Electrodiagnostic Assessment of Hyperexcitable Nerve Disorders

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KEYWORDS

• Peripheral nerve hyperexcitability • Myokymia • Neuromyotonia • Isaacs syndrome • Morvan syndrome • Cramp-fasciculation syndrome • VGKC-complex antibodies

KEY POINTS

- Peripheral nerve hyperexcitability (PNH) constitutes a variety of disorders along an electroclinical spectrum of cramps, fasciculations, myokymia, neuromyotonia, dysautonomia, and encephalopathy.
- Disorders of PNH include cramp-fasciculation syndrome, Isaacs syndrome, and Morvan syndrome. Myokymia, neuromyotonia, and dysautonomia are features of both Isaacs and Morvan syndromes, and central nervous system dysfunction is a defining characteristic of Morvan syndrome.
- Sensitivity of detecting myokymia and neuromyotonia on needle electromyography in Isaacs and Morvan syndromes increases with sampling of distal muscles.
- Patients with myokymia or neuromyotonia associated with leucine-rich glioma-inactivated 1 (LGI1) or contactin-associated protein-2 (CASPR2) antibodies may have an underlying neoplasm.

INTRODUCTION

The syndromes of peripheral nerve hyperexcitability (PNH) are relatively rare disorders characterized by involuntary muscle twitching, cramping, and muscle stiffness. Other symptoms include exercise intolerance, hyperhidrosis, mood irritability, insomnia, and encephalopathy. Characteristic electrodiagnostic (EDX) findings include fasciculation potentials, cramp potentials, myokymia, and neuromyotonia. Over the years, numerous investigators proposed several descriptive and eponymous names for PNH syndrome.[1,2] This article focuses on 3 PNH disorders: cramp-fasciculation syndrome (CFS), Issacs syndrome, and Morvan syndrome, recognizing that core clinical and EDX features differentiate these clinical entities (**Fig. 1**).

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	CFS	Isaacs	Morvan
Male Preponderance	X	X	XXX
Cramps/Fasciculations	X	X	X
Myokymia/NMT on EDX		X	X
Dysautonomia		X	XX
CNS Dysfunction			X
Cancer		X	XX
Neural Autoantibodies	X	XX	XXX

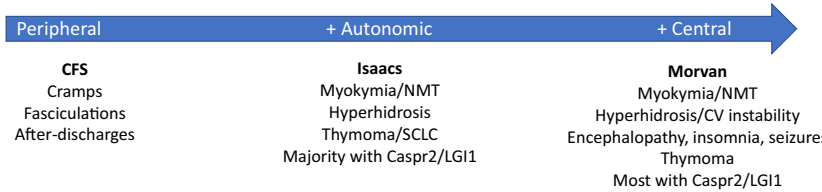

Fig. 1. Comparison of clinical and EDX features of cardinal disorders of PNH.

HISTORY

Disorders of PNH first were described approximately 130 years ago when, in 1890, Augustin Morvan first reported on his eponym of mixed peripheral nervous system (PNS) and central nervous system (CNS) dysfunction when he described 5 patients with "fibrillary chorea," referring to the apparent dancing of muscle fibers underneath the skin in patients.[3] These patients also demonstrated signs of autonomic dysfunction, fluctuating encephalopathy, and insomnia. In the ensuing decades, sparse reports of similar cases ensued (reviewed by Serratrice and Azulay[4]). The original description of the second syndrome of PNH was published 1961, wherein Hyam Issacs[5] coined a term for a syndrome of "continuous muscle fiber activity" (subsequently referred to as Isaacs syndrome) in 2 patients who presented with gradually progressive generalized muscle stiffness with muscle twitching and hyperhidrosis. Isaacs syndrome is phenotypically different from Morvan syndrome due to the absence of CNS symptomatology (including insomnia, hallucinations, personality change, and encephalopathy). The final major manifestation of PNH was described in 1991 by Tahmoush and colleagues,[6] who described a milder syndrome of myalgia, cramps, stiffness, and exercise intolerance in what they called CFS.

