DIAGNOSIS AND TREATMENT UPDATE

Voltage-Gated Potassium Channel Antibody-Mediated Syndromes: A Spectrum of Clinical Manifestations

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Immune-related neurologic disorders have long been recognized. A number of specific targets have been identified, including neurons, Purkinje cells, and pre- and postsynaptic receptors. Over the past decade, antibodies against voltage-gated potassium channels (VGKCs) have been reported in a number of neurologic syndromes, such as neuromyotonia, limbic encephalitis, and Morvan's syndrome. Recent advances have supported the pathologic mechanism of VGKC in these disorders, their response to therapy, and the possible mechanisms of peripheral, central, and autonomic dysfunctions seen in these disorders. We present a patient with 1 of these syndromes and review the literature of these disorders.


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A 31-year-old right-handed man presented with a 2-month history of brief episodes of “daydreaming,” visual and olfactory hallucinations, memory loss, poor attention, confusion, and sleep disturbances. He also reported autonomic symptoms such as hyperhidrosis, hot and cold flashes, palpitations, and paroxysmal diarrhea. His wife reported that he would forget simple daily activities shortly after being reminded of them, wake frequently throughout the night, and have periods of insomnia lasting days. She had observed staring spells, which the patient reported as sometimes corresponding to his visual and olfactory hallucinations and daydreaming. The patient had a nonspecific viral
syndrome 2 months prior to the onset of symptoms, characterized by fever and upper respiratory symptoms. He had no history of head trauma, seizures, or known central nervous system (CNS) infection, and the family history was unremarkable.

On examination, the patient was hypertensive (blood pressure, 150/90 mm Hg) with intermittent orthostatic hypotension. Neurological assessment revealed impaired attention and memory with 1 of 3 objects remembered at 5 minutes. He had fluctuating periods of piloerection and diffuse, patchy hydrosis accompanied by tachycardia. The remainder of the neurological examination provided normal results.

MRI revealed hyperintensity on T2-weighted sequences of the left hippocampus with decreased signal on T1-weighted sequences, patchy enhancement, and mild mass effect (Figure 1 A and B). Positron emission tomography (PET) showed left temporal hypermetabolism and perfusion imaging revealed increased perfusion. Cerebrospinal fluid was clear with no nucleated cells, his glucose level was 58 mg/dL, and his protein level was 45 mg/dL. Hyponatremia was present (serum Na⁺ = 132 mEq/L). Herpes polymerase chain reaction; cryptococcal antigen; Lyme titers; a CT of the abdomen, chest, and pelvis; thyroid function tests, rheumatoid factor test, streptolysin antibody test, rapid plasma reagin, and transesophageal echocardiogram results were all normal; 24-hour urinary metanephrine and norepinephrine were initially elevated, but repeat testing found normal levels.

Based on the presence of memory and sleep impairment, autonomic dysfunction, hallucinations, and hippocampal changes evident on MRI, a voltage-gated potassium channelopathy was suspected. Voltage-gated potassium channel (VGKC) antibody level was found to be 1000 pmol/L (normal < 115 pmol/L). Video electroencephalogram (EEG) monitoring revealed bilateral temporal lobe dysfunction with epileptiform discharges originating in both temporal lobes (Figure 2). Autonomic changes were not associated with changes in EEG but periodic sinus tachycardia was observed. Initial neuropsychological testing revealed significant impairment in memory, language, and executive functioning, along with substantial anxiety and depression. Plasmapheresis and high-dose steroid treatment resulted in slow improvement in symptoms.

