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Fatal mitochondrial cardiomyopathy in Kearns-Sayre Syndrome

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Summary. The clinical and postmortem findings in a 26 year old man with Kearns-Sayre syndrome are described. In the last years of his life he suffered from cardiac arrhythmias and a congestive cardiomyopathy, dying of cardiac pump failure. The heart was enlarged, especially the left ventricle which was fibrotic and excessively dilated. Histological and fine structural investigation revealed an excessive loss of myofibrils and an increase of enlarged mitochondria with lamellar and atypically tubular cristae in widespread heart muscle cells. Mitochondrial anomalies were also observed in some cells of the conductive system. This patient thus suffered not only from a mitochondrial myopathy with ragged red fibers but also from a fatal mitochondrial cardiomyopathy. The anomalies observed in the mitochondria of the conductive system cells suggest that the well-known conductive abnormalities in patients with Kearns-Sayre syndrome might be at least partly caused by disturbed function of these mitochondria.

Key words: Kearns-Sayre syndrome – Progressive external ophthalmoplegia – Mitochondrial cardiomyopathy – Conductive heart muscle cells – Ragged red fibers

Introduction

In progressive external ophthalmoplegia (PEO) skeletal muscles are regularly affected by a disseminated mitochondrial myopathy with so-called ragged red fibers. These patients often suffer from a pigmentary retinopathy and cardiac conduction defects among other symptoms (Kearns-Sayre Syndrome; Kearns and Sayre 1958; Kearns 1965; Bastiaensen 1978). Whereas the conduction defects in these patients are quite common (Roberts et al. 1979) myocardiac lesions seem to be very rare. Davies and coworkers (1983)

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even state that in PEO "frank cardiac failure which would suggest involvement of contractile myocardial fibers does not occur".

In this paper we present the case of a young man with Kearns-Sayre syndrome who died at the age of 26 years with the signs of a severe congestive cardiomyopathy. Autopsy revealed disseminated mitochondrial cardiomyopathy as cause of the cardiac pump failure.

Case report

This male patient at the age of 11 years suffered from a bilateral ptosis. At 15 years neurological examination revealed severe oculomotor impairment. Cerebral arteriography, cerebrospinal fluid and EMG were normal. At the age of 18 a progressive weakness of the musculature of the shoulder girdle and the trunk developed, and one year later the patient had difficulties with swallowing. A skeletal muscle biopsy from the left M. biceps showed myopathy with so-called ragged red fibers, i.e. disseminated muscle fibers with fat droplets and accumulation of enlarged atypical mitochondria with intramitochondrial paracristalline inclusions (Fig. 1). Thus the already presumed diagnosis of progressive external ophthalmoplegia (PEO) was confirmed. – When first admitted to the hospital at the age of 24 years, the patient was dyspnoeic and suffered from severe biventricular heart failure. The consulting ophthalmologist found a pigmentary retinopathy in addition to a near complete external ophthalmoplegia. The patient

