Neuromyotonia and myokymia
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Introduction

Overview

Neuromyotonia and myokymia are related disorders of peripheral nerve hyperexcitability manifest respectively as muscle stiffness and twitching. Both conditions are typically related to disorders of the voltage-gated potassium channel and caused by autoimmune, toxic, or genetic processes. In this update, the author offers a clinical and electromyographic guide to the diagnosis and treatment of these intriguing syndromes.

Key points

• Generalized neuromyotonia is usually an autoimmune disease characterized by widespread muscle stiffness and delayed muscle relaxation after voluntary movement. It is accompanied by continuous muscle twitching known as myokymia.
• Electromyography of the affected muscles shows either electrical neuromyotonia (high-frequency trains of decrementing motor unit discharges that start and stop abruptly) or electrical myokymia (grouped discharges recurring semi-rhythmically at a rate of 2 to 10 Hz).
• These phenomena also occur in episodic ataxia type 1, an autosomal dominant hereditary disease.
• Autoimmune neuromyotonia responds to treatment with sodium channel-blocking drugs (carbamazepine, phenytoin, mexiletine), corticosteroids, plasmapheresis, and high-dose intravenous human immunoglobulin.

Historical note and terminology

The terms “neuromyotonia” and “myokymia” have both been used to describe clinical phenomena as well as distinct patterns of abnormal electrical discharge recorded during needle electromyography. This dual nomenclature has created confusion over the years, but no other set of clearer definitions has yet been universally accepted. In this review, we will address and distinguish the clinical syndromes of neuromyotonia and myokymia, the electromyographic discharges defined by these terms, and their relationships.

Clinical neuromyotonia is a syndrome of persistent muscle stiffness, delayed muscle relaxation, and continuous muscle twitching due to abnormal electrical discharges of motor nerves. Originally described by Gamstorp and Wohlfart in 1959, it has also been called “Isaacs syndrome” (Isaacs 1961) and “myokymia with impaired muscle relaxation” (Gardner-Medwin and Walton 1969), but it is now mostly called “neuromyotonia” (Mertens and Zschocke 1965). Needle EMG recordings from affected muscle show abnormal electrical activity of either the type known as electrical neuromyotonia or the type known as electrical myokymia, or both. These EMG findings are discussed in this article.

Clinical myokymia refers to the presence of focal or generalized continuous muscle twitching, often exhibiting a rippling, “bag of worms” appearance under the skin. Needle EMG recordings from the twitching muscle can show either very frequent fasciculations, electrical neuromyotonia, or electrical myokymia.

Clinical manifestations

Presentation and course

Focal neuromyotonia has mainly been reported in the extraocular muscles. Ocular neuromyotonia causes episodic diplopia lasting a few seconds when an ocular muscle contracts spontaneously or remains contracted after voluntary eye deviation (Shults et al 1986). There are several reported cases of focal neuromyotonia affecting the third and fourth fingers on 1 hand, resembling Dupuytren contracture or focal dystonia. All of the patients had chronic
obstructive lung disease and had been treated with a beta-sympathomimetic drug (Modarres et al 2000; Jamora et al 2006; Gantenbein et al 2010).

In generalized neuromyotonia, there is persistent muscle stiffness that is more pronounced in the distal than in the proximal limbs and occurs more in the limbs than in the trunk or cranial muscles. The hands often have adducted fingers resembling the posture of tetany. The stiffness worsens during activity, and there is delayed muscle relaxation after voluntary movement resembling active myotonia; however, there is no percussion myotonia. Posture may be abnormal with exaggerated kyphosis, and movement is stiff and slow. Weight loss is common. The muscles may be well-developed, and sweating may be prominent, possibly because heat is generated by the excessive and constant muscle activity (Auger 1994). However, direct autonomic nervous system involvement could also explain the hyperhydrosis. Dyspnea may result from tightening of the respiratory muscles. Bulbar and laryngeal muscles may be affected. The tongue and jaw become stiff, making swallowing difficult, and the voice turns hoarse (Isaacs 1961). In addition to the abnormal stiffness, there is usually continuous muscle twitching (clinical myokymia), which is most pronounced in the distal limbs. This abnormal muscle activity persists during sleep and is not relieved by general anesthesia or spinal anesthesia; it is reduced but not abolished by proximal peripheral nerve blocks and is abolished by curare or botulinum toxin. The discharges are, therefore, thought to arise in the nerve rather than in the perikaryon or neuromuscular junction.