ELECTRODIAGNOSTIC FINDINGS IN PERIPHERAL NERVE HYPEREXCITABILITY

The classic EDX abnormalities seen in PNH constitute abnormal insertional and spontaneous motor unit activity noted on needle electromyography (EMG). Volitional motor unit morphology and recruitment generally are normal unless there is an underlying neuromuscular condition contributing to secondary PNH. A diverse array of discharges has been described, including (1) fasciculations, (2) cramp potentials, (3) myokymic discharges, and (4) neuromyotonic discharges.[7] Nerve conduction studies (NCSs) may show abnormal afterdischarges (ADs) after routine motor NCSs, with assessment of late responses, such as F-responses and H-reflexes, and after repetitive nerve stimulation (RNS).

Fasciculation Potentials

Fasciculations present clinically as irregular muscle twitching, which may be observed when superficial muscle fibers are activated by the spontaneous depolarization of a motor axon. This twitching does not cause movement across a joint, and fasciculations involving deeper regions of muscle or under thick subcutaneous tissue may be identified only by needle examination. Denny-Brown and Pennybacker[8] first described the fasciculation potential in 1938 as the spontaneous discharge of an individual motor unit, which constitutes an anterior horn cell, its associated axon, and all the muscle fibers it innervates. The source generator of this discharge is the motor nerve or the axon terminal, in spite of the classic association of these discharges with diseases of the anterior horn cell.[9,10] On needle examination, fasciculation potentials fire erratically. The irregular and typically slow firing pattern requires patience, because fasciculations may be missed if an examiner is rushed during the examination. When multiple fasciculations are noted, the morphology of each fasciculation potential typically is variable because different potentials reflect spontaneous activation of different motor units (**Fig. 2**). Most fasciculation potentials have normal motor unit morphology for the muscle from which they are recorded, unless there is an underlying neuromuscular disorder associated with chronic reinnervation changes.

Cramp Potentials

Cramps manifest clinically as painful and palpable muscle tightening (of a single muscle) that is relieved by stretching. Cramps are common among the general population and generally associated with electrolyte derangements, dehydration, and multiple medications.[11] The generator of a cramp potential historically is the motor unit, although there is some evidence that the distal motor unit, in particular the intramuscular nerve terminals, constitutes the predominant source generator.[10] Cramps typically are associated with muscle activation (eg, exercise) but may be spontaneous. In isolation they are nonspecific for cause but in the setting of muscle twitching and muscle stiffness cramps may herald PNH.

On EMG, muscle cramps are composed of continuous motor unit potentials (MUPs) firing at frequencies up to 150 Hz. During the evolution of a cramp discharge, the frequency of firing and amplitude of the discharge increase and then slowly subside.[10,12] They typically are preceded by recurrent fasciculations, which also may be observed after cessation of the cramp discharge. Stimulus-induced cramp discharges also may be recorded with surface electrodes and identified when the frequency of ADs increases such that individual ADs cannot be identified (**Fig. 3**).

Myokymia

The EDX features of myokymic discharges first were described in 1948 by Denny-Brown and Foley.[13] Myokymia is a descriptive term stemming from the clinical observation of undulating movement of the overlying skin or mucous membranes (eg, the tongue) as a result of spontaneous repetitive discharges from 2 or more motor

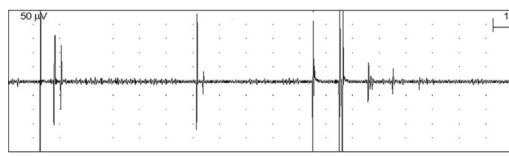

Fig. 2. Multiple fasciculation potentials are depicted on this tracing. Note the slow sweep speed of 1 s/division. (*Adapted from* Rubin DI. Normal and abnormal spontaneous activity. Handb Clin Neurol. 2019;160:257-279; with permission.)

