Invited Editorial Comment

Epileptic Disord 2005; 7 (3): 177-9

Temporal lobe seizures, amnesia and autoantibodies – identifying a potentially reversible form of non-paraneoplastic limbic encephalitis

Angela Vincent[1], Christian G. Bien[2]

[1] Neurosciences Group, Department of Clinical Neurology, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK
[2] Department of Epileptology, University of Bonn, Germany

Limbic encephalitis is a relatively rare disorder traditionally described as a paraneoplastic neurological disease. The presentation includes memory loss, confusion, personality change and seizures. MRI shows high intensity signals in the medial temporal lobes and cerebrospinal fluid analysis shows some lymphocytes and oligoclonal bands. The presence of serum antibodies to one of the paraneoplastic antigens, usually HuD, Ma/Ta proteins (Ma1/Ma2), av CRMP-5 (CV2), helps confirm the diagnosis of a paraneoplastic disorder and points to the most likely tumour (small cell lung cancer, thymoma, breast, testis and others depending on the antibody detected and the age and sex of the patient). In general, paraneoplastic limbic encephalitis and other neurological manifestations are progressive. They may stabilize with treatment of the tumour, or with immunosuppressive therapies, but the prognosis is poor, except in the case of some Ma2 antibody-associated patients (for a review see Bataller and Dalmau 2004). In the past, this may have led to a pessimistic approach to the treatment of these patients, even when a specific paraneoplastic antibody and/or primary tumour has not been identified. Over the last five years or so, however, it has become clear that there is a non-paraneoplastic, immunotherapy-responsive, form of limbic encephalitis, sometimes presenting with temporal lobe epilepsy (Bien *et al.* 2000), and a proportion of these patients have antibodies to voltage-gated potassium channels (VGKCs; Vincent *et al.* 2004, Thieben *et al.* 2004). VGKC antibodies are occasionally associated with thymoma or small cell lung cancers (Buckley *et al.* 2001, Pozo-Rosich *et al.* 2003), but there is increasing evidence for high VGKC antibody levels in patients with no apparent tumour. VGKC-antibody-associated non-paraneoplastic limbic encephalitis (VGKC-NPLE) is clinically indistinguishable from the paraneoplastic form at onset, although probably less likely to progress to involve other brain regions. Although there are no epidemiological data, the number of VGKC antibody positive patients identified during the last three years in Oxford from sera referred from the UK (> 30 new cases) suggests that VGKC-NPLE is more common

than the paraneoplastic form and, most importantly, follow-up data suggest that substantial improvement can be obtained by immunosuppressive treatments (Vincent *et al.* 2004 and unpublished data).

How diverse are the clinical presentations of this potentially reversible disorder and how can it be recognized? To date, most of the reported cases have presented with amnesia and temporal lobe seizures evolving during the first days or weeks. However, there are a few cases of a similar syndrome in temporal lobe epilepsy is the main and presenting feature (J. Adcock, C. Buckley and A. Vincent, in preparation). The paper in this issue by Wieser, Kelemen *et al.* 2005 (p. 205-12), from centres in Zurich and Budapest, describes a 42-year-old man who presented with frequent bouts of piloerection, shivering and flushing on one or both sides of his body that became more frequent until they reached a status-like state. At this stage there were psychotic symptoms and severe retrograde amnesia. Paraneoplastic and autoantibody screens were negative (although Ma2 was not looked for specifically, which could have been important because of the possibility of testicular cancer). Anti-epileptic drugs were ineffective and, interestingly, the patient developed an allergic skin reaction to carbamazepine, and a low serum sodium, both of which, although seen in other forms of epilepsy, seem to be relatively common among the VGKC-NPLE patients (Vincent *et al.* 2004). VGKC antibodies were not measured initially but, based on the history and MRI changes, intravenous methylprednisolone was given followed by oral steroids and azathioprine, as an additional immunosuppressive and steroid-sparing agent. Although there was substantial improvement, this was not sustained when first steroids and then azathioprine were withdrawn; at this stage, MRI changes were still present and VGKC antibodies were found to be raised (481pM, normal values < 100 pM). Steroids were reintroduced and the patient again improved and is now well controlled on antiepileptic drugs, although a repeat VGKC antibody was (unusually) higher (3031 pM) than the first.

VGKC antibodies are found in a range of different neurological conditions. They were first identified in about 40% of patients with an autoimmune peripheral nerve hyperexcitability syndrome, acquired neuromyotonia. In this condition, the VGKC antibodies are thought to reduce the number of VGKCs in the motor nerve axons and terminals, leading to increased excitability and repetitive bursts of motor nerve activity (Newsom-Davis *et al.* 2003). The patients develop muscle fasciculations, cramps, pseudomyotonia and sometimes weakness. They often complain of excessive sweating (which the patient of Wieser, Kelemen *et al.* 2005 suffered from initially). The condition can be treated with antiepileptic drugs and/or immunosuppression. Some patients are found to have central nervous system involvement with anxiety, sleep problems or memory disturbance, but true seizures are infrequent (Hart *et al.* 2002). Morvan's syndrome is a very rare condition which presents with florid neuromyotonia, central and also autonomic symptoms, such as cardiac arrhythmias, constipation and hypersecretions (Liguori *et al.* 2001); about half the cases have VGKC antibodies (Vincent unpublished observations). By contrast, patients with VGKC-NPLE seldom have neuromuscular or autonomic dysfunction, unless associated with seizures as in the current case report.

There are many questions concerning this newly-defined condition. Does it only occur in adults (all cases defined so far are over 30 years of age)? Are the VGKC antibodies of different fine specificity in patients with neuromyotonia, Morvan's syndrome, and VGKC-NPLE, that might explain the different clinical syndromes? Why, how and where do the antibodies gain access to the central nervous system in VGKC-NPLE and Morvan's syndrome? What is the full clinical spectrum of VGKC-antibody associated neurological disorders.