In addition to the above findings, physical examination demonstrates normal or depressed tendon reflexes, sometimes with a mild coexisting sensorimotor peripheral neuropathy. Carpopedal spasm with flexion of the wrist, extension of the fingers, and plantar flexion of the feet may be seen, resembling tetany, but serum calcium and magnesium are normal.

A rare type of generalized neuromyotonia known as Morvan syndrome consists of neuromyotonia, hyperhidrosis, burning pain, and a fluctuating encephalopathy manifest by insomnia, delirium, and hallucinations (Lee et al 1998; Barber et al 2000; Liguori et al 2001).

In laboratory studies, CSF is normal except for the presence of oligoclonal IgG bands in about half of the cases. Antibodies that immunoprecipitate [125I]alpha-dendrotoxin-labeled voltage-gated potassium channels extracted from mammalian brain tissue (VGKC antibodies) are likewise present in 40% to 50% of cases (Newsom-Davis and Mills 1993). As explained in the Etiology section, in most cases, the true target of these antibodies is either contactin-associated protein 2 (Caspr2) or leucine-rich glioma inactivated 1 (Lgi1), and these antibodies can now be assayed directly (Irani et al 2010). Nerve conduction tests may reveal a mild sensorimotor axonal polyneuropathy.

Electromyography shows either electrical neuromyotonia or myokymia (Table 1), or a combination of the two. Electrical neuromyotonia consists of high-frequency (150 to 300 Hz) trains of decrementing single motor unit discharges, which usually start and stop suddenly and can last for up to several seconds. The decrement in amplitude occurs within the train, although the train starts and stops abruptly. When processed and subjected to audio output on an EMG system, these high-frequency discharges can produce sounds ranging from a “ping” to a high-pitched whine. They can occur spontaneously or may be induced by electrical stimulation, nerve ischemia, percussion of the nerve, or needle movement (Gutmann 2001a; Gutmann and Gutmann 2004). After voluntary activation, there are typically prolonged neuromyotonic afterdischarges corresponding to the delayed muscle relaxation. In other cases, EMG reveals electrical myokymia, which consists of rhythmic or semirhythmic bursts of waveforms representing single motor units firing as doublets, triplets, or multiplets. The individual spike frequency within each burst averages from 30 to 40 Hz but ranges from 2 to 62 Hz, and total burst duration is usually 100 to 900 ms. The bursts usually repeat at a frequency of 2 to 10 Hz but may be as slow as 0.05 Hz (1 burst every 20 seconds). Myokymic discharges are usually spontaneous and are not affected by electrical stimulation, needle movement, percussion, or sleep and may or may not be precipitated by exercise.

<table>
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<th>Table 1. EMG Characteristics of Neuromyotonia and Myokymia</th>
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<td>Neuromyotonia</td>
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• Single MUAP firing rapidly
• 150 to 300 Hz discharges in long trains
• Trains occur at random intervals
• Train duration up to several seconds
• Decrementing train
• Trains start and stop abruptly
• Spontaneous or induced by electrical stimulation, nerve ischemia, percussion of the nerve, needle movement, or voluntary activation

Table 2. Causes of Myokymia

**Focal myokymia**

*Peripheral nervous system*
- Bell palsy
- Neurovascular cranial nerve compression

*Central nervous system*
- Neoplastic/inflammatory meningoencephalitis
- Anoxic and ischemic rhombencephalopathy
- Syringobulbia
- Cardiopulmonary arrest
- Subarachnoid hemorrhage

*Generalized myokymia*
- Chronic inflammatory demyelinating polyneuropathy
- Episodic ataxia with myokymia (EA1)
- Timber rattlesnake envenomation
- Mercury poisoning

