

Isaacs' Syndrome (Autoimmune Neuromyotonia) in a Patient with Systemic Lupus Erythematosus

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ABSTRACT. Patients with systemic lupus erythematosus (SLE) often produce autoantibodies against a large number of antigens. A case of SLE is presented in which muscle twitching and muscle cramps were associated with an autoantibody directed against the voltage-gated potassium channel of peripheral nerves (Isaacs' syndrome). (J Rheumatol 2005;32:757-8)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS
ISAACS' SYNDROME

AUTOIMMUNE NEUROMYOTONIA
CHANNELOPATHY

Systemic lupus erythematosus (SLE) is a multi-system illness characterized by autoantibody production and inflammatory damage to tissues and organ systems. Neuromuscular symptoms may be the result of inflammatory myopathy or peripheral neuropathy. Inflammatory myopathy may be discovered by electromyography (EMG) and muscle biopsy. Peripheral neuropathy is diagnosed by nerve conduction studies and sural nerve biopsy.

The SLE patient in this case report developed muscle twitching and muscle cramps. Isaacs' syndrome (autoimmune neuromyotonia) was diagnosed by typical EMG findings and the discovery of an autoantibody to the voltage-gated potassium channel (VGKC) of motor nerve axons. The association of SLE with Isaacs' syndrome has been observed infrequently.

CASE REPORT

The patient is a 45-year-old white woman who developed SLE at age 28. The patient's illness began with joint pain, fever, malar rash, cough, dyspnea, and oral ulcers. A cytoid body was observed in the left fundus. Laboratory abnormalities included leukopenia, anemia, hypocomplementemia, antinuclear antibodies (1:5120), and anti-DNA antibody binding (58.6%) by the Farr assay. Urinalysis revealed 2+ proteinuria and microscopic hematuria. Twenty-four hour urine protein excretion was 1300 mg and creatinine clearance was 77 ml/min. Chest radiograph revealed bilateral interstitial infiltrates and pleural effusions. Renal biopsy showed an increase in mesangial cells.

The patient was treated initially with prednisone 60 mg daily. Joint pain became the patient's main complaint once the acute illness had subsided and methotrexate (MTX) was added. The dose of prednisone was tapered and the patient was treated with MTX, nonsteroidal antiinflammatory drugs, and intermittent low doses of prednisone with fair suppression of the joint symptoms. At age 41 the patient noted bilateral calf muscle twitching which progressed over the next year to involve the proximal leg muscles,

trunk and abdominal muscles, muscles in the arms, and rarely the muscles of the face. The muscle twitching was worse with exertion and was associated with cramping in the arm and leg muscles.

There was no muscle weakness on examination. Diffuse continuous fasciculations were observed in the muscles of the legs, particularly in the calf. Mental status, cranial nerves, reflexes, and sensory examination were all normal. Sodium, potassium, calcium, magnesium, creatine phosphokinase, parathyroid hormone, liver function tests, and thyroid function tests were all normal. Single motor unit discharges in doublets, triplets, and occasional quadruplets were observed by EMG examination of muscles of the upper and lower extremities, most prominently in the gastrocnemius muscles. Fasciculations were also reported. Nerve conduction studies of upper and lower extremity nerves were normal. After 18 months of symptoms VGKC antibodies were measured at 0.06 nmol/l by Mayo Medical Laboratories, Rochester, MN, USA. Normal values are less than 0.02 nmol/l. Repeat measurement 3 years later was 0.02 nmol/l. Because of the clinical and EMG findings, Isaacs' syndrome (autoimmune neuromyotonia) was diagnosed and the patient was treated with gabapentin and clonazepam with some improvement in muscle twitching. Carbamazepine was tried but was not tolerated by the patient. Other treatments reported to be effective in Isaacs' syndrome such as plasmapheresis were not considered due to the relatively mild nature of the patient's symptoms.

