Autoimmune channelopathies: new antibody-mediated disorders of the central nervous system

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Abstract

Contrary to established wisdom, there now appear to be antibody-mediated central nervous system (CNS) disorders. Over the last few years, a number of patients have been defined with antibodies to voltage-gated (VGKC) or ligand-gated (NMDAR, GlyR) ion channels or ungated water (AQP4) channels. Some of the disorders improve spontaneously over time, others may be more chronic and relapsing-remitting, but immunotherapies reduce antibody levels and improve clinical outcomes. These are exciting developments that herald a new era of immunotherapy-responsive CNS diseases, and they raise interesting questions regarding the aetiological and pathogenic mechanisms mediating these conditions.

Introduction and context

Autoimmune channelopathies are becoming one of the exciting areas of neurological diseases in clinical practice because, though relatively uncommon (collectively perhaps 20 per million per year), diagnosis of these conditions usually indicates a significant clinical improvement following immunotherapies that reduce autoantibody levels. The field stems from three decades of research into myasthenia gravis and the Lambert-Eaton myasthenic syndrome [1,2]; in these conditions, autoantibodies to muscle nicotinic acetylcholine receptors (AChRs) or voltage-gated calcium channels (P/Q-type), respectively, are the main pathogenic agents and cause destruction and/or downregulation of their targets, leading to neuromuscular junction transmission failure (Table 1) which can be demonstrated in animal models. Newer disorders of peripheral neurotransmission include (a) peripheral nerve hyperexcitability syndromes with antibodies binding to ¹²⁵I-dendrotoxin-labelled *shaker*-type (Kv1) voltage-gated potassium channels (VGKCs) extracted from mammalian cortex [3] and (b) autonomic neuropathies with antibodies to ¹²⁵I-epibatidine-labelled ganglionic nicotinic AChRs [4].

Over the last decade or so, a new family of antibody-associated diseases has emerged that is beginning to overturn previous concepts that regarded the brain as immune-privileged and protected by an impermeable blood-brain barrier. First, glutamate receptor (GluR3) antibodies were present in children with the very rare but devastating form of epilepsy called Rasmussen encephalitis [5], but these findings were not always confirmed in other cohorts of patients [6], and the main pathology is now thought to be cellular rather than antibody-driven [7]. The paradigm shift really began with the finding of very high VGKC antibody levels in patients with limbic encephalitis – which includes seizures, psychological disturbance, memory loss and high signal on magnetic resonance imaging (MRI) in the medial temporal lobes – who responded convincingly to immunotherapies such as plasma exchange (which removes circulating plasma components such as antibodies and replaces them with substitute plasma proteins; see Figure 1) [8-10]. Until then, limbic encephalitis was almost always recognised as ‘paraneoplastic’ (that is, associated with a T cell-mediated immune response to a tumour [11]) and with a poor response to treatments. The VGKC

Table 1. Peripheral nervous system autoimmune channelopathies

	Myasthenia gravis	Lambert-Eaton myasthenic syndrome	Peripheral nerve hyperexcitability syndromes	Autonomic neuropathy
Typical symptoms	Muscle weakness and fatigue	Muscle weakness	Muscle twitching, cramps, sweating	Hypotension, constipation, papillary abnormalities, sicca syndrome (dry eyes and mouth)
Target	Muscle nicotinic AChR	VGCC P/Q-type	Dendrotoxin-binding VGKC Kv1.1, 1.2, 1.6 complexes extracted from mammalian cortex	Ganglionic nicotinic AChR (alpha 3)
Tumour association or other pathology	Thymoma, thymic hyperplasia or idiopathic	Small-cell lung cancer common in adults (about 50%)	Thymoma, small-cell lung cancer in about 20%	Small-cell lung cancer or other tumours uncommon
Main pathogenic mechanism	Complement-mediated damage, increased AChR degradation, some direct block of AChR function	Increased VGCC degradation, no evidence of complement-mediated damage	Probably increased VGKC degradation with no apparent complement-mediated damage	Direct block of function and increased degradation
Disease course	Usually chronic, rare spontaneous remissions	Usually chronic, may improve with tumour removal	Can be chronic or monophasic, postinfectious or postallergic	Monophasic or chronic, postinfectious

AChR, acetylcholine receptor; VGCC, voltage-gated calcium channel; VGKC, voltage-gated potassium channel.