Focal myokymia is associated with diverse syndromes and disorders of both the central and peripheral nervous system. Radiation plexitis, Guillain-Barré syndrome, multiple sclerosis, pontine tumor, timber rattlesnake envenomation, and ocular myokymia due to neurovascular compression are all potential causes of focal myokymia. Myokymia appears in 60% to 70% of radiation-induced brachial or lumbosacral plexopathies; it may involve a few muscles with relatively preserved strength and can persist for many years after irradiation. The presence of myokymia in a symptomatic extremity following radiation of a mass lesion in the vicinity of the plexus favors radiation injury over tumor recurrence, although myokymic discharges may rarely appear with tumor infiltration of the plexus as well. Transient myokymia occurs in 17% of Guillain-Barré cases and may last up to 6 weeks. It is more common in the face (where it is usually bilateral), involves mildly weak muscles, and is seen more often in women. In multiple sclerosis, myokymia is also more common in the face and is also transient, but it can last up to 3 months. It is usually unilateral, involves nonparetic muscles, can recur on the same or opposite side, and may respond to injection with botulinum toxin type A. In contrast, posterior fossa tumors cause persistent and unilateral myokymia. Although pontine glioma is the most likely neoplasm to cause myokymia, it may also appear with cerebellar astrocytomas, schwannomas, and pontine metastases. Facial myokymia and myokymia in a bitten extremity are also features of timber rattlesnake envenomation. In these cases, facial myokymia is caused by a hematogenous spread of the venom and resolves within several hours of antivenin administration. Myokymia produces an abduction and adduction tremor of the fingers when the arm is bitten or a vertical tremor of the toes when the leg is attacked, each of which typically resolves over 3 days (Gutmann 1991). Persistent facial myokymia may also be a focal manifestation of K⁺ channel antibody syndrome (Gutmann et al 2001b).

Generalized myokymia is present as part of any of the neuromyotonic syndromes. It may be one feature of mercury poisoning, which also causes hyperhidrosis, neuromyotonia, constipation, tremor, and encephalopathy. Generalized myokymia can also be seen in timber rattlesnake envenomation, episodic ataxia with myokymia (EA1), and a few cases of chronic inflammatory demyelinating polyneuropathy (Gutmann 1991; Browne et al 1994).

**Prognosis and complications**

Clinical neuromyotonic syndromes may remit after immunotherapy, and in rare cases may resolve spontaneously (Auger 1994).
The prognosis of clinical myokymia is dependent on the associated disorder causing it. Myokymia associated with Guillain-Barré syndrome is transient, whereas that associated with multiple sclerosis is also transient, but can recur. Myokymia in brainstem tumors is usually persistent, unless antineoplastic therapies are successful. In cases of postirradiation plexopathy, myokymia can persist for many years.

**Clinical vignette**

**Clinical neuromyotonia.** For 3 years, starting at 42 years of age, this man noted progressive limb muscle stiffness. At first there were cramps and twitching in both calves, which gradually spread to involve the arms, trunk and face. The stiffness was worse with exercise, but improved if he continued the activity. His wife reported that the stiffness persisted in sleep, and he was occasionally awakened by the cramps. He complained of excessive fatigue and generalized weakness and had lost 30 pounds. The rigidity made walking difficult, and tightening of the chest wall muscles occasionally produced shortness of breath. Speech and swallowing were unaffected. There were no sensory symptoms.

He had no other clinical disorders. He took no medications and had no allergies. He had smoked until 30 years of age, drank alcohol socially, and had never used illicit drugs. No one in his family suffered from any neurologic or autoimmune disorders.

On examination he had prominently well-developed muscles of the trunk and limbs, which were in a state of constant contraction. Twitching was observed in the thighs and upper arms. He was sweating despite normal ambient temperature. Examination of the cranial nerves was unremarkable. Strength was mildly reduced in the proximal muscles of the arms and legs. Muscles relaxed slowly after contraction, but there was no carpal or pedal spasm. Tendon reflexes were normal. Coordination and sensory examinations were normal. Gait was slow and stiff. Laboratory evaluation revealed normal serum potassium, calcium and magnesium concentrations. Thyroid studies were normal. Serum creatine kinase was mildly elevated at 260 (less than 195 = normal). Serum anti-voltage-gated potassium channel antibodies were elevated. Oligoclonal bands were present in otherwise unremarkable cerebrospinal fluid. Chest CT showed no evidence of thymoma or tumor of the lung. Nerve conduction studies were normal, but EMG revealed both neuromyotonic and myokymic discharges along with fibrillations and fasciculations in multiple tested muscles of the arms and legs, worse distally.

A course of plasmapheresis (6 exchanges over 12 days) resulted in marked improvement in stiffness. He was subsequently given oral prednisone at a dose of 1 mg/kg per day. Symptoms continued to improve and the dose was slowly tapered over the next 11 months. Eventually, he stopped the steroids entirely without relapse. He remained well 2 years later off all medications.

**Clinical myokymia.** A 35-year-old woman with relapsing-remitting multiple sclerosis for 7 years presented with a 2-week history of persistent twitching of the right facial muscles. No facial weakness or numbness was reported. There was no double vision and speech and swallowing were unaffected.