Except for mild proteinuria at SLE onset at age 28 the patient's renal function tests remained normal until age 45 when proteinuria was again detected. Urine sediment was benign, creatinine clearance was 77 ml/min, and 24-h urine protein excretion was 2200 mg. Renal biopsy revealed mesangial proliferative lupus glomerulonephritis and segmental membranous nephropathy. Treatment with prednisone 60 mg daily and azathioprine 100 mg daily was begun for renal disease and for symptoms of joint pain and severe fatigue. With this treatment the patient's muscle twitching failed to improve and fasciculations could still be observed. There was some reduction in muscle cramping.

DISCUSSION

Isaacs' syndrome was first described in 1961 in 2 patients with persistent generalized muscle stiffness and weakness in whom spontaneous rapid discharges of motor unit potentials were observed by EMG¹. Isaacs' syndrome is characterized by widespread myokymia (muscle twitching) and cramps and may be associated with muscle hypertrophy, muscle weakness or stiffness, pseudomyotonia (delayed muscle relaxation), increased sweating, and rarely paresthesia².

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When accompanied by central nervous system symptoms such as insomnia and hallucinations, the illness is designated Morvan's syndrome. The hallmark of neuromyotonia is the spontaneous burst discharge of single motor units as doublets, triplets, or multiplets as demonstrated by EMG². Neuromyotonia may be either inherited or acquired.

Resting potential of neurons and action potentials responsible for impulse conduction are generated by ion currents and ion channels. Most ion channels are gated, meaning that they can transition between conformations that are open or closed to ion conductance. Individual ion channels are distinguished by the specific ions they conduct and by whether they directly sense voltage or ligands such as neurotransmitters. Action potentials are normally generated by the opening of sodium channels and the inward movement of sodium ions. Depolarization of the neuronal membrane opens potassium channels, resulting in outward movement of potassium ions, repolarization, and closure of the sodium channel.

Immune-mediated channelopathies were first shown in disorders of the neuromuscular junction in which the acetylcholine receptor (ligand-gated sodium channel) was found to be the target channel protein in myasthenia gravis³. Subsequently antibodies against the voltage-gated calcium channel were discovered in the Eaton-Lambert myasthenic syndrome⁴. Most recently, acquired neuromyotonia has been associated with antibodies directed against the proteins of the VGKC⁵.

Acquired neuromyotonia is considered an autoimmune disorder because of the presence of antibodies against the VGKC in most patients. Acquired neuromyotonia may be associated with other autoimmune disorders such as myasthenia gravis and with tumors that are recognized to produce autoantibody-mediated, paraneoplastic disorders such as thymoma⁶. One case of autoimmune neuromyotonia has been linked to administration of penicillamine, a drug known to precipitate autoimmune disease⁷. Single case reports have been published describing the association of autoimmune neuromyotonia with systemic sclerosis, juvenile rheumatoid arthritis, and dermatomyositis⁸⁻¹⁰. In a review of 42 patients with clinical and EMG evidence of neuromyotonia, 38% had raised titers of VGKC antibodies and one patient was noted to have SLE with anti-dsDNA antibodies¹¹. Plasma exchange and immunosuppressive drug treatment have resulted in clinical and EMG improvement in patients with acquired neuromyotonia.

A functional VGKC comprises 4 transmembrane alpha subunits that associate with 4 intracellular beta subunits. Six VGKC alpha subunit genes have been isolated. Autoantibodies have been detected against 3 of the 6 gene products in patients with autoimmune neuromyotonia¹². Mutations have been identified in alpha subunit genes in patients with hereditary neuromyotonia¹³. The hyperexcitability of peripheral nerves in patients with neuromyoto-

nia is likely due to a reduction in the number of functional voltage-gated potassium channels.

SLE is a chronic disorder of unknown cause in which a dysregulated immune system results in the production of autoantibodies which, in concert with inflammatory mediators, damage tissues. Antibodies have been detected against histones, ds and ssDNA, cardiolipin, RNA-protein complexes, and immunoglobulins as well as many less common and often uncharacterized autoantibody specificities^{14,15}. Autoantibodies in SLE contribute to pathogenesis in clinical illness, for example, anti-dsDNA antibody in patients with nephritis. Based upon the findings in our patient, it is tempting to speculate that the autoimmune neuromyotonia and VGKC autoantibodies were related to her SLE.

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