Over the next year the patient’s symptoms waxed and waned, but at no point was he symptom free. He had periods of worsening related to elevated levels of serum VGKC antibodies. The patient was treated with intermittent plasmapheresis or intravenous immunoglobulin (IVIg) in addition to receiving steroids (prednisone, 20 mg/d), with resulting subjective improvement in symptoms over time and decreased VGKC antibody levels. He was treated with levetiracetam and carbamazepine, which showed improvement in hallucinations and sleep disturbance. Marked sleep disturbance on EEG during 1 episode rapidly normalized after 1 session of plasmapheresis. Subsequent EEG monitoring variably revealed left, right, or bilateral temporal lobe cortical hyperexcitability. Follow-up MRI revealed increased T2 signal and hippocampal atrophy consistent with mesial temporal damage (Figure 1C). Monthly IVIg infusion was initiated with normalization of VGKC antibody levels; subjective improvement in sleep, autonomic, and memory symptoms and decreased frequency of hallucinations was noted. Repeat neuropsychological testing revealed continued global cognitive dysfunction with improvement in some domains. Eighteen months after diagnosis, the patient was working part-time, was seizure free on levetiracetam, and on a 6- to 8-week interval course of IVIg and prednisone (15 mg/d). Neuropsychologic testing revealed moderate improvements in cognitive areas.

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![Figure 1. MRI showed increased T2-weighted signal in the right mesial temporal lobe (A) with gadolinium enhancement (B). Follow-up MRI showed mesial temporal atrophy and cortical thinning (C).](image-url)
The patient’s presentation typifies a spectrum of clinical manifestations of VGKC antibody-mediated syndromes. Memory loss, confusion, and agitation are consistent with limbic encephalitis (LE), whereas the presence of autonomic disruptions, sleep disturbances, and myokymia suggests Morvan’s syndrome.

VGKC Channelopathy Syndromes

Three clinical syndromes have been associated with VGKC antibodies: acquired neuromyotonia (NMT),1-7 LE,8-11 and Morvan’s syndrome.12-15 NMT is characterized as peripheral nerve hyperexcitability (PNH), whereas LE is characterized by memory impairment and disturbance of consciousness. Morvan’s syndrome is a combination of peripheral nervous system (PNS), CNS, and autonomic nervous system (ANS) dysfunction. The different clinical manifestations of the 3 syndromes, the concept of the syndromes as part of a spectrum of VGKC channelopathies, and the role VGKC antibodies play in the pathophysiologic mechanism are still under exploration.

Neuromyotonia

NMT is characterized primarily by PNH; the term PNH has been used to describe a collection of similar neurological disorders including NMT, Isaacs syndrome, continuous muscle fiber activity, generalized myokymia, undulating myokymia, and cramp-fasciculation syndrome—all of which involve peripheral nerve hyperexcitability.15,16 The hyperexcitable state of the neuron causes continuous muscle fiber activity manifesting clinically in various combinations of muscle cramps, fasciculations, myokymia (both at rest and exercise-induced),

Figure 2. Electroencephalogram revealed bilateral temporal dysfunction.
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Although NMT occurs in a number of genetic disorders, it is usually an acquired condition.18 It has been associated with myasthenia gravis, thymoma, and small cell lung cancer.17 The association with autoimmune and neoplastic processes, along with the observation that plasmapheresis results in both symptomatic and electrophysiological improvement18 has stimulated investigations of an immune-mediated etiology.

Limbic Encephalitis

In contrast to NMT, LE is defined by CNS involvement without peripheral dysfunction; patients usually present with subacute onset of memory loss, confusion, seizures, and psychiatric symptoms.11 Insomnia or other sleep disturbances are common.10 Hyponatremia may be present as a syndrome of inappropriate antidiuretic hormone secretion.9

Neuropsychiatric testing usually reveals high signal in the medial temporal lobes,16,22,23 poral lobe hypermetabolism, also seen in patients with Morvan’s syndrome have normal scans.12,14,16,29 However, our patient’s MRI revealed significant temporal lobe hypermetabolism despite the absence of sleep cycles.36 Classically, patients with LE demonstrate increased signal in the medial temporal lobes on brain MRI, whereas patients with Morvan’s syndrome have normal scans.12,14,16,29 However, our patient’s MRI revealed significant temporal lobe abnormalities despite the absence of sleep cycles.36 Classically, patients with LE demonstrate increased signal in the medial temporal lobes on brain MRI, whereas patients with Morvan’s syndrome have normal scans.12,14,16,29 However, our patient’s MRI revealed significant temporal lobe abnormalities despite the absence of sleep cycles.36 Classically, patients with LE demonstrate increased signal in the medial temporal lobes on brain MRI, whereas patients with Morvan’s syndrome have normal scans.12,14,16,29 However, our patient’s MRI revealed significant temporal lobe hypermetabolism. However, in our patient whose clinical findings are consistent with Morvan’s syndrome), the PET scan revealed temporal lobe hypermetabolism, also atypical with the classical distinction of LE and Morvan’s syndrome.

