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Cardiomyopathy associated with Leigh's disease*

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Summary. Clinical and postmortem findings in a female infant, suffering from Leigh's disease and cardiomegaly are described. The cardiac enlargement was due to symmetrical thickening of both ventricular walls and the septum. On light microscopy a widespread fibre disarray with a slight predilection for the ventricular septum was observed. Ultrastructural changes included an extreme reduction in the number of myofibrils and an excess of mitochondria. Abnormalities of the mitochondrial structure with tubular and myelinic transformation of the cristae suggested that a mitochondriopathy is responsible for the cardiomegaly in Leigh's disease.

Key words: Cardiomyopathy – Leigh's disease – Mitochondriopathy – Ultrastructure

Introduction

With varying frequencies, hereditary neuromuscular diseases are combined with myocardial changes (Welsh et al. 1963; Perloff et al. 1966; Hewer 1969; Perloff 1971; MacKay et al. 1976; Rahlf and Bachmann 1982) and Friedreich's ataxia with hypertrophic cardiomyopathy is the best known (Smith 1977). In Leigh's disease in recent years several cases of cardiomyopathy have been observed (Rutledge et al. 1982). This autosomal recessive disease, mostly occurring in the newborn and in children, is characterized by a progressive subacute necrotizing encephalomyopathy (Leigh 1951). Occasionally abnormally structured mitochondria appear in cerebellar neurons and coincidently in skeletal muscle cells (Crosby and Chou 1974; Willems et al. 1977; Walter 1981) and thus a hereditary mitochondriopathy has been though to be pathogenic (Egger et al. 1982). While defects of mitochondrial

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enzymes (Tassin and Brucher 1982) with numerical increase and abnormal structure of mitochondria have been found in several congenital skeletal muscle diseases (Walter 1981; Schmitt 1982) few observations of diffuse mitochondrial changes in cardiomyopathy exist (Bogousslavsky et al. 1982; Hübner and Grantzow 1983). To our knowledge thorough light and electron microscopical investigations of cardiomegaly in Leigh's disease have not previously been performed. Here we report the cardiac findings of a female infant who died at the age of 8 weeks, presenting the clinical and morphological signs of Leigh's disease with coexisting mitochondrial cardiomyopathy.

Case report

The female infant was delivered as second child two weeks before term, following a normal pregnancy, with a body weight of 2.44 kg and a body height of 48 cm.

Clinical evaluation revealed insufficiency of the sucking and swallowing reflexes, distinct muscular hypotonia, missing proprioreceptive reflexes and temporary horizontal nystagmus. Hypothermia with a minimum body temperature of 95° F (35.2° C) and occasional slight hyperthermia (max. 100.4° F (37.9° C)) were evident.

The CT-scan of the brain revealed a hydrocephalus with vacuolation and was suggestive of leucodystrophy. Severe lactic acidosis was apparent from the first days of life. The chest radiograph presented distinct enlargement of the heart with globular configuration. The ECG showed elevation of the ST-segment to 0.6 mV.

From the third postnatal week the patient required mechanical ventilation with 30–40% O_2 because of progressively impaired respiratory functions. The patient died on the 58th day of life due to regulatory disorder of the central nervous system.

Autopsy was performed 8 h after death.

Methods

Light microscopy. After fixation with 4% formalin the heart was cut parallel to the base in horizontal discs, each 5 mm in thickness. Paraffin sections were stained with haematoxylin-eosin, Elastic van Gieson, and PAS.

Electron microscopy. Myocardial specimens from the midwall-region of the left and right side walls were fixed with 2.5% cacodylate-buffered glutaraldehyde, postfixed with 1% OsO_4 and embedded in epon. Staining of the semithin sections was carried out as described by Richardson et al. 1960; the ultrathin sections were contrast stained with lead citrate and uranyl acetate.

Results

The morphological changes of the brain were characteristic of Leigh's disease. Detailed neuropathological findings are presented elsewhere (Seitz et al. 1984).

Macroscopic data. Postmortem opening of the thorax revealed dilatation of the pericardium and 30 ml of pericardial effusion. The heart was distinctly ball-shaped and enlarged (Fig. 1a), causing extensive compression atelectases of the lung (weight of the heart 65 g, normal: 21.4 g). The epicardium was smooth and glistening without thickening. No valvular defects were apparent. The coronary arteries were of normal size and arranged normally. The atrial and ventricular lumina were regular. Anatomical obstruction of the left ventricular outflow tract was not seen, the endocardium was normal