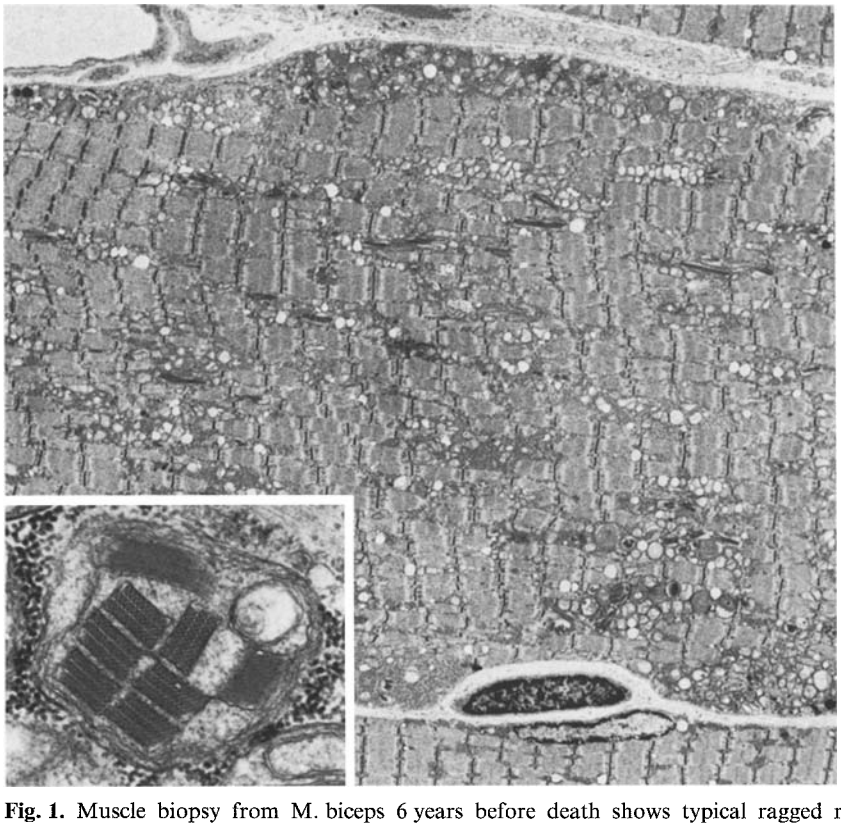

Fig. 1. Muscle biopsy from M. biceps 6 years before death shows typical ragged red fiber with lipid droplets and accumulation of enlarged abnormally structured mitochondria. × 1800. *Inset:* × 37,000

showed malignant arrhythmias which at first were treated sucessfully with amiodarone. Later a heart pacer had to be implanted for a left bundle block. Afterwards he returned to work, but soon the cardiac disease replapsed. In the last 2 years of life he had to be hospitalized eight times, always with signs of severe right and left heart failure with pulmonary oedema, ankle oedema, ascites and cardiogenic shock. The ejection fraction was down to 21%. Endomyocardial biopsy, which for technical reasons could only be investigated with the light microscope, revealed a congestive cardiomyopathy with interstitial fibrosis. The patient was set on the list for cardiac transplantation. Soon afterwards he died at the age of 26 years with the signs of cardiac pump failure. (Further details of the clinical findings and the course of disease will be published elsewhere (Park et al. 1986).

Autopsy

Autopsy was carried out 3 h after death. The heart (heart weight 400 g, body weight 63 kg) showed an excessive dilatation of the left ventricle with a thinning of the wall especially in the rounded-out apical region (wall thickness here 0.5 cm, otherwise 1 cm). The right ventricle was hypertrophic and dilated. In both ventricles small patches of interstitial fibrosis occured. The coronary arteries displayed small spots of lipoidosis without stenosis of the lumen. There was chronic congestion of the lungs with basal atelectasis on both sides, caused by pleural effusions. Liver, spleen and kidneys were extremely congested, as well as the mucosa of the stomach and intestinum. Oedema of both legs was noted. The muscles of the shoulder girdle were atrophic.

Material and methods

Tissue for light microscopic investigation was fixed in formalin and embeddded in paraffin. Sections were stained with H. and E., after van Gieson and with the PAS-reaction. For electron microscopy specimens from the mid-wall part of the left ventricle, from the upper left vetricular septum, from the M. pectoralis major, M. quadriceps femoris and the M. deltoideus as well as from liver, kidney and pancreas were fixed in glutaraldehyde (6,25%), postfixed in 2% buffered osmic acid solution for 2 h, and embedded in Epon. Semithin sections were stained in Azur-II-Methylen blue solution (Richardson et al. 1960). Ultrathin sections were contrasted with uranyl acetate and lead citrate.

Results

Light microscopy

Both ventricles and both atria of the heart display a diffuse interstitial fibrosis. The heart muscle cells often show an irregular arrangement; some of them appear enlarged, whereas other cells are thinner than usual. The hypertrophic cells contain big nuclei with irregular contours. Other heart muscle cells hold few myofibrils but masses of fine granular material. In the Epon-embedded semithin sections these cells contain many small vesicles with a loss of myofibrils (Fig. 2).

