Bradley, W. G., Bay, P., Stommel, E. W., Shi, X., Torbick, N. M., Caller, T. A., & Sabel, C. E. (2015). Spatial cluster analysis of population amyotrophic lateral sclerosis risk in Ireland. *Neurology*, 85(20), 1822-3. <https://doi.org/10.1212/01.wnl.0000473800.89178.a9>

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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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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 Wheeler⁵ 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

near water bodies with cyanobacteria blooms was a risk factor for ALS.³

It is likely that sporadic ALS is a multifactorial disease, resulting from the interaction of multiple environmental risk factors with multiple genetic predisposing factors. Therefore, studies of regional distribution of cases and of underlying genetic factors may fail if they do not focus on individual risk factors.

Author Response: James P. Rooney, Anthony Staines, Orla Hardiman, Dublin: We thank Bradley et al. for their interest and comments on our article.¹ We agree that “If cases are aggregated over large areas, the effect of a localized toxic exposure may be lost.” Therefore, we have undertaken a new study where we replicated our analysis at a higher spatial resolution of over 18,000 small areas consisting of no more than 200 residences each.⁶

We also agree that “sporadic ALS is a multifactorial disease, resulting from the interaction of multiple environmental risk factors with multiple genetic predisposing factors.” There is recent epidemiologic evidence for this in the form of multistep models for ALS.⁷ We are also cognizant of the ecological fallacy (i.e., inappropriately ascribing group-level correlations to individual-level variables), and agree that individual risk factors are important to include in models wherever possible.

However, our study did report positive results. Our methods were sensitive enough to find 2 statistically significant low-risk areas, as well as detect 5 cases that presented late and 2 that presented cross-border. The algorithms used are agnostic to hot or cold spots; therefore, if hot spots did exist, we are confident we would have detected them.

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CORRECTION

CNS neutrophilic vasculitis in neuro-Sweet disease

In the Clinical/Scientific Note “CNS neutrophilic vasculitis in neuro-Sweet disease” by R. Charlson et al. (*Neurology*® 2015;85:829–830), there is an error in the discussion and the references. The last name of the first author of reference 2 should be Hisanaga, not Hisanga as originally published. The authors regret the error.

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Spatial cluster analysis of population amyotrophic lateral sclerosis risk in Ireland

Walter G. Bradley, James P. Rooney, Elijah W. Stommel, et al.

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