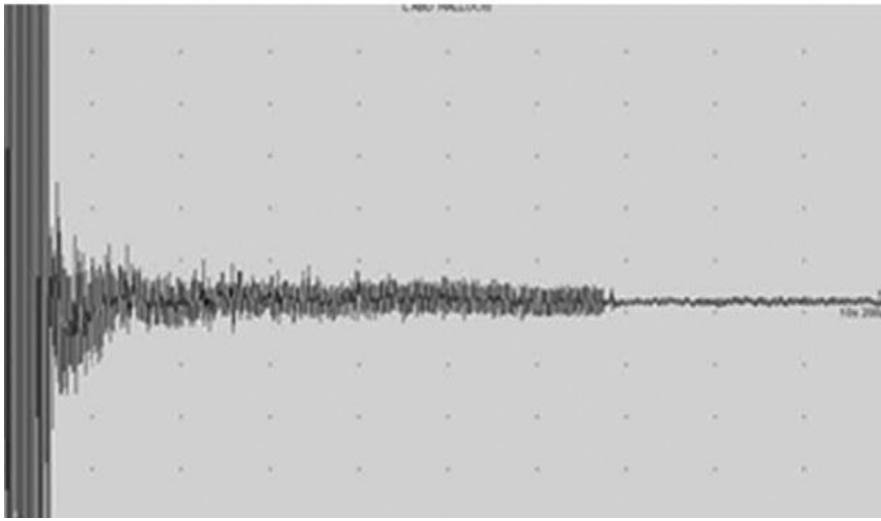

Fig. 3. Stimulus-induced cramp discharge stimulating the tibial nerve and using surface electrodes over abductor hallucis brevis. Note onset of cramp potential is immediately after stimulation and innumerable Ads contribute to the waveform. Sweep speed is 1 s/division and gain is 100 μV/division. (*From* Benatar M, Chapman KM, Rutkove SB. Repetitive nerve stimulation for the evaluation of peripheral nerve hyperexcitability. J Neurol Sci. 2004;221(1-2):47-52; with permission.)

units.[9,12] Although myokymia can be observed clinically, this not always is the case, particularly when the affected muscle is deep either within the bulk of muscle or under deep subcutaneous tissue.

Double, triple, and multiple discharges reflect the spontaneous firing of 2 or more MUPs of similar morphology and amplitude that occur in a similar sequence during each burst.[12] The interval between each discharge usually is in the range of 2 milliseconds (ms) to 20 ms, with the duration between the second and third action potentials often exceeding that between the first 2 (**Fig. 4**). The generator is the motor unit or motor axon and essentially synonymous with fasciculation potentials. They can be thought of as grouped fasciculations, classically associated with tetany from hypocalcemia or hypomagnesemia, which is important to consider in the differential diagnosis.[14]

Myokymic discharges occur most typically as double or multiple discharges (up to 10) with rhythmic or semirhythmic bursts, typically described as the sound of marching soldiers.[12,14] These spontaneous bursts cycle as a group between bursts and silence. The intraburst (within the burst) frequency (5–60 Hz) is faster than the interburst (between-burst) frequency, which typically is 2 Hz or less. There is much variability on burst morphology and both intraburst and interburst frequency, because myokymic discharges can contain bursts of more than 100 motor units and burst frequency as slow as every 20 s[15] (**Fig. 5**).

Myokymic discharges can be localized (focal) or generalized, the latter typically associated with disorders of PNH. Focal myokymia may be restricted to facial musculature, 1 limb, or the distribution of a spinal root or motor nerve. There are multiple causes of focal myokymia (**Box 1**).[16] Myokymia can be confused with other spontaneous discharges, such as complex repetitive discharges or tremor (**Table 1**).