In all the inspected skeletal muscles typical "ragged red fibers" occur.

The bulbus oculi shows a pigmentary retinopathy without the typical picture of retinitis pigmentosa, thus confirming the diagnosis of the Kearns-Sayre Syndrome (Mc Kechnie et al. 1985).

Electron microscopy

In both specimens of the heart the cells are surrounded by bundles of collagen fibrils. They have a width of up to 35 μm. Most of them show the

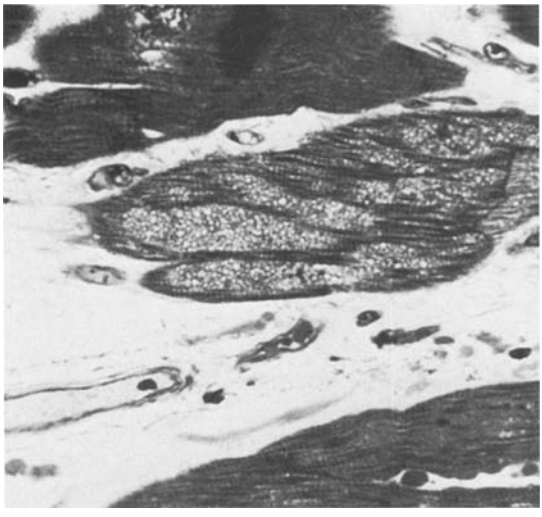

Fig. 2. Heart muscle, left ventricle. Heart muscle cells filled with indistinct vacuoles and severe loss of myofibrils. Azur methylene blue stained semithin section. ×450

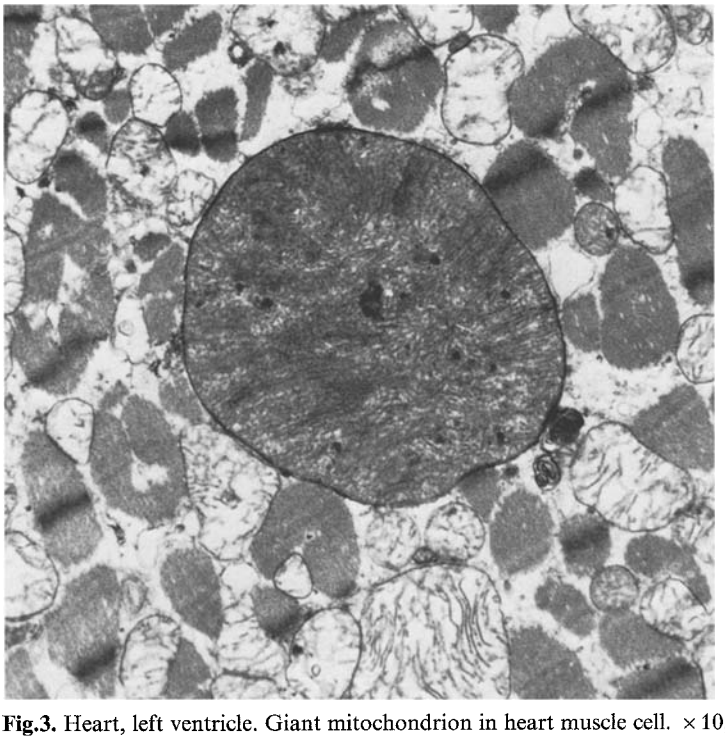

Fig.3. Heart, left ventricle. Giant mitochondrion in heart muscle cell. ×10,000

typical artefacts of autopsy material, especially swollen mitochondria (1,2–2,5 μm ∅) with ruptured cristae. In a few cells there occur single giant mitochondria (∅ up to 5 μm) with many cristae in a dense matrix (Fig. 3). Some other heart muscle cells contain autophagic vacuoles as sign of cell degeneration. No fatty infiltration of the heart muscle cells is seen.