The pathophysiology of Morvan’s syndrome is not well defined. The syndrome has been reported in conjunction with a variety of diseases or suspected etiologies, such as associations with gold and manganese exposure, or comorbid autoimmune disease (myasthenia gravis) or neoplasm (thymoma and small-cell carcinoma).12,14,26-30 The observation that VGKC autoantibodies are present in both paraneoplastic and idiopathic cases1-15 has led to further investigation into an autoimmune, antibody-mediated etiology.

Common Pathophysiology of the VGKC Antibody-Mediated Channelopathies

Increasing evidence supports an autoimmune origin for NMT, LE, and Morvan’s syndrome. The association with autoimmune diseases and
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Neoplasms, the presence of VGKC autoantibodies in the 3 syndromes, and observations of both clinical and electrophysiological responses to decreasing antibody titers1,7,12,14,18,37 substantiate an immune mechanism. VGKCs are located in the plasma membrane of neurons and glial cells4 throughout the PNS, CNS, and ANS. Immunocytochemical studies with mouse brain suggest a concentration of VGKCs are present in the membranes of both neurons and glial cells.3-5 One study proposed that patients with NMT may have antibodies that bind only to VGKC expressed in peripheral motor neurons, whereas patients with LE may have antibodies that bind to VGKCs expressed primarily within the hippocampus.46 Kleopa and colleagues8 identified the hippocampus as a binding site for VGKC antibodies from the serum of a patient with LE. As in peripheral motor neurons, VGKCs are known to play a role in repolarization of the neuron between action potentials.2,4,17

Passive transfer studies in mice and in vitro electrophysiological experiments with NMT patient sera and IgG showed a direct effect on VGKC currents and neuronal excitability.2,7,40 In peripheral motor neurons, the VGKC antibodies cause a hyperexcitable state in the motor nerve terminal, which leads to increased acetylcholine release into the neuromuscular junction, which in turn results in the excessive muscle fiber activity that clinically defines NMT. Experiments with neuromuscular blocking agents and nerve blocking cause elimination of the excessive muscle fiber activity, supporting the peripheral nerve as the inception point of the hyperexcitable state. Furthermore, 4-aminopyridine, which specifically blocks VGKCs, causes hyperexcitability in the peripheral nerve,7 supporting the idea that the antibodies are heterogeneous and have been shown to bind to Kv1.1, Kv1.2, and Kv1.6.3,5 One study proposed that patients with NMT may have antibodies that bind only to VGKCs cause PNH.

VGKC antibodies also lead to CNS manifestations in both LE and Morvan’s syndrome. VGKCs are present in the membranes of both neurons and glial cells.4 VGKC antibodies may cross the blood-brain barrier12,14 at circumventricular sites where the blood-brain barrier is more permissive and cause encephalopathy, behavioral changes, and insomnia. Buckley and colleagues6 identified the hippocampus as a binding site for VGKC antibodies from the serum of a patient with LE. As in peripheral motor neurons, VGKCs are known to play a role in repolarization of the neuron between action potentials, leaving it hyper-excitability.2,4,17

The effect of VGKC antibodies on the autonomic system in Morvan’s syndrome is less clear. VGKC antibodies may act directly on secretory tissue resulting in hyperhidrosis, hypersalivation, and hyperlacrimation present in patients with Morvan’s syndrome.8 VGKC antibodies may indirectly affect autonomic function by altering secretion of neurohormones in the periphery14 or disrupt central autonomic regulatory centers.