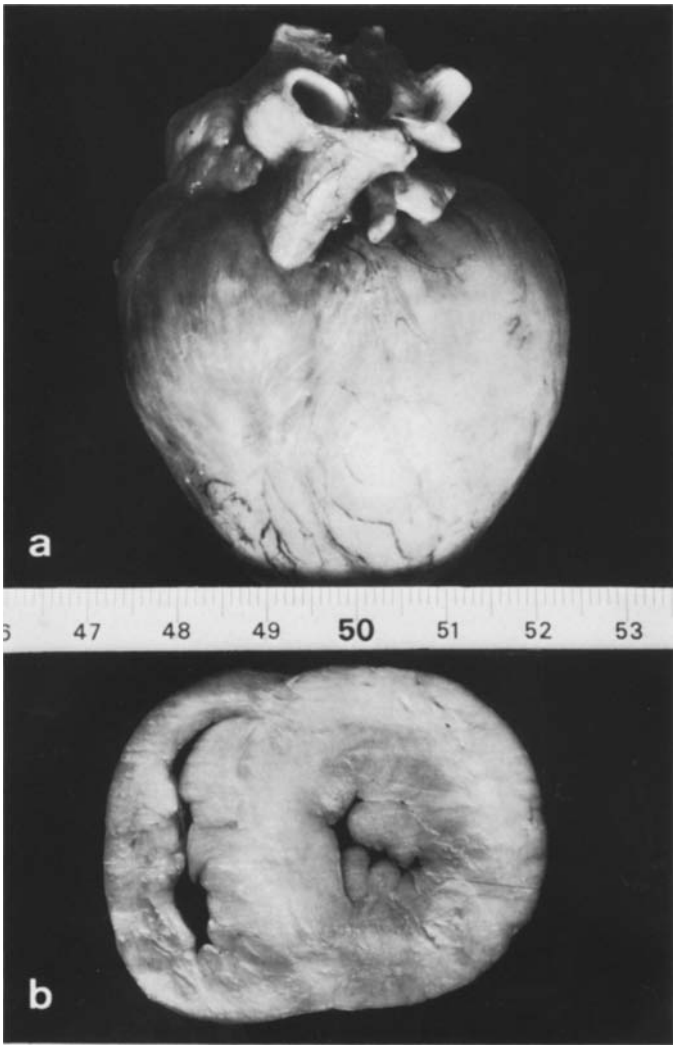

Fig. 1. a Ball-shaped, symmetrical enlargement of the heart. **b** Horizontal section of the ventricular part. Distinct thickening of both ventricles and the septum, with small ventricular cavities

and no parietal thrombosis was seen. Cross-sections parallel to the base of the heart were cut and a uniform thickening of the septum, left and right ventricular wall was evident (Fig. 1 b).

Light microscopy. Haematoxylin-eosin-stained sections show a moderate to distinct increase in width of the muscle fibres with a pale, slightly granulated cytoplasm in the perinuclear region. Numerous abnormally arranged muscle fibres show obtuse-angled exceptionally wide-spread branching in the septum (Fig. 2). The methylene-blue-stained semithin sections reveal marked reduction of myofibrillar structures (Fig. 3). There is no interstitial fibrosis,