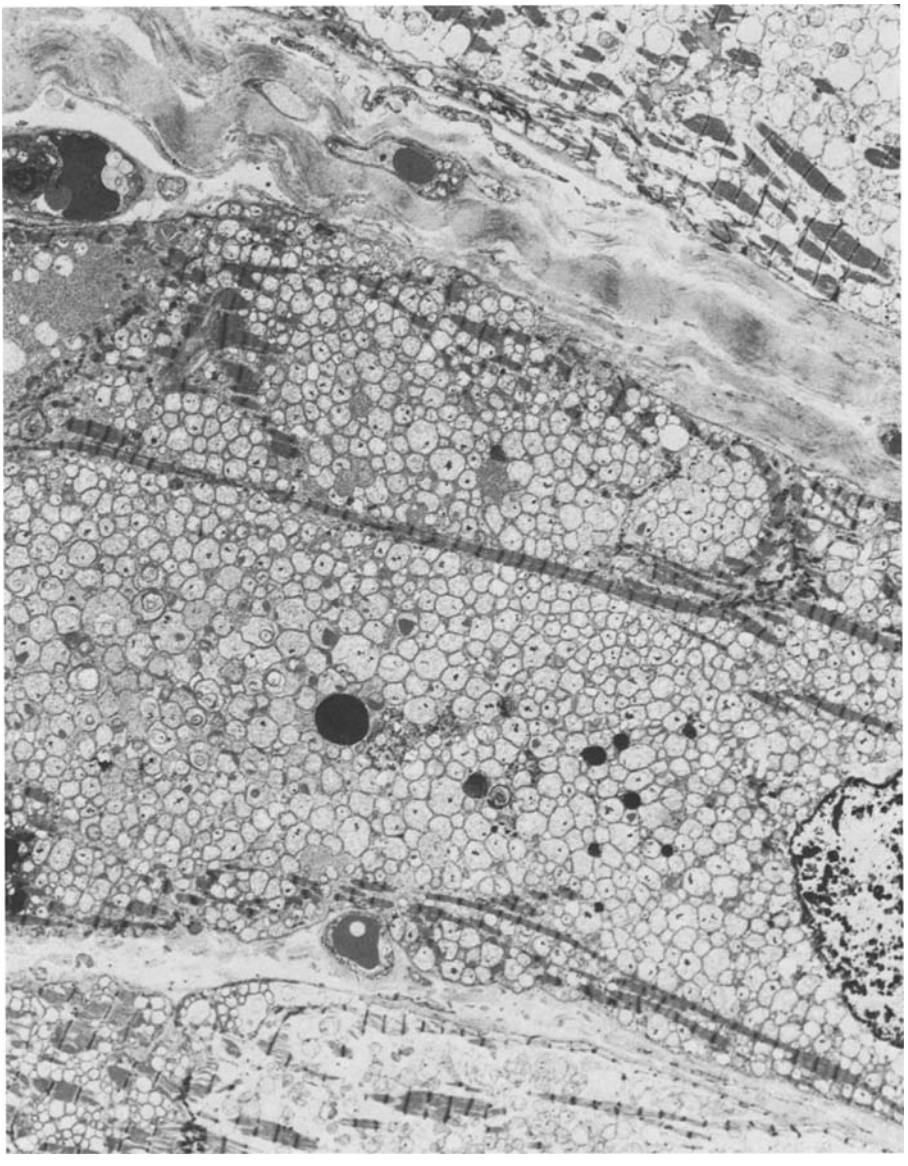

Fig. 4. Heart, left ventricle. Heart muscle cell with loss of myofibrils and excessive accumulation of moderately enlarged mitochondria. Interstitial fibrosis. × 2,500

About 2–5% of heart muscle cells show an extreme loss of myofibrils and an excessive accumulation of moderately enlarged mitochondria (∅ 2.5 μm up to 5 μm) (Fig.4). They contain some stacks of lamellar cristae, but mostly many tubular cristae (Fig. 5). The nuclei of these cells are enlarged and irregularly formed. Some of them display intranuclear tubular inclusions obviously arising from the nuclear membrane (Fig. 6).

