Myasthenia Gravis, Muscle Twitch, Hyperhidrosis and Limb Pain Associated with Thymoma: Proposal of Possible New Myasthenic Syndrome

YOSHIHIRO WAKAYAMA, SADAYOSHI OHBU and HITOSHI MACHIDA

Division of Neurology, Department of Medicine, Showa University Fujigaoka Hospital, Yokohama 227


We describe a 54-year-old man with myasthenia gravis, thymoma, systemic muscle twitch particularly of both lower limbs, hyperhidrosis and lower limb pain. The muscle twitch resembled to fasciculation rather than to myokymia and was persistent after discontinuation of anti-acetylcholinesterase drug. No attenuation nor disappearance of the muscle twitch was educed by spinal anesthesia. However, it disappeared when a nondepolarizing type muscle relaxant (pancuronium bromide) was used. The muscle twitch was thus considered to originate from peripheral axons. Thymoma was considered to be involved in the pathogenesis of these unusual clinical manifestations which may constitute a new myasthenic syndrome.

In myasthenia gravis (MG) spontaneous muscle twitch, such as fasciculation, is rare except for special situations such as overdose of an anti-acetylcholinesterase drug or coexistence of hyperthyroidism. We experienced a patient with MG who had, in addition, muscle twitch mainly in both lower limbs, hyperhidrosis and lower limb pain, as cardinal manifestations. We previously reported this patient in Japanese literature (Wakayama and Ohbu 1982) when thymoma was not found. Thymoma found later is now considered to be important in the pathogenesis of this condition. As far as we know, there have been a few descriptions of MG and
these complex clinical features associated with thymoma (Kitahara et al. 1981; Kawamura et al. 1984). It would thus be interesting and important to present this case, and to consider the cause of this muscle twitch in relation to thymoma. We also feel that MG, thymoma, muscle twitch, hyperhidrosis and limb pain may constitute a constellation of neuromuscular symptoms and signs that can presumably be attributed to the thymoma and autoimmune mechanism.

CASE REPORT

A 54-year-old man who was engaged in clerical work was healthy until November 1979 when he noticed diplopia. In our clinic in April 1980 diplopia and right blepharoptosis, which were improved by edrophonium chloride, were found. He was diagnosed as having MG and the administration of anti-acetylcholinesterase drug was initiated. In June he began to have weakness of his proximal upper limbs despite the use of an anti-acetylcholinesterase drug. From December 1980, in addition to these signs and symptoms, severe muscle twitch appeared in his upper and lower limbs especially in his calves. He also had profound perspiration which required him to change underwear every hour, and lower limb pain began. He was admitted to our clinic in February 1981. Past history revealed epididymitis and lung tuberculosis, but no family history of neuromuscular disease.

General physical examination revealed nothing unremarkable on admission. Neurological examination revealed a mild to moderate degree of bilateral blepharoptosis more marked in the right side and mild to moderate limitation of upward gaze in both eyes more marked in the left side. Other cranial nerves were intact. Deep tendon reflexes were normal. Mild to moderate degree of muscle weakness was detected in the proximal muscles of 4 limbs without muscle atrophy. Generalized muscle twitch, which was considered to be fasciculation, was observed and was particularly severe at his calves. No sensory disturbance was noted. Pain in both lower limbs and remarkable hyperhidrosis were present.

The laboratory studies. Complete blood count, urinalysis, serum electrolytes including calcium and phosphate, serum protein, serum creatine phosphokinase and aldolase, blood urea nitrogen, serum cholesterol, transaminases and lactate dehydrogenase, routine test of cerebrospinal fluid content, thyroid function (T3, T4, T3-U, thyrotropin stimulating hormone), and serum IgG, IgA and IgM were normal. Chest roentgenogram showed the presence of old pulmonary tuberculosis. Serum anti-acetylcholine receptor antibody was measured three times by the methods of Lindstrom et al. (1976). The results were 15.0 nmol/l (normal value less than 0.5) on March 11, 25.1 on April 30, and 18.0 on July 1, 1981. Serum anti-striated muscle antibody was also positive.

Needle electromyogram showed the presence of fasciculation potentials composed of polyphasic motor unit potentials at rest. At maximal contraction, full interference patterns were observed. The repetitive stimulation of right deltoid muscle revealed the waning phenomenon at relatively low frequencies such as 5 and 10 Hz.

The surface electromyogram showed the motor unit potentials at rest (Fig. 1). The motor conduction velocity was 52.7 m/sec for the right median nerve, 60.6 m/sec for right ulnar nerve, and 47.1 m/sec for right tibial nerve. The sensory conduction velocity was 69.4 m/sec for right median nerve and 44.0 m/sec for right tibial nerve.

Muscle biopsy of the right vastus lateralis muscle under local anesthesia was macroscopically normal. The cryosections were stained with hematoxylin and eosin (HE), Gomori's trichrome, nicotinamide adenine dinucleotide (NAD) dehydrogenase and adenosine triphosphatase (ATPase). In HE and Gomori's trichrome stain, the muscle was normal and no lymphorrhage was evident. Histochemical preparation using NAD dehydrogenase and ATPase staining showed a tendency of fiber type grouping (Fig. 2). Paraffin embedded biopsied sural nerve was stained with HE, Masson's trichrome and Bodian's silver stains.
These specimens were all normal.

