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Chronic progressive external ophthalmoplegia (CPEO) with 'ragged red fibers'

— A Case Report —

Jong Sung Kim, M.D.,* Chong Jai Kim, M.D.,* Je G. Chi, M.D., and** Ho Jin Myung, M.D.

Department of Neurology, Asan Medical Center, Seoul Korea
Department of Pathology and Department of Neurology, Seoul National University, Seoul, Korea*

Chronic progressive external ophthalmoplegia (CPEO) is a rare clinical syndrome characterized by slowly progressive parlaysis of extraocular muscles. We report a male patient who had a 20 year history of CPEO. Histological examination of left deltoid muscle showed characteristic ragged red fibers. Electron microscopy revealed a number of abnormal mitochondria which contain paracrystalline inclusion boides.

Key words: *CPEO, ragged red fibers*

INTRODUCTION

CPEO is a clinical syndrome characterized by slowly progressive paralysis of extraocular muscles. With its classification still being debated, many of the cases were reported to share other neurologic manifestations. Since many of the patients show histological abnormalities of mitochondria, this syndrome is currently regarded as a form of mitcchondrial metabolic disorders. We report a 53-year-old male patlent who had a very long history of CPEO. Muscle biopsies revealed charateristic ragged red fibers on modified Gomori trichrome stain. Literature is briefiy reviewed.

CASE REPORT

This 53-year-old male patient had a 20 year history of slowly progressive external ophthalmoplegia. It has very slowly progressed so that diplopia was not noticed. Amost simultaneously, his right facial muscle became paralysed and progressively worsened.

At the time of admission, he appeared flabby, but alert. He had been a high school teacher for more than twenty years. Family history was denied. Neurologic examination revealed moderate bilateral ptosis

Address for correspondence: Jong Sung Kim, M.D. Department of Neurology, Asan Medical Center, Seoul, Korea (Tel. (02) 480-3093)

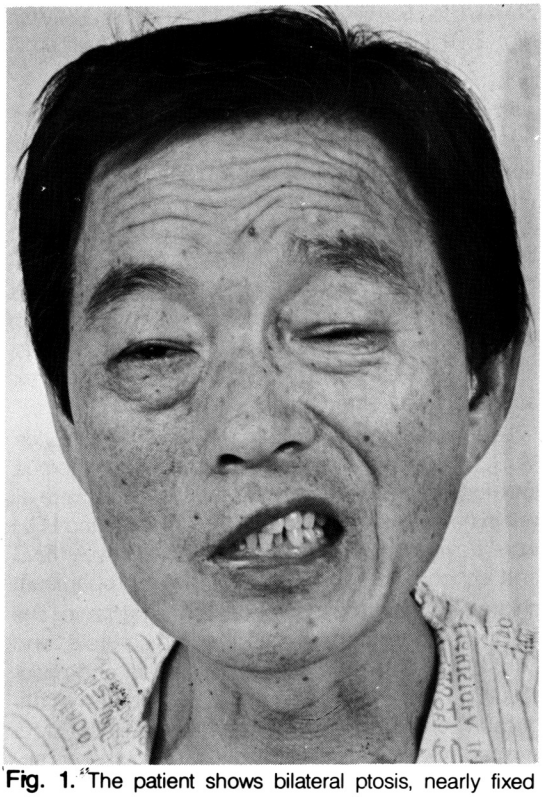

Fig. 1. The patient shows bilateral ptosis, nearly fixed eyeballs, and right sided facial muscle weakness.

