MITOCHONDRIAL NEUROGASTROINTESTINAL ENCEPHALOMYOPATHY (MNGIE)

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Abstract- Mitochondrial neurogastrointestinal encephalo-myopathy (MNGIE) is a rare autosomal recessive disease caused by thymidine phosphorylase (TP) gene mutation. Here we report a patient with MNGIE in whom sensorimotor polyneuropathy was the first presenting symptom and had a fluctuating course. This 26-year-old female patient developed acute-onset demyelinating polyneuropathy from the age of 6 with two relapses later on. In addition, she had gastrointestinal symptoms (diarrhea, recurrent abdominal pain), progressive weight loss and ophthalmoparesis. Brain magnetic resonance imaging showed white matter abnormalities, and muscle biopsy showed ragged red fibers. This constellation of clinical and laboratory findings raised the diagnosis of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). This report highlights the uncommon clinical characteristics of this rare disease.

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Key words: MNGIE, mitochondrial encephalomyopathy, neuropathy, cachexia, ophthalmoparesis

INTRODUCTION

Mitochondrial neurogastrointestinal encephalo-myopathy (MNGIE) is a rare autosomal recessive disease caused by thymidine phosphorylase (TP) gene mutation (1). It is clinically characterized by ptosis, progressive external ophthalmoplegia, gastrointestinal dysmotility, cachexia, peripheral neuropathy, mitochondrial myopathy and leukoencephalopathy (2). The age at onset varies considerably. It may begin between 6 months and 40 years of age (3). Gastrointestinal symptoms are the most common initial manifestations. It is a chronic and progressive disease which causes death in early to middle adulthood (3).

Here we report a patient with MNGIE in whom sensorimotor polyneuropathy was the first presenting symptom and had a fluctuating course.

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CASE REPORT

This 26-year-old woman was the product of an uncomplicated pregnancy and delivery. Parents were first cousins. Psychomotor development was normal. At the age of 6, she developed acute symmetrical limb weakness with numbness and burning sensation in hands and feet which evolved in a few days. Her condition gradually improved after a month with complete recovery. Since the age of 7, she complained of recurrent abdominal pain, diarrhea, borborygmi, loss of appetite and dry mouth. She had a slender body habitus. Hirsutism was noted from early teens and her evaluation including pelvic sonography and hormonal work-up were normal. At age 19, she weighed 41 kg and was 162 cm tall. At that time, she developed secondary amenorrhea. 8 months later, she developed weakness more prominent distally, tingling in hands and feet and mild diplopia. There was mild loss of vibration and pinprick sensations in distal lower extremities. Deep tendon reflexes were absent. She was able to walk only with aid. Nerve conduction studies were interpreted as demyelinating sensorimotor polyneuropathy.

She was diagnosed as Guillain-Barre syndrome (GBS) but received no specific treatment. Over the following weeks, she had a notable spontaneous improvement. She achieved the ability to ambulate independently but with residual distal weakness and numbness in her feet. During the past few years, she had muscle cramps lasting a few minutes in her legs and gradually began to experience mild dysphagia.

In April 2003, she underwent an extensive evaluation for weight loss and gastrointestinal discomfort. Upper gastrointestinal contrast radiography revealed hypotonic stomach and dilated duodenum. Biopsy samples obtained during an upper GI endoscopy showed mild non-specific inflammatory changes. Barium enema and colonoscopy were normal. Blood tests including creatine kinase, total proteins and lipids, thyroid function tests, folic acid, vitamin B12, liver function tests, anti-gliadin and anti-endomysial antibodies and glucose tolerance test were normal. A mild increase in stool fat content (9.1 gram/24 hours) was observed. Nerve conduction studies demonstrated prolonged distal latency of median and ulnar motor responses with decreased conduction velocities (Table 1). She had no family history of a similar illness. She was diagnosed with anorexia nervosa and depression and was treated with nortriptyline. After treatment with a course of oral antibiotics, she reported partial improvement in gastrointestinal problems. 4 months later there was an acute clinical deterioration consisting of generalized weakness, increased paresthesia and transient diplopia. Neurologic examination revealed limitation of eye movement in all directions but no ptosis, mild facial and neck flexor weakness, severe distal weakness and muscle atrophy, absent deep tendon reflexes and loss of vibration and pinprick sensations in a glove-stocking distribution. Fundi were normal.

She had clubbing in her fingers and severe cachexia (weight = 31 kg). Nerve conduction studies showed loss of motor and sensory responses (Table 1). CSF analysis revealed an elevated protein (295 mg/dL) with no cells. Brain MRI showed white matter abnormalities in cerebrum, brainstem and cerebellum on T2-weighted and FLAIR images and minor changes in thalami and basal ganglia (Fig.1). Serum arylsulfatase A and creatine kinase were normal. Muscle biopsy revealed ragged red fibers on Gomori-trichrome staining.

