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CNS autoimmunity: new findings and pending issues

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During 2011, the area of neuroimmunology has shown an enhanced interest in disorders associated with antibodies against cell-surface or synaptic proteins. This interest is reflected in the plethora of studies that have expanded on the phenotype and treatment of these disorders and the many investigations on new synaptic autoantigens and related syndromes.

The idea that encephalitis could be mediated by antibodies that target synaptic proteins is fairly new. This notion has expanded enormously in the past few years, supporting the clinical impression that encephalitis—or at least some subtypes of the disorder—is not rare, and presents important challenges at both clinical and research levels. In the past 3 years, antibodies against synaptic targets have been characterised or redefined (table). For example, researchers have shown that antibodies against voltage-gated potassium channels (VGKCs) in fact target associated channel proteins—ie, leucine-rich glioma inactivated 1 (LGI1)¹ and contactin-associated protein-like 2 (CASPR2)^{2,3}—rather than the potassium channel itself. In 2011, several studies have contributed to the understanding of how these antibodies might cause neuronal dysfunction, and have identified clinical aspects that could improve diagnosis.

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is the most common type of autoimmune encephalitis. The clinical range of the disease has been described extensively in a recent series of 400 patients.⁴ Encephalitis typically presents with psychosis, followed by seizures, language disintegration, abnormal movements, catatonia, and dysautonomia. This large series confirms that the frequency of ovarian teratoma is highest (58%) in women older than 18 years. Clinical recovery takes place in more than 75% of patients treated with immunotherapy. However, recovery is slow, patients typically need second-line therapy, and relapses arise in 20–25% of them, particularly in those without tumours. An important issue when considering the most appropriate immunotherapy regimen for anti-NMDAR encephalitis is to find out if intrathecal synthesis of NMDAR antibodies is happening. If antibody synthesis is taking place, therapeutic approaches that are effective in peripheral autoimmune disease—such as plasma exchange in myasthenia gravis—might not work. Findings of previous studies, in which NMDAR antibody concentrations were compared in serum and CSF, suggested intrathecal synthesis of antibodies.⁴ Neuropathological analysis of the brains of five patients with anti-NMDAR encephalitis disclosed many infiltrates of plasma cells and plasmablasts in perivascular, interstitial, and Virchow-Robin spaces. The presence of these antibody-secreting cells supports intrathecal synthesis of NMDAR antibodies.⁵ Whether this neuropathological feature is also present in encephalitis mediated by antibodies against other synaptic antigens remains to be elucidated.

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Limbic encephalitis associated with LGI1 antibodies is the second most common autoimmune encephalitis. Anti-LGI1 limbic encephalitis in adults is more predominant in men than women and is not associated with cancer. Hyponatraemia can sometimes be diagnostic for this encephalitis. Three recent studies describe two symptoms^{6–8} that might antedate full-blown limbic encephalitis and, if recognised, could lead to early diagnosis and prevention of irreversible neurological damage. In the first study,⁶ sleep disorders were noted in a group of patients with antibodies to VGKC, without further specification of the target antigen. The study showed that limbic encephalitis associated with anti-VGKCs can present with REM sleep behaviour disorder (as previously recognised) and severe insomnia, which is a well-known symptom of Morvan's syndrome.⁶ Considering that CASPR2 is most usually associated with Morvan's syndrome than limbic encephalitis, a useful step would have been to establish whether CASPR2, rather than LGI1, was the main antigen in the few patients with limbic encephalitis who presented with insomnia. A second symptom that could antedate limbic encephalitis associated with LGI1 antibodies is development of brief (few seconds) frequent episodes (median 50 per day) of abnormal unilateral and bilateral movements of the arms, sometimes the ipsilateral muscles of the face, and more rarely the leg. Video electroencephalography (EEG) has shown^{7,8} the epileptic origin of these myoclonic-like movements which, although described as faciobrachial dystonic seizures,⁷ represent epileptic tonic seizures.⁸ Irrespective of the name, the important issue is that regular EEG with scalp electrodes might not reveal an ictal pattern and the patient might not be treated with antiepileptic drugs. Furthermore, if the symptom and associated LGI1 antibodies are recognised promptly, immunotherapy could potentially prevent progression to limbic encephalitis, which in one study arose after a median delay of 36 days⁷ but could take place after many months.⁹ Further work is needed to ascertain whether early immunotherapy, undertaken as soon as seizures are recognised, effectively prevents development of limbic encephalitis.

