THELANCETNEUROLOGY-D-16-00045
S1474-4422(16)00025-9
Linked to: 0694
Embargo: Feb 19, 2016—23:30 (GMT)
CL

Autoimmune encephalitis: paving the way for early diagnosis

Lancet Neurol 2016
Published Online
February 19, 2016
http://dx.doi.org/10.1016/S1474-4422(16)00025-9
See Online/Position Paper
http://dx.doi.org/10.1016/PII

A major and fascinating development in neuroimmunology in the past 10 years has been the impressive rise in the number of antibodies identified that recognise neuronal cell-surface or synaptic proteins.[1] Identification of these antibodies has enabled the characterisation of new forms of autoimmune encephalitis (eg, anti-NMDA receptor encephalitis)[2] or new patterns of presentation (eg, faciobrachial dystonic seizures in autoimmune encephalitis associated with LGI1 antibodies).[3] Overlap in the presence of these antibodies between neurological syndromes has highlighted complexities in the differential diagnosis—eg, NMDA receptor antibodies in some cases of herpes simplex virus encephalitis, which can sometimes precede anti-NMDA receptor encephalitis.[4]

By contrast with the onconeural antibodies identified in the 1980s, which react with intracellular antigens and are now regarded as biomarkers of a paraneoplastic origin,[5] evidence shows that specific antibodies against cell-surface or synaptic proteins are frequently responsible for specific autoimmune encephalitis disorders, and that these disorders might respond to immunotherapy. However, treatment regimens should not be identical for all patients because, for example, anti-NMDA receptor encephalitis frequently needs intensive immunosuppression, whereas encephalitis associated with LGI1 antibodies usually responds to steroids alone.[2,6,7] Early diagnosis of these disorders is, therefore, needed. In a Position Paper[8] in this issue of *The Lancet Neurology*, Francesc Graus and colleagues propose new guidelines for the diagnosis of autoimmune encephalitis.

Early diagnosis can be difficult in practice because of the wide range of symptoms and signs of autoimmune encephalitis disorders. The combination of neurological, psychiatric, and sometimes general symptoms in an acute or subacute setting often leads patients to the emergency room, the intensive care unit, or even the psychiatry department, where practitioners are not always aware of these disorders. Furthermore, antibody testing laboratories are not easily accessible at all times, commercial kits are not often updated to incorporate new or rare antigens, and results are not always rapidly available. The guidelines set out in the Position Paper[8] aim to address these challenges to enable diagnosis on the basis of conventional neurological assessment and standard diagnostic tests that are available to most clinicians.

The scope of the guidelines is deliberately restricted to limbic encephalitis, anti-NMDA receptor encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis, and Hashimoto's encephalopathy because they present as acute or subacute disorders and share several clinical features. These guidelines are intended to be used from the early phase of the diagnostic process, when antibody confirmation is not yet available, and when immunomodulatory treatment is being considered. The guidelines follow a step-wise progression, relying on the analysis of clinical manifestations and MRI, EEG, and CSF findings to reach the level of possible and then probable autoimmune encephalitis. Sets of criteria are proposed for the diagnosis of possible autoimmune encephalitis and each of the aforementioned disorders. Differential diagnosis will, of course, play a crucial part, and useful guidance about diseases that should be ruled out is provided. The authors also describe several pitfalls, particularly with MRI or CSF analysis, which can be misleading. A key point is that the antibody status is often needed for a definite diagnosis. An important contribution of this Position Paper[8] is that it provides guidelines on how the search for antibodies in the serum and CSF can be used to refine diagnosis and how the results should be interpreted.

Clinicians sometimes encounter patients for whom no antibody can be identified, particularly in cases of limbic encephalitis. For some patients, analysis of CSF with immunohistochemistry shows reactivity against neuronal proteins, which suggests the presence of previously unknown antibodies. The serum and CSF of these patients should be tested in research laboratories for the identification of new antibodies. This is a crucial step for future development and the guidelines provide welcome criteria that help the clinician in the identification of these cases.

Restriction of the scope of any new guidelines is unavoidable and the inclusion of several disorders in the autoimmune encephalitis classification could be debated. For example, one could question why Hashimoto's encephalopathy is included in the criteria for probable autoimmune encephalitis and

not considered as a related syndrome when no clear evidence exists that it is a genuine disease entity. To overcome this problem, the authors provide in the appendix a comprehensive list of disorders that have some relation to autoimmune encephalitis, together with their main characteristics.

To conclude, these guidelines, which result from a welcome consensus, will no doubt support clinicians considerably in making early diagnoses and help to provide the framework for classifying the different autoimmune encephalitis syndromes. The next step will be to test them for sensitivity and specificity in clinical practice.

Jean-Christophe Antoine
Department of Neurology, University Hospital of Saint-Etienne, 42055 Saint-Etienne, France
j.christophe.antoine@chu-st-etienne.fr

I have received grants from French Ministry of Health, non-financial support from LFB Biomédicaments and CSL Behring, and personal fees from Biomarin. I have a patent for a CV2 CRMP5 diagnostic tool with royalties paid to Athena Diagnostics, and a patent on FGFR3 issued.

1 Linnoila JJ, Rosenfeld MR, Dalmau J. Neuronal surface antibody-mediated autoimmune encephalitis. *Semin Neurol* 2014; **34:** 458–66.
2 Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011; **10:** 63–74.
3 Irani SR, Schott JM, Vincent A, Smith SJ. Tonic seizures: a diagnostic clue of anti-LGI1 encephalitis? *Neurology* 2011; **77:** 2140–41.
4 Armangue T, Moris G, Cantarin-Extremera V, et al. Autoimmune post-herpes simplex encephalitis of adults and teenagers. *Neurology* 2015; **85:** 1736–43.
5 Didelot A, Honnorat J. Update on paraneoplastic neurological syndromes. *Curr Opin Oncol* 2009; **21:** 566–72.
6 Zekeridou A, Karantoni E, Viaccoz A, et al. Treatment and outcome of children and adolescents with N-methyl-D-aspartate receptor encephalitis. *J Neurol* 2015; **262:** 1859–66.
7 Malter MP, Frisch C, Schoene-Bake JC, et al. Outcome of limbic encephalitis with VGKC-complex antibodies: relation to antigenic specificity. *J Neurol* 2014; **261:** 1695–705.
8 Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet *Neurol* 2016; published online Feb 19. http://dx.doi.org/10.1016/S1474-4422(15)00401-9.