antibody-associated central nervous system (CNS) phenotypes are now recognised widely, are usually nonparaneoplastic and include patients with some form of epilepsy [12,13] or Morvan syndrome [14]. However, despite colocalisation with antibodies to different Kv1 subtypes on brain tissue and in transfected HeLa cells expressing different Kv1 subtypes, the specificity of the antibodies is not altogether clear [15]; a new finding is that many of the antibodies bind not to the Kv1s themselves but to other juxtaparanodal proteins, such as contactin-associated protein 2 (Caspr2), that form part of the VGKC complex after extraction from brain tissue. Antibodies to Caspr2 are particularly frequent in patients with Morvan syndrome (S Irani, S Alexander, A Vincent, unpublished data).

Major recent advances

Some patients presenting with symptoms of cognitive problems, psychiatric disturbance or epilepsy were found to have antibodies that bound to the proximal dendrites of the hippocampal neuropil [16], distinct from the binding of VGKC antibodies more distally [8,16]; many of these antibodies were subsequently shown to be directed against *N*-methyl-D-aspartate receptors (NMDARs) (NR1/NR2B) [17], with NR1 as the main target [18]. Most of these patients progressed to a more complex phenotype with movement disorders or catatonias, mutism, sleep disturbance and autonomic dysfunction [17,18]. At first, the syndrome was associated with ovarian teratomas in young women, but in these cases, unlike the traditional paraneoplastic disorders [11], the conditions improved when the tumour was removed and immunotherapies given [17]. Now many nonparaneoplastic cases are being identified and the phenotype is widening to include both male and female adults, teenagers, and even young children [18,19]

(S Irani, A Vincent, unpublished data). These NMDAR antibodies may be different from those measured by binding to linear peptide sequences of NR2A/NR2B seen in neuropsychiatric patients [20] and have the potential to be pathogenic since they target extracellular domains on NR1/NR2B transfected human embryonic kidney cells and substantially reduce the expression of these subunits in primary cultures of hippocampal neurons [18]. The NMDAR antibodies were most easily detected in the cerebrospinal fluid (CSF) (at 1:10) compared with serum (at 1:400), and there is substantial intrathecal synthesis of the specific antibody [18] (Table 2); nevertheless, in absolute terms, serum levels are higher than CSF levels. Recently, antibodies to AMPAR (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) GluR1/GluR2 were identified in another form of limbic encephalitis that was mostly cancer-related. These patients also showed treatment responses but tended to relapse [21].

Meanwhile, a completely different condition was found to be associated with antibodies to a water channel. Neuromyelitis optica (NMO, or Devic disease) has usually been considered to be part of the spectrum of inflammatory demyelinating disorders, of which multiple sclerosis is the best known. However, NMO is a distinct inflammatory condition of the optic nerves which involves severe visual failure and inflammation of the spinal cord causing longitudinally extensive transverse myelitis (at least three spinal cord segments with high signal on MRI), that leads to para- or tetraparesis, sensory deficits and bladder disturbances. Patients show variable recovery with immunomodulatory treatments but accumulate disability over time, and mortality is high if the disease is not appropriately treated [22]. In 2004, antibodies binding around small vessels, under

Figure 1. Aspects of the new autoimmune channelopathies

(a)
VGKC-Ab limbic encephalitis

High signal in hippocampal regions

Antibodies to VGKC identified by immunoprecipitation of ^{125}I -alpha-dendrotoxin-VGKCs in patient with limbic encephalitis **(b)**
NMDAR-Ab encephalitis