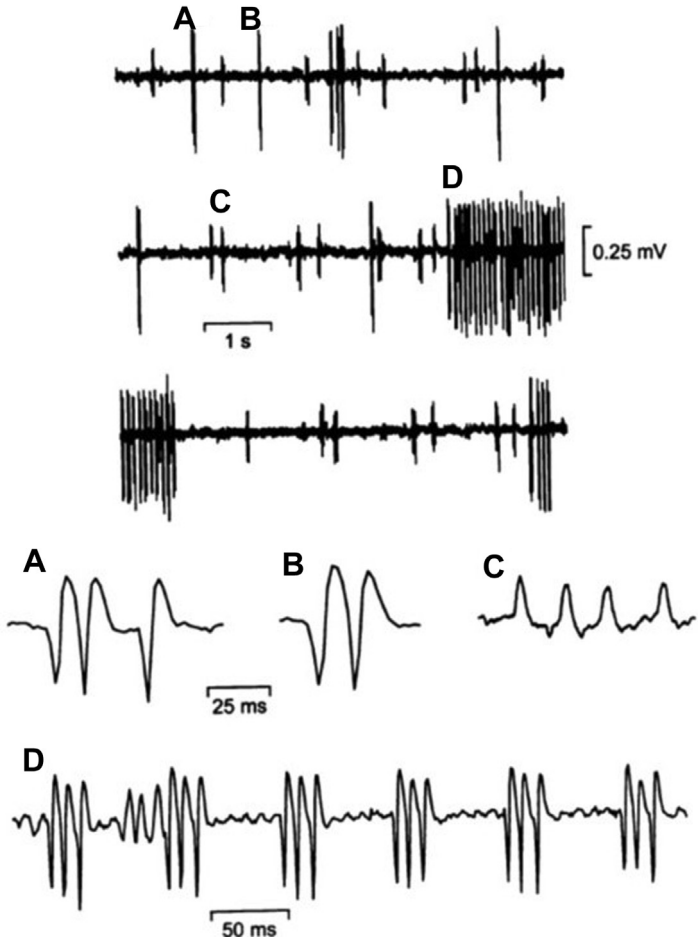

Fig. 4. Upper trace is a 25-s continuous needle EMG recording from medial gastrocnemius. Different motor units are seen to fire spontaneously and irregularly as double discharges (B), triple discharges (A), and multiple discharges (C), with intraburst frequencies of up to 120 Hz. The prolonged discharge in the middle of the recording consists of rapidly firing triple discharges of more than 1 motor unit (D). (*From* Maddison P, Mills KR, Newsom-Davis J. Clinical electrophysiological characterization of the acquired neuromyotonia phenotype of autoimmune peripheral nerve hyperexcitability. Muscle Nerve. 2006;33(6):801-808; with permission.)

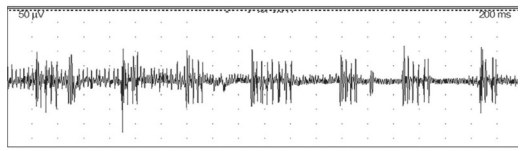

Fig. 5. Schematic of myokymic discharge. Sweep speed is 200 ms/division and gain is 50 μV/division. (*From* Rubin DI. Normal and abnormal spontaneous activity. Handb Clin Neurol. 2019;160:257-279; with permission.)

Box 1
Disorders associated with focal and generalized myokymia

Facial
- Pontine lesions (multiple sclerosis, glioma, and others)
- Cerebellopontine angle masses (schwannomas)
- Vascular compression (basilar invagination)
- Facial neuropathies (Bell's palsy, Guillain-Barré syndrome, sarcoidosis, and basilar meningitis)
- Motor neuron disease (eg, Kennedy disease)

Regional
- Myelopathy
- Radiculopathy (structural or demyelinating)
- Plexopathy (eg, postradiation injury)
- Mononeuropathy (compressive or traumatic)

Generalized
- PNH syndromes (Isaacs and Morvan syndromes)
- Hereditary diseases (episodic ataxia type 1, axonal neuropathy with neuromyotonia, and Charcot-Marie-Tooth disease)
- Acquired demyelinating neuropathies (acute and chronic acquired demyelinating polyneuropathies)Motor neuron diseases (amyotrophic lateral sclerosis)
- Toxic exposures (heavy metals, penicillamine, and timber rattlesnake envenomation)
- Thyrotoxicosis

Adapted from Katirji B. Peripheral nerve hyperexcitability. Handb Clin Neurol. 2019;161:281-290; with permission.

Neuromyotonia

The EDX features of neuromyotonia originally were described in 1965 by Mertens and Zschocke.[17] Neuromyotonic discharges are very high frequency (150–300 Hz) bursts of MUPs that wane in amplitude throughout the burst and start/stop abruptly, either spontaneously or as a result of needle movement or voluntary contraction[12] (**Fig. 6**).

Clinically, neuromyotonia is manifest as persistent muscle contraction.[18] Some investigators posit that myokymic and neuromyotonic discharges exist along a frequency spectrum but have the same significance.[18] Neuromyotonia constitutes a more specific finding for PNH, because myokymia is associated with more diverse pathologic entities, as discussed previously.