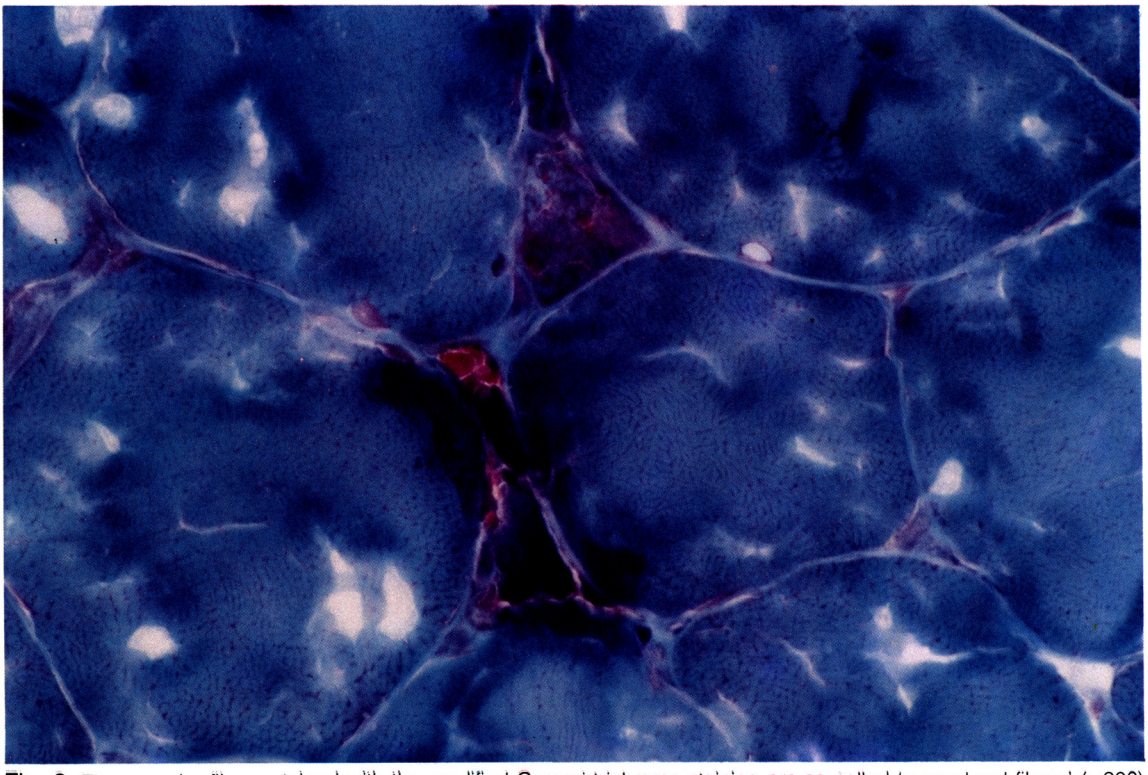

Fig. 2. The granular fibers, stained with the modified Gomori trichrome staining are so called 'ragged red fibers.' (×200)

and marked limitation of conjugate gaze in all directions. Nystagmus was absent. His visual acuity and field were normal. Neither retinal pigmentary degeneration nor optic atrophy was found. Pupils were round and regular, equal in size, and promptly reacted to light. He had right sided facial muscle weakness (Fig 1). Nasal speech was evident. Other cranial nerves were generally intact. There was mild proximal limb muscle weakness with some atrophies in those muscles. DTR's were hypoactive. Other neurological examination was unremarkable.

Laboratory findings including CBC, UA, electrolytes, VDRL, ANA, C reactive protein, calcium, phosphorous, liver function tests, and thyroid function tests were all within normal limits or negative. Serum CPK and LDH were elevated to 310 and 369 mg/dl respectively. EKG and echocardiography were normal. Edrophonium chloride test for myasthenia gravis was negative. The CSF was under normal pressure, without cells, and with 48 mg of protein per deciliter. Brain and nasopharynx CT scans were normal. EEG and nerve conduction velocity tests were within normal limits. EMG showed normal motor units without spontaneous activities. Visual, auditory, and somatosensory evoked potentials were all unremarkable.

Biopsy was performed on the left deltoid muscle. Histologic examination on H&E stain was consistent with mild myopathy showing scattered degenerating fibers. On modified Gomori stain, scattered 'ragged red fibers' were seen (Fig. 2). Electronmicroscopy showed enlarged abnormally shaped mitochondria with increased, irregularly oriented cristae (Fig. 3). Many of these organelles contained paracrystalline inclusion bodies of rectangular shape (Fig. 4).

Prednisolone had been given with 40 mg/day for about one month. However, there was no overt improvement so that he stopped to take the medication. His clinical signs progressively worsened. Four years later, he revealed complete external ophthalmoplegia and bilateral facial palsies. His proximal muscle weakness became worsened. Nasal speech was more prominent. However, he was still able to perform his daily tasks.