In 2010, antibodies to inhibitory γ -aminobutyric acid-B receptor (GABA_BR) were characterised in 15 patients with limbic encephalitis, associated with small-cell lung cancer in five patients or concomitant glutamic acid decarboxylase (GAD) antibodies in three.¹⁰ In a subsequent study,¹¹ anti-GABA_BR antibodies were identified in seven (70%) of ten patients with limbic encephalitis and small-cell lung cancer without Hu or other onconeural antibodies, suggesting that anti-GABA_BR could be the most common antibodies in patients with limbic encephalitis and small-cell lung cancer previously judged seronegative (50% of cases). In the same study,¹¹ anti-GABA_BR were not seen in a series of 77 patients with different syndromes associated with anti-GAD antibodies (stiff-person syndrome, cerebellar ataxia, and epilepsy). By contrast, anti-GABA_BR antibodies were detected in two (20%) of ten patients with limbic encephalitis associated with anti-GAD antibodies, both as a paraneoplastic manifestation of small-cell lung cancer.¹¹ Therefore, these findings do not accord with the idea that anti-GABA_BR antibodies arise frequently in anti-GAD-associated syndromes and are the main cause of symptoms.

Comparable to the discovery of onconeural antibodies at the end of the 20th century, the list of antibodies against extracellular epitopes of synaptic proteins seems far from being closed. For example, antibodies to metabotropic glutamate receptor 5 (mGluR5) have been described in two patients with limbic encephalitis and Hodgkin's disease (sometimes called Ophelia syndrome).¹² Interestingly, mGluR5 shares 85% amino acid sequence homology with mGluR1, and antibodies against mGluR1 have been identified in four patients with autoimmune cerebellar ataxia, two of them with a remote history of Hodgkin's disease.

The discovery that synaptic autoimmunity causes several subtypes of encephalitis and cerebellitis suggests that similar pathogenic mechanisms could operate in subgroups of other prevalent neurological and psychiatric disorders, such as epilepsy or psychosis.

Demonstration that some antibodies have structural or functional effects on target antigens has reinforced the importance of these disorders.¹ For 2012, we envisage an exponential increase of studies from neuropsychiatry and other clinical and basic disciplines, resulting in discovery of new syndromes and autoantigens, mechanisms of disease, and how to provide better treatment.

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Table

Antibodies against cell-surface or synaptic antigens associated with encephalitis

	Syndrome	Cancer	Comments
NMDAR	Encephalitis	Ovarian teratoma (rare in children, present in 58% older than 18 years)	Children, young women; 20% relapses, higher in idiopathic cases
LGI1	Limbic encephalitis	None	Men, hyponatraemia, myoclonic-like faciobrachial, with or without crural movements (tonic seizures)
GABA _B R	Limbic encephalitis	SCLC (70%)	Seizures predominant
AMPA	Limbic encephalitis	SCLC, breast, thymus (60%)	Frequent relapses
CASPR2	Morvan's syndrome	Thymoma (20%)	Unusual in isolated neuromyotonia
GlycineR	PERM	None	Clinical range to be defined

AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. CASPR2=contactin-associated protein-like 2. GABA_BR=γ-aminobutyric acid-B receptor. GlycineR=glycine receptor. LGI1=leucine-rich glioma inactivated 1. NMDAR=N-methyl-D-aspartate receptor. PERM=progressive encephalomyelitis with rigidity and myoclonus. SCLC=small-cell lung cancer.