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IMMUNOTHERAPY-RESPONSIVE PAIN IN AN ABATTOIR WORKER WITH FLUCTUATING POTASSIUM CHANNEL-COMPLEX IgG

In late 2007, a neurologic disorder was identified in the midwestern United States among swine abattoir workers who were exposed to aerosolized brain tissue.^{1,2} All patients reported positive sensory symptoms with pain. Neurologic signs and electrophysiologic testing abnormalities were limited and compatible with a sensory-predominant painful polyradiculoneuropathy.¹ Serologic analysis revealed an unusual profile of neural-specific autoantibodies.^{1,3} Here we describe an early presenting case from this outbreak who was followed longitudinally with pain-predominant symptomatology, a newly recognized manifestation of voltage-gated potassium channel (VGKC)-complex autoimmunity.⁴ In the course of IV immune globulin therapy, the patient's pain symptoms paralleled fluctuating levels of VGKC-complex autoantibodies.

Case report. A middle-aged woman presented in February 2007 with severe aches and lancinating pain in the lower extremities, which was worse on the left and precluded ambulation.¹ Muscle power was limited by pain, as assessed by manual testing, but was judged minimally reduced; cramps and fasciculations were noted. Reflexes were reduced in the upper and lower extremities. Sensory testing revealed distal extremity hyperalgesia. The pain spread to involve trunk and upper extremities, further interfering with routine activities. Nerve conduction abnormalities were limited and characteristic of those found in other abattoir employee patients: prolonged distal motor latencies and absent F-wave responses.¹ Sural nerve biopsy findings showed normal myelinated fiber density (5,800 myelinated fibers/mm²; age/sex matched control value: 6,500 myelinated fibers/mm²) with occasional epineurial inflammatory infiltrates. Serologic evaluation revealed an autoantibody profile typical of the entire patient cohort with occupational autoimmune polyneuropathy,^{1,3} and was dominated by a neural-specific "signature" immunoglobulin G (IgG) and VGKC-complex-IgG (4.70 nmol/L; CASPR2-IgG and LGI1-IgG negative in this case).

Gabapentin, pregabalin, and OxyContin afforded minimal or no benefit. Four months after symptom on-

set, the patient received IV methylprednisolone (1 g/day for 5 days), then IV immune globulin (0.4 g/kg weekly, for 12 weeks). The subsequent improvement in pain allowed the patient to resume daily activities including ambulation and work, and to discontinue narcotics. Neurologic examination normalized and hyperesthesia was no longer present. However, 3 weeks after completing this treatment, the patient experienced gradual recurrence of paresthetic pain, muscle cramps, leg aching and fatigue, and walking difficulties. Neurologic examination revealed recurrent leg muscle fasciculations and hyperesthesia. Symptomatic resolution followed resumption of alternate week IV immune globulin therapy, but at approximately 3–5 days before each treatment the patient experienced recurrence of severe leg pain, cramps, and painful tingling.

During the next 42 months of immunotherapy, improvement was documented in symptoms, neurologic examination, electrophysiologic findings, and serology (figure). Attempts to discontinue treatment or increase the interval between treatments invariably resulted in symptomatic relapse with accompanying autoantibody elevation. At evaluation, in February 2009 and February 2011 (figure), significant pain resolution was reported. At both times, neurologic signs were lacking and VGKC-complex autoantibody was undetectable. Discontinuation of treatment resulted in recurrence of pain symptoms and autoantibody reappearance. Within 4 months of commencing methotrexate therapy (20 mg/week), maintenance IV immune globulin therapy was able to be reduced, without pain exacerbation, from 0.4 g/kg weekly to 0.3 g/kg alternate weekly (followed 10 weeks at this dose). Gradual immune globulin dose reduction is continuing.

Discussion. Pain was the predominant symptom in all abattoir employee patients in the reported outbreak.¹ IgG reactive with VGKC-complex components was the most frequent autoantibody specificity defined in the patients (79%) and was detected in 100% of experimental mice exposed to aerosolized porcine brain tissue.³ At last follow-up, 3 of 4 patients who remained seropositive for VGKC-complex IgG had persistent neuropathic pain despite resolution of objectively measurable neurologic deficits.³

At initial presentation, the patient of this report had the highest VGKC-complex autoantibody level re-

Figure Timeline of the patient's serum levels of voltage-gated potassium channel (VGKC)-complex autoantibody, and courses of IV immune globulin (IVIg) therapy and reported complaints of pain

Relative pain, analog scale (1–10) paralleled VGKC-complex autoantibody levels. Relapse of pain and a rise in serum VGKC-complex autoantibody level followed each attempt to discontinue, or extend the interval between, courses of IVIg therapy.

corded among all abattoir cases. VGKCs are an important physiologic regulator of membrane potentials in nociceptive sensory neurons as well as in motor neurons.⁵ As in this patient, motor nerve hyperexcitability, muscle fasciculations, and cramps are commonly encountered in patients with idiopathic VGKC-complex autoimmunity.⁶ Although paresthesia (interpreted as sensory nerve hyperexcitability) has been reported with VGKC-complex autoimmunity,⁷ pain is newly recognized as a syndromic manifestation of idiopathic VGKC-complex autoimmunity.⁴ The case we present here provides further evidence linking VGKC-complex autoimmunity and chronic neuropathic pain, and illustrates the efficacy of immunotherapy in treating autoantibody-mediated pain. Neural autoantibody profiles aid the diagnosis of potentially immunotherapy-responsive pain.

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