DISCUSSION

Progressive external ophthalmoplegia is a striking but nonspecific clinical sign that occurs in a variety

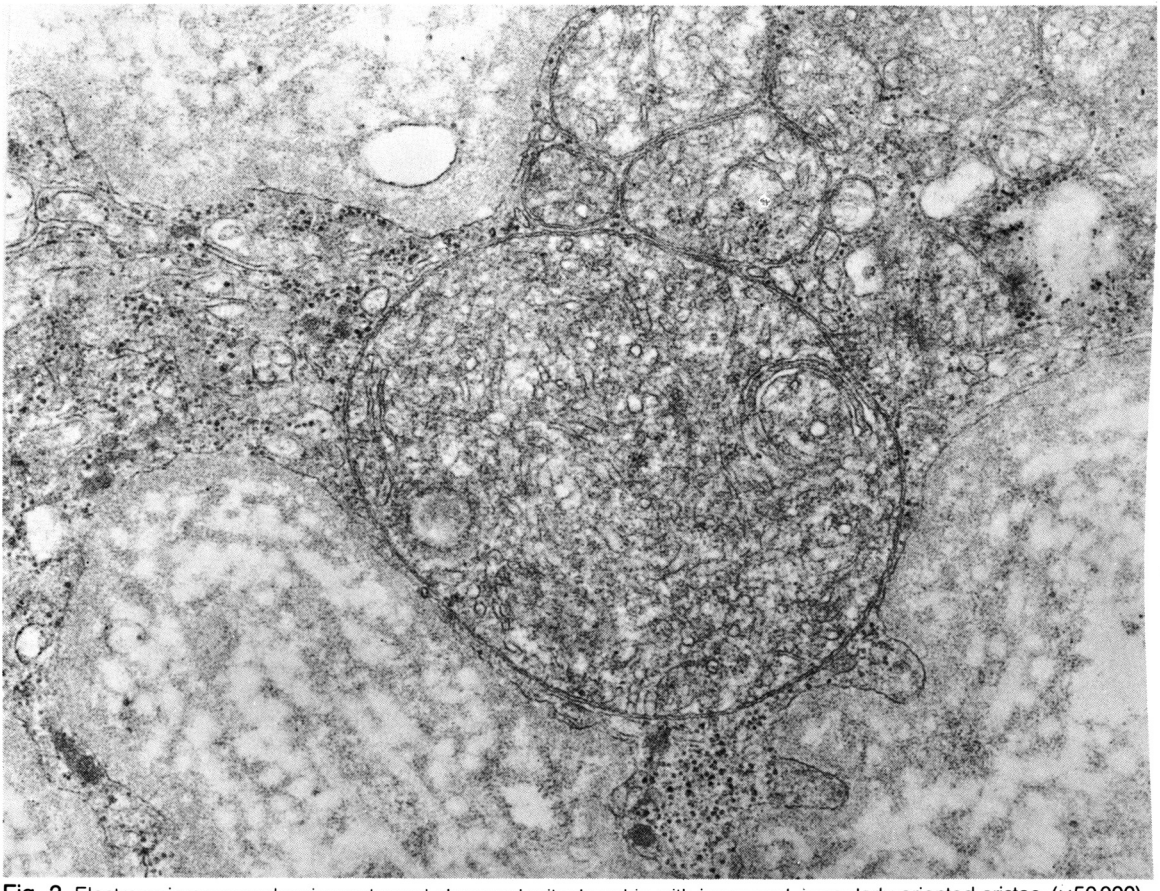

Fig. 3. Electronmicroscopy showing enlarged abnormal mitochondria with increased, irregularly oriented cristae. (×50,000)

of disease states such as myasthenia gravis, thyrotoxicosis, Guillain-Barre syndrome, Refsum's disease, Bassen-Kornzweig disease (Olson et al. 1972, Drachmann 1968). Excluding these entities, conditions idiopathic progressive ophthalmoplegia remain, which have often been called as CPEO (Daroff 1969, Mitsumoto et al. 1983). These entities may exist as an isolated abnormality, but are more commonly seen with weakness of facial or extremity muscles (Daroff 1969).