Although it is established that VGKC antibodies can be present in patients with all 3 syndromes, the basis for the diversity of clinical manifestations both among and within the 3 syndromes remains speculative. One theory proposes that various VGKC subtypes are represented at different levels throughout the PNS and CNS in a patient-dependent manner and that the pattern of clinical manifestations may be the result of differences among patients in antibody specificity and/or affinity for the different VGKC subunits. Indeed, antibodies are heterogeneous and have been shown to bind to Kv1.1, Kv1.2, and Kv1.6.3,5 One study proposed that patients with NMT may have antibodies that bind only to VGKCs expressed in peripheral motor neurons, whereas patients with LE may have antibodies that bind only to VGKCs expressed mainly within the hippocampus.46 Kleopa and colleagues8 found that although sera from patients with all 3 syndromes colocalized with Kv1.1 and Kv1.2 in peripheral myelinated axons, sera from patients with LE bound with greater affinity to Kv1.1 channels, and sera from patients with NMT and Morvan’s syndrome bound preferentially to Kv1.2 and Kv1.6 channel subtypes. Interestingly, only sera from patients with LE bound to hippocampal axon terminals, suggesting the presence of a channel subtype recognized only by antibodies in patients with LE but not NMT or Morvan’s syndrome. A case of pathologic startle response responsive to immunotherapy has been reported in a patient with antibodies to VGKC with Kv1.6 pattern, suggesting that even patients with similar antibodies may have different clinical manifestations.
VGKC antibodies are not present in all patients. Reports addressing all 3 syndromes have found other humoral factors that target both known and novel antigens within the neuromuscular junction and hippocampal neuropil. These additional antibodies have been implicated in both VGKC antibody-negative and -positive patients. Some of these antibodies are known paraneoplastic antibodies that occur in associative patterns with specific tumors, whereas others are not associated with neoplasms. Further study is needed to explore the antigenic targets of the novel antibodies.

The possibility that additional autoantibodies in combination with VGKC antibodies are responsible for the varied clinical presentation must be considered. This is illustrated by a report from Maselli and coworkers on a patient with Morvan’s syndrome who had concomitant thymoma. Multiple autoantibodies were identified, and the authors suggested a pathogenic mechanism involving multiple targets throughout the PNS, CNS, and ANS, based on identification of known autoantibodies targeting a variety of antigens, including motor nerve end-plate acetylcholine receptor channels, voltage-gated calcium channels, and VGKCs.

**Diagnosis**

NMT is diagnosed in patients presenting with PNH by the classic finding of myokymic and neuromyotonic discharges on electromyography. LE should be considered in patients presenting with subacute encephalopathy and seizures. Morvan’s syndrome should be suspected clinically in the presence of neuromyotonic muscle dysfunction, CNS abnormalities, insomnia, and dysautonomia. Because NMT, LE, and Morvan’s syndrome have all been associated with neoplasm, thorough investigation for an occult malignancy in all cases is warranted. MRI results may be normal or show temporal T2 hyperintensity. Cerebrospinal fluid typically shows a mild pleocytosis with slightly elevated protein, but is normal in 25% of patients. 

Unusual features found on common observation or routine laboratory testing such as myokymia, hyperhidrosis, hyponatremia, or hypothermia may help guide the diagnosis.

Diagnosis may be further supported by (but does not require) serological testing for VGKC antibodies. Immunoprecipitation assays use 125I-α-dendrotoxin (VGKC specific) to label VGKCs. Serum from the patient is applied, and immunoprecipitation indicates the presence of VGKC antibodies. An immunohistochemical assay employing Xenopus oocytes injected with VGKC alpha-subunit complementary RNA may have greater sensitivity.

**Treatment**

Though no randomized controlled trials exist due to the rare nature of these disorders, immunotherapy involving plasmapheresis, IVIg, corticosteroids, and other immunosuppressants are the primary therapeutic strategy for patients with a VGKC channelopathy. Observations that the 3 syndromes improve in direct relation to declining serum antibody levels support the idea of a reversible, antibody-mediated pathophysiology. In addition to clinical improvement, electrophysiological and imaging improvements have been noted.