Afterdischarges

ADs are repetitive or sustained firing of action potentials that occur after stimulation and persist beyond stimulus cessation. ADs have been noted after routine motor NCSs and during late responses in patients with PNH.[19–23] In the setting of F-waves, ADs may obscure the late response (**Fig. 7**). A gain of 200 μV and a time base of 20 ms/division may facilitate the identification of ADs during routine motor NCSs (**Fig. 8**).[20,24]

RNS has been proposed as potentially useful for identifying stimulus-induced ADs with surface electrodes. Various studies have reported the identification of abnormal ADs, many of which reported qualitive data about the presence or absence of ADs.[6,25,26] Various recording setups have been utilized, with a sweep speed of 100 ms—1 s/division and a gain of 100 μV/division to 200 μV/division most commonly reported. Because the distal axon and motor end plate are suspected to contribute to the generation of the spontaneous discharges in PNH, distal stimulation is performed in a standard fashion for routine motor NCSs. The tibial nerve may provide optimal sensitivity and specificity, concordant with reports noting neuromyotonia and

Table 1
Myokymia mimics

EMG Discharge	Source Generator	Morphology	Firing Characteristics
Myokymia	Motor unit	Looks like grouped fasciculations, on speaker sounds like marching solders. Number of intraburst potentials may vary.	Intraburst (within-burst) frequency of 5–60 Hz Interburst (between-burst) frequency of 2 Hz or less
Complex repetitive discharge	Muscle fiber, with ephaptic spread to adjacent fibers	Regular, high frequency (20–-150 Hz) polyspike discharge. Morphology may change due to drop out or additional involvement of nearby muscle fibers. Machine-like sound on amplifier.	Begins and stops abruptly
Tremor	Central cause stimulates a variable population of anterior horn cells	Motor units within each burst vary	Interburst frequency of 4–19 Hz depending on cause of tremor (Parkinson disease, essential tremor, orthostatic tremor)

myokymia are more prominent distally than proximally and more prominent in the legs than arms.[22,26] Various stimulation frequencies have been employed, ranging from 1 Hz to 30 Hz, with sensitivity optimized at high RNS rates and specificity improved with low stimulation frequencies.[25,26] It is important to be careful to not misinterpret voluntary muscle activation or impaired relaxation on surface EMG as being indicative of PNH.

The clinical relevance of ADs, particularly with regard to ADs provoked by RNS, is questionable. Evaluation of ADs in normal controls and patients with polyneuropathy

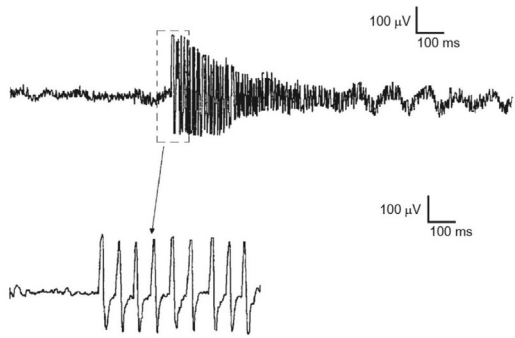

Fig. 6. Neuromyotonic discharge. Note the decrementing response. The top is recorded with a long sweep speed of 100 ms/division while the insert is at a regular sweep speed of 10 ms/division. Note the very-high-frequency (150–250 Hz) repetitive discharge of a single motor unit. (*From* Preston DC, Shapiro BE. (2013). Electromyography and neuromuscular disorders, third edition. London: Elsevier/Saunders; with permission.)

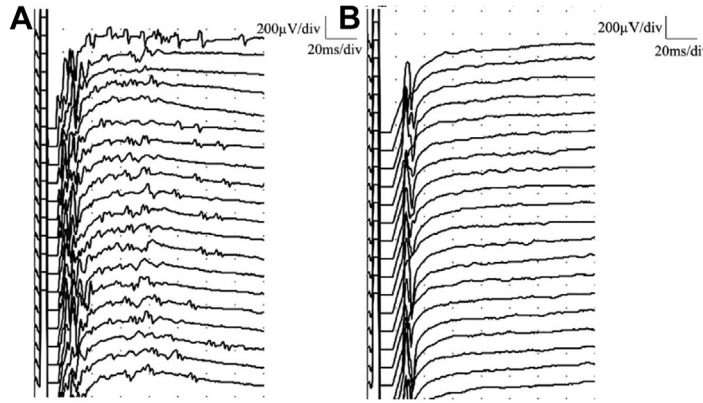

Fig. 7. Prolonged ADs noted after median f-responses, note the ADs obscure the median f responses. (*From* Niu J, Guan H, Cui L, Guan Y, Liu M. Afterdischarges following M waves in patients with voltage-gated potassium channels antibodies. Clin Neurophysiol Pract. 2017;2:72-75; with permission.)

