Autoimmune pain

An emerging concept

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Neurology® 2012;79:1080–1081

Autoantibodies to the voltage-gated potassium channel (VGKC) complex have been implicated in a number of autoimmune neurologic conditions, including limbic encephalitis, neuromyotonia, and Morvan syndrome (neuromyotonia, insomnia, and autonomic dysfunction).[1,2] Although these antibodies are measured by radioimmunoprecipitation of brain tissue extracts labeled with ^{125}I-α-dendrotoxin (a snake toxin that binds various VGKC subtypes), it is now clear that many are directed against the VGKC-complex proteins, principally leucine-rich glioma-inactivated 1 protein (LGI1) and contactin associated protein-like 2 (CASPR2).[3,4] Although pain, often neuropathic, has been reported previously in some VGKC-complex antibody positive patients, particularly those with CASPR2 antibodies,[2,3] the report in this issue of *Neurology*® suggests that pain is common and often chronic in these patients.[5]

The medical records of 316 VGKC-complex antibody neurology patients were evaluated at the Mayo Clinic. Pain was present in 50% (159), a higher percentage than found in patients in the study with other autoantibodies (9%); pain was the sole symptom in 45/159 patients. In patients with follow-up data, the pain became chronic, requiring multiple analgesics. Importantly, 80% of 16 antibody-positive patients (despite highly variable titers and other clinical features in 15/16) had improvement in their pain with immunotherapies.

The VGKC-antibody titers were often low (0.02–0.1 nM [20–100 pM]). Antibodies to the VGKC-complex proteins LGI1 or CASPR2 were present in 89/316 overall (28%), but CASPR2 antibodies were more common in patients with pain (n = 25, 16%) than those without pain (n = 11, 7%), consistent with earlier reports.[3] Since 70% of the VGKC-complex antibodies were not associated with detectable antibodies to these antigens, it is possible that pain is associated with antibodies to another, so-far undefined, antigenic target within the VGKC-complex; previous work indicates[3] that not all the VGKC-complex antigens have yet been defined.

The pain descriptors included allodynia, paraesthesia, lancinating, and burning pain. Pain most commonly affected the extremities but in some cases the whole body or the head and face. The patients were more likely to have features of neuropathy (often with minor distal sensory loss) or peripheral nerve hyperexcitability (cramp, myokymia, and fasciculation) than those patients without pain, but patients with pain were less likely to have manifestations of cortical dysfunction (cognitive impairment and seizures). The authors suggest that the latter could reflect lack of verbalization of pain, but it is also possible that patients with cortical dysfunction have a different spectrum of VGKC-complex antibodies.

Are these antibodies causative—the treatment responses suggest that they could be—and what are the potential mechanisms by which VGKC-complex antibodies generate chronic pain? In many of the patients, structural and functional measures did not provide evidence of neural injury, suggesting that the pain is not simply a maladaptive response to injury, as may be seen following traumatic nerve injury. It is more likely that VGKC-complex antibodies lead to enhanced excitability of the somatosensory system. VGKCs are important determinants of neuronal excitability, and antibodies to LGI1 and CASPR2 may modulate nociceptive processing in a number of ways. CASPR2 is an adhesion molecule that forms a complex with Kv1.1 and 1.2 in the juxtaparanodal region of the node of Ranvier. VGKCs modulate internodal resting potential, although CASPR2 knockout animals with dispersed VGKCs do not demonstrate peripheral nerve hyperexcitability,[6] possibly due to compensatory changes. However, a number of clinical features indicate C-fiber dysfunction in the Mayo patients, including burning pain and heat hyperalgesia, suggesting that the pathogenic

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Study funding: D.L.H.B. is a Wellcome Trust senior research fellow in clinical science and member of the London Pain Consortium. Work in A.V.'s group is supported by the NIHR Oxford Biomedical Research Centre.

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effects of the antibodies are not restricted to the node of Ranvier, and could be operating on the soma of C-fiber nociceptors that express VGKC currents,[7] blockade of which enhances neuronal excitability. In addition, synaptic plasticity is a key substrate for pain hypersensitivity and is a further potential target of these antibodies: it is possible that binding to LGI1 complexed with Kv1.1 at presynaptic nerve terminals modulates the inactivation kinetics of these channels[8] such that LGI1 antibodies lead to central sensitization.

Should we be testing patients with chronic pain for VGKC-complex antibodies and if so, which patients? Symptoms and signs of peripheral nerve excitability, autonomic dysfunction, and hyperhidrosis, irrespective of pain symptoms, suggest a diagnosis of neuromyotonia, or Morvan syndrome if accompanied by insomnia,[2] and should trigger testing for VGKC-complex antibodies. The more problematic issue is those patients whose sole complaint is pain without any additional abnormalities. Larger focused studies and more detailed pain phenotyping will be required to determine the true prevalence of VGKC-complex antibodies in chronic pain cohorts, but unfortunately, apart from 6% with an initial diagnosis of fibromyalgia, the present report does not suggest any potential subgroups that would be prime subjects for further study. On a cautionary note, the Mayo group recently identified VGKC antibodies (often very high titer) and other antibodies in patients with painful neuropathies and mice undergoing exposure to porcine brain material.[9] This suggests that VGKCs/VGKC-complexes are highly immunogenic, but also implies that some of the lower titers they report here may be merely part of a wider autoimmune reaction.

Are these findings relevant to other, well-defined, pain syndromes? Complex regional pain syndrome (CRPS) is a chronic pain syndrome, not seen in this study, usually affecting 1 extremity with autonomic and trophic features. Recently reported patients with CRPS had antibodies to the β2 adrenergic receptor and muscarinic-2 receptor[10] and a small randomized controlled trial of IV immunoglobulin reported encouraging results.[11] We may, therefore, be entering an exciting phase in which autoantibodies to neural antigens are recognized as having a role in the etiology of a number of hitherto poorly understood chronic pain states, opening new avenues for treatment.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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