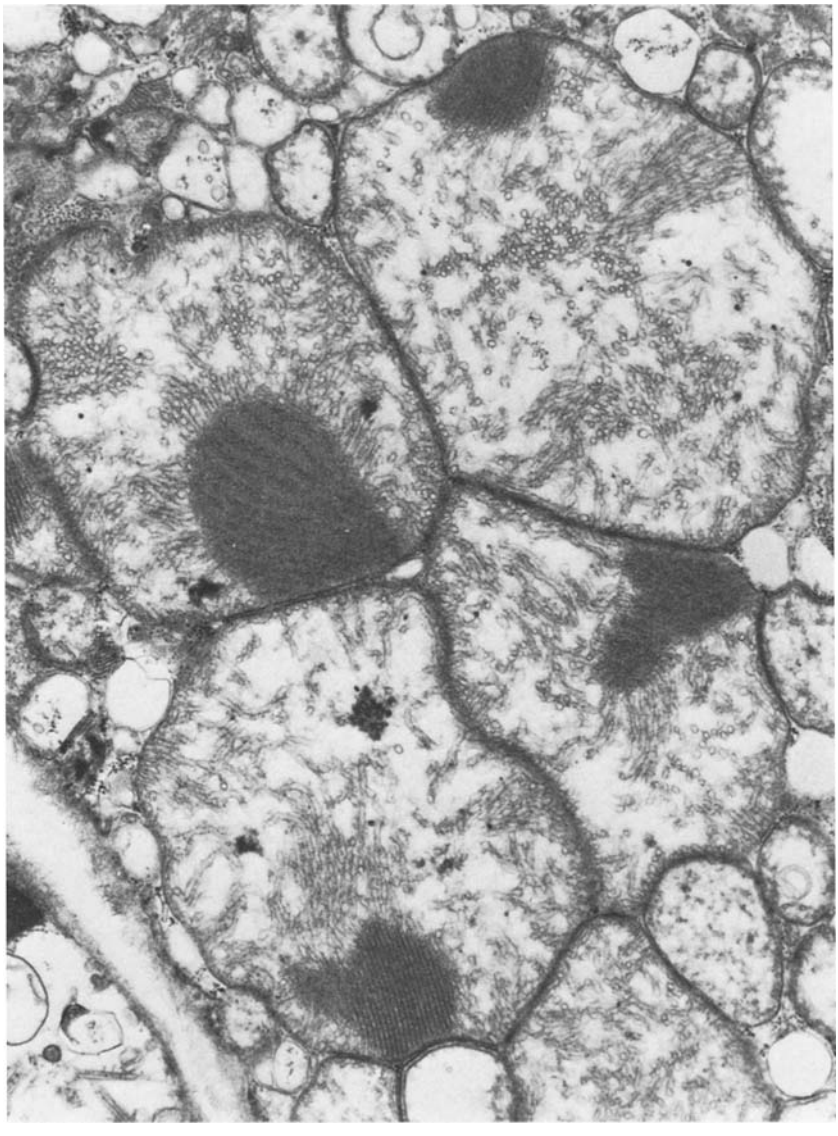

Fig. 5. The same cell as in Fig. 4 shows densely packed moderately enlarged mitochondria with some lamellar, but mostly tubular cristae. ×27,000

The cells filled with abnormal mitochondria are in contact with the neighbouring cardiomyocytes by intercalated discs. In the specimens from the septum cells of the conductive system occured. Most of them show the usual fine structural organisation with few myofibrils and masses of glycogen particles. They contain a few oval swollen mitochondria (∅ up to 2.5 μm). Some other cells however, also filled with glycogen, contain

