Diseases Associated with Antibodies to Voltage-Gated Potassium Channels

Potassium channelopathies are caused either by autoantibodies directed against the potassium channels or by mutations in their encoding genes. Benign neonatal febrile convulsions[1] and hereditary deafness syndromes[2] are associated with mutations in the KCNQ family of voltage-gated potassium channels (VGKCs) whereas neuromyotonia,[3] episodic ataxia[4] and intractable epilepsy[5] are associated with mutations in the Shaker family of VGKCs. The phenotype of neurological disorders occurring in patients with autoantibodies against subunits of Shaker VGKCs is rapidly expanding and will be the focus of this review.

Shaker VGKCs are composed of four transmembrane α subunits associated with four intracellular β subunits (Figure 1). The α subunits (Kv 1.1 – Kv 1.7) can combine homotypically or heterotypically to generate an enormous diversity of functional VGKCs which are widely distributed throughout the peripheral and central nervous system, and are important in controlling membrane excitability. VGKC antibodies impair channel function resulting in clinical syndromes of hyperexcitability in the peripheral and central nervous systems.

Syndromes of peripheral nervous system (PNS) hyperexcitability

The spectrum of disorders of peripheral nerve hyperexcitability ranges from the mild cramp fasciculation syndrome (CFS) to the more disabling neuromyotonia (NMT). Patients with neuromyotonia usually present with muscle twitching and cramps often associated with increased sweating.[6] They may have sensory symptoms, especially dysaesthesia without numbness, which is probably a consequence of hyperexcitability of the sensory nerves.[7] Rarely, hand posturing resembling dystonia can be present.[8] On examination there is visible myokymia and muscle cramps often accompanied by muscle hypertrophy. Pseudomyotonia (but rarely percussion myotonia), pseudotetany, and mild distal sensory loss may occur.

Electromyography reveals fibrillations and fasciculation potentials at rest and the characteristic multiple responses to a single stimulus. The serum creatine kinase level may be mildly elevated, and VGKC antibodies can be detected by radioimmunoprecipitation in approximately 40% of patients.[6] The clinical syndrome is indistinguishable between patients with and without antibodies, and there appears to be no correlation between antibody titre and clinical or EMG severity.

Some patients can tolerate their symptoms without treatment once reassured as to the underlying cause, whilst others attain symptomatic relief from phenytoin, carbamazepine or lamotrigine. In the minority with persistent disabling symptoms, immunomodulatory therapies can produce clinical and electrophysiological improvement.[9]

Pathophysiology of PNS hyperexcitability

An immune-mediated pathology underlying NMT is suggested by the clinical response to immunomodulatory therapies, the association with other autoimmune diseases, and the observation that 15% of patients have a thymoma.[6] Moreover there is experimental evidence indicating that the antibodies themselves are pathogenic. Passive transfer of IgG from NMT patients to mice results in increased quantal content at the motor endplates,[10] and application of NMT sera to a neuroblastoma cell line (Nb-1) causes reduction in amplitude of VGKC currents.[11]

Syndromes of central nervous system (CNS) hyperexcitability

Limbic Encephalitis

VGKC antibodies have recently been identified in the serum of patients presenting with non-paraneoplastic limbic encephalitis.[12] VGKC-associated LE appears to be at least as common as paraneoplastic limbic encephalitis associated with neuronal antibodies (table 1), is more common in men and has a mean age at diagnosis of 65 years. The typical presentation is with sub-acute onset of short-term memory loss, disorientation, confusion and seizures. Agitation, sleep disturbance, hallucinations and paranoid ideation can be prominent.[13] Interestingly there is usually no clinical or electrophysiological evidence of PNS hyperexcitability. Investigations reveal hyponatraemia with urine and serum osmolarities consistent with the syndrome of inappropriate ADH secretion. VGKC antibody titres are usually greater than 400 pM and frequently above 1000 pM (normal < 100 pM). EEG reveals slowing of the background rhythms and often demonstrates an epileptogenic focus. MRI is abnormal in 75% with high signal often restricted to the hippocampi and best visualised on coronal images attained with T2 weighted FLAIR sequence (Figure 2). Neuropsychology confirms disorientation and severe impairment in verbal and visual anterograde and retrograde memory, often accompanied by confabulation.

The optimum treatment regime remains unclear but acute therapy with plasma exchange or intravenous immunoglobulin, accompanied by high dose alternate day oral steroids, often results in striking clinical improvement. The disorientation, seizures and hyponatraemia respond initially, followed by improvement in memory.

Dr Camilla Buckley is Clinical Lecturer in Neurology at the University of Oxford and Specialist Registrar at the Radcliffe Infirmary. Her research interest is autoimmune neurological disorders particularly antibody-mediated diseases of the central nervous system.

