Myasthenia Gravis with Concomitant Severe Paraspinal Muscle Degeneration and Mitochondrial DNA\textsuperscript{4977} Deletion

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Abstract

Recent reports have discussed the many causes of dropped head syndrome and bent spine syndrome. We described a case of myasthenia gravis with concomitant severe degeneration of spinal muscle, mitochondrial DNA\textsuperscript{4977} deletion and sensorineural deafness. These associations were thought to be independent, however this is an important case to consider the etiology of bent spine syndrome.

Key words: myasthenia gravis, mitochondrial DNA\textsuperscript{4977} deletion, paraspinal muscle degeneration, sensorineural deafness

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Introduction

Recent reports have discussed the many causes of dropped head syndrome and bent spine syndrome. We describe a case of myasthenia gravis with concomitant severe degeneration of erector spinae muscle, mitochondrial DNA\textsuperscript{4977} deletion and sensorineural deafness.

Case Report

A 56-year-old woman had had trouble running from about the age of 10 years old. At age 15, she first experienced difficulty ascending and descending stairs without manual assistance. However, the severity of these symptoms fluctuated considerably. At age 27, she was diagnosed as having hyperthyroidism and began therapy with thiamazole. Soon after, she suffered dysphagia, diplopia, muscle weakness of the extremities and dysarthria after dinner. At age 28, she was admitted to our hospital and diagnosed as having myasthenia gravis because of a positive edrophonium chloride test and evidence of waning on a repetitive nerve stimulation test. Needle EMG revealed myogenic changes; her serum creatine kinase (CK) level fluctuated between 100-185 IU (14-105 IU). She was then treated with pyridostigmine bromide. At age 29, thiamazole treatment was stopped, but the level of antithyroid antibody remained high. At age 31, she began to suffer bilateral deafness. At age 39, an extended thymectomy was performed; pathological examination of the thymus revealed hyperplasia. During surgery, an intercostal muscle biopsy was performed, and the biopsy specimens showed myogenic changes including variation in fiber diameters and increased presence of central nucleus; but ragged-red fiber was not detected. The anti-acetylcholine receptor (ACh-R) antibody titer was 747 nmol/l (<0.2). Subsequently, alternate-day prednisolone treatment was started. The dose was gradually increased to 100 mg, and then gradually decreased. The patient was able to continue with her ordinary daily activities without myasthenic symptoms. Prednisolone treatment was stopped after 2 years. At age 41, her audiogram revealed sensorineural deafness, particularly at 2000 Hz/110 dB. She was treated with 120 mg pyridostigmine bromide. There was no evidence of muscle weakness in the extremities, and she was able to squat and stand, but she complained muscle weakness in her waist. At age 47, abdominal CT scan performed, because of questionable cholecystolithiasis, revealed degeneration of left erector spinae muscle (Fig. 1a). At age 48, sensorineural deafness deteriorated and mitochondrial DNA\textsuperscript{4977} deletion was detected; however, serum lactic and pyruvate acid levels remained normal. Ubidecarenone 90 mg/day was started, but there was no clinical improvement. At age 51, the patient...
was unable to bend her back to an angle 20 degrees from standing position. And also mitochondrial DNA
3243, DNA3271 (MELAS) and DNA8344 (MERRF) deletions were negative (by PCR-RFLP method). At age 56, her extremity muscle strength is 5/5, except for her head forward flexion muscle, lumbar level T2-weighted MRI image showed about same conditions as shown in the CT scan at age 47 (Fig. 1b). Skeletal muscles MRI revealed slight atrophic changes with fatty degeneration in the bilateral biceps femoris, semitendinosus and semimembranosus muscles (Fig. 1c).

**Family history**

At age 26, our patient gave birth to a girl who later died of meningitis. At age 29, she had a second girl. The infant suffered from asphyxia and was considered as having neonatal myasthenia gravis. She had bilateral facial paralysis, bilateral deafness, and could not speak until 2 years old. At age 16, serum CK was normal, and anti ACh-R antibody titer was 0.33 nmol/l. At age 17, congenital anomalies of bilateral auditory ossicles were detected. Subsequently, she had a replacement operation of bilateral artificial stapes. Then, her hearing improved and she no longer needed a hearing aid. At age 19, mitochondrial DNA4977 deletion was detected. Now she is 27 years old, and she has no muscle weakness and is even able to go to skiing.

