Oculopharyngeal myopathy with distal and cardiomyopathy

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SUMMARY Two patients are described with distinctive clinical features including an insidious onset, slow progression, bilateral ptosis, weakness of facial muscles, dysphagia, muscle atrophy, and weakness with a distal distribution in the extremities, and cardiomyopathy with conduction system disorders. Electromyographic studies and muscle biopsy showed features highly suggestive of a myopathic disorder. One case is considered to be sporadic. The other seems to be a familial disorder, because of the presence of a mild atroventricular block and right incomplete bundle branch block in the patient's son and the presence of eyelid ptosis in his sister. This may be a variant of oculopharyngeal myopathy with distal and cardiomyopathy. It will be necessary to perform long-term follow-up studies in these families.

A syndrome which included ptosis, external ophthalmoplegia, dysphagia or muscle atrophy or both, and weakness in the extremities has been reported by many authors (Fuchs, 1890; Dutil, 1892; Taylor, 1915; Langden and Cadwalader, 1928; Kiloh and Nevin, 1951; Andrews, 1961; Lakin and Locke, 1961; Lees and Liwersedge, 1962; Victor et al., 1962; Lundberg, 1962; Peterman et al., 1964; Schotland and Rowland, 1964; Bray et al., 1965; Satoyoshi et al., 1965; Roberts and Bamforth, 1968).

Recently, several authors (Olson et al., 1972; Schneck et al., 1973; Karpati et al., 1973; Tamura et al., 1974; Julien et al., 1974) have reported this syndrome with prominent mitochondrial abnormalities in skeletal muscles, some of which had cardiomyopathy.

However, as far as we know, ocular myopathy with dysphagia, distal and cardiomyopathy with no mitochondrial abnormalities or central nervous system lesions, has not been described, and in this paper we report two cases.

Case 1

This 48 year old male was born and has always lived on Iki island, a small Japanese island with a population of 42 000. When he was 42 years old, he began to have difficulty in swallowing and with hearing in the right ear associated with tinnitus. He also developed a nasal voice and bilateral eyelid ptosis without diplopia. These symptoms became gradually worse. He was noted to have cardiomyopathy on his chest radiograph at the age of 46 years, but he did not complain of any weakness in any of his extremities. He had no family history of neurological diseases and there was no parental consanguinity.

Physical examination revealed bradycardia (43/min), pulse arrhythmia, a grade II systolic murmur at the apex of the heart, and mild enlargement of the liver.

He had bilateral eyelid ptosis (Fig. 1), a mild degree of weakness of the orbicularis oculi and oris muscles with myopathic facies, a nasal voice, decreased hearing on the right, poor movement of the soft palate, dysphagia, and a decreased gag reflex. There was no tongue atrophy. There was paresis of the vocal cords and a mild weakness of neck flexion. No weakness was found in the sternocleidomastoid or trapezius muscles. Striking weakness and atrophy of the thenar, interosseous, peroneal and anterior tibial muscles were present bilaterally, and a moderate weakness and atrophy in the forearms (Figs. 2 and 3). Difficulty in walking because of bilateral foot drop was a prominent feature. The deep reflexes were absent in all four extremities. Pathological reflexes were not elicited. No sensory impairment was found.

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Fig. 1  Case 1. Bilateral ptosis.

Fig. 2  Case 1. Bilateral wasting of the forearm and intrinsic hand muscles.

Fig. 3  Case 1. Distal muscle wasting in lower extremities.

The serum CPK was slightly elevated (38 U/l; normal value less than 20 U/ml). Serum alanine and aspartate transaminases (SGPT and SGOT) and LDH were also elevated. The following laboratory studies were normal: CBC, urine, faeces, ESR, serum protein electrophoresis, cholesterol, phospholipid, triglyceride, alkaline phosphatase, blood urea nitrogen, serum electrolytes, thyroid function, glucose tolerance test, and CSF. The serological test for syphilis was negative. Radiological examination of the chest showed a diffuse enlargement of the heart (CTR: 58%). Audiograms revealed a hearing loss with positive recruitment in both ears, milder in the left, which suggested an inner ear impairment. The EEG showed no remarkable abnormalities. A routine ECG revealed atrial fibrillation, abnormal left axis deviation, idioventricular rhythms, ventricular premature beats and an intraventricular block (Fig. 4). Radiological examination of the oeso-
phagus revealed retention of a large amount of barium in the piriform recess.

The biceps brachii, triceps brachii, first dorsal interosseous, vastus medialis, and anterior tibial muscles were examined by electromyography. There were no spontaneous discharges at rest. Motor unit action potentials were of low amplitude and short duration. There were full interference patterns. There was neither a response to edrophonium nor a myotonic reaction. The motor conduction velocities of the right ulnar and tibial nerves were normal at 55.4 m/s and 46.6 m/s, respectively. Muscle biopsy specimens (right anterior tibial and triceps muscles) showed that muscle fibres of various sizes were irregularly mixed, and there were central nuclei, vacuolar changes, and moderately increased connective tissue. Neither ragged-red fibres nor mitochondrial abnormalities were seen.