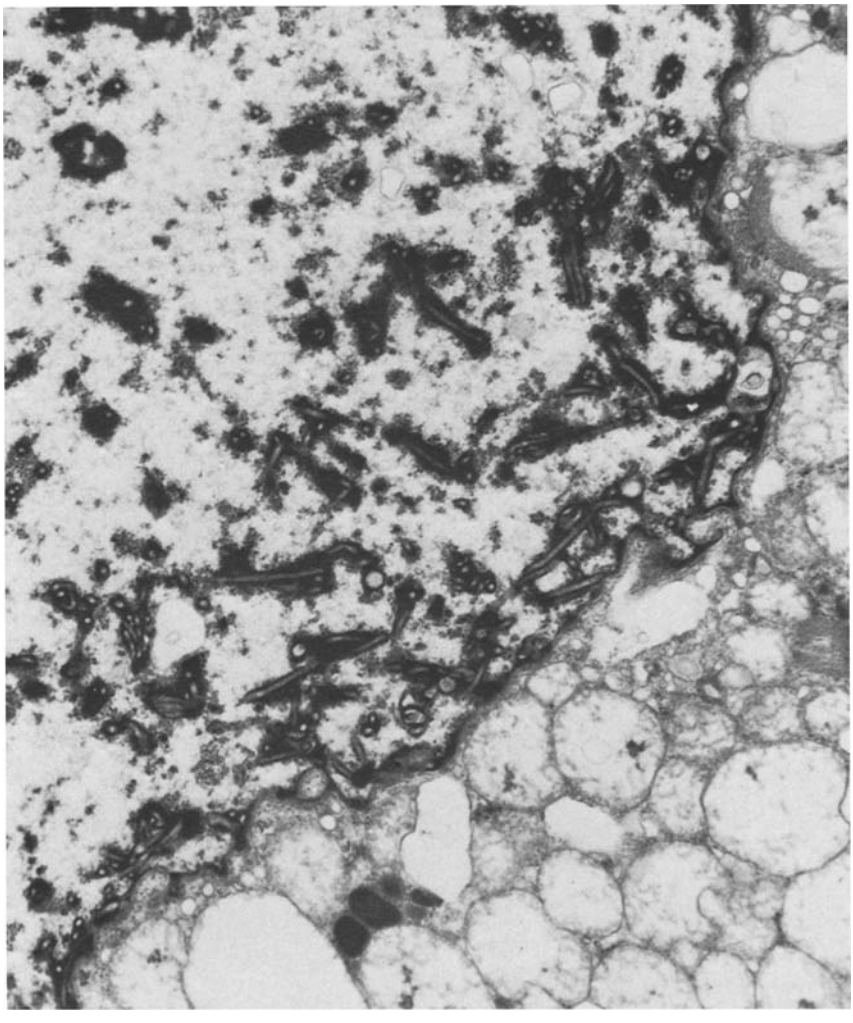

Fig. 6. Heart, left ventricle. Nucleus of heart muscle cell with abnormal accumulated mitochondria displays tubular inclusions. × 10,000

rounded mitochondria with a dense matrix (∅ up to 1.7 μm). They possess abnormal tubular cristae (Fig. 7). Also in this region all cells are surrounded by bundles of collagen fibrils.

Fine structural examination of liver, kidney and pancreas revealed no mitochondrial abnormalities.

Biochemical investigation

The carnitin content of the heart was within the normal range.