She had no medical problems other than multiple sclerosis and had not had any surgeries. She had been on interferon beta 1a for 4 years. Other medications included baclofen for leg spasticity and oxybutynin for a hyperactive bladder. Family history was unremarkable.

Examination revealed continuous fine, worm-like movements of the right facial muscles. The remainder of the cranial nerve examination was normal except for a partial right sixth cranial nerve palsy.

Needle EMG of the right frontalis, orbicularis oculi, nasalis and orbicularis oris showed myokymic discharges. MRI of the brain showed a small demyelinating lesion in the right pons.

She declined treatment with carbamazepine for fear of side effects. The abnormal movements stopped spontaneously 2 weeks later. They recurred twice, for 3 weeks and 1 week respectively, over the next 2 years.

**Biological basis**

**Etiology and pathogenesis**

Generalized neuromyotonia is usually a sporadic autoimmune disease (Newsom-Davis and Mills 1993; Newsom-Davis...
A minority of neuromyotonic syndromes is hereditary and occurs either in isolation or with periodic ataxia or inherited neuropathies. Most patients with episodic ataxia type I have clinical or electrophysiological neuromyotonia, mainly in facial and hand muscles. This autosomal dominant disorder is caused by mutations in the KCNA1 potassium channel gene (Tomlinson et al 2013). An autosomal recessive form of hereditary axonal motor neuropathy associated with neuromyotonia has been linked to loss-of-function mutations of HINT1, which encodes histidine triad nucleotide-binding protein 1, a type of purine phosphoramidase. Mutations of this gene were found in 11% of patients with autosomal recessive peripheral neuropathy, and in 76% of patients with axonal neuropathy plus neuromyotonia (Zimon et al 2012).

Neuromyotonia is a prominent feature of a rare autosomal recessive genetic disease known as the Schwartz-Jampel syndrome, or chondrodystrophic myotonia. Affected children have a very distinctive appearance, including wry facies, short stature, spondylo-epiphyseal dysplasia, a hunched posture due to muscle stiffness, slow muscle relaxation after voluntary contraction, and percussion myotonia (Taylor et al 1972). Electromyography demonstrates continuous high-frequency electrical discharges at rest; these are abolished by curare, which also produces muscle relaxation (Taylor et al 1972). The disorder is caused by mutations of the gene coding for perlecan, the major heparan sulfate proteoglycan of basement membranes. Studies of perlecan-deficient mice suggest that the abnormal nerve activity arises in distal motor nerves, perhaps in nerve terminals (Bangratz et al 2012). The presence of percussion myotonia, however, implies that the excitable muscle membrane is also affected (Taylor et al 1972).

A 53-year-old man developed paroxysmal neuromyotonia at the age of 40 (Pulkes et al 2012). The attacks lasted 5 to 6 hours, were provoked by exercise, and responded to acetazolamide plus carbamazepine. Although the family history was negative, the syndrome resembles a hereditary disorder, such as a channelopathy.