has failed to identify differences in AD duration between groups.[27] Furthermore, the average duration of stimulus-induced ADs following stimulation at various frequencies (between 2 Hz and 20 Hz) in patients with CFS with and without voltage-gated potassium channels (VGKCs) antibodies did not discriminate between seropositive and seronegative patients.[28] Thus, RNS-induced ADs in patients undergoing evaluation for CFS should be interpreted cautiously, given the common presence of ADs in the normal population and apparent lack of specificity.[27,29] More information is needed regarding the typical duration of ADs in the normal population and the prevalence of

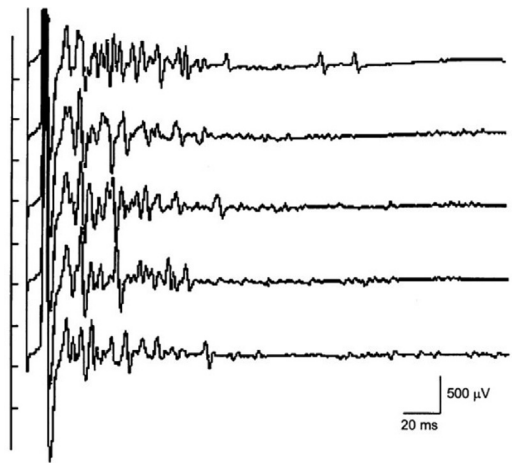

Fig. 8. ADs following supramaximal stimulation of the posterior tibial nerve; 5 consecutive compound muscle action potentials are followed directly by trains of asynchronous ADs. (*From* Maddison P, Mills KR, Newsom-Davis J. Clinical electrophysiological characterization of the acquired neuromyotonia phenotype of autoimmune peripheral nerve hyperexcitability. Muscle Nerve. 2006;33(6):801-808; with permission.)

ADs in common neuromuscular diseases to determine if ADs can discriminate between those with and without CFS.[27]

THE CLINICAL SPECTRUM OF PERIPHERAL NERVE HYPEREXCITABILITY

The causes of PNH are myriad and largely can be divided into primary (presumed autoimmune, paraneoplastic, or hereditary) and secondary etiologies (related to varied pathology affecting motor nerves or neurons). Conceptually, disorders of PNH can be considered to lie along an electroclinical spectrum with more benign disease typically limited to the PNS, as in CFS, and more severe disease associated with additional dysfunction of the CNS and autonomic nervous system (ANS), as in Isaacs and Morvan syndromes. The presence of an associated neural autoantibody becomes increasingly more likely as abnormal spontaneous activity is seen on EMG or when CNS or ANS dysfunction are apparent. A proportion of patients are found to have a paraneoplastic disorder, with thymoma, non–small cell lung carcinoma, and thyroid cancer the most commonly associated neoplasms.[30–32] Hereditary causes of PNH include episodic ataxia type 1 and axonal neuropathy with neuromyotonia.[33,34]

PNS hyperexcitability commonly is ascribed to dysfunction of VGKCs, which function to repolarize the nerve and, in disease, reduce the threshold to nerve depolarization.[35] The association of PNH with VGKC-complex antibodies first was suspected by Newsom-Davis and Mills in 1993.[36] The specific antigens were later clarified to be associated with the VGKC-complex rather than the actual channel (**Fig. 9**).[36,37] Contactin-associated protein 2 (Caspr2) is involved in the clustering of potassium channels at the juxtaparanodal region on myelinated axons and also is found centrally in the cerebellum and hippocampus.[38] Leucine-rich glioma-inactivated 1 (LGI1) modulates synaptic transmission and is expressed mainly in the hippocampus and temporal cortex, hence its association with limbic encephalitis and faciobrachial dystonic seizures (FBDS).[37] Although Caspr2 is associated more commonly with Isaacs and Morvan syndromes and LGI1 with limbic encephalitis and FBDS, the clinical