In addition, this and other cases raise an issue of particular relevance to epilepsy. Pilomotor seizures are a rare form of partial seizures usually originating from the temporal lobe. Temporal lobe epilepsy is relatively common, and usually associated with disturbances of episodic memory. The most common morphological correlate of the epileptogenic region in temporal lobe epilepsy is hippocampal sclerosis which is readily identifiable on appropriate T2 and FLAIR weighted coronal brain MRI sections, angulated perpendicularly to the hippocampal axis, by the two criteria of hippocampal atrophy and signal increase (Von Oertzen *et al.* 2002). In the present interesting case report, the 42-year-old VGKC-NPLE patient is described as developing temporal lobe seizures and – after several months – a hippocampal lesion that is indistinguishable from hippocampal sclerosis. Similar observations have been made in two other cases with similar features (Fauser *et al.* 2005, Soeder *et al.* 2005). Histopathological studies of VGKC-NPLE hippocampi have not yet been performed and it remains a matter of speculation if they indeed show the same pattern of neuronal loss and gliosis as "classical" hippocampal sclerosis. If this proves to be the case, VGKC-ab-associated limbic encephalitis might turn out to be one of the possible causes of this histopathological entity – but it will be important to test for these antibodies early in the disease, since they can fall spontaneously over one to two years (Buckley *et al.* 2001). In the meantime, the following features should make the neurologist think of this potentially reversible form of recent onset temporal lobe epilepsy:

– Disease onset in adult life;
– Subacute development of high seizure frequency,

considerable deficits of episodic memory, or "limbic" neuropsychiatric abnormalities;
– Brain MRI: hyperintense uni- or bilateral signal of temporomedial regions.
In such cases – as exemplified by the case of Wieser, Kelemen *et al.* 2005 – a thorough search for tumour and for paraneoplastic antibodies is indicated (although a paraneoplastic cause cannot be formally excluded without long-term follow up). If these are negative and, especially if high VGKC antibodies are found, consequent immunosuppressive treatments may reduce the severity of epilepsy and the chronic cognitive deficits The main differential diagnosis in the early stage of unilateral VGKC-NPLE is a temporomedial glioma or ganglioglioma (Luyken *et al.* 2003) or status epilepticus-induced hippocampal damage (probably caused by edema; Scott *et al.* 2002, Pohlmann-Eden *et al.* 2004). The exclusion of these is usually possible by the detection of VGKC antibodies, the MRI (especially the MRI course during the first few months after onset of the disease) or – if not otherwise possible – by brain biopsy. □

Acknowledgements. We are grateful to the neurologists and patients who have provided information essential to these studies.

References

Bataller L, Dalmau JO. Paraneoplastic disorders of the central nervous system: update on diagnostic criteria and treatment. *Semin Neurol* 2004; 24: 461-71.

Bien CG, Schulze-Bonhage A, Deckert M, *et al.* Limbic encephalitis not associated with neoplasm as a cause of temporal lobe epilepsy. *Neurology* 2000; 55: 1823-8.

Buckley C, Oger J, Clover L, *et al.* Potassium channel antibodies in two patients with reversible limbic encephalitis. *Ann Neurol* 2001; 50: 73-8.

Fauser S, Talazko J, Wagner K, *et al.* FDG-PET and MRI in potassium channel antibody-associated non-paraneoplastic limbic encephalitis: correlation with clinical course and neuropsychology. *Acta Neurol Scand* 2005; 111: 338-43.

Hart IK, Maddison P, Newsom-Davis J, Vincent A, Mills KR. Phenotypic variants of autoimmune peripheral nerve hyperexcitability. *Brain* 2002; 125: 1887-95.

Liguori R, Vincent A, Clover L, *et al.* Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. *Brain* 2001; 124: 2417-26.

Luyken C, Blumcke I, Fimmers R, *et al.* The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. *Epilepsia* 2003; 44: 822-30.

Newsom-Davis J, Buckley C, Clover L, *et al.* Autoimmune disorders of neuronal potassium channels. *Ann N Y Acad Sci* 2003; 998: 202-10.

Pohlmann-Eden B, Gass A, Peters CN, Wennberg R, Blümcke I. Evolution of MRI changes and development of bilateral hippocampal sclerosis during long lasting generalised status epilepticus. *J Neurol Neurosurg Psychiatry* 2004; 75: 898-900.

Pozo-Rosich P, Clover L, Saiz A, Vincent A, Graus F. Voltage-gated potassium channel antibodies in limbic encephalitis. *Ann Neurol* 2003; 54: 530-3.

Scott RC, Gadian DG, King MD, *et al.* Magnetic resonance imaging findings within 5 days of status epilepticus in childhood. *Brain* 2002; 125: 1951-9.

Soeder BM, Urbach H, Elger CE, Bien CG, Beyenburg S. Limbic encephalitis associated with autoantibodies against voltage-gated potassium channels. *Nervenarzt* 2005; 76: 760-2.

Thieben MJ, Lennon VA, Boeve BF, Aksamit AJ, Keegan M, Vernino S. Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. *Neurology* 2004; 62: 1177-82.

Vincent A, Buckley C, Schott JM, *et al.* Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004; 127: 701-12.

Von Oertzen J, Urbach H, Jungbluth S, *et al.* Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. *J Neurol Neurosurg Psychiatry* 2002; 73: 643-7.

Wieser S, Kelemen A, Barsi P, *et al.* Pilomotor seizures and status in non-paraneoplastic limbic encephalitis. *Epileptic Disord* 2005; 7: 205-12.