Using [125I]alpha-dendrotoxin immunoprecipitation assay VGKC antibodies are found in 40% to 50% of patients with acquired neuromyotonia (Vincent 2000; Gutmann 2001a; Van Parijs et al 2002). However, recent laboratory investigations have revealed that the antibodies rarely bind to potassium channel subunits. Instead, 2 main antigen targets have been discovered: leucine-rich glioma-inactivated 1 (Lgi1) and contactin-associated protein-2 (Caspr2) (Irani et al 2010; Lai et al 2010). Both proteins are complexed with VGKCs in extracts of mammalian brain tissue. Lgi1 is the principal target of VGKC antibodies in patients with limbic encephalitis, whereas Caspr2 is the principal target of VGKC antibodies in patients with neuromyotonia and Morvan syndrome. Of 56 patients with limbic encephalitis attributed to VGKC antibodies in a laboratory, 49 had Lgi1 antibodies and 7 had Caspr2 antibodies; of 13 patients with VGKC-antibody neuromyotonia or Morvan syndrome, 10 had Caspr2 antibodies and 3 had Lgi1 antibodies (Irani et al 2010). In a study of 29 patients with Morvan syndrome, of whom 93% were male, Irani and colleagues detected VGKC-complex antibodies in 79% (Irani et al 2012). Of 24 sera tested, only Caspr2 antibodies were found in 6 patients, both Caspr2 and Lgi1 antibodies in 15 patients, and only Lgi1 antibodies in 3 patients. Tumors, mainly thymoma, were associated with Caspr2 antibodies and a poor prognosis, whereas hyponatremia was associated with Lgi1 antibodies. It is not yet known whether antibodies to Lgi1 or Caspr2 can be found in the serum of neuromyotonia patients who lack VGKC antibodies. A role for aberrant immunologic activation in acquired clinical neuromyotonia is strongly supported not only by the presence of the aforementioned antibodies in the serum, but also by oligoclonal bands in the CSF and by clinical improvement following immunomodulatory therapy with plasmapheresis or IVlg. Further suggestive clinical evidence includes a clear association with thymoma, myasthenia gravis, lung cancer, and neuronal ganglionic anti-acetylcholine receptor antibodies (Vernino et al 1998; Hart et al 2002). The neurologic disorder appears at the same time or after the diagnosis of myasthenia in patients with clinical neuromyotonia associated with myasthenia gravis, but in patients with lung cancer, the hyperexcitability syndrome may predate the tumor diagnosis by an average of 2 years (Hart et al 2002). Passive transfer of clinical neuromyotonia to animals can be achieved by injection of purified IgG from patients with neuromyotonia into mice, in which an antibody-mediated attack on peripheral nerve potassium channels can be demonstrated in vitro (Sinha et al 1991). The neuromyotonic variant, Morvan syndrome, is also associated clinically with thymoma, myasthenia gravis, psoriasis, and atopic dermatitis, and serologically, it can be associated with anti-ganglionic-acetylcholine receptor antibodies or anti-voltage gated K channel antibodies (Lee et al 1998; Barber et al 2000; Liguori et al 2001).

Although most cases of thymoma-related neuromyotonia are associated with VGKC (usually Caspr2) antibodies, one such patient lacking VGKC antibodies was found instead to have ANNA-1 (anti-neuronal nuclear) antibodies (Tsivgoulis et al 2014). After total resection of the tumor, both the antibodies and the neuromyotonia disappeared.

Clinical neuromyotonia may also appear as a consequence of intoxication with mercury, 2,4-dichlorophenoxyacetic
acid, dichlorophenyldichloroethylene and with drugs such as penicillamine (Newsom-Davis and Mills 1993) and oxaliplatin (Wilson et al 2002). VGKC-antibody positive neuromyotonia has been reported after a wasp sting (Turner et al 2006). A patient with MuSK antibodies without myasthenia exhibited frequent fasciculations and neuromyotonia of facial and bulbar muscles, probably originating in hyperactive motor nerve terminals (Simon et al 2013). A case of generalized neuromyotonia was reported after human papilloma virus immunization (Cerami et al 2013). Paraneoplastic neuromyotonia has been reported with thymoma (Newsom-Davis and Mills 1993), hypernephroma (Canovas et al 2007), bronchogenic carcinoma, bladder carcinoma (Forte et al 2009), and Hodgkin disease (Lahrmann et al 2001). Clinical neuromyotonia has also been described in central pontine myelinolysis, essential thrombocytethemia, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, spinal epidural abscess, amyloidosis, and chronic graft-versus-host disease. A patient with focal neuromyotonia of both legs, especially when walking, was found to have compression of the lumbosacral nerve roots by severe spinal stenosis (Raut et al 2013).

A review of the literature on ocular neuromyotonia revealed that 16 of 30 patients had received radiation therapy to the sellar and parasellar regions, and 8 cases of ocular neuromyotonia resulted from compressive lesions such as supraclinoid aneurysm, basilar artery dolichoectasia, mucormycosis of the cavernous sinus, arachnoiditis, and Graves disease (Yuruten and Ilhan 2003). In a case of ocular neuromyotonia, vascular compression of the oculomotor nerve by the posterior cerebral and superior cerebellar arteries was identified by 3D MRI and successfully treated by surgical microvascular decompression (Inoue et al 2012). Paroxysmal ocular neuromyotonia involving a single eye muscle has recently been described in 2 girls with brainstem demyelinating disease, one with multiple sclerosis and the other with probable neuromyelitis optica (Menon et al 2014).

Clinical myokymia, in contrast, most commonly occurs as a component of other disorders (See Table 2). Although it rarely causes serious symptoms directly, it remains important as a possible presenting symptom of much more serious disease.