The clinical course. Muscle twitch, hyperhidrosis, and lower limb pain appeared about 8 months after administration of anti-acetylcholinesterase drug. We considered that these clinical manifestations were probably due to administration of excessive anti-acetylcholinesterase drug, so the drug was discontinued for at least one month. The muscle twitch decreased in frequency, but was still present, and discontinuation of the drug for more than one month did not abolish the muscle twitch. To analyze the origin of the muscle twitch, we performed spinal anesthesia, with the patient's permission, on October 1, 1981. The muscle twitch neither decreased nor disappeared under the spinal anesthesia. Paresthesia of both feet occurred around June, 1981. Pleural effusion appeared at the beginning of November, 1981 and at that time a mediastinal tumor was found by computed tomography (Fig. 3A). The pleural effusion was disappeared by the chemotherapy, and thoracotomy was performed on December 16, 1981. Neuromuscular junction block, using pancuronium
bromide at the time of the operation abolished the muscle twitch completely. The tumor was revealed by the histological examination to be thymoma. The thymoma was composed of round-oval neoplastic epithelial cells intermingled with a small number of spindle cells plus a moderate infiltration of lymphocytes (Fig. 3B). After the operation, most of the clinical manifestations subsided (Fig. 4). The muscle twitch and diplopia disappeared soon, but the blepharoptosis was still present slightly in January, 1991. Serum anti-acetylcholine receptor antibody titers remained elevated until January, 1991. At that time the patient still had slight blepharoptosis of the right eye.

**DISCUSSION**

This patient had MG, since serum acetylcholine receptor antibody was
remarkably high and clinical and electrophysiological features were consistent with those of MG. The muscle twitch, hyperhidrosis, limb pain and paresthesia seen in this case were an unusual combination. The muscle twitch was considered to be fasciculation rather than myokymia, since clinically the muscle twitch was very rapid contraction of individual muscle bundles rather than slow undulating muscle mass movement.

Kitahara et al. (1981) reported a 43-year-old housewife who had tumor shadow on her chest x-ray film for about 10 years and developed hyperhidrosis, decreased body weight and continuous undulatory muscle movement in her calves without myotonia. Thoracic open biopsy disclosed thymoma on histological examination. After operation bulbar myasthenic symptoms appeared and proximal limb weakness worsened. Peripheral nerve block by procaine did not abolish the myokymia. The case reported by Kitahara et al. was clinically, and probably pathophysiologically, very similar to ours. Kawamura et al. (1984) also described a 30-year-old man with similar clinical manifestations, but the muscle twitch appeared after thymectomy and concomitant marked increase of urinary excretion of catecholamine was noted. Other similar cases have been reported in the literature as Isaacs syndrome (Isaacs 1961) or neuromyotonia (Nakanishi et al. 1975). However, our case showed neither the muscle stiffness nor myotonia, that others reported. The association of muscle twitch, hyperhidrosis and limb pain with MG in our patient was of particular interest, since MG responds pharmacologically in an opposite way from myotonia and most drugs that are therapeutically for MG clinically worsen the myotonia of Isaacs syndrome. The present
case thus suggests that muscle twitch, hyperhidrosis and limb pain could occur independent of myotonia in Isaacs syndrome. Therefore, clinical manifestations such as muscle twitch, hyperhidrosis and limb pain in patients with MG associated with thymoma may constitute a new myasthenic syndrome.

The pathogenesis of muscle twitch in our patient was unknown, so we conducted spinal anesthesia which neither decreased nor abolished the muscle twitch. On the other hand, the pancuronium bromide which has the same pharmacological effect as curare was used to block the neuromuscular junction at the time of the operation on the mediastinal tumor. This resulted in complete disappearance of the muscle twitch. We thus concluded that the muscle twitch came from hyperactive peripheral axons, although it was unknown why excessive release of acetylcholine from the motor nerve ending did not improve the muscle weakness, but induced the muscle twitch.

Greenhouse et al. (1967) speculated that hyperhidrosis may be a result of peripheral neuropathy. Coërs et al. (1981) reported a case with generalized muscle twitching, profuse sweating, and occasional painful muscular stiffness whose muscle biopsy showed fiber type grouping. The muscle biopsy finding was similar to that of our case, and suggested the presence of motor neuropathy. It is possible to speculate that the same mechanism at the motor nerve ending could be applied to autonomic nerve ending and that the excessive acetylcholine release from the pilomotor nerve ending may result in hyperhidrosis. Although the precise origin of the limb pain is unknown and the biopsied sural nerve in our case did not have the abnormalities described by Welch et al. (1972), the neuropathic nature of the limb pain seemed plausible.

These clinical manifestations by our patient may constitute a new myasthenic syndrome and the thymoma may play a central role in the pathogenesis of this particular syndrome by triggering the autoimmune mechanism. The peripheral neuropathy due to the dysimmune mechanism may provoke these manifestations. Further detailed studies for the detection of specific antibodies against axonal and/or myelin sheath components of peripheral nerves may throw light onto the pathogenesis of this syndrome.

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References


