Case Report

Isaac's Syndrome Associated with CIDP and Pregnancy

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Abstract

Neuromyotonia with all its synonyms is a disorder of peripheral nerve hyperexcitability characterized by regular or irregular myokymia, muscle cramps and stiffness, delayed muscle relaxation after contraction, and hyperhidrosis associated with well-described spontaneous electromyographic features. Herein, we report clinical and electrodiagnostic findings of a pregnant woman with neuromyotonia who also suffered from chronic inflammatory demyelinating polyneuropathy. We treated the patient with plasma exchange, 50 mL/kg (twice weekly, for six weeks). After two weeks of treatment, cramps and stiffness were substantially reduced. After four weeks, she looked normal with a relatively smooth gait. After eight weeks, the patient was entirely well with no cramps or stiffness. Repeat EMG showed no myokymic discharges. After four months she was in good health and the plasma exchanges continued every other week without the use of corticosteroids or cytotoxic agents. Afterwards, we discontinued the plasma exchange and only visited the patient regularly. One year later, we repeated a five-day course of plasma exchange to overcome mild recurrence of myokymia in her thighs. Now, after four years, she is healthy without any disability or problem. The patient's child has been healthy throughout without any evidence of neuromyotonia.

Keywords: chronic inflammatory demyelinating polyneuropathy, Isaac's syndrome, neuromyotonia, pregnancy

Introduction

Neuromyotonia with all its synonyms is a paradoxical entity, in part because of its remarkable clinical pleomorphism, uncertain natural history and anecdotal response to an assortment of treatments.[1] It is a disorder of peripheral nerve hyperexcitability characterized by regular or irregular myokymia, muscle cramps and stiffness, delayed muscle relaxation after contraction (pseudomyotonia), and hyperhidrosis associated with well described spontaneous electromyographic features. Neuromyotonia is usually an acquired immuno-mediated disorder occurring in isolated form or associated to autoimmune diseases, such as myasthenia gravis.[2–6]

Herein, we report clinical and electrodiagnostic findings of a pregnant woman with neuromyotonia who, after further investigations was diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP).

Case Report

A 24-year-old female patient referred to our electrodiagnosis laboratory for evaluation of muscle cramps. Previously, the impression of myotonia congenita had been proposed for her.

She was a young, alert, slender lady with chief complaints of severe cramps in her arms and legs. Gait was extremely stiff and laborious with superficial similarity to the movements of reptiles (armadillo gait). The symptoms appeared nine months before during the fourth month of her pregnancy with myokymia, muscle cramps and night sweats. Four months before, she had delivered a healthy boy through normal vaginal delivery without any complications. She had severe cramps and stiffness in all four limbs, most noticeably in the legs. Muscle stiffness were persisted during sleep. She had been prescribed phenytoin and carbamazepine in the last nine months, which were ineffective to relieve her symptoms; however, the symptoms had progressed relentlessly and generated a great disability.

The patient did not report any history of fever, chills, joint pain, and rash. There was no history of toxic exposures and she had been completely healthy before the pregnancy. General examination including skin, respiratory, cardiovascular, gastrointestinal, and urinary systems was also normal. On neurological examination, she was alert and oriented with intact cranial nerves. On motor examination, there was reduced bulk and atrophy in all four limbs; in addition, accurate estimation of strength was not possible because of severe cramps and stiffness in all four limbs. She had diffuse myokymia, especially in the lower limbs. On sensory examination, loss of pain, temperature, and vibration were detected in the distal parts of all four limbs. She exhibited reduced deep tendon reflexes (grade 1) at the biceps, triceps, and brachioradialis on both sides. Likewise, the deep tendon reflexes were absent on both knees and ankles, bilaterally. Plantar reflex was also flexor on both sides and cerebellar tests were normal as well.

In electrodiagnostic studies (EDX) all sensory and motor nerve conduction velocities (NCVs) were reduced and conduction block was detected in most of the examined motor nerves (Table 1). In electromyography, there were detectable diffuse fasciculation potentials in all four limbs associated with continuous motor unit activity (CMUA) and bursts of motor unit potentials along with intraburst frequencies of 40 – 100 HZ.

Frozen and paraffin embedded sections of nerve biopsy from the sural nerve revealed demyelination and mild epineural, endoneural and perivascular infiltration of lymphocytes without evidence of fibrinoid necrosis. On CSF examination, there was evidence of increased protein (93 mg/dL) in the cerebrospinal fluid with no increase in the number of white blood cells (albuminocytologic dissociation).

With the possible impression of neuromyotonia, an immunoprecipitation assay applying alpha dendrotoxin was used for detection of anti-VGKC antibody, which was positive [titer=684 Pico moles (pM); titer greater than 100 pM was considered positive].

The laboratory tests for vasculitis including anti-nuclear antibody, anti-double strand DNA, anti-phospholipid antibody, anti-cardiolipin antibody and LE-cell were negative. No evidence of thymoma or lung cancer was found on thoracic CT scan. Ace-

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Table 1. Motor and sensory nerve conduction studies of the patient before and after plasma exchange (PE).

