

## SCIENTIFIC COMMENTARY

## A new cause of limbic encephalopathy

The spectrum of antibody-associated encephalopathy seems ever increasing. In 2004 Vincent *et al.* described, in this journal, a series of patients with a reversible limbic encephalopathy associated with antibodies against the voltage-gated potassium channels (VGKC-Ab). In this issue, Ances *et al.* (2005) have described yet another cause of limbic encephalopathy, this time a paraneoplastic disorder. Furthermore, they have suggested a classification to aid the physician in diagnosis and treatment and allow one to predict prognosis.

Beau Ances and colleagues describe seven patients with the subacute onset of a limbic encephalopathy. The serum of one of their patients contained VGKC-Ab and resembled in all respects the patients described by Vincent *et al.* (2004). That patient did not have cancer and recovered after treatment with intravenous immunoglobulin and corticosteroids. As with the patients described by Vincent and colleagues the cerebrospinal fluid (CSF) did not contain white cells and there was no evidence of intrathecal synthesis of the antibody. The other six patients were different. Their serum and CSF contained an antibody that reacted not as in most previously described paraneoplastic syndromes with the nucleus or cytoplasm of neurons, but instead with the neuropil of the hippocampus or the cerebellum; in only one patient was an intracellular antibody identified. Unlike the patients with VGKC-Ab, five of the six patients described in this paper had tumours. In addition, all had CSF pleocytosis and intrathecal synthesis of antibody. All, save the patient with the intracellular antibody, made a nice recovery with the treatment of the tumour, immunosuppression or both. The immunohistochemical identification of these antibodies required the use of tissue prepared differently from that which had previously been used in the study of paraneoplastic antibodies.

We believe there are several points that the clinician can learn from this study. First, autoimmune limbic encephalopathy is probably more common than most of us have heretofore believed (Graus and Saiz, 2005). Secondly, there is a logical approach to the evaluation of such patients. As indicated by Ances and colleagues, magnetic resonance imaging (MRI) of the brain and lumbar puncture are required first steps. If the MRI is not helpful, a brain positron emission tomography (PET) scan should be performed. Since treatment of the tumour is the best way of either stopping progression or reversing the neurologic symptomatology for most paraneoplastic syndromes, a search for a tumour [either benign or malignant (Taylor *et al.*, 1999)] should include imaging of

the entire body by CT or MRI and, if these are negative, by PET scan. The serum should be examined for antibodies against neural tissue. Although commercial laboratories have the capacity for identifying many paraneoplastic and other antibrain antibodies, this paper and others suggest that if the initial search is negative, serum should be sent to an academic medical centre studying paraneoplastic syndromes for a more thorough study (Darnell and Posner, 2003). Unfortunately, identification of these antibodies takes time and some patients may develop irreversible symptomatology while awaiting results. Accordingly, if there is ample evidence of an autoimmune limbic encephalopathy (i.e. herpes simplex encephalitis has been ruled out), we believe that one should begin immunosuppression using intravenous immunoglobulin without delay. Thirdly, laboratory evaluation is extremely helpful in establishing the prognosis. If the CSF is acellular and there is no evidence of cancer, VGKC-Ab is the likely culprit. If the CSF is cellular, a paraneoplastic syndrome is more likely and depending on the antibody, the neurologic symptoms may resolve with treatment of the cancer and/or immunosuppressive therapy or the neurological symptoms may be permanent even if the cancer is cured.

What can the investigator learn from this study? First, as we already know, identical clinical pictures (in this case, limbic encephalopathy) can be either paraneoplastic or non-paraneoplastic and can be associated with several different antibodies. Secondly, there are probably more antibodies than we have yet discovered. New more sensitive techniques, such as those described by Ances and colleagues are required to identify these antibodies. With our current techniques, we have still been unable to identify the antibody that is almost certainly present in children with neuroblastoma-associated opsoclonus (Antunes *et al.*, 2000). Thirdly, we must learn more about the pathogenesis of these syndromes. Ances and colleagues have suggested that the paraneoplastic syndromes associated with intracellular antibodies are T-cell mediated, and perhaps that is the reason they do not respond to intravenous immunoglobulin.

Solimena *et al.* (1988) have demonstrated that stiff-person syndrome is associated with autoantibodies that very specifically stain the neuropil, whether the disorder be autoimmune (with anti-GAD antibodies) or paraneoplastic (with anti-amphiphilic antibodies) (David *et al.*, 1996). Patients with anti-GAD antibodies respond remarkably well to benzodiazepines, suggesting a specific anti-GAD disruption in these patients, although it appears that there is both an

antibody and T-cell component to the disorder, whereas anti-amphiphilic antibodies have been reported to be capable of passively transferring stiff-person syndrome to animals (Sommer *et al.*, 2005). The complexity of the issue is seen in our understanding of the pathogenesis of Lambert Eaton myasthenic syndrome and myasthenia gravis, where antibodies can clearly transfer disease, and yet where an increasing role for T-cells is beginning to be appreciated. Although it is currently unclear whether a general rule regarding antibody type and pathogenesis in antibody-associated neurologic disorders exists, further understanding of disease pathogenesis is clearly of clinical as well as biological importance.

In the meantime, Ances and colleagues have given us the new syndrome to ponder and have suggested a new classification of limbic encephalitis. Following their approach should allow us to identify and successfully treat more patients than we have in the past.

Robert B. Darnell<sup>1</sup> and Jerome B. Posner<sup>2</sup>

<sup>1</sup>The Rockefeller University, 1230 York Avenue and

<sup>2</sup>Memorial Sloan-Kettering Cancer Center,

1275 York Avenue, New York, USA

E-mail: posnerj@mskcc.org

#### References

- Ances BM, Vitaliani R, Taylor RA, Liebeskind DA, Voloschin A, Houghton DJ, et al. Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. *Brain* 2005.
- Antunes NL, Khakoo Y, Matthay KK, Seeger RC, Stram DO, Gerstner E, et al. Antineuronal antibodies in patients with neuroblastoma and paraneoplastic opsoclonus-myoclonus. *J Pediatr Hematol Oncol* 2000; 22: 315–20.
- Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. *N Engl J Med* 2003; 349: 1543–54.
- David C, McPherson PS, Mundigl O, De CP. A role of amphiphysin in synaptic vesicle endocytosis suggested by its binding to dynamin in nerve terminals. *Proc Natl Acad Sci USA* 1996; 93: 331–5.
- Graus F, Saiz A. Limbic encephalitis: a probably under-recognized syndrome. *Neurologia* 2005; 20: 24–30.
- Solimena M, Folli F, Denis-Donini S, Comi GC, Pozza G, De Camilli P, et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. *N Engl J Med* 1988; 318: 1012–20.
- Sommer C, Weishaupt A, Brinkhoff J, Biko L, Wessig C, Gold R, et al. Paraneoplastic stiff-person syndrome: passive transfer to rats by means of IgG antibodies to amphiphysin. *Lancet* 2005; 365: 1406–11.
- Taylor RB, Mason W, Kong K, Wennberg R. Reversible paraneoplastic encephalomyelitis associated with a benign ovarian teratoma. *Can J Neurol Sci* 1999; 26: 317–20.
- Vincent A, Buckley C, Schott JM, Baker I, Dewar B.-K, Detert N, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004; 127: 701–12.