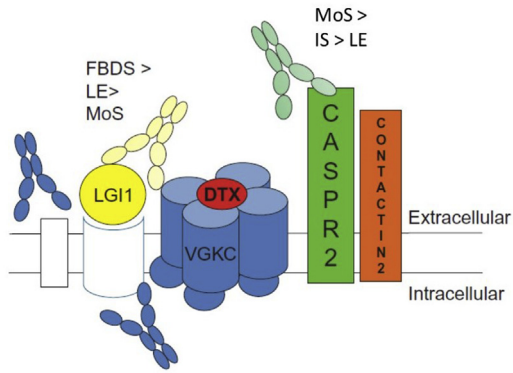

Fig. 9. Depiction of the VGKC-complex labeled with dendrotoxin (DTX), the snake neurotoxin that binds strongly to VGKC, to show antibodies known to bind the extracellular domains of LGI1 (in patients with limbic encephalitis [LE], FBDS, and Morvan syndrome [MoS]), and Caspr2 in patients with MoS more frequently than in Issacs syndrome (IS) or LE. Contactin-2 antibodies are rare. Some antibodies may bind the intracellular domains of some molecules within the VGKC-complex (blue antibody). (*Modified from* Irani SR, Vincent A. Voltage-gated potassium channel-complex autoimmunity and associated clinical syndromes. Handb Clin Neurol. 2016;133:185-197; with permission.)

phenotypes associated with these autoantibodies overlap considerably, and both are capable of causing PNS as well as CNS pathology.[35,39] Antibodies against components of the cell-surface VGKC-complex may interfere with this function in a variety of ways: modulating channel activity, channel cross-linking and internalization, and complement-mediated destruction.[39–41]

As a group, men are affected more commonly with PNH than are women, and the male preponderance increases greatly if neural autoantibodies or CNS features are present (93% male in Morvan syndrome). Morvan patients tend to be older (median age of 57) whereas those with CFS and Isaacs are most commonly in their 40s.[2,28,42]

When a patient presents with symptoms and signs compatible with PNH, routine sensory and motor nerve conductions should be performed in at least 1 symptomatic limb, with at least 2 limbs preferred. Motor responses as well as late responses should be reviewed carefully for ADs. EMG should focus on at least 1 symptomatic limb, sampling both proximal and distal musculature, as well as another limb to determine whether there is a regional or generalized pattern of PNH. EDX abnormalities may fluctuate over time, which emphasizes importance of repeat EDX testing in patients with worsened clinical symptoms and/or signs in spite of having a previously unremarkable examination.[2]

Cramp-Fasciculation Syndrome

With manifestations restricted to peripheral motor nerves, CFS is considered the least severe phenotype of PNH. Muscle cramps, twitching, muscle stiffness, and exercise intolerance are symptoms commonly reported.[6,25] Although weakness may be a reported symptom, weakness rarely is found on examination. Cramps may be induced or exacerbated by exercise or muscle activation, which is common among all disorders of PNH. Sensory symptoms also may be present, typically in the setting of an underlying polyneuropathy. Besides fasciculations, the examination otherwise is normal unless CFS is secondary to an underlying neuromuscular condition, such as polyneuropathy or radiculopathy. CFS phenotypically is different from Issacs and Morvan syndromes because neuromyotonia and myokymia are not noted on EMG and CNS and ANS symptoms or signs are absent.

Routine motor and sensory NCSs should be conducted to exclude baseline disease of the nerve. Stimulus-induced ADs or cramps on RNS and fasciculation potentials on EMG can be seen, noting that the role of RNS-induced ADs and cramps are unclear at this time.[6] Neural antibodies (mostly against the VGKC-complex) are relatively uncommon, ranging from 16% to 32%, and rarely in association with tumor which is most commonly thymoma (in 6%).[28,30]

Isaacs Syndrome

The additional findings of dysautonomia, clinical myokymia, and EDX evidence of abnormal spontaneous motor unit activity (myokymic and/or neuromyotonic discharges) help differentiate Isaacs syndrome from CFS.[22] Hyperhidrosis is the primary dysautonomia, although other less common forms have been described, including dysphagia, sialorrhea, piloerection, and tachycardia.[16] Some investigators have posited that hyperhidrosis reflects the metabolic impact of continuous motor unit activity as opposed to true dysautonomia. The neurologic examination may reveal fasciculations and myokymia, pseudomyotonia (impaired relaxation after muscle activation), and hypertrophied muscles (most commonly affecting the calves, likely from continuous motor unit activity). Trousseau sign (carpopedal spasm caused by inflating the blood-pressure cuff to a level above systolic pressure for 3 minutes) and Chvostek sign (twitching of the facial muscles in response to tapping over the

facial nerve) have been reported but appear to be uncommon. It is not uncommon for patients to complain of pain, which can be diffuse and tends to be length-dependent (eg, worse in the legs than the arms).[43]