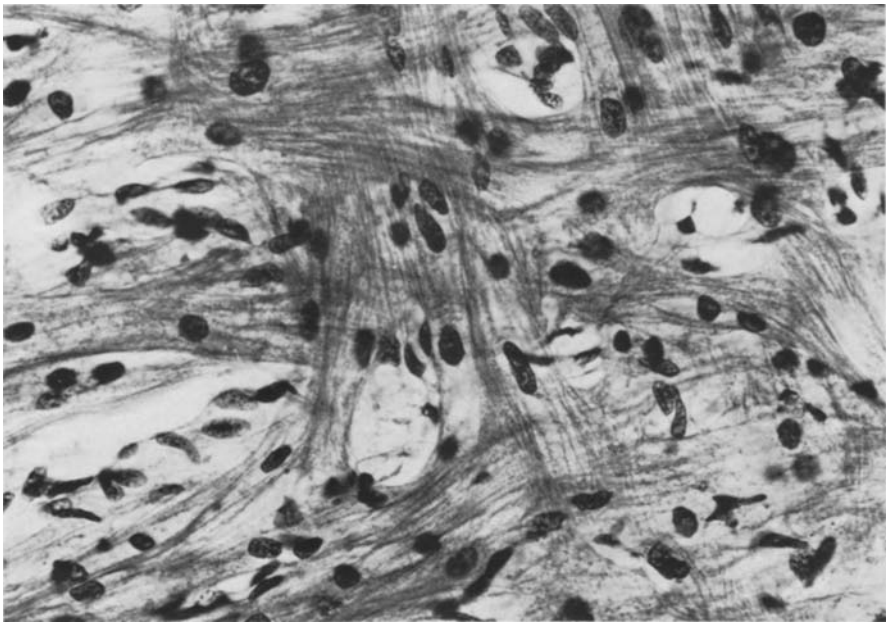

Fig. 2. Marked muscle fibre disarray in the septum. HE, ×400

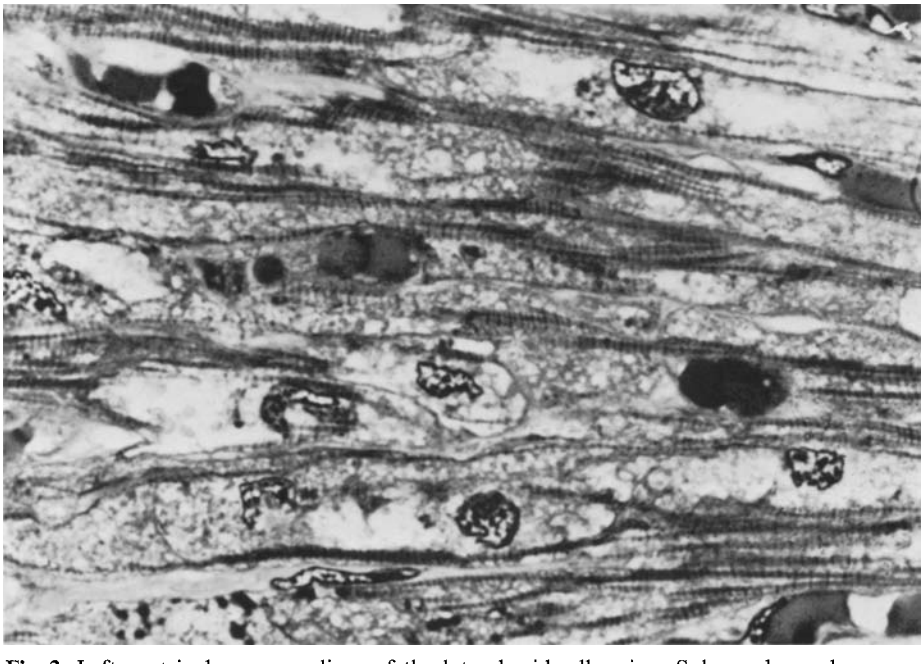

Fig. 3. Left ventricular myocardium of the lateral midwall-region. Subsarcolemmal arrangement of reduced myofibrils. Broad perinuclear areas with corpuscles of different size. Semithin section, Richardson stain, ×850

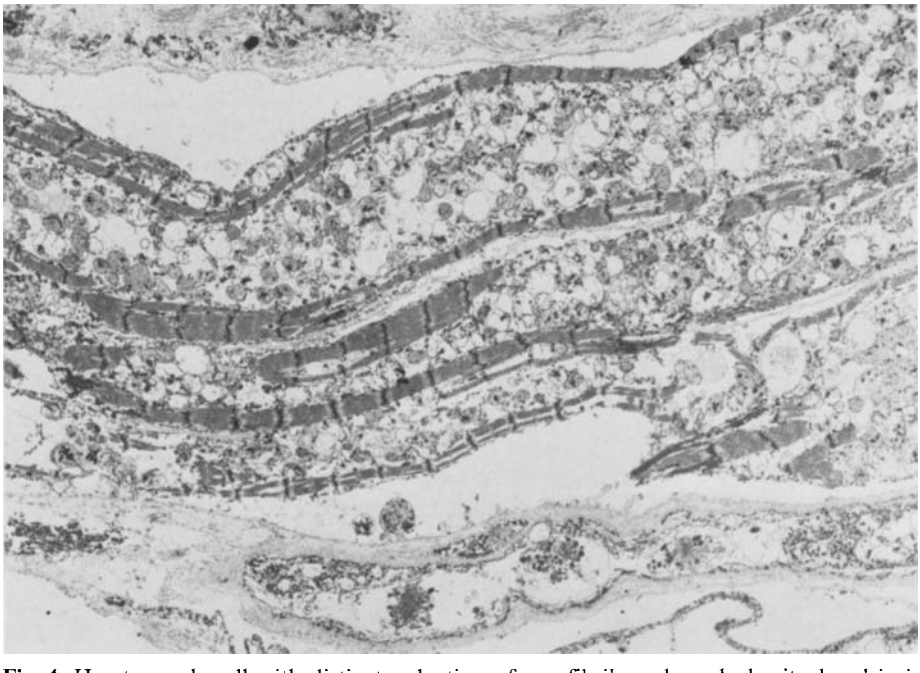

Fig. 4. Heart muscle cell with distinct reduction of myofibrils and marked mitochondriosis, × 3,600

