Autoimmunity Reviews 12 (2013) 678–681

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Developments in autoimmune channelopathies

Angela Vincent *

Neuroimmunology Group, Nuffield Department of Clinical Neurosciences, Level 5/6 John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom

ARTICLE INFO

Article history:
Accepted 27 October 2012
Available online 30 November 2012

Keywords:
Autoantibodies
Autoimmune encephalitis
Demyelination
Devic's disease
Neuromyelitis optica
Limbic encephalitis
Encephalopathy

ABSTRACT

Autoimmune forms of encephalopathy have become a hot topic in neurology. These conditions are now known to be associated with antibodies to neuronal or glial cell surface proteins, such as ion channels, receptors or associated proteins. The most common conditions are a form of limbic encephalitis associated with antibodies to voltage-gated potassium channel complex proteins, and a more complex encephalopathy with antibodies to the NR1 subunit of the N-methyl-D aspartate receptor, a class of glutamate receptor. In addition, a very inflammatory disease of the nervous system, neuromyelitis optica, associated with blindness as well as spinal cord damage, can be distinguished by the presence of antibodies to aquaporin-4, a water channel. Many other antibodies are now being identified, but their frequencies are less clear. Most importantly, these new antibody-mediated diseases are being identified in patients of all ages, and in the majority of cases, the patients improve substantially with immunotherapies.

Contents

1. Introduction

Antibodies binding to proteins that are expressed on the surface of neurons (mainly voltage-gated potassium channel complex (VGKC-complex) proteins, N-methyl-D-aspartate receptors (NMDAR)), astrocytes or myelin (aquaporin-4 (AQP4) and myelin-oligodendrocyte glycoprotein (MOG)) are now being recognised as a likely cause of spontaneous, often monophasic, neurological disorders. Some of these disorders are associated with tumours, but many patients do not have tumours. All can make good recoveries with immunotherapies although recovery may take time. [1]. It is important to appreciate that these cell-surface antibodies are different from those in patients with typical paraneoplastic neurological diseases, in which the antibodies are directed to intracellular antigens (e.g., Hu, Yo, and Ri) and are not thought to be pathogenic.

The number of patients with the new antibodies is also collectively more common than that of those with typical paraneoplastic antibodies. There are also many patients with similar syndromes without the defined antibodies and who are beginning to be treated with immunotherapies on the basis of their subacute onset, magnetic resonance imaging or cerebrospinal fluid evidence of inflammation and lack of evidence for other (e.g., infectious or neoplastic) causes for their illness. [2].

* Tel.: +44 1865 234630.
E-mail address: Angela.vincent@ndcn.ox.ac.uk.

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http://dx.doi.org/10.1016/j.autrev.2012.10.016

2. Limbic encephalitis (LE) with VGKC-complex antibodies (Table 1)

LE typically presents with acute or subacute onset of memory loss, confusion and seizures, with high signal in the mediotemporal lobes on MRI. There may be CSF evidence of inflammation. Many of the patients have antibodies to the VGKC-complex antigens [3] and a smaller proportion with LE have antibodies to AMPAR, $GABA_BR$, GAD or NMDAR (for a review see 1).

VGKCs are potassium channels that modulate neuronal excitability in the central and peripheral nervous system. In situ they are complexed with other proteins including leucine-rich glioma inactivated protein 1 (LGI1) and contactin-associated protein 2 (CASPR2) [4–6]. The VGKC-complex antibodies can be measured by radioimmunoprecipitation of the VGKC-complexes from mammalian brain tissue extracts but are directed to LGI1 or CASPR2 or other components of the complex which have not yet been defined.

In this form of LE, the CSF is often normal, oligoclonal bands are uncommon [3], and the MRI may also be uninformative. There are, however, two particular clues that can help in the recognition of the syndrome. Firstly up to 60% of patients have hyponatraemia at onset which resolves following treatment and up to 40% of the patients have a specific form of seizures which often precede the limbic encephalitis [4]. These 'faciobrachial dystonic' seizures (FBDS) are very brief (a few seconds) but can occur up to 200 times a day, and typically they respond poorly, often with adverse effects, to typical antiepileptic drugs [6] but respond well to immunotherapies. Moreover, identifying them and treating appropriately may prevent the subsequent onset of cognitive problems. Most of these patients also have VGKC-LGI1 antibodies. Patients with LE and VGKC-LGI1 antibodies seldom have tumours, but those with CASPR2 antibodies have a relatively high incidence of thymomas [5].

In general, this condition is treated with intravenous methylprednisone acutely followed by high dose oral steroids, plasma exchange or intravenous immunoglobulins (IvIg), or both. The antibody levels often fall rapidly [3–5], the seizures cease and cognition improves substantially. Nevertheless, hippocampal atrophy is relatively frequent long-term and anterograde memory problems often persist.

Table 1
Different forms of limbic encephalitis.