Neuromyotonic discharges are more common in distal than proximal muscles and more commonly are in the legs than the arms.[2,22] In a study of autoimmune neuromyotonia associated with VGKC-complex antibodies, the most frequently seen findings on EMG were double, triple, or multiple discharges of high intraburst frequency (between 40 Hz and 350 Hz) in at least 1 symptomatic muscle.[22] VGKC-complex antibodies are present in up to half of cases (54%), ganglionic acetylcholine receptor antibodies in a minority (14%), and 1 or both in 63%. Thymoma and small cell lung cancer are the most commonly associated tumors; 16% of cases are paraneoplastic.[30] Issacs syndrome can be associated as a comorbid autoimmune phenomenon with myasthenia gravis and if the appropriate clinical history and examination are elicited, further evaluation for myasthenia is warranted.

Morvan Syndrome

In addition to the PNH stigmata seen in Isaacs syndrome, Morvan patients with Morvan syndrome typically have prominent sleep disturbances (insomnia, dream-enactment, and daytime hypersomnolence), a fluctuating encephalopathy, and vivid hallucinations.[19] Personality change with anxiety and agitation may be reported. Limb paresthesias and pain as well as skin lesions and pruritis are common.[19,42,43] Hyperhidrosis (86.2%) and cardiovascular instability (48.3%) are the most common dysautonomias.[19] Seizures and cerebellar dysfunction are present in one-third and weight loss in one-half.[42]

The primary approach to diagnosis of Morvan syndrome relies on the recognition of simultaneous PNS and CNS involvement (nearly all have neuromyotonia and neuropsychiatric disturbances), supported heavily by EDX findings of PNH and supplemented by neural antibody testing. VGKC-complex antibodies are present in most (70%–90%), usually against Caspr2 but also LGI1, either alone or in combination.[39,42] Magnetic resonance imaging of the brain typically is normal, which can help discriminate Morvan from limbic encephalitis.[19,39,44] Spinal fluid abnormalities (unmatched oligoclonal bands or elevated protein levels) are present in fewer than half.[2] Autonomic testing (sweating and cardiovascular abnormalities) and polysomnography (lack of sleep architecture and loss of REM atonia) can be useful adjunctive tests. Tumors (41%), especially thymoma, and myasthenia gravis (31%) are common associations.[37,42] Up to a third of patients eventually may succumb to Morvan syndrome, much more commonly when in association with cancer.[37,42]

TREATMENT CONSIDERATIONS

Management of PMH largely has been informed by the experience of case reports and various case series. In general, those with minor symptoms limited to the PNS can be managed symptomatically whereas those with more severe peripheral disease or involvement of the CNS or ANS should be considered for immunotherapy.

Symptomatic treatment is helpful for the manifestations of PNH in most patients, regardless of underlying etiology. Drugs that stabilize neuronal membranes (antiepileptic drugs primarily) have been reported as most useful, including carbamazepine, phenytoin, and gabapentin, which have been reported to improve symptoms in a majority of patients.[1,45] Various case reports note the possible utility of oxcarbazepine, pregabalin, lamotrigine, mexiletine, acetazolamide, topiramate, and valproate (reviewed by Elangovan and colleagues[32]).

In those cases of a suspected autoimmune basis, immunotherapy often is necessary, and regimens are similar to those used for the autoimmune encephalitides (for a detailed review of treatment strategies for autoimmune neurologic conditions, see Linnoila and Pittock[46]). Steroids, intravenous immunoglobulins, and plasmapheresis commonly are employed to induce remission, either as monotherapies or in combination.[42,47,48] Although clinical presentation classically is subacute with clinical nadir by 4 months, patients still may respond to treatment despite prolonged symptom duration of months to years.[49] In refractory cases, escalation to second-line treatments (rituximab and cyclophosphamide) may be necessary.[47] Maintenance therapies have included mycophenolate mofetil and azathioprine.[42,47]

In the setting of Caspr2 antibodies, a good or full response to immunotherapy (with tumor treatment if necessary) can be expected in approximately half of patients, with the remainder experiencing either a partial (44%) or no response (7%).[47] In patients with LGI1 antibodies, first-line immunotherapies initially are effective in 80%, with up to 67% experiencing a favorable outcome.

DISCLOSURE

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