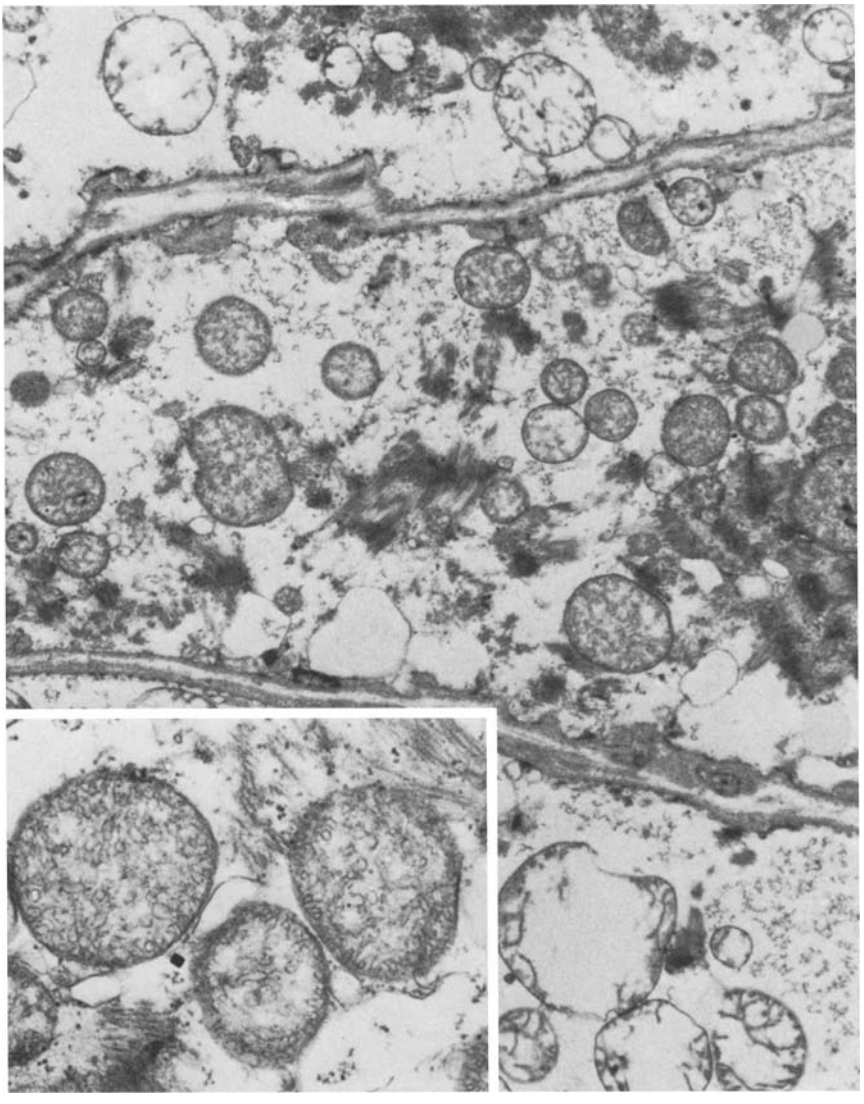

Fig. 7. Heart, left ventricle. Cell of the left branch of the His'bundle contains mitochondria with tubular cristae and a dense matrix. ×10,000. Inset: ×27,000

Discussion

It is well known that hereditary neuromuscular disease is often combined with cardiomyopathy. This is especially the case in spinocerebellar ataxia (Friedreich), in muscular dystrophy (type Duchenne) and in myotonic dystrophy (Welsh et al. 1963; Rahlf et al. 1982). In these patients defects in the cardiac conduction system with interstitial fibrosis usually occur (Davies et al. 1983). As already mentioned, primary involvement of the heart muscle

cells seems to be very rare. Our report now deals with a young man with Kearns-Sayre syndrome showing the typical myopathy with ragged red fibers, who died from frank cardiac failure as consequence of a disseminated mitochondrial cardiomyopathy.

Mitochondrial cardiomyopathies are rare. Many reports deal with the so called histiocytic or oncocytic fatal mitochondrial cardiomyopathy always occuring in small children with severe arrythmias. In this lesion clusters of heart muscle cells are transformed into rounded cells filled with abnormal enlarged mitochondria (for literature see Silver et al. 1980). Amini et al. (1980) suggested that this entity of mitochondrial cardiomyopathy might be regarded as a diffuse lesion not of the common myocardium but of the cardiac conductive system. In a case of histiocytic cardiomyopathy Papradimitriou et al. (1984) found a deficiency of reducible cytochrome-b in the mitochondria. Skeletal muscle is not afflicted in this group of cardiomyopathies.

Hug and Schubert (1970) reported a six month old girl with diffuse mitochondrial cardiomyopathy and abnormal giant mitochondria in the heart and in the liver. A diffuse mitochondrial cardiomyopathy in a female infant with Leigh's disease has been reported by Langes (Langes et al. 1985).