Table 1. Nerve conduction studies

	Apr 2003	**Sep 2003**	**Jun 2004**
Sural sensory	NR	NR	NR
Median sensory	NR	NR	NR
Ulnar sensory	NR	NR	NR
Median motor (APB)			
Latency (ms)	6.5	NR	NR
Amplitude, wrist/elbow (mv)	1.8/1.5		
Velocity (m/s)	19.9		
Ulnar motor (ADM)			
Latency (ms)	5.4	NR	5.2
Amplitude, wrist/below elbow/above elbow (mv)	12.4/10.9/9.9		0.1/ 0.1/ 0.1
Velocity, elbow-wrist/across elbow (m/s)	23.7/21.9		19.3/36.2
Peroneal motor (EDB)	NR	NR	NR
Peroneal motor (TA)			
Latency (ms)	7.7	6.6	5.5
Amplitude, fibular head/knee (mv)	1.1/1.2	2.1/2.3	0.1/0.2
Velocity, knee-fibular head (m/s)	23	27.9	24
Tibialis motor (AH)	NR	NR	NR

Abbreviations: NR, no response obtainable; APB, abductor pollicis brevis; ADM, adductor digiti minimi; EDB, extensor digitorum brevis; TA, tibialis anterior; AH, abductor hallucis.

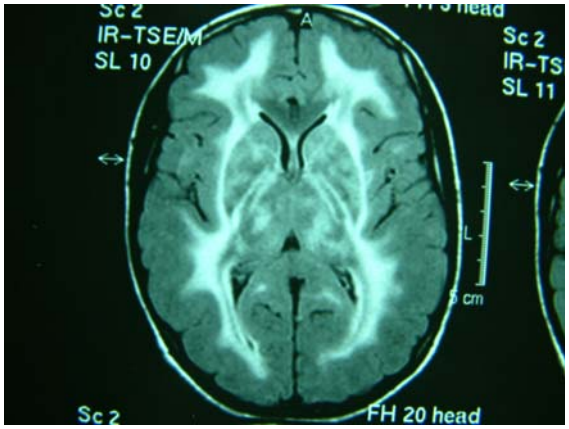

Fig. 1. Axial FLAIR MR, displaying signal abnormalities in white matter, thalami and basal ganglia.

Over the next few months, she had a slight improvement in symptoms attributed to her neuropathy, but she lost another 5 kilograms of weight. Another nerve conduction study in June 2004 showed no significant change (Table 1).

DISCUSSION

Clinical and laboratory characteristics in this patient including symmetric weakness with a fluctuating course, areflexia, impaired proprioceptive sense, elevated CSF protein and electrophysiologic findings are indicative of a demyelinating neuropathy. A few diseases may cause these features including chronic inflammatory demyelinating polyneuropathy (CIDP), recurrent GBS, Refsum disease and mitochondrial disorders. Although ophthalmoparesis and cerebral white matter abnormalities have been described in CIDP patients (4, 5), they are infrequent. A long interval between first and second relapses (14 years), cachexia and gastrointestinal manifestations make CIDP quite unlikely. In some GBS patients, one or more recurrences have been reported (6). Our patient had 3 recurrences of acute neuropathy but the presence of leukoencephalopathy and severe cachexia are suggestive of other underlying diseases.

Refsum disease is an inherited neuropathy which is prone to recurrence (7). Absence of ichthyosis, retinitis pigmentosa and deafness and presence of cerebral white matter abnormalities and also ophthalmoparesis in our patient are against this diagnosis. Metachromatic leukodystrophy is a lysosomal storage disorder associated with white matter abnormalities and demyelinating neuropathy (8). However, normal amounts of serum arylsulfatase A and presence of other clinical findings (such as cachexia and ophthalmoparesis) besides absence of ataxia and pyramidal signs, removes it as a diagnostic possibility.

In accordance with clinical features and presence of ragged red fibers on muscle biopsy, this case has been diagnosed as MNGIE. In MNGIE patients, peripheral neuropathy has been described as a clinical feature with insidious onset and a progressive or relapsing course (9). To the best of our knowledge, this is the first patient with MNGIE in whom peripheral neuropathy had several acute onset relapses.

Peripheral neuropathy is a consistent feature of all MNGIE patients, but is uncommon as the initial symptom (3). Our case suffered from a demyelinating peripheral neuropathy which was the first presentation of the disease.

Leukoencephalopathy is one of the diagnostic criteria in MNGIE (3) and is a very useful finding in differentiating MNGIE from pseudo-MNGIE. Previous studies did not mention any abnormalities of gray matter. In this patient, increased signal intensity in thalami and basal ganglia which was evident on T2-weighted and FLAIR images, were suggestive of gray matter involvement (Fig.1).

Diarrhea, abdominal cramps and borborygmi in MNGIE are thought to be the result of dysmotility and neuromuscular dysfunction (3). Bacterial overgrowth may also play a role and improvement of gastrointestinal symptoms with antibiotic therapy in our patient maybe suggestive for this.

As mentioned earlier, this patient also had hirsutism and clubbing of fingers. Hirsutism is reported as a clinical manifestation in some mitochondrial diseases other than MNGIE (10). In this patient, normal hormonal study and pelvic sonography indicate that hirsutism may be due to MNGIE. Since there is no better explanation for her finger clubbing, this may also be the result of her mitochondrial disease.

In summary, our MNGIE patient had an acute onset fluctuating neuropathy. It is important to consider mitochondriopathy in any patient with neuropathy and multi-organ involvement.

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