Focal myokymia may be caused by multiple sclerosis, pontine tumors, Guillain-Barré syndrome, radiation plexitis, and, rarely, timber rattlesnake envenomation. Facial myokymia may also be seen in Bell palsy, syringobulbia, polyradiculoneuropathy, central pontine myelinolysis, tuberculosis, meningeval carcinomatosis, meningeal sarcoidosis, lymphocytic meningoradiculitis, basilar invagination, phosgene poisoning, and hemifacial spasm. Facial myokymia can also occur spontaneously after brain death (Saposnik 2001). Limb myokymia occurs in chronic inflammatory demyelinating polyneuropathy, rare compressive neuropathies, syringomyelia, spinal stenosis, conus medullaris teratoma, radiculopathy, neurocysticercosis, subarachnoid hemorrhage, and following cardiopulmonary arrest.

As we have seen, generalized myokymia is a major feature of clinical neuromyotonia. Myokymia is also an important feature of episodic ataxia type 1, which is caused by mutations of the voltage-gated potassium channel, KCNA1. Some individuals with this mutation have had isolated neuromyotonia (Pessa and Hanna 2009). An autosomal dominant familial syndrome of dyskinesia and facial myokymia has also been reported (Fernandez 2001). Myokymia of the lower face and tongue, increased by voluntary activation, is a characteristic feature of Kennedy disease or X-linked spinal and bulbar muscular atrophy (Olney et al 1991). Myokymic discharges and, occasionally, clinical myokymia may sometimes be seen in other denervating disorders such as neuropathy.

The abnormal electrical activity of neuromyotonia arises from peripheral nerves. The activity takes the form of motor unit potentials or fragments thereof, and the frequency of the discharges (up to 300 Hz) is much higher than can arise from motor neurons. Nerve block experiments suggest that discharges arise at various sites along the nerve because distal nerve blocks tend to reduce the activity to a greater extent than proximal nerve blocks, but only the blockade of neuromuscular transmission with curare or botulinum toxin completely abolishes the activity.

In autoimmune neuromyotonia, it is thought that antibodies directed against Caspr2, Lgi1, or other unidentified antigens alter the expression of VGKCs in the plasma membrane of peripheral nerve, preventing potassium efflux and chronically lowering the resting membrane potential, which results in decreased repolarization and neuronal hyperexcitability (Sinha et al 1991; Newsom-Davis and Mills 1993). In Morvan syndrome, the combination of encephalopathy and clinical neuromyotonia suggests that these antibodies may affect VGKCs in both the central and peripheral nervous system (Barber et al 2000). Hart and colleagues (Hart et al 1997) demonstrated the reactivity of neuromyotonic IgG with dendrotoxin-sensitive VGKCs (“fast” K+ channels), and later patch clamp studies demonstrated that both sera and IgG from patients with neuromyotonia suppressed voltage-gated outward K+ current through indirect mechanisms (Nagado et al 1999). These findings suggest that the autoantibodies may decrease
channel density, either through increased degradation or by decreased expression of VGKCs (Arimura et al 2002).

The VGKC is also involved in episodic ataxia type 1, an autosomal dominant disorder characterized by myokymia and episodes of cerebellar ataxia lasting up to several minutes. The symptoms are due to mutations in highly conserved regions of the VGKC subunit Kv1.1, with high expression in the basket cells of the cerebellum and in the axons of peripheral nerves (Browne et al 1994; Pessia and Hanna 2009).

Clinical myokymia (focal and generalized) results from the myokymic discharge of 1 or several motor units, producing brief tetanic contractions 1 to 2 centimeters wide in neighboring muscle segments. These slow, irregular and independent contractions result in a continuously rippling appearance of the skin overlying the muscle (Kimura 2001). Myokymia may result from disruption of the biochemical microenvironment of an injured axon, causing regional and repetitive membrane hyperexcitability. As with neuromyotonic discharges, the site of origin of myokymic discharges can include virtually any segment of the motor axon, from the perikaryon to the terminal branches. Terminal branch generators are probably less common in myokymia than in neuromyotonia, however, because local nerve block often abolishes these discharges (Gutmann 1991). In an animal model, myokymic-like discharges originated in experimentally demyelinated axons at the site of demyelination. A number of mechanisms appeared to contribute to these discharges, including local ephaptic transmission (ie, the abnormal spread of an action potential between 2 or more injured axons at a point of abnormal physical or electrical contact); a proximal impulse of unidentified source; and spontaneously depolarization of the membrane at the point of demyelination (Gutmann 1991).