Initially, the pathogenesis of this disorder was thought to be linked to certain myopathic process on the ocular muscles with occasional involvement of other muscles (Sandifer 1946, Kiloh and Nevin 1951). However, subsequent reports have revealed a number of cases where CPEO was associated with other neurologic signs including pharyngeal weakness, peripheral neuropathy, cerbellar ataxia, spasticity, deafness, optic atrophy, and dementia (Drachman, 1968). Drachman (1968) thus called this entity 'ophthalmoplegia plus' and defined this entity as a degenerative process of obscure etiology. Naturally, considerable debates have arisen as to its pathogenesis, which were extensively reviewed by Daroff (1969). Biopsies of ocular muscles have revealed the changes compatible with myopathy (Sandifer 1946, Kiloh and Nevin 1951), but there have also been morphologic evidences of nervous system involvement (Langdon and Cadwalader 1928, Brion and DeRecondo 1967). Furthermore, according to Drachman et al. (1969), myopathic changes are seen in the denervated ocular muscles of experimental animals. Then it may be impossible to make a definite etiological diagnosis when based on biopsy material alone.

In 1972, Olson et al. found ragged red fibers in the muscles of their patients on modified Gomori trichrome stain, which are consistent with subsarcollemmal and intermyofibrillar accumulations of abnormal mitochondria. They thus called this entity 'oculocraniosomaic neuromuscular disease with ragged red

