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Editors' Note: In WriteClick this week, Drs. Finke and Prüss comment on influenza-associated encephalitis (IAE) as discussed in "Clinical Reasoning: A 57-year-old woman who developed acute amnesia following fever and upper respiratory symptoms," and suggest patients with suspected IAE be tested for neuronal antibodies. In reference to "Spatial cluster analysis of population amyotrophic lateral sclerosis risk in Ireland," Drs. Bradley et al. and authors Rooney et al., who have published further work, discuss methodologic considerations in testing for amyotrophic lateral sclerosis clusters.

—Megan Alcauskas, MD, and Robert C. Griggs, MD

CLINICAL REASONING: A 57-YEAR-OLD WOMAN WHO DEVELOPED ACUTE AMNESIA FOLLOWING FEVER AND UPPER RESPIRATORY SYMPTOMS

Carsten Finke, Harald Prüss, Berlin: McCray et al.[1] described a patient with an influenza-associated encephalitis (IAE). As they stated, IAE is believed to be caused by an immune-mediated mechanism rather than direct viral toxicity. Their patient did not respond to antiviral therapy but improved after immunomodulatory treatment with steroids and immunoglobulins.

The recent discovery of antibodies to neuronal surface proteins has revolutionized clinical neurology and has led to the identification of several new autoimmune encephalitides. A viral trigger has been considered in many of these conditions and has been demonstrated for herpes simplex virus type I and varicella-zoster virus, both of which can trigger anti–NMDA receptor (NMDAR) encephalitis.[2,3] Moreover, a past influenza A infection can predispose to the development of serum NMDAR antibodies,[4] and positive influenza serology is common in acute NMDAR encephalitis.[5] In contrast to the authors' notion, autoimmune encephalitides can occur with rapid onset and acute deterioration as well as with normal CSF leukocyte count.

Perhaps patients with suspected IAE should be tested for neuronal antibodies using cell-based and CNS tissue assays to rule out antibody-mediated autoimmune encephalitis. In addition, this testing would further our understanding of parainfectious autoimmune encephalitides.

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2. Pruss H, Finke C, Holtje M, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. Ann Neurol 2012; 72:902–911.
3. Schabitz W, Rogalewski A, Hagemeister C, Bien CG. VZV brainstem encephalitis triggers NMDA receptor immunoreaction. Neurology 2014;83:2309–2311.
4. Hammer C, Stepniak B, Schneider A, et al. Neuropsychiatric disease relevance of circulating anti-NMDA receptor autoantibodies depends on blood-brain barrier integrity. Mol Psychiatry 2014;19:1143–1149.
5. Pruss H, Dalmau J, Harms L, et al. Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. Neurology 2010;75:1735–1739.

SPATIAL CLUSTER ANALYSIS OF POPULATION AMYOTROPHIC LATERAL SCLEROSIS RISK IN IRELAND

Walter G. Bradley, Palmetto Bay, FL; Elijah W. Stommel, Xun Shi, Hanover; Nathan M. Torbick, Newmarket; Tracie A. Caller, Hanover, NH; Clive E. Sabel, Bristol, UK: We read with interest the article by Rooney et al.,[1] who reported no significant high-risk clusters of patients with amyotrophic lateral sclerosis (ALS) in the Irish ALS Register. They referred to reports, including our own, of statistically increased frequency of ALS in Finland, northern New England, and France.[2–4] Methodologic, conceptual, and real differences between risk factors in one region and another may explain the differences between studies. If cases are aggregated over large areas, the effect of a localized toxic exposure may be lost.

Sabel et al.[4] and Wheeler[5] showed that the kernel density function method revealed statistically significant areas of increased risk for ALS in Finland and leukemia in Ohio that were not detected with SaTScan and other methods. Our studies of ALS clusters in northern New England originated from recognition of a cluster of patients with ALS who lived near Lake Mascoma in New Hampshire, which has frequent cyanobacteria blooms. We found 11 clusters of statistically significant high incidence in northern New England, supporting our hypothesis that living