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VERY HIGH TITERS OF VOLTAGE-GATED POTASSIUM CHANNEL ANTIBODIES IN A PATIENT WITH AMYOTROPHIC LATERAL SCLEROSIS

Voltage-gated potassium channel (VGKC) antibodies have been implicated in a spectrum of immunotherapy-responsive neurological conditions, including peripheral nerve hyperexcitability (PNH), a heterogeneous syndrome that may present with fasciculations, cramps, and stiffness.[1,2] These antibodies are reported rarely in association with amyotrophic lateral sclerosis (ALS).[2–4] We report the case of a patient with very high titers of VGKC antibodies.

A 61-year-old man presented with a 9-month history of impaired right hand dexterity and a 2-month history of right hand weakness and limb cramping. He had no leg weakness or bulbar disturbances. Examination demonstrated fasciculations in all limbs, mild wasting of both first dorsal interossei, and grade $4^+/5$ weakness of the palmar and dorsal interossei bilaterally, but no tongue wasting or fasciculation. Reflexes were generally brisk. Sensory examination was normal. Nerve conduction studies were unremarkable, but electromyography (EMG) showed profuse fasciculation potentials and myokymic discharges in both upper and lower extremities suggestive of PNH. The right genioglossus, right deltoid, and bilateral tibialis anterior muscles showed moderately reduced recruitment with some discrete motor unit potentials (MUPs) of normal amplitude and duration firing at abnormally rapid rates. No fibrillation potentials or positive sharp waves were seen. The combination of fasciculation potentials and reduced recruitment raised concerns about ALS. VGKC antibodies were strongly positive at 1028 pM (0–100). A comprehensive work-up for malignancy, which included serum paraneoplastic antibodies and positron emission tomography, was unremarkable. Cerebrospinal fluid examination was normal. Carbamazepine eased the cramps, but the weakness progressed to involve all limbs despite a 6-month trial of intravenous immunoglobulin (2 g/kg) administered every 6 weeks. Repeat VGKC antibody titers were 1343 pM.

EMG repeated 6 months later showed myokymic discharges but also fibrillation potentials and positive sharp waves in the right abductor hallucis, bilateral tibialis anterior, and right rectus abdominis muscles. Long-duration, high-amplitude, rapidly firing, discrete MUPs were present in muscles innervated by cranial, cervical, thoracic, and lumbosacral segments. These electrodiagnostic findings were indicative of ALS with superimposed PNH. His symptoms have continued to worsen, but there is no clinical bulbar involvement 26 months into the illness. The reflexes remain brisk. There has been no cognitive impairment or seizures to suggest limbic encephalitis.

A number of autoimmune conditions have been described in association with ALS.[5] A potential association between VGKC antibodies and ALS has been reported in a retrospective cohort of 54 patients.[3] Sixteen (29.6%) patients had an antibody titer of >100 pM, with a maximum of 439 pM. The mean titers were also higher in ALS patients than in a cohort with peripheral nervous system disorders.[3] VGKC antibodies have been implicated in axonal dysfunction after spinal cord injury, indicating a potential spinal cord substrate for expression of VGKC antibodies.[6] Similarly, axonal hyperexcitability has been shown to be neurotoxic in experimental animals.[7] A causal relationship between VGKC antibody-associated PNH and ALS remains uncertain. It is possible that VGKC autoimmunity is an epiphenomenon, particularly because immunomodulatory therapies have been ineffective in halting progression of the patient's disease.

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TWO, THREE, OR FOUR-LIMB TESTING? OR THE DIFFICULTIES OF OPTIMIZING ELECTRODIAGNOSIS FOR SUSPECTED CIDP

I read with great interest the study by Vo et al. who retrospectively compared 3-limb with 2-limb electrophysiological testing in chronic inflammatory demyelinating polyneuropathy (CIDP).[1]

They found that studying a third limb/fifth nerve increased the degree of diagnostic certainty, particularly in atypical forms of CIDP. They otherwise state that testing 8 nerves with proximal stimulation is not done routinely in clinical practice. Although this may be the case in many laboratories, this situation is not necessarily appropriate in the attempt to reach a diagnosis. The results of a previous analysis which we conducted showed that with exclusively distal forearm and foreleg studies, diagnostic sensitivity increases by increasing the number of limbs and therefore of nerves tested. In that study, we retrospectively applied different hypothetical electrophysiological protocols of varying extensiveness in patients with clinically suspected CIDP.[2] The results showed that, using what we found at the time to be the most sensitive combination of electrodiagnostic criteria,[3,4] 4-limb testing of forearm and foreleg nerve segments was considerably more sensitive than unilateral, 2-limb studies (90% vs. 45%). Exclusive upper limb studies with proximal stimulation was also highly sensitive (90%).[2]

Vo et al. demonstrate increased level of diagnostic certainty to "definite CIDP" in a cohort of subjects who had all been preselected on the basis of having at least "possible CIDP" as per latest EFNS/PNS electrodiagnostic criteria.[5] This is an important point, as the issue of increasing the level of diagnostic certainty in those with at least 1 demyelinating feature beforehand differs from that of increasing diagnostic sensitivity, *per se,* i.e., that of the justification for continuing testing when precisely no demyelinating features are found after studying 1, 2, or 3 limbs. Sensitivity may ultimately be what really matters in *de novo* patients with the suspected diagnosis. Otherwise, the issue of reduced specificity, not raised in this study, deserves mention. It is similarly relevant with more extensive studies, as we have also described.[6]

It is interesting that Vo et al. found that 2-limb testing was sufficient to diagnose 12/13 of typical CIDP patients, but it was less sensitive for asymmetrical or distal forms. This may suggest more extensive testing is justified in asymptomatic regions. In another prospective analysis, we found that 50% of demyelinating features are located in asymptomatic regions in CIDP, which highlights the value of extending testing to clinically unaffected territories.[7] In that study, we also found more frequent demyelination in the upper limbs and more axonal loss in the lower limbs, in keeping with the length-dependent axonal loss also reported by others.[8] In contrast, Vo et al. report more frequent demyelinating features in the lower limbs.

Another key issue, which may partly explain this discrepancy could be the electrophysiological parameters considered. Prolongation of distal compound muscle action potential duration was included in the last EFNS/PNS Guidelines with cut-offs derived with low-cut filter settings of 20 Hz.[9] We have since shown in a multicenter European study that these cut-offs were inadequate for low cut filters of 2, 3, or 10 Hz.[10] The authors do not provide their filter settings, but they found this parameter was the second most frequent electrophysiological abnormality in their study.[1] This is of interest, as overdiagnosis may occur as a result of use of the latest EFNS/PNS Guideline cut-offs.

Nonetheless, this study is useful and of direct clinical relevance, and the authors should be commended, particularly given the persistent absence of data on optimal electrodiagnostic methodology in the setting of suspected CIDP. Ideally, future studies should be prospective and multicenter but with standardized protocols, and they should analyze treatment-responsive patients.

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REPLY: COMPARISON OF 2-LIMB VERSUS 3-LIMB ELECTRODIAGNOSTIC STUDIES IN THE EVALUATION OF CIDP

We appreciate the thoughtful comments from Dr. Rajabally regarding our recent article,[1] and we agree that the electrophysiological findings in our cohort merit further discussion.

Rajabally and Jacob have shown the high sensitivity of proximal limb stimulation in the diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP).[2] We agree that this is a valuable practice, but it is not always done due to technical difficulties, including the need for