Correspondence to:
Dr Camilla Buckley,
Lecturer in Clinical Neurology,
Department of Clinical Neurology,
Radcliffe Infirmary,
Woodstock Road,
Oxford OX2 6HE, UK.
Tel: 01865 224172,
Email: camilla.buckley@clinical-neurology.oxford.ac.uk

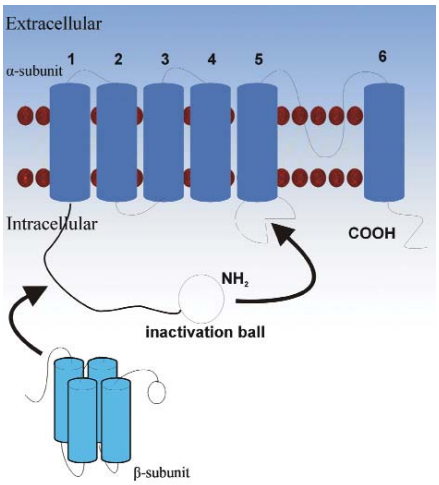

Figure 1: Cartoon showing the basic structure of the alpha and beta subunits of the voltage-gated potassium channel. Each alpha subunit is composed of six transmembrane domains with the "pore" occurring between the fifth and sixth domains, and the fourth domain serving as the voltage sensor due to its high positive charge. Each beta subunit is composed of four domains without any membrane-spanning sequences and they bind to the alpha subunits and determine the electrophysiological properties of the channel.

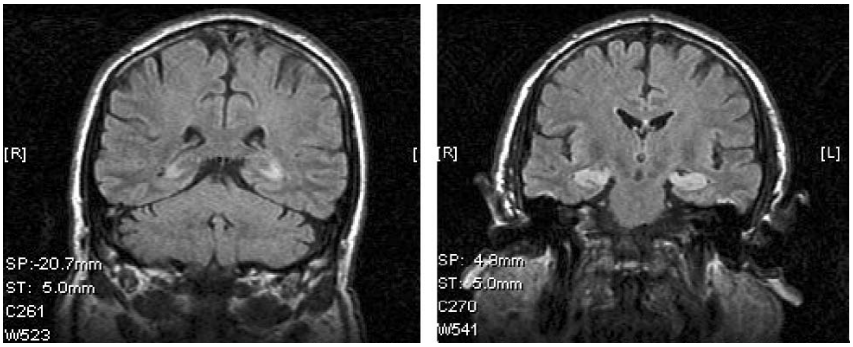

Figure 2: Coronal T2 weighted FLAIR magnetic resonance image of the brain showing the classical appearance of bilateral hippocampal high signal in a patient with VGKC-associated LE.

After several months anti-convulsant and immunomodulatory therapies can be reduced and stopped with many patients remaining free of seizures and regaining near normal memory function. This clinical improvement is accompanied in most cases by improvement on neuropsychological scores and rapid reduction in antibody titre, and in some cases by resolution of MRI changes.

Morvan's Fibrillary Chorea (MFC)

Patients with florid neuromyotonia associated with memory disturbance, disorientation, disordered sleep and autonomic dysfunction with sweating and cardiac arrhythmias were first described by Morvan over 100 years ago. Recently serum VGKC antibodies and a clinical response to immunomodulatory therapy have been described in a few patients with this rare condition.[14]

Pathophysiology of CNS hyperexcitability

In contrast to paraneoplastic LE where neuronal antibodies are probably markers of cell mediated immunopathology,[15] VGKC antibodies may be pathogenic: VGKC subtypes recognised by patients' antibodies are expressed in the CNS (including the hippocampus) as transmembrane proteins that would potentially be accessible to circulating antibodies; memory dysfunction and seizures can occur in Kv1.1 knock out mice[16] and in patients with inherited mutations in the Kv1.1 gene[5]; and there is often a striking temporal correlation between the appearance and disappearance of VGKC antibodies and the development and subsequent resolution of the clinical syndrome[12, 13]. Direct evidence of pathogenicity from passive and active immunisation experiments is awaited.

The factors determining the phenotype of disease in an individual patient remain unknown but are likely to include the exact composition of channels in the PNS versus the CNS, the relative affinities of antibodies from different patients for individual subunits, and variations in blood brain barrier permeability.

The clinical phenotypes associated with VGKC antibodies continue to expand, and now include patients with slower presentations of more restricted symptoms including isolated memory loss, or intractable temporal lobe seizures, who also appear to respond well to immunomodulatory therapies. Irrespective of whether the antibodies are pathogenic their identification is important as it suggests novel therapeutic options with associated improved clinical outcomes.