**Discussion**

The present patient was diagnosed as having autoimmune myasthenia gravis because of fluctuated muscle weakness in the extremities, ptosis, dysphagia, dysarthria, a positive edrophonium chloride test, evidence of waning on a repetitive nerve stimulation test, a positive anti-ACh-R antibody, the presence of anti-thyroid antibody, and because of the effectiveness of anticholinesterase medications. However, the presence of mild serum CK elevation and unusual needle EMG and muscle biopsy findings suggest myopathy of unknown etiology.

Mitochondrial DNA4977 deletion is associated with neurodegenerative disorders including ALS, Alzheimer disease and Parkinson’s disease, as well as with sensorineural deafness, cardiomyopathies and aging. We have never seen the association with myasthenia gravis in the literature. Although this deletion has typically been described in relatively older persons (1), however, Ueda et al. (2) found that the presence of this deletion is not correlated with age. In-
Indeed our patient’s daughter had the same deletion. Although our patient had selective degeneration of her skeletal muscles, there was no ragged-red fiber in the intercostal muscle biopsy specimens, and lactic and pyruvate acid levels were normal. Mitochondrial myopathy can be difficult to differentiate from myasthenia gravis, because both are characterized by ptosis and easy fatigability (3, 4). There have been only a few reports of an association between myasthenia gravis and mitochondrial myopathy (5, 6). Therefore, we think this case who has a common mitochondrial DNA4977 deletion, does not have so-called mitochondrial myopathy.

Both dropped head syndrome and bent spine syndrome are caused by paraspinal muscle degeneration, and many potential causes have been reported (Table 1). Examinations of paraspinal muscle have revealed myogenic changes (7, 8, 9), with occasional detection of ragged-red fibers and cytochrome oxidase negative fibers; a small number of cases with neurogenic changes have been reported (10). There is only one report detailing the histochemical examination of both skeletal and paraspinal muscles (7): unfortunately the findings were contradictory. Myogenic changes were noted on EMG, but fibrillation potentials suggesting denervation were sometimes detected. Serum CK levels were normal or slightly elevated. Some authors discuss different etiology between these two syndromes (11).

Myasthenia gravis associated with paraspinal muscle degeneration was reported in 2 patients with dropped head syndrome (12, 13). Mitochondrial myopathy associated with bent spine syndrome has also been reported (7, 9). The region of paraspinal muscle degeneration is cervical and/or upper thoracic levels in dropped head syndrome, and lower thoracic and/or lumbar levels in bent spine syndrome. Severe paraspinal muscle degeneration evident on CT or MRI images, as in our patient, is rare, but cases of mitochondrial myopathy (7), inflammatory myopathy (9), old poliomyelitis and progressive muscular dystrophy (14) have been reported.

We have examined and treated 320 patients with myasthenia gravis over the past 35 years. Although assessment routinely included MRI or CT scan to detect thymoma, we have never before encountered a patient with paraspinal muscle degeneration. In the present patient, paraspinal muscle degeneration began many years before; serum CK levels had been elevated for the previous 28 years and the first CT scan was taken 9 years before. We speculate that the paraspinal muscle degeneration is a result of idiopathic generalized myopathy, because she also had skeletal muscle abnormalities. In this patient, although paraspinal muscle degeneration was present, her spine was still straight. This finding is compatible with reports suggesting that bent spine syndrome and dropped head syndrome occur in relatively old persons. Further investigation will needed, when her spine starts to bend.

Table 1. Secondary Forms of Paraspinal Muscle Degeneration

<table>
<thead>
<tr>
<th>Spinal disorders</th>
<th>Postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis</td>
<td>Spinal osteoid osteoma</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>Spasmodic torticollis</td>
</tr>
<tr>
<td>Torsion spasm</td>
<td>Neurovascular diseases</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Duchenne dystrophy</td>
</tr>
<tr>
<td>Limb girdle dystrophy</td>
<td>Facioscapulohumeral dystrophy</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Progressive spinal atrophy</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Nemaline myopathy</td>
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<tr>
<td>Mitochondrial myopathy</td>
<td>Metabolic disorders</td>
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<tr>
<td>Pompe disease,</td>
<td>McArdle disease</td>
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<tr>
<td>Carnitine deficiency</td>
<td>Psychiatric</td>
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<tr>
<td>Camptocormia</td>
<td>Hysterical</td>
</tr>
<tr>
<td>Manic depressive disease</td>
<td>Normal age-progressive phenomenon</td>
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</tbody>
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References

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