	Helpful clinical features	Which antibodies?	Tumour associations
Limbic encephalitis Subacute memory loss, psychiatric or behavioural disturbance, seizures MRI typically shows high signal in the medial temporal lobes (MTL) CSF variable but can be pleocytosis, mildly raised protein or oligoclonal bands	May be preceded by facio-brachial dystonic seizures Serum hyponatremia common	VGKC-complex antibodies; commonly directed against LGI1	Tumours uncommon
	Rapidly progressing LE with features of acute psychosis	AMPA receptor (GluR 1/2)	Often paraneoplastic; SCLC, breast, thymoma (70%)
	Seziures as the predominant symptom, usually of temporal lobe onset with secondary generalisation	$GABA_BR$	Often paraneoplastic: SCLC (47%)
	Temporal lobe seizures with less evident cognitive involvement	Glutamic acid decarboxylase	Tumours rare; diabetes

3. Encephalitis with other antibodies

Limbic encephalitis can occur with other antibodies such as those to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR-Abs) or gamma-amino-buyric acid $(GABA)_B$ receptors but these forms are much less common, although they are important because the patients have a high probability of tumours. Despite the tumour association, they usually respond well to immunotherapies, although with a tendency to relapse (for a review see [1]).

Another form of LE that is being recognised is associated with antibodies to glutamic acid decarboxylase (GAD). These patients tend to be young adult females with temporal lobe epilepsy. Although seldom tumour-associated, they are relatively resistant to immunotherapies and antibody titres do not decrease substantially following treatments, contrasting with the fall in VGKC-LGI1 antibodies after similar therapies [7].

4. Encephalitis with NMDAR antibodies (Table 2)

The other main disorder is associated with antibodies to NMDARs which are glutamate-gated ion channels that mediate excitatory neurotransmission in the CNS. These antibodies were first described in a form of limbic encephalitis with ovarian teratomas in young females [for a review see 8] often presenting with behavioural disturbance or psychiatric features, but it became clear that they had a more extensive and complex encephalopathy. Cognitive problems and seizures are present but seldom dominate. Headache and fever are not infrequent at onset and there is often CSF leukocytosis, suggesting a possible infectious aetiology. However, within days, striking and defining features occur. These include dyskinesias (orofacial grimacing, dystonic posturing and choreoathetoid movements), autonomic instability and reduction in consciousness requiring ventilatory support [8]. By this time, the CSF may be normal, but oligoclonal bands may have appeared [9]. NMDAR antibodies are almost invariably present in the CSF as well as the serum, and there is substantial intrathecal synthesis of the NMDAR antibodies. Nevertheless, serum levels are higher in absolute terms, and most commercial assays for the antibodies use serum. A recent review covers the clinical and paraclinical findings in detail [8].

Many patients now, both male and female, are being identified in whom no tumour is ever found [9]. However, even with aggressive immunotherapies, recovery can be slow suggesting the possibility of an occult malignancy, and systematic searches need to be carried out. High dose steroids, plasma exchange and IvIg are used as first line therapy in most patients but many require second line treatments such as rituximab or cyclophosphamide. Even with these, the response can be very slow with weeks or months spent in intensive care [8].

Table 2
Features of NMDAR-antibody encephalitis.

Clinical features	Demographics	Treatment responses
May have prodromal viral-like symptoms but seldom a preceding infection. Neurological presentation with cognitive and behavioural changes Over days to weeks progress to choreoatheroid movement disorders, orofacial dyskinesia, dysautonomia, mutism. MRI normal or mild abnormalities usually outside the medial temporal lobes CSF shows lymphocytic pleocytosis at onset, oligoclonal bands appear over time	Younger adult females and children are most common. But males and females of all ages can be affected.	Removal of ovarian teratoma if present is mandatory Immunotherapies appear to be helpful but improvement can take weeks to months. Substantial recovery can occur eventually

Surprisingly, ultimately most patients make a considerable recovery, with a proportion restored to good health, while others are left with cognitive impairment including amnesia, and relapses. It's not yet clear whether long-term immunosuppression should be used to prevent relapses; these are probably more common in patients who have been inadequately treated at the first episode [9]. A high proportion of patients with NMDAR-antibodies are children, including some who would otherwise be given the diagnosis of encephalitis lethargic [10,11].

5. Morvan's syndrome

This combination of neuromyotonia (muscle fasciculations and cramps), autonomic disturbance and insomnia is rare, but can be misdiagnosed as schizophrenia [12]. The VGKC-complex antibodies are directed most often to CASPR2 but LGI1 antibodies may also be present at lower titres [12]. Morvan's syndrome can present in patients with recurrent or aggressive thymomas, and coexisting myasthenia.

6. Stiff person syndrome (SPS) and progressive encephalomyelopathy with rigidity and myoclonus (PERM)

SPS is a rare disorder with muscle rigidity and spasms affecting the lumbar, thoracic, paraspinal and proximal leg muscles [13]. Typically there are antibodies to glutamic acid decarboxylase (GAD) but in the relatively few patients with a paraneoplastic form of SPS, antibodies to amphiphysin or other onconeural antigens may be present. Many of the patients have type 1 diabetes but the GAD antibodies are typically much higher titre than those found in diabetes alone. Although this is widely thought to be an immune-mediated disease, immunotherapies are not necessarily effective, and most patients require symptomatic treatments such as benzodiazepines and baclofen [13]. SPS is a chronic disease and spontaneous or therapy-induced remission is very uncommon.