Nerves		Latency (ms)		Amplitude (mv)		NCV (m/s)		Proximal amplitude decrement (%)*	
		Before PE	After PE	Before PE	After PE	Before PE	After PE	Before PE	After PE
Motor nerves	Rt median	4.8	4.4	4.3	4.4	33	38	74	60
	Lt median	4.4	4.3	4.9	4.9	35	40	52	41
	Rt ulnar	4.1	3.8	5.2	5.4	31	39	65	52
	Lt ulnar	3.9	3.6	4.8	4.9	28	32	66	48
	Lt tibial	7.1	7.0	2.9	2.9	24	29	45	42
	Rt tibial	8.3	7.9	2.8	2.9	27	30	38	33
	Lt peroneal	6.9	6.8	2.1	2.4	30	33	77	51
	Rt peroneal	7.7	7.2	2.3	2.5	31	34	63	53
Sensory nerves	Rt median	3.9	3.7	8.4	10.8	38	39		
	Lt ulnar	4.4	4.1	10.9	12.4	33	35		
	Lt sural	6.4	5.8	6.2	7.1	29	31		

*Conduction block=proximal amplitude decrement of more than 50% in comparison with distal part. Rt=right; Lt=left; ms=millisecond; mv=millivolts; m/s=meter per second; NCV=nerve conduction velocity.

tylcholine receptor antibody and test for thyroglobulin antibody were negative. Total abdominal sonography detected no lymph node enlargement.

She was treated with plasma exchange of 50 cc/kg, twice weekly for six weeks. After two weeks of treatment, cramps and stiffness relieved radically. After four weeks, she looked normal with a relatively smooth gait.

Repetition of the nerve conduction study revealed improvement of nerve conduction velocities in both sensory and motor nerves (Table 1) and profound decrease of CMUA. Myokymic discharges overshadowed by CMUA in a previous study were apparent.

After eight weeks, the patient was entirely well with no cramps or stiffness. On the third EMG, there were no myokymic discharges noted. After four months, she was in good health; the plasma exchanges were administered every other week without the use of corticosteroids or cytotoxic agents. Afterwards, we discontinued the plasma exchange and only visited the patient regularly. One year later, we repeated a five-day course of plasma exchange to overcome mild recurrence of myokymia in her thighs. Currently, after four years, she is healthy without any disability or problem. The patient's child has continual follow up visits by a pediatric neurologist; he is also healthy without any evidence of neuromyotonia.

Discussion

Our patient is the first instance of Isaac's syndrome associated with CIDP during the pregnancy that terminated in normal vaginal delivery of a live, healthy boy. This case is unique from several aspects: i) this is the first instance of Isaac's syndrome associated with CIDP that initiated during pregnancy; ii) pregnancy continued for about five months without any complications, thus neuromyotonia may not have adverse effects on the course of pregnancy; iii) vaginal delivery was uneventful without complications; and iv) finally, after three years of follow up, the patient's son is completely healthy with no signs of neuromyotonia found in repeated visits, which suggests that anti-VGKC antibodies may not pass through the placenta.

Isaac's syndrome has been postulated to be an autoimmune channelopathy, probably by affecting voltage gated potassium channels (VGKC) leading to excitation and abnormal discharges.[7–10] It is significant that the patient's plasma or IgG can transfer the electrophysiological features to mice and reduce VGKC currents *in vitro*.[11] Spontaneous discharges seem to be mostly generated at sites distal to the terminal axon branching points.[12]

Most patients present with muscle cramps, delayed relaxation, muscle hypertrophy, increased sweating, slowly progressive weakness, muscle spasms and stiffness, fasciculations, and myokymia.[13,14] Our patient also presented with cramps, stiffness, sweating, and myokymia. Isaac's syndrome occurs most often as a paraneoplastic syndrome in patients with cancers of the immune system, such as lymphoma and thymoma.[6,15] It is also associated with other immune mediated diseases, including systemic lupus erythematosus, myasthenia gravis, Hashimoto's thyroiditis, dermatomyositis[7,8,16,17] and chronic hepatitis B infection.[18] Peripheral neuropathy is sometimes present and some reports describe the association of neuromyotonia and neuropathy.[6,7,19–23] Recently, other associated disorders noted are chronic obstructive pulmonary disease, episodic ataxia and congenital heart disease.[16,24,25] Nerve conduction studies are usually normal,[13] but may be slowed due to accompanying peripheral neuropathy.[26] Hyperexcitability of the nerves, demonstrated by repetitive discharges which follows M-wave, are occasionally observed[27] and high amplitude, long duration, and polyphasic F-waves after either tibial nerve or peroneal nerve stimulation have been described.[28] Needle EMG shows continuous motor unit activity at rest with bursts of rapid-firing discharges and myokymic discharges which are unaffected by spinal anesthesia but diminished by peripheral nerve block and completely abolished by local curarization.[13,14] Muscle biopsy may show type two-fiber atrophy[13] and nerve biopsy may be normal or show evidence of axonal degeneration and demyelination.[6,14]

Muscle cramping, twitching and stiffness are usually responsive to phenytoin and carbamazepine.[13,14] Most patients show moderate to marked response to plasma exchange.[7,15,28] Response to prednisone and azathioprine has also been mentioned.[14]

In our patient, all the above mentioned secondary causes were ruled out by appropriate tests. Only peripheral neuropathy was detected in the form of CIDP. It is noticeable that only one case of CIDP associated with Isaac's syndrome has been reported in the literature.[14] The exact mechanism provoking excess muscle activity in acquired neuropathy is not defined, but the activity is believed to originate in the peripheral nerves at the sites of focal demyelination. Factors that could contribute to the generation of CMUA at the sites of focal demyelination include alteration in sodium and potassium currents, change in the composition of the extracellular fluid, and stretch-sensitive ion channels at the sites.[29,30]

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