Management of Voltage-Gated Potassium Channel Antibody Disorders

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KEYWORDS

• Voltage-gated • Potassium channel • Antibody
• Neuromyotonia • Limbic encephalitis • Morvan syndrome

Antibodies to voltage-gated potassium channels (VGKC) can cause 3 major syndromes: neuromyotonia (NMT), limbic encephalitis (LE) and Morvan syndrome (MVS), with the latter encompassing elements of the others. Although the peripheral nervous system (PNS) is primarily involved in NMT, and the central nervous system (CNS) is the main target in LE and MVS, some clinical overlap of symptoms does occur. It took several years to realize the common pathogenesis of these syndromes. Pathologic neuronal overactivity or hyperexcitability, common to each disorder, occurs when membrane VGKC are reduced or blocked, preventing the normal potassium influx for membrane repolarization and termination of neuronal activity.[1] Greater antibody affinity for certain VGKC subunits seems to determine which syndrome becomes clinically manifest in a particular patient.[2] Anti-VGKC titers may be higher when the CNS is involved, in LE and MVS, than when the PNS is mainly involved (NMT), because current assays use cortical neuron VGKCs.[3] A serum anti-VGKC titer should be checked in any patient having the usual clinical features of NMT, LE, or MVS, as described later, because most cases benefit from immunosuppressive therapy. However, the selection of an immunosuppressive treatment is based on anecdotal experience because no controlled treatment trials currently exist for these diagnostically challenging and rare syndromes.

NMT

NMT is considered a clinical syndrome of peripheral nerve hyperexcitability, where motor units fire spontaneously, even continuously, creating persistent muscle contraction, manifest as stiffness, and occasionally as impaired muscle relaxation, yet different from myotonia. In NMT, affected muscles are often observed to have

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fasciculations, appearing as focal or multifocal single twitches, or myokymia, with numerous twitches spreading in irregular wavelike fashion over the muscle. With electromyography (EMG), the hallmark finding is the continuous, or nearly continuous, firing of motor unit potentials (MUPs) at rest, either as doublet, triplet, or multiple (multiplet) discharges, with intraburst frequencies of 5 to 300 Hz.[4,5] The discharges themselves are often called myokymia, if the bursts repeat in a rhythmic fashion, or neuromyotonic discharges if non-rhythmic and at higher frequency; however, this nomenclature is imprecise and the distinction is often of little value.

In 1961, before the recognition of VGKC antibodies, Isaacs[6] reported 2 patients with twitching of limb and trunk muscles, and diffuse muscle stiffness, so severe as to impair posture and mobility. The symptoms were relieved by phenytoin. Unexplained tachycardia, low-grade fevers and continuous sweating in both patients suggested involvement of the autonomic nervous system. Years later, Tahmoush and colleagues[7] coined the term ''cramp-fasciculation syndrome,'' to describe patients with the ''acute onset of muscle aching, cramps, and exercise intolerance without weakness or muscle atrophy,'' often relieved by carbamazepine. In these patients, repetitive electrical stimulation of motor nerves triggered off showers of potentials, or afterdischarges, following the evoked compound muscle action potential (CMAP). EMG revealed fasciculations in several muscles, but no continuously firing bursts of MUPs. Activities of patients with the cramp-fasciculation syndrome were limited by painful muscle cramps, yet this seemed less disabling than the widespread muscle stiffness of Isaacs syndrome.

In 1993, Newsom-Davis and Mills[4] reported that 2 of 3 patients with acquired neuromyotonia, or Isaacs syndrome, greatly improved with plasma exchange, corticosteroids, and azathioprine. After a diagnostic serum assay for VGKC antibodies was developed, 1 of these patients was later found to have an increased titer.[8] Larger series of peripheral nerve hyperexcitability cases found VGKC antibodies in about 20% to 50% of patients.[1,9,10] It is unclear to what extent (1) more anti-VGKC cases would have been detected with a more sensitive assay, (2) different, unrecognized antibodies were responsible, or (3) some neuromyotonia cases were not immune-mediated at all. It became evident also that VGKC antibodies could be present not only in cases of NMT but also in cramp-fasciculation or rippling muscle syndromes, suggesting a clinical spectrum more than distinct types of peripheral nerve hyperexcitability.[10] Moreover, peripheral nerve hyperexcitability could be associated with other autoimmune diseases, as a paraneoplastic syndrome, as a hereditary potassium channelopathy, or related to nonimmune disorders like timber rattlesnake bites or amyotrophic lateral sclerosis (ALS).[9] Indeed, Hart and colleagues[9] noted that 2 cases apparently presenting with NMT later went on to develop ALS, indicating the need for vigilance in observing and carefully following these patients. The spontaneous motor unit activity in NMT apparently can be generated from the anterior horn cell, although most early reports[1,4] favored terminal motor nerve branches as the source of the abnormal discharges. This was based on motor nerve activity persisting after anesthetic nerve block, but not after administration of curare.

Table 1 shows the typical clinical profile and abnormal diagnostic testing for anti-VGKC mediated NMT, based on 73 cases from the literature in which sufficient details were provided,[4,5,9,11–16] plus the current case report. Age at onset for NMT is 46 years for men, and 48 years for women, with a male predominance of about 2:1. Included here are some patients who responded to immunotherapy, but before the anti-VGKC assay was available. The largest series by Hart and colleagues[9] provided aggregate clinical data, not separating the anti-VGKC positive and negative cases. In general, the main signs and symptoms of anti-VGKC mediated NMT include painful