In humans, local axonal disturbance leading to myokymia may be caused by demyelination (multiple sclerosis, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, radiation plexopathy), edema (pontine tumors), toxins (rattlesnake envenomation and clozapine administration), and ischemia, but not usually by nerve compression without the above changes. Nerve lesions associated with myokymic discharges are more likely to be chronic than acute.

Epidemiology

Clinical neuromyotonia is uncommon, and neuromyotonic discharges remain extremely rare. Clinical and electrical myokymia are much more common. No specific data about the precise incidence or prevalence of either condition are available in the literature.

Prevention

Apart from the avoidance of known toxins or medications (ie, penicillamine, oxaliplatin, clozapine), there are no known preventative measures for either neuromyotonia or myokymia.

Differential diagnosis

The muscle stiffness of neuromyotonia could be confused with stiff-person syndrome, and the delayed muscle relaxation could be mistaken for myotonia. Both diagnoses are easily ruled out on clinical and electromyographic grounds. In stiff-person syndrome, muscle rigidity is usually greatest in the trunk and axial muscles, is accompanied by reflex muscle spasms, is not accompanied by myokymia, and is very painful. The abnormal activity is abolished by spinal anesthesia or peripheral nerve block. On EMG, one observes motor unit discharges at frequencies not exceeding 50 Hz, as would be expected from a central disorder. The delayed muscle relaxation of active myotonia is accompanied by percussion myotonia, as well as by typical myotonic discharges on EMG; percussion myotonia does not occur in neuromyotonia, and the EMG findings are different.

Clinical myokymia (focal and generalized), in its purest form, is usually more easily separated from other disorders, but should be taken seriously as a possible indicator of a more significant, separate disease process, especially when focal. The undulating sensation under the skin may be confused with diffuse fasciculations and motor neuron disease. However, no upper motor neuron signs are present on exam, no muscular atrophy or weakness is noted, and EMG clearly distinguishes myokymia from fasciculation. Facial myokymia may be confused with a variety of other disorders, including blepharospasm (dystonic contractions of the orbicularis oculi muscle) and hemifacial spasm (manifested by tonic and clonic contractions of facial muscles). Hemimasticatory spasm is a similar condition affecting the trigeminal nerve and muscles of mastication. These disorders produce distinctly different findings on EMG, with myokymia demonstrating characteristic bursts of motor unit activation and blepharospasm demonstrating intermittent full
contractions indistinguishable from voluntary activation. Hemifacial spasm may be more difficult to distinguish, as it produces irregular, rhythmic bursts of motor unit activity, although most patients with this disorder have more dramatic muscle activation than patients with myokymia. Both myokymia and hemifacial spasm can develop after facial nerve lesions, including Bell palsy. Isolated orbicularis oculi myokymia frequently occurs as a benign phenomenon in otherwise normal individuals, producing twitching of the lower eyelid, exacerbated by stress, sleep deprivation and the use of caffeine and other stimulants. Tetany (due to hypocalcemia or alkalosis) may resemble myokymia on EMG, but electrolyte measurements and the Trouseau test help to define tetany.

Diagnostic workup

Electromyography is the primary diagnostic tool. The EMG characteristics of neuromyotonia and myokymia have already been defined.

In cases of clinical neuromyotonia, serum studies should include a complete blood count, calcium, magnesium, phosphate, potassium, sedimentation rate, thyroid function tests, and immunologic function tests. Serum creatine kinase activity is usually mildly elevated. Assays for antibodies to VGKC, Caspr2, and Lgi1 are commercially available. Although lumbar puncture is not mandatory in all cases, CSF analysis may show elevated gamma-aminobutyric acid levels (Sakai et al 1983) and oligoclonal bands (Kimura 2001). A CT or MRI of the chest should be performed to rule out a thymoma, lung cancer, or other tumor. Muscle biopsy may be indicated in some cases, depending on the clinical manifestations.

Clinical or electrical myokymia necessitates a search for an underlying etiology. An EMG must be performed. Serum studies should include a complete blood count and serum electrolytes, including calcium and magnesium. Imaging of the brain and spinal cord, usually with contrast, may be necessary to rule out a structural lesion. CSF examination may be needed to search for signs of multiple sclerosis, Guillain-Barré, and other causes of meningeal inflammation.

