel-based morphometry (5), as well as conventional imaging and neuropsychologic testing, the authors sought...
to establish whether there are in fact imaging signatures of this autoimmune condition that might escape detection by standard clinical MRI sequences.

Indeed, although there were no gray matter morphologic differences between patients and controls, the investigators did find a number of significant alterations of structural and functional connectivity in anti-NMDAR encephalitis patients. Specifically, patients had reduced functional connectivity between the hippocampi and the anterior default mode network. (This brain network shows functional activation when patients are not actively engaged in a cognitive task and is felt to be relevant to episodic memory, autobiographic processing, and other non–stimulus-dependent states (6).) Of importance, the degree of hippocampal functional connectivity predicted memory performance in the anti-NMDAR patients, highlighting the clinical relevance of these specialized imaging findings. In addition, structural connectivity imaging revealed that there were quite extensive changes in white matter integrity (as measured by fractional anisotropy) in the patient group as compared with controls, particularly in the cingulum, and the degree of white matter integrity loss correlated with global disease severity, though not with specific cognitive features.

These findings serve to answer some questions regarding anti-NMDAR encephalitis (and may speak to autoimmune encephalitides more broadly as well) yet raise more questions than they answer. For example, they help us to understand that despite the normal or near-normal appearance of gray and white matter on conventional imaging in this disorder, there are important and substantial changes in connectivity in the anti-NMDAR state, both locally and globally in the brain, and these may play a critical role in the underlying pathophysiology of the disorder.

Among the questions raised by these findings, though, are the following:

1. What happens to brain structural and functional connectivity during the acute phase of this disorder? MR imaging in this study was not performed until an average of 31 months after the onset of initial symptoms (range, 9–72 months). Indeed, by the time of the imaging, some patients no longer had detectable anti-NMDAR titers.

2. What is the mechanism by which neuronal cell surface antibodies lead to widespread connectivity defects but no gray matter morphologic changes? A proposed theory of pathogenesis is that these autoantibodies cause internalization of synaptic NMDA receptors, particularly in GABAergic neurons, and thus disinhibition within brain circuits.

This is a good opportunity to reflect on a broader perspective of anti-NMDAR encephalitis: Within a period of only several years, we have been introduced to and have learned much about what appears now to be one of the most common autoimmune causes of epilepsy we can currently identify (2). Anti-NMDAR encephalitis may be more prevalent than the many other such syndromes, paraneoplastic and otherwise, that we frequently test for in unexplained cases of encephalitis, and importantly, is one that may be quite readily treatable with immunosuppressive therapy (7, 8).

Even more, as further work emerges on the underlying molecular, cellular, and system-based pathobiologic mechanisms of seizures and cognitive/behavioral dysfunction in anti-NMDAR encephalitis, it may serve as an instructive model for our understanding of inflammatory causes of epilepsy and even for psychiatric diseases like schizophrenia, which share some of its clinical and mechanistic features.

In other organ systems, and indeed in other disorders of the nervous system, autoimmunity has turned out to be a complex, informative, and prevalent mechanism of disease. It is not surprising that this may be the case in epilepsy as well.

by Bernard S. Chang, MD

References

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

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3.  Are you the Main Assigned Author?  ☑ Yes   ☐ No

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4.  Manuscript/Article Title: Paradox Lost: Exploring the Clinical-Radiologic Dissociation Seen in Anti-NMDA Receptor Encephalitis

5.  Journal Issue you are submitting for:  14.3

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