One case series has shown subsequent development of classical temporal lobe epilepsy and medial temporal sclerosis (MTS) after VGKC antibody-associated and other immune-mediated LE, raising the possibility that some cases of MTS may be the consequence of prior LE.

Although some patients have been noted to have spontaneous decreases in serum VGKC antibody levels, it seems prudent to treat all patients immediately in order to relieve symptoms, prevent dangerous complications (eg, status epilepticus, hyponatremia, cardiac arrhythmias, and sudden cardiac death), and minimize permanent CNS damage (eg, cerebral atrophy and long-term cognitive impairments). Clinical response is short term, and optimal therapy may include repeated courses of plasmapheresis and/or IVIg, along with long-term immunosuppression maintenance with corticosteroids. Additional agents, such as azathioprine, cyclophosphamide, and rituximab, have also been reported to be beneficial.

Therapy aimed at symptoms such as seizures, muscle dysfunction, hyperhidrosis, and insomnia is also important. PNH in both NMT and Morvan’s syndrome is often relieved by anticonvulsant medications such as carbamazepine and phenytoin. Carbamazepine has also been noted to improve insomnia, agitation, and autonomic symptoms in Morvan’s syndrome.

**Prognosis**

The reversibility and generally good neurological outcome of the non-paraneoplastic autoimmune forms of NMT, LE, and Morvan’s syndrome are in contrast to the paraneoplastic counterparts of all 3 syndromes. Although the paraneoplastic forms also often have associated humoral factors, their autoantibodies are usually directed at intracellular targets such as Hu, CV2/CRMP5, and Ma2. The presence of intracellularly directed antibodies is associated with poor response to treatment. In contrast, the presence of VGKC antibodies or
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The presence of VGKC antibodies or novel CNS neuropil antibodies (directed at cell membrane antigens) decreases the possibility of a concurrent neoplasm and indicates probable good response to immunotherapy. Follow-up MRI in patients with VGKC antibodies or other antibodies directed at neuronal cell membrane antigens after immunotherapy tends to show resolution of previous pathology. In contrast, serial MRI in patients with neoplasm-associated intracellularly directed antibodies shows increasing pathologic features, even after therapy.

Conclusions

VGKC antibodies may be present and play a pathologic role in both paraneoplastic and idiopathic NMT, LE, and Morvan’s syndrome. These syndromes are amenable to both symptomatic treatment and immunosuppressive therapy. Although these syndromes have historically been defined as distinct entities, the patient presented here represents a continuous spectrum of VGKC antibody-mediated clinical manifestations. Future studies should attempt to delineate easier recognition and optimal treatment of these uncommon neurologic diseases.

Main Points

- Three clinical syndromes have been associated with voltage-gated potassium channel (VGKC) antibodies: acquired neuromyotonia (NMT), limbic encephalitis (LE), and Morvan’s syndrome.
- NMT is characterized primarily by peripheral nerve hyperexcitability. In contrast to NMT, LE is defined by CNS involvement without peripheral dysfunction. Morvan’s syndrome is a combination of peripheral, central, and autonomic nervous system manifestations.
- Increasing evidence supports an autoimmune origin for NMT, LE, and Morvan’s syndrome; the association with autoimmune diseases and neoplasms, the presence of VGKC autoantibodies in the 3 syndromes, and observations of both clinical and electrophysiologic responses to decreasing antibody titers substantiate an immune mechanism.
- Because NMT, LE, and Morvan’s syndrome have all been associated with neoplasm, thorough investigation for an occult malignancy in all cases is warranted. Unusual features found on common observation or routine laboratory testing such as myokymia, hyperhidrosis, hyponatremia, or hypothermia may help guide the diagnosis.
- The presence of VGKC antibodies or novel CNS neuropil antibodies (directed at cell membrane antigens) decreases the possibility of a concurrent neoplasm and indicates probable good response to immunotherapy.

References

VGKC Antibody-Mediated Syndromes continued