Management

Sodium channel-blocking drugs such as phenytoin, carbamazepine, and mexiletine, which act as membrane-stabilizing agents, are often helpful in reducing muscle stiffness in patients with neuromyotonia. The drugs are not always effective, however, and some patients respond, inexplicably, to centrally acting agents such as valproic acid (Auger 1994) or baclofen (Newsom-Davis and Mills 1993). One patient with thymoma-associated generalized neuromyotonia refractory to other treatments responded dramatically to dronabinol, a cannabinoid agent (Meyniel et al 2011). There are a number of anecdotal reports testifying to the effectiveness of various immunomodulatory treatments for acquired generalized neuromyotonia. These include corticosteroids, azathioprine, mizoribine, plasmapheresis, and intravenous immunoglobulin. None of these treatments has been efficacious in all cases, although plasmapheresis seems to have the best record (Bady et al 1991; Sinha et al 1991; Newsom-Davis and Mills 1993; Ishii et al 1994; Heidenreich 1998; van den Berg et al 1999; Nakatsuji et al 2000). Although intravenous immunoglobulin has been effective as a sole agent in 2 cases (Ho and Wilson 1993; Alessi et al 2000), it was ineffective in one (van den Berg et al 1999) and detrimental in another (Ishii et al 1994). After immunoglobulin failed in the latter 2 of these cases, plasmapheresis proved effective. A combination of a sodium channel-blocking drug and immunomodulating therapy may be more effective than either drug alone (Newsom-Davis and Mills 1993).

In the largest series of patients with "neuromyotonia," 19 patients treated with intravenous methylprednisolone, 1 gm/day for 5 days, had "significant amelioration of complaints" persisting during follow-up of 1 to 2 years (Panagariya et al 2006). However, the physical findings were not well documented, and although all patients had myokymia, only 5 had stiffness before treatment. Prolonged remission has been described in other cases (Isaacs 1974), but usually lifelong treatment is required.

Clinical myokymia, either focal or generalized, usually responds to phenytoin and carbamazepine in antiepileptic doses (Gutmann 1991). Myokymia alone usually does not pose a functional problem, and many patients may not require treatment. However, a full work-up for an underlying etiology is mandatory.

Special considerations

Anesthesia

Little information is available in the literature about anesthesia in patients with Isaacs syndrome. A patient with
neuromyotonia showed increased sensitivity to rocuronium, a nondepolarizing muscle relaxant (Ginsburg et al 2009). Shyr and colleagues reported a patient with neuromyotonia who was anesthetized with propofol without effect on the abnormal muscle activity. Administration of the nondepolarizing muscle relaxant atracurium produced complete relaxation. Anesthesia was maintained with propofol and nitrous oxide without any complications (Shyr et al 1997). Interestingly, although diazepam and baclofen produced no effect on the abnormal muscle activity preoperatively, a small dose of diazepam was effective in the immediate postoperative period.

Clinical and electrical neuromyotonia respond to muscle relaxants working at the neuromuscular junction but not to general or spinal anesthesia.

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**References especially recommended by the author or editor for general reading.

**Former authors**

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**ICD and OMIM codes**

**ICD codes**

ICD-9:
Facial myokymia: 351.8

ICD-10:
Facial myokymia: G51.4

**OMIM numbers**

Dyskinesia, familial, with facial myokymia: %606703

**Profile**

**Age range of presentation**

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance**

male=female

**Family history**

family history may be obtained

**Heredity**
heredity may be a factor

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

- upper motor neuron lesions
- compressive myelopathy
- amyotrophic lateral sclerosis
- myotonic disorders
- myotonia congenita
- stiff person syndrome
- tetanus
- strychnine
- diffuse fasciculations
- motor neuron disease
- blepharospasm
- hemifacial spasm
- hemimasticatory spasm
- hypocalcemic tetany
- hypomagnesemia

**Associated disorders**

- Acute inflammatory demyelinating polyneuropathy
- Continuous autosomal dominant familial dyskinesia
- Facial myokymia
- Familial paroxysmal kinesigenic ataxia
- Guillain-Barré syndrome
- Isaacs syndrome
- Morvan syndrome
- Multiple sclerosis
- Normocalcemic tetany
- Ocular neuromyotonia
- Pseudomyotonia
- Quantal squander

**Other topics to consider**

- Central nervous system complications of radiation
- Charcot-Marie-Tooth disease type 1B and mutations of the myelin protein zero
- Gold neurotoxicity
- Ion channels and neurologic disorders
- Nocturnal leg cramps
- Paraneoplastic syndromes
- Paroxysmal dyskinesias
- Radiation plexopathy