References

1. Singh NA, Charlier C, Stauffer D, DuPont BR, Leach RJ, Melis R, et al. *A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns.* Nat Genet 1998;18(1):25-9.
2. Neyroud N, Tesson F, Denjoy I, Leibovici M, Donger C, Barhanin J, et al. *A novel mutation in the potassium channel gene KVLQT1 causes the Jervell and Lange-Nielsen cardio auditory syndrome.* Nat Genet 1997;15(2):186-9.
3. Eunson LH, Rea R, Zuberi SM, Youroukos S, Panayiotopoulos CP, Liguori R, et al. *Clinical, genetic, and expression studies of mutations in the potassium channel gene KCNA1 reveal new phenotypic variability.* Ann Neurol 2000;48(4):647-56.
4. Browne DL, Gancher ST, Nutt JG, Brunt ER, Smith EA, Kramer P, et al. *Episodic ataxia/myokymia syndrome is associated with point mutations in the human potassium channel gene, KCNA1.* Nat Genet 1994;8(2):136-40.
5. Zuberi SM, Eunson LH, Spauschus A, De Silva R, Tolmie J, Wood NW, et al. *A novel mutation in the human voltage-gated potassium channel gene (Kv1.1) associates with episodic ataxia type 1 and sometimes with partial epilepsy.* Brain 1999;122(Pt 5):817-25.
6. Hart IK, Maddison P, Newsom-Davis J, Vincent A, Mills KR. *Phenotypic variants of autoimmune peripheral nerve hyperexcitability.* Brain 2002;125(Pt 8):1887-95.
7. Lance JW, Burke D, Pollard J. *Hyperexcitability of motor and sensory neurons in neuromyotonia.* Ann Neurol 1979;5(6):523-32.
8. Tuite PJ, Navarette C, Bril V, Lang AE. *Idiopathic generalized myokymia (Isaacs' syndrome) with hand posturing resembling dystonia.* Mov Disord 1996;11(4):448-9.
9. Sinha S, Newsom-Davis J, Mills K, Byrne N, Lang B, Vincent A. *Autoimmune aetiology for acquired neuromyotonia (Isaacs' syndrome).* Lancet 1991;338(8759):75-7.
10. Shillito P, Molenaar PC, Vincent A, Leys K, Zheng W, van den Berg RJ, et al. *Acquired neuromyotonia: evidence for autoantibodies directed against K+ channels of peripheral nerves.* Ann Neurol 1995;38(5):714-22.
11. Arimura K, Watanabe O, Kitajima I, Suehara M, Minato S, Sonoda Y, et al. *Antibodies to potassium channels of PC12 in serum of Isaacs' syndrome: Western blot and immunohistochemical studies.* Muscle Nerve 1997;20(3):299-305.
12. Buckley C, Oger J, Clover L, Tuzun E, Carpenter K, Jackson M, et al. *Potassium channel antibodies in two patients with reversible limbic encephalitis.* Ann Neurol 2001;50(1):73-8.
13. Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N, et al. *Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis.* Brain 2004;127(Pt 3):701-12.
14. Liguori R, Vincent A, Clover L, Avoni P, Plazzi G, Cortelli P, et al. *Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels.* Brain 2001;124(Pt 12):2417-26.
15. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. *Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients.* Brain 2000;123(Pt 7):1481-94.
16. Smart SL, Lopantsev V, Zhang CL, Robbins CA, Wang H, Chiu SY, et al. *Deletion of the K(V)1.1 potassium channel causes epilepsy in mice.* Neuron 1998;20(4):809-19.

Table 1: Comparison of the main clinical features in patients with limbic encephalitis (LE) and VGKC antibodies and patients with paraneoplastic LE and anti-neuronal antibodies

	VGKC antibodies	*Neuronal antibodies (Hu, Ma2, CV2, CRMP5)*
Location of antigen	*Transmembrane*	*Intracellular*
Regional specificity of antibody staining	*Yes; mainly hippocampus and cerebellum*	*None; any part of neuraxis*
CSF abnormalities	*Rare*	*Pleocytosis, raised protein*
Hyponatraemia	*Usual*	*Rare*
Tumour Association	*Rare (occasional thymoma)*	*Usual (SCLC, thymoma, testicular)*
Hyperintensity on T2 Weighted FLAIR MRI	*Often restricted to hippocampi*	*Several limbic areas and may extend to brainstem*
Response to treatment	*Frequent. Antibody titre decreases in months*	*Rare (except young men with Ma2). Antibodies remain detectable*
Clinical Course	*Relapses may occur and are treatable*	*Progressive until stabilisation or death*

SCLC: small cell lung cancer, CSF cerebrospinal fluid

Table 2: Characteristic clinical findings in patients with antibodies against voltage-gated potassium channels (VGKC)

	Cramp Fasciculation syndrome	*Neuromyotonia*	*Morvan's syndrome*	*Limbic Encephalitis*
Muscle twitching and cramps	++	+++	++	+/-
Neuromytonic discharges on EMG	-	++	++	+/-
Increased sweating	-	++	++	+/-
Additional autonomic features	-	-	++	-
Agitation	-	+/-	++	+++
Seizures	-	-	-	+++
Short term memory loss	-	-	+	+++