Progressive encephalomyelitis with rigidity and myoclonus (PERM) is a variant of SPS in which rigidity and spasms are accompanied by brainstem signs such as oculomotor disturbance and autonomic features [13]. In some patients there is rapid deterioration and death may occur. The CSF may show lymphocytic pleocytosis and oligoclonal bands, but imaging is often uninformative. Antibodies to the glycine receptor alpha1 subunit have now been identified in patients with PERM and these patients appear to respond well to immunotherapies [14–16]. Tumours are uncommon but thymomas have been identified in two patients.

7. Neuromyelitis optica (NMO)

This is a chronic relapsing condition mostly affecting the optic nerves and spinal cord, which can easily be misdiagnosed as multiple sclerosis. Patients present with loss of vision, weakness or sensory disturbance associated with optic nerve inflammation or extensive spinal cord lesions which can be identified on MRI. Classically the patients then improve but relapse subsequently. With each relapse there is progressive disability, and many become wheel-chair bound within five years [17].

The identification of antibodies to aquaporin-4 (AQP4) in up to 80% of patients has made a substantial impact on the diagnosis and of NMO [18] and helped to ensure that the patients are treated earlier and more aggressively in an attempt to prevent further relapses and increasing disability. Treatments are usually given steroids during the relapses, and maintained with azathioprine or other immunosuppression. Antibodies to myelin-oligodendrocyte glycoprotein (MOG) may also be helpful in patients who present with an NMO-like phenotypes [19].

8. Future prospects

It is likely that further antibody-mediated CNS diseases will be identified in the future, and it is also evident that some patients with more common diseases such as idiopathic forms of epilepsy, pyschosis, dementia or movement disorders will have an antibody-mediated condition. At present, the newer cell surface antibodies (LGI1, CASPR2, NMDAR, etc.) are measured by indirect immunofluorescence on cell lines expressing the antigen of interest. This is a sensitive method in the right hands, as recently demonstrated for AQP4 antibodies in a multi-centre study [20], but time-consuming and not widely available. There is a need for better and faster diagnosis which requires development of commercial assays that can be used locally. Finally, although most of the diseases described herein do respond to current immunotherapies, the responses can be slow and the therapies have unwanted side effects. Treatments that target more specifically those B cells or plasma cells that produce the specific antibodies would clearly be preferable.

Take-home messages

- Antibody-mediated central nervous system (CNS) diseases are a new and important area.
- The antibodies bind to neuronal or glial cell surface proteins, such as receptors or channel proteins.
- They cause a range of neurological symptoms involving different areas of the nervous system.
- They can be identified in patients of all ages who often respond clinically to immunotherapies.

Conflicts of interest

A.V. and the Department of Clinical Neurology in Oxford receive royalties and payments for Ab assays. A.V. is the inventor on patent application WO/2010/046716 entitled “Neurological Autoimmune Disorders.” The patent has been licensed to Euroimmun AG for the development of assays for LGI1 and other VGKC-complex Abs. A.V. acts as a paid consultant for Athena Diagnostics, and is employed by Oxford University and University College London. A.V. and S.R.I. may receive royalties for testing of VGKC complex Abs.

Acknowledgements

The work of the Oxford Clinical Neuroimmunology Group receives support from the NIHR Oxford Biomedical Research Centre.

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Raised IL5 in the Th2 – immune response of airways microenvironment in Churg-Strauss syndrome patients

Churg-Strauss syndrome (CSS) is a systemic vasculitis typically characterized by eosinophilia and asthma. This study by Jakiela B et al. **(Rheumatol. 2012;51:1887-93.)** aimed to analyze the local immune response in CSS patients' airways during diverse disease phases. For this purpose, BALF samples were taken by fiberoptic bronchoscopy from 11 patients affected by active CSS, 11 patients during disease remission and 9 controls with bronchial asthma. BALF and blood eosinophilia (> 450 eosinophils/μL) was detected in all active CSS cases ($p < 0.01$). The levels of IL5, CCL17, CCL22 and CCL26 were tested using ELISA while T helper cell related gene expression was measured by real-time PCR array. The results displayed higher expression of STAT6, STAT3, GATA3, IL4, IL5, and IL10 in patients with active CSS than asthmatic controls and also increased STAT5A, CCR4, FoxP3, IL4, IL5 and IL10 transcripts compared to the inactive CSS group. Furthermore, IL4, IL5, IL10 and STAT5A expression was closely correlated with disease activity as measured by the Birmingham Vasculitis Activity Score or BVAS and eosinophilia ($r > 0.6$ in each comparison). The Th2 dominant trascriptome profile of BALF cells in active CSS and the crucial role of IL5 as well as other eosinophil active chemokine secretions such as eotaxin3 by airway cells were deemed lung eosinophilia inducers of the CSS exacerbations. This understanding has allowed the advancement of IL5 and CCL26 as CSS biomarkers as well as anti-IL5 (or chemokine receptor) targeted therapies especially for refractory or relapsing CSS.

Maurizio Rinaldi