The symptoms described were very slowly progressive. Three years later, the heart was more diffusely enlarged on chest radiography (CTR: 66%). The ECG revealed the same findings as before. At this time the EMG showed the same findings as before, that is, no spontaneous discharge at rest, brief and small amplitude motor unit potentials, an increased incidence of polyphasic potentials, and full interference patterns (Fig. 5). The motor conduction velocities of the right ulnar and tibial nerves were 50 m/s and 41.1 m/s, respectively. Biopsy of the right triceps muscle showed that muscle fibres of various sizes were irregularly mixed with mild to moderate increases in endomysial and perimysial connective tissues and vacuolar changes. Small groups of small fibres were occasionally seen. No mitochondrial abnormalities or ragged-red fibres were seen (Fig. 6).
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Another 48 year old male who was born and has lived on Iki island all his life, developed hoarseness and mild weakness of upper extremities during childhood. His symptoms were not progressive until he was 43 years of age. Since then he has become aware of eyelid ptosis and of gradually increasing weakness of his upper and lower extremities, particularly on the right. These symptoms progressed slowly and he was admitted to the Kyushu University Hospital on 8 January 1976.

His 16 year old son had a mild atrioventricular block and right incomplete bundle branch block, his 12 year old daughter had epilepsy, his sister had eyelid ptosis, and his paternal aunt had hoarseness. There was no parental consanguinity.

Physical examination revealed the following: pulse rate was 60 beats per minute, irregular; blood pressure was 146/80 mmHg supine. A grade II systolic murmur was heard at the heart apex with no signs of cardiac decompensation, lipomas were present on the left occipital region (5 × 5 cm) and the right shoulder region (10 × 15 cm).

On neurological examination, mentation was normal. Bilateral eyelid ptosis (Fig. 7), mild limitation of ocular movement in all direction without diplopia, bilateral facial weakness with myopathic facies, poor movement of the soft palate, dysphagia, decreased gag reflex, and paresis of the vocal cords were observed. No weakness was found in the sternocleidomastoid or trapezius muscles. There was mild weakness of neck flexion. Striking weakness and wasting of bilateral thenar,
interosseous, peroneal and anterior tibial muscles was present with moderate weakness and wasting in forearms and legs. He had bilateral foot drop. The deep reflexes were absent in all extremities with no pathological reflexes. The sensory examination was normal.

The serum CPK was slightly elevated (28 U/ml; normal value less than 20 U/ml). The serological test for syphilis was negative. The following laboratory studies were normal: CBC, urine, faeces, ESR, RA test, CRP, ASLO, serum protein, electrophoresis, cholesterol, LDH, SGOT, SGPT, LE test, serum electrolytes, triosorb, TSH, and CSF. The pulmonary function test was normal. The EEG showed a mild abnormality with bursts of irregular theta waves in the left anterior temporal area. Chest radiograph showed diffuse enlargement of the heart (CTR: 53%). Audiograms showed only a loss of 25 decibels for 4000 Hz and 30 decibels for 8000 Hz in both ears. The ECG showed ventricular premature beats, left ventricular hypertrophy, and an anteroseptal myocardial infarction. The vector electrocardiogram revealed impairment of the intraventricular conduction.

Electromyography was performed in the right deltoid, extensor carpi radialis, first dorsal interosseous, and anterior tibial muscles using a concentric needle electrode. Fibrillation potentials graded as +1 were found in the right first dorsal interosseous and right anterior tibial muscles. Insertion activities were slightly increased in these muscles. Motor unit potentials, voluntarily activated, were of decreased duration, and the incidence of polyphasic potentials was increased in all of the muscles sampled (Fig. 8). With maximal effort there were full interference patterns. The motor conduction velocity of the right ulnar nerve (elbow to wrist) was 51.0 m/s and the distal motor latency (DML) was 2.6 ms; distance 63 mm. The MCV of the right peroneal nerve (knee to ankle) was 46.8 m/s, and the DML was 4.1 ms; distance 90 mm. The sensory peak latency of the right median nerve (index finger to wrist) was 3.2 ms; distance 130 mm, and the amplitude of the sensory potential was 19 μV. There was no evidence of neuromuscular transmission block with the Harvey-Masland test. Muscle biopsy (right biceps muscle) showed that muscle fibres of various sizes were irregularly mixed with small groups of small fibres. Central nuclei, vacuolar changes, and mild increased connective tissues were observed in frozen sections (Fig. 9). Neither mitochondrial abnormalities nor ragged-red fibres were seen.

Family studies
Four generations have been traced in these two families by the census register which is the personal and family registration system and there is no evidence from this that these two patients are related.