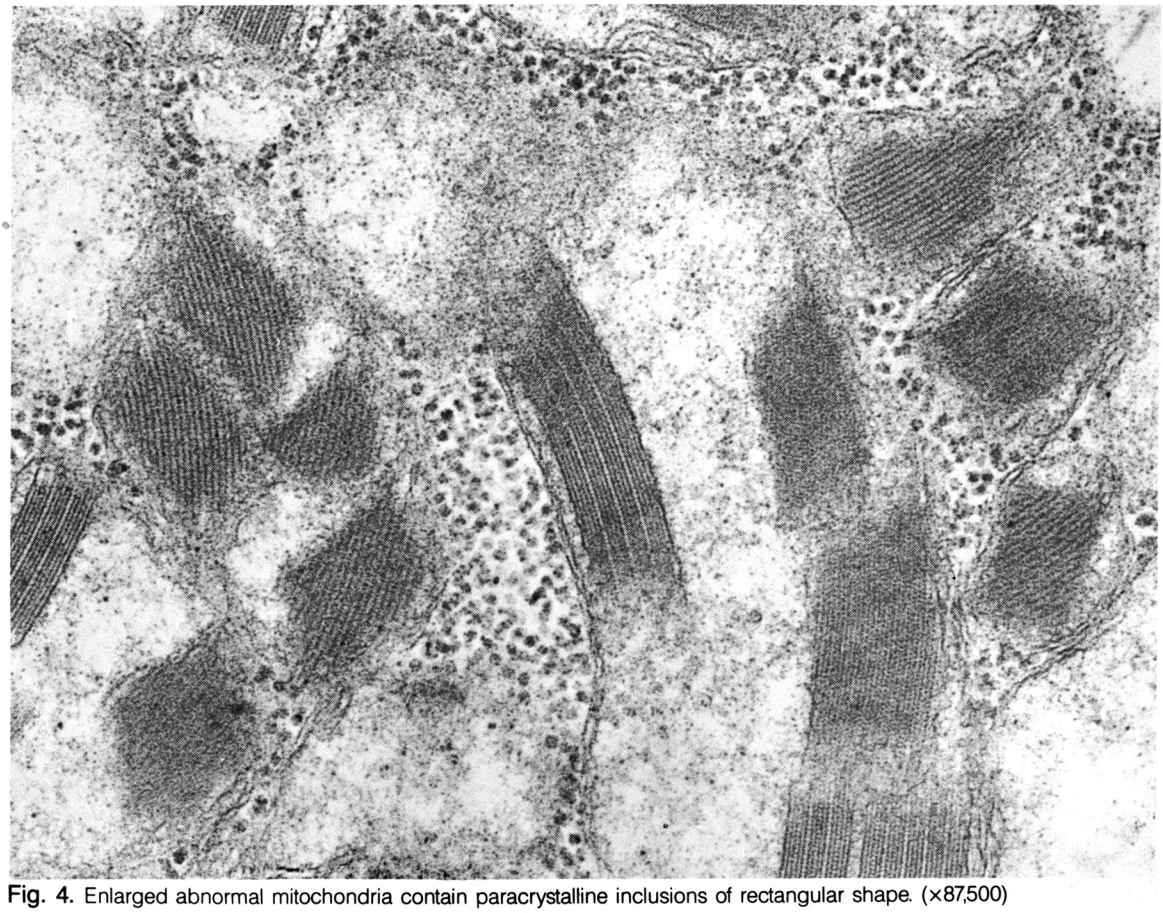

Fig. 4. Enlarged abnormal mitochondria contain paracrystalline inclusions of rectangular shape. (×87,500)

fibers'. This term is not only too long but seems incongruent since some of the subsequently reported cases did not reveal ragged red fibers (Bastiaensen et al. 1987, Mitsumoto et al. 1983). However, their work has triggered recent morphological and biochemical investigations in this and related disorders (Mitsumoto et al. 1983, DiMauro et al. 1985).

When reviewed with electronmicroscopy, the mitochondria in affected muscle fibers appear more variable in size and often contain paracrystalline inclusions. Abnormal mitochondria have also been demonstrated in the brain, liver, sweat glands, and vascular endothelium (Gonatas et al. 1967, Karpati et al. 1973, Schneck et al. 1973, Okamura et al. 1976). Spongiform changes of brain, cerebellar and brain stem abnormality and CT scan abnormality have been described (Daroff et al. 1966, Cullen et al. 1973, Horwitz and Roessmann 1978, Seigel et al. 1979, Okamoto et al. 1981). The old question whether CPEO is a neurogenic or myogenic condition thus seemed to be answered when we consider CPEO as a multisystem mitochondrial disorder affecting both muscular and nervous systems (Bastieansen et al. 1978).

Our patient showed progressive ptosis and external ophthalmoplegia for about 20 years. Clinically, he showed a mixed picture of neurogenic and myogenic invoivement. On imitial examination facial paralysis was nearly limited to the right side and thus appeared identical with idiopathic peripheral facial palsy aside from its gradual development. However, his proximal limb muscle weakness and histological findings of muscle fibers were consistent with myopathy. Muscle biopsy showed typical ragged red fibers with modified Gomori trichrome stain. Electronmicroscopy revealed abnormal mitochondria which contain a number of inclusion bodies. Morphologically these findings are identical to those seen in the patient of MELAS syndrome previously presented by us (Myung et al., 1987) where seizures and early onset strokes were the most prominent signs.

Ragged red fibers which are indicative of mitochondrial metabolic error were observed in a number of disease entities with different symptomatologies. Included under the headings of mitochondrial myopathy, mitochondiral cytopathy or mitochondrial encephalomyopathy (Shapira et al. 1977, Egger and Wilson 1981, DiMauro et al. 1985) are numerous clinical entities such as CPEO, progressive muscle weakness, syndrome of exercise intolerance, facioscapulohumeral syndrome, nonthyroidal hypermetabolism as well as newly described syndromes of MERRF (myoclonic epilepsy and ragged red fiber) and MELAS (mitochondiral myopathy, encephalopathy, lactic acidosis, stroke-like episodes). According to Petty et al. (1986), CPEO occupys the majority among these syndromes.

Recent attentions were focused on the biochemical defects in these disorders. Biochemical disorders such as alterations of pyruvate metabolism, loose oxidation-coupling, and defects of the respiratory chain such as complex I, III, IV etc. have been identified (DiMauro et al. 1985, Peterson et al. 1988). Up to now, however, rational classification of the mitochondrial diseases is far from satisfactory. One of the most confusing facts is that biochemical and clinical classifications occasionally do not agree in these syndromes; Distinctly different clinical syndromes have been described in association with apparent deficiency of the same enzyme complex while similar clinical syndromes have been reported with deficiency of different respiratory enzymes (DiMauro 1985, Petty et al. 1986, Peterson et al. 1988). According to Petty et al. (1986), the wide spectrum of presentations occurring with each identified biochemical defect may be due either to random variation in the distribution of defective mitochondria or, more likely, to heterogeneity at a molecular level. Whatever is the truth, studying more cases with further biochemical investigation is obviously needed to clarify this fascinating syndrome.

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