Whereas in some of the above mentioned cases other organs apart from the heart may be found with abnormal mitochondria, the skeletal muscle was not afflicted. However, in 1976 Mackay et al. had reported on a cardiac endomyocardial biopsy of an eleven year old boy with an unusual type of proximal myopathy and a hypertrophic cardiomyopathy. The heart muscle cells were filled with giant, often ring-shaped (cup-shaped?) mitochondria. The skeletal muscle however showed no abnormalities morphologically.

A report of Sengers et al. (1975) deals with seven children from three families with hypertrophic cardiomyopathy and skeletal muscle myopathy. All patients had cataracts, the heart showed a diffuse mitochondrial myopathy with intensive fatty infiltration.

Another series of cases coming from a family with a X-linked recessive mitochondrial cardiomyopathy with enlarged and structurally abnormal mitochondria was demonstrated by Neustein et al. (1979). In this family one boy revealed mitochondrial abnormalities in the heart and also in liver, kidney and skeletal muscle. – Finally a diffuse mitochondrial cardiomyopathy combined with a mitochondrial myopathy in a 21 month old girl was reported by ourselves (Hübner and Grantzow 1983). This girl died in cardiac failure.

Our case deals with a disseminated mitochondrial cardiomyopathy in a patient with Kearns-Sayre syndrome. Few reports on the morphology of the heart muscle in such cases are published. McComish et al. (1976) gave an account on a 32 year old man with progressive external ophthalmoplegia, and atrio-ventricular and left bundle block. The endomyocardial biopsy showed hypertrophy of the heart muscle cells and an increased number of normally structured mitochondria, whereas Charles et al. (1981) in a similar case also found, in a endomyocardial biopsy, hypertropic heart

muscle cells with a probably concomitant increased number of enlarged mitochondria without structural peculiarities. – The other reports on mitochondrial cardiomyopathy in Kearns-Sayre syndrome were published only in abstracted form: Harati et al. (1977) gave an account of a heart biopsy of a 14 years old boy with Kearns-Sayre syndrome about similar changes in the heart muscle cells as in the ragged red fibers of the musculature. Isolated mitochondria had a reduced respiratory rate to about 30% of normal. Oxidative phosphorylation was partially uncoupled. No cardiac insufficiency was found. Recently Schwartzkopff et al. (1985a) reported on endomyocardial biopsies in 5 patients with Kearns-Sayre syndrome and a variation in form and size of the cardiac mitochondria. In 4 cases they observed abnormal muscle cells with degenerative changes in the mitochondria in the form of parallel louped or ring-like cristae, but little change in contractile elements. The function of the heart at rest was normal in all patients; under stress one patient however showed reduced cardiac function, (Schwartzkopff et al. 1985a, 1985b).

As in many other cases our patient suffered from cardiac arrhythmias. They were successfully treated by modern therapy, and finally with a heart pacer. In the cells of the conduction system we observed abnormal dense rounded mitochondria with tubular cristae. This finding suggests that the conductive disturbances of the heart in Kearns-Sayre syndrome might be, at least partially, caused by disturbed function of the mitochondria with such abnormalities. – The patient died with right and left heart failure in consequence of a disseminated mitochondrial cardiomypathy. That means, that in patients with Kearns-Sayre syndrome or progressive external ophthalmoplegia, both parts of the striated muscle system, i.e. the skeletal muscle as well as the heart muscle (both heart muscle cells and conductive heart muscle cells) can be the target of a mitochondrial lesion the cause of which is not known. Such an injury, as discussed earlier (Hübner und Grantzow 1983) could lead to a proliferation of mitochondria in a frustrated attempt to compensate for the defect. In this case, in the heart muscle cells the mitochondrial lesions might result in the proliferation of abnormal mitochondria, leading to a mitochondrial cardiomyopathy which was finnally fatal. For these patients, a heart transplantation might be the therapy of last resort.

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