Discussion
Many authors (Taylor, 1915; Lees and Liversedge, 1962; Victor et al., 1962; Schotland and Rowland, 1964; Satoyoshi et al., 1965) have described cases in which various clinical manifestations are associated with ptosis and external ophthalmoplegia. This syndrome, usually termed ocular myopathy in the literature, is called variously progressive vagus-glossopharyngeal paralysis with ptosis (Taylor, 1915), descending ocular myopathy (Lees and Liversedge, 1962), oculopharyngeal muscular dystrophy (Victor et al., 1962), progressive muscular dystrophy with ptosis and dysphagia (Peterman et al., 1964), ocular myopathy with dysphagia (Bray et al., 1965), and ocular muscular dystrophy (Roberts and Bamforth, 1968). Tamura et al.
(1974) described a familial oculocranioskeletal neuromuscular disease which included ptosis, external ophthalmoplegia, and mitochondrial abnormalities with or without facial and proximal muscle weakness. On the other hand, Matsunaga et al. (1973) reported oculopharyngeal involvement with and without muscle involvement in familial neurogenic muscular atrophy.

Roberts and Bamforth (1968) reported that nine of 25 cases of ocular myopathy had dysphagia. Lundberg (1962) described seven cases of ocular myopathy with and without dysphagia in a family, some of which had myopathy in the extremities. Gerber et al. (1970) reported two cases of ocular myopathy with dysphagia in a family. Bray et al. (1965) concluded that the mean age of onset was 40 years in ocular myopathy with dysphagia and 23 years in ocular myopathy without dysphagia.

Our cases had an insidious onset, manifestation of the disease in adult life, slow progression, bilateral ptosis, weakness of facial muscles, and dysphagia. Moreover, our cases had muscle atrophy and weakness with a distal distribution in the extremities, particularly hand and anterior tibial muscles. Case 1, in the absence of any clear family history of similar disorders, is considered to be a sporadic example of the disease. The family history in case 2 shows that the patient's 16 year old son has mild atrioventricular block and right incomplete bundle branch block, his sister had eyelid ptosis, and his paternal aunt had hoarseness. Therefore, case 2 may be thought to be a familial disorder, although the hereditary aspect remains to be clarified. These two patients who live on the small island of Iki do not appear to be related.

The distribution of the distal muscle atrophies in the extremities in our cases is similar to that of Welander's report (Welander, 1951). Although Gowers (1902) described distal myopathy with facial and sternocleidomastoid weakness in a young male, Welander (1951) and Walton and Gardner-Medwin (1974) suggested that his patient may have had myotonic dystrophy.

Our cases must be differentiated from myotonic dystrophy. They did not exhibit clinical or electrical myotonia in their long clinical course. Therefore, we are able to rule out myotonic dystrophy, although it may be difficult to distinguish them from myotonic dystrophy without myotonia. Distal myopathy must also be differentiated from Charcot-Marie-Tooth disease and the distal type of spinal muscular atrophy. In our cases, however, electromyographic and muscle biopsy studies suggest that the distal muscle weakness and atrophy are not of neurogenic origin, but of myopathic process. Andrews (1961) described a new type of ocular myopathy with distal myopathy. Since then, several other cases of ocular myopathy with dysphagia and distal myopathy have been reported (Lakin and Locke, 1961; Lundberg, 1962; Schotland and Rowland, 1964; Satoyoshi et al., 1965).

Besides involvement of the ocular, facial, bulbar, and distal muscles, the present cases have cardiomyopathy with conduction defects.

Cardiomyopathy has been described in various types of Iki.

**Fig. 9 Case 2. Transverse section of right biceps brachii muscle showing focal loss of mitochondria and no increase of mitochondria. Frozen section; DPNH dehydrogenase. ×190.**
of progressive muscular dystrophy, myopathy, and neurogenic muscle atrophies. Pateisky et al. (1970) reported four cases of ocu
cardiac myopathy with giant mitochondria and glycogen storage. Kearns and Sayre (1958) described two cases with external ophthalmoplegia, retinitis pigmentosa and complete atrioventricular block. Sandifer (1946) reported a case with external ophthalmoplegia and bundle branch block. Lind and Prame (1963) described two cases with ptosis, external ophthalmoplegia, proximal weakness of the extremities, mental retardation, and cardiopathy. Mawatari and Katayama (1973) reported scapuloperoneal muscle atrophy with cardiopathy.

Our cases do not have mitochondrial abnormalities, glycogen storage in skeletal muscles, central nervous system involvement, or retinitis pigmentosa, and do not show findings suggestive of a neurogenic disorder. Moreover, they do not have manifestations suggestive of hypertension, arteriosclerosis, hyperlipaemia or endocrine disturbances. We, therefore, suggest that the myocardial damage in our cases is not related to mitochondrial abnormalities, neurogenic disorders, or ischaemic heart damage, but is of myogenic origin like the skeletal muscle damage, although additional detailed investigations are still to be performed.

As described above, our cases showed involvement of the levator palpebrae, orbicularis oculi and oris, pharyngeal, laryngeal, neck flexor, distal limb, and heart muscles. This affliction may be a variant of ocularpharyngeal myopathy with distal and cardiac involvement. Similar cases have never been reported as far as we know. It is necessary to perform long-term follow-up studies in these families and in families with similar manifestations, in order to elucidate the ocularpharyngeal myopathy.

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