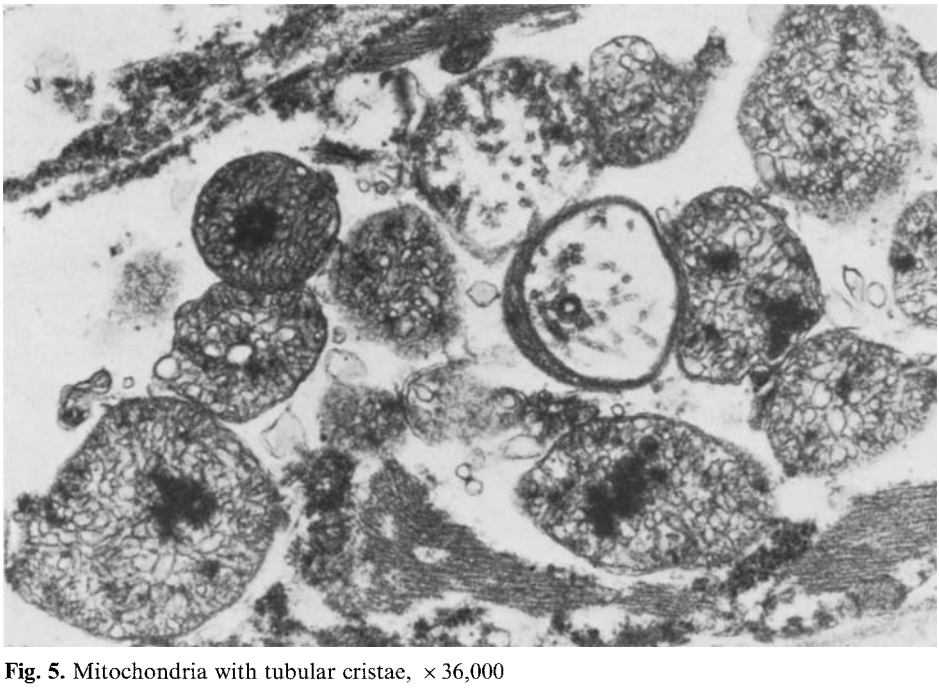

Fig. 5. Mitochondria with tubular cristae, × 36,000

inflammatory infiltrations or lipomatosis. The walls of the intramural vessels are not thickened.

Electron microscopy. All myocardial cells show almost the same changes. The myofibrils are markedly reduced, the myocytes often exhibiting only one or two subsarcolemmic myofibrils (Fig. 4). The myocardial cells are filled with mitochondria which are often enlarged. Most of them (40–60%) are abnormally structured and contain tubular cristae or dense plump inclusions (Fig. 5). Numerous mitochondria are transformed into vesicular corpuscles, delimited by a double-membrane, resembling myelin-figures of different size.

Neither the central nor the peripheral nervous system nor the skeletal muscles reveal any mitochondrial disorders (Seitz et al. 1984).

Discussion

From the clinical symptoms a tentative diagnosis of Leigh's disease was made which was confirmed by macroscopic and microscopic findings in the brain. A further essential pathological finding was marked cardiomegaly. Occasionally Leigh's disease has been observed in combination with a hypertrophic cardiomyopathy (Rutledge et al. 1982). Thorough histological and electron microscopical investigations of such hearts have not been performed.

The most frequent reasons for cardiac enlargement in infancy, e.g. a cardiac anomaly, myocarditis, storage diseases (glycogenosis) or carnitine deficiency were excluded. On light microscopy the myocardial cells revealed perinuclear vacuolization and peripheral displacement of the myofibrils. In storage diseases (Pompe's disease, Fabry's disease) identical alterations are seen but on the basis of histochemical and electron microscopical studies a correct differential diagnosis can be made. The myocardial cells presented an enormous increase in mitochondria, many of them being abnormal. Mitochondrial swelling with enlargement of dense inclusions is generally an artefact due to hypoxia or autolysis (Trump et al. 1965) but the tubular transformation of mitochondrial cristae represents a real structural abnormality. We therefore suggest that the cardiomegaly in Leigh's disease is a mitochondrial cardiomyopathy. A few reports of diffuse mitochondrial changes as the causative factor of cardiomyopathy have been made. Hug and Schubert (1970) found a similar mitochondriosis with tubular cristae in an infant, 6 months old, suffering from hypertrophic cardiomyopathy, Hübner and Grantzow (1983) described largely similar mitochondrial changes in the heart and skeletal muscles of a 21 months old girl. An increase of mitochondria with circular arrangement of cristae was found by MacKay et al. (1976) in a myocardial biopsy of an 11 years old boy with an uncommon myopathy. A distinction should be made between the mitochondrial cardiomyopathy that we observed and the so-called oncocytic or "histiocytoid" cardiomyopathy (Ferrans et al. 1976; Silver et al. 1980) in which the myocardial cells are focally rounded and stuffed with mitochondria and contractile elements are not present or present only as leptofibrils.

Diseases associated with abnormal mitochondrial number or shape have been called mitochondriopathies (Ernster et al. 1959; Luft et al. 1962) and it has been suggested that the structural changes of mitochondria are due to a deficiency or inhibition of