Patient's serum IgG (1:40) binding to NR1/NR2b/EGFP transfected cells

Patient's serum IgG (1:250) binding to 17 day live RAT hippocampal neurons

(c)
Neuromyelitis optica

Patient's serum IgG (1:20) binding to AQP4-EGFP expressing cells

Antibodies to AQP4 identified by immunoprecipitation of EGFP-tagged AQP4

(a) Above, magnetic resonance imaging evidence of hippocampal inflammation and swelling (arrows) in a patient with voltage-gated potassium channel (VGKC) antibodies. Below, graph of dramatic decrease in the antibodies after successful treatment in another patient. **(b)** In the images above, antibodies (red anti-human IgG) bind to human embryonic kidney cells expressing *N*-methyl-D-aspartate receptors (NMDARs) (coexpressed with enhanced green fluorescent protein [EGFP]; some cells express EGFP without detectable NMDARs) in a young girl who developed an encephalopathy with mutism and catatonia and made a complete recovery after immunotherapies (see [32] and the video available online). In the image below, NMDAR antibodies (green) bind to unpermeabilised hippocampal neurons in culture, which were then fixed, permeabilised and stained for synaptophysin (blue) and NR1 (red) (the binding of antibodies to the live cell surface does not colocalise well with the intracellular NR1 which appears throughout the neuron). **(c)** In the images above, antibodies to aquaporin-4 (AQP4) in a patient with neuromyelitis optica (NMO) bind to cells transfected with AQP4-EGFP. In this case, the directly tagged AQP4-EGFP can also be solubilised from the cells and, as seen in the graph, the antibodies can be measured quantitatively by counting the fluorescence in the immunoprecipitates [34]. In these assays, sera from healthy individuals and from patients with unrelated diseases are negative. Ab, antibody; NDs, neurological diseases. Images courtesy of S Irani, L Zuliani, MI Leite, P Waters and B Lang.

the pia and in Virchow-Robin spaces were defined by immunofluorescence [23], and the target was subsequently identified as aquaporin-4 (AQP4), the only water channel expressed strongly in the brain (and also in kidney and stomach) [24]. Antibodies to AQP4 bind to the astrocyte endfeet that abut CNS blood vessels and are thought to be important contributors to the integrity of the blood-brain barrier. The antibodies lead to substantial loss of surface AQP4 by internalisation and activate complement with formation of the membrane attack complex, leading to cellular damage [25]. They

also reduce astrocyte expression of excitatory amino acid transporter 2 (EAAT2) with reduced reuptake of glutamate [26] and hence potential excitotoxic damage. Interestingly, it seems that AQP4 and EAAT2 are part of a macromolecular complex [25]. Whether these changes alone lead to the substantial inflammatory infiltrates, areas of demyelination, loss of AQP4 and sometimes necrosis that are found in lesions [27,28] is not yet clear, but increases in antibody levels are associated with clinical relapses, and AQP4 antibodies decrease in parallel with clinical improvement after

Table 2. Central nervous system autoimmune channelopathies

Examples	VGKC-Ab-limbic encephalitis	NMDAR-Ab encephalitis	AMPA-Ab encephalitis	Neuromyelitis optica	Glycine receptor antibody-associated disorder
Typical symptoms	Memory loss, seizures, psychiatric or psychological disturbance	Psychosis, bizarre behaviours, mutism, catatonia, movement disorders, hypothalamic dysfunction	Memory loss, confusion, seizures, agitation Sometimes downbeat nystagmus	Optic nerve inflammation with visual loss Spinal cord inflammation leading to paralysis, loss of sensation	Excessive startle, rigidity, myoclonic jerks
Target	Dendrotoxin-binding CNS VGKC (Kv1.1, 1.2, 1.6)	NMDAR, probably principally NR1	GluR1/2 dimers, epitopes on GluR1 or GluR2	AQP4	GlyR alpha 1a
Tumour association or other pathology	Thymoma	Ovarian teratomas in young women	Breast cancer, small-cell lung cancer, thymoma	Very rare	Not common
Main pathogenic mechanism	Increased internalisation	Increased internalisation Complement-mediated mechanisms not explored	Increased internalisation Complement-mediated mechanisms not explored	Complement-mediated mechanisms important Increased internalisation of AQP4 and increased turnover of EAAT1 in astrocytes	No evidence to date
Disease course	Self-limiting in most cases Immunotherapies hasten recovery and reduce long-term disability	Tumour cases do well after removal and treatments Nontumour cases may do less well and have a tendency to relapse	Responds to immunotherapies but has tendency to relapse	Historically a severe relapsing remitting disease with bad prognosis May do better with intensive immunotherapies	First patient described returned to work after intense immunotherapies
Intrathecal synthesis of specific antibody	1.5 to 40, variable but sometimes high	10 to 30, High	High	Little or none (<1.5)	1.5 to >50, variable but sometimes very high
Normal <1.5 ^a					

^aThis is calculated as (cerebrospinal fluid [CSF] titre of specific antibody/concentration of CSF IgG) / (serum titre of specific antibody/concentration of serum IgG). Values above 1.5 are usually considered indicative of synthesis within the CSF compartment rather than the result of passive leakage. The values given are based on our unpublished experience and from data presented in [18,21]. It needs to be appreciated that the normal serum IgG concentration is about 400 times higher than the normal CSF IgG concentration. Therefore, even in the presence of substantial intrathecal synthesis, the serum concentration of specific antibody will be higher than the CSF concentration. Ab, antibody; AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AQP4, aquaporin-4; CNS, central nervous system; EAAT1, excitatory amino acid transporter 2; GluR, glutamate receptor; GlyR, glycine receptor; NMDAR, N-methyl-D-aspartate receptor; VGKC, voltage-gated potassium channel.

immunosuppression [29]; overall, there seems little doubt that the antibodies contribute to the pathology [22].

Finally, another receptor target is emerging in patients with rare spinal and brain stem syndromes. In one adult male who presented with excessive startle and progressive encephalomyelitis with rigidity and myoclonus (PERM), a form of stiff person syndrome, antibodies to glycine receptor alpha 1 pentamers (GlyR1s) were identified [30]. The GlyR1 antibodies disappeared with treatment and the patient made a substantial clinical recovery. These antibodies are now being found in other patients with related disorders (A Vincent, I Leite, H-M Meinck, unpublished data).

Future directions

There are some important lessons that arise out of these exciting advances. Once defined, the antibodies are best identified by binding to native proteins extracted from mammalian tissue in mild detergents (VGKCs), or better still to the native protein expressed in an appropriate

human cell line (NMDARs, AMPARs, AQP4, GlyR), rather than to short peptides that do not represent the native conformation of the target antigen. The protein must be expressed on the cell surface and the cells should be unpermeabilised so that only cell surface-binding antibodies are detected (this ensures that they are potentially pathogenic, in contrast to those antibodies to intracellular components found in paraneoplastic disorders). Clustering of the antigen by use of intracellular scaffolding proteins can increase sensitivity and specificity as recently demonstrated for AChR antibodies [31]. In addition, the antibodies should be shown to bind to the extracellular surface of neurons or astrocytes cultured from mammalian tissues and to induce relevant biological changes in such cultures. In the future, one hopes that these studies will extend to examining the effects of these recently discovered antibodies on neuronal activity in brain slices *in vitro* and in animal models *in vivo*.

Considering the diversity of ion channels and receptors in the nervous system, it would be strange if there were no other autoimmune channelopathies to be discovered,

diagnosed and treated. Until now, most of the target channels have been identified by a candidate approach, but if the target for binding to the cultured cells is sufficiently abundant, as appears to be the case for AMPARs [21], it is possible to immunoprecipitate the target using the relatively pure CSF IgG from the patients [21]; this technique has potential for identifying new targets in the future. Even the total patient plasma IgG can be used to identify antigens by this approach when a suitable cell preparation or cell line is identified [32].

In each of these diseases, CSF antibodies are found, and there is often evidence of high concentrations of CSF-specific antibody relative to CSF IgG concentration when compared with similar measurements in serum ('intrathecal synthesis', Table 2), but the absolute concentration of antibody is still higher in serum than in CSF. A major question, therefore, is whether the antibodies that are pathogenic come directly from the blood into the CNS parenchyma via a 'leaky' or damaged blood-brain barrier or whether the disorders require the presence of specific antibodies in the CSF. The latter could be the result of passive diffusion across the choroid plexus and/or intrathecal synthesis by B cells that have gained entry to the CNS and synthesise the antibodies in the intrathecal compartment. These considerations are not purely academic. Does intrathecal synthesis decrease with current systemic treatments and increase if the patient relapses? Do immune responses ever begin in the CNS and remain undetectable in the serum? And importantly, should drugs and therapies be specifically targeted to the CSF compartment rather than to the systemic immune system? These are just some of the questions that arise from the identification of these new autoimmune disorders, and the answers will likely come from both focused human studies and animal models.

Abbreviations

AChR, acetylcholine receptor; AMPAR, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AQP4, aquaporin-4; Caspr2, contactin-associated protein 2; CNS, central nervous system; CSF, cerebrospinal fluid; EAAT2, excitatory amino acid transporter 2; GluR, glutamate receptor; GlyR1, glycine receptor alpha 1 pentamer; MRI, magnetic resonance imaging; PERM, progressive encephalomyelitis with rigidity and myoclonus; NMDAR, N-methyl-D-aspartate receptor; NMO, Neuromyelitis optica; VGKC, voltage-gated potassium channel.

Competing interests

The author and her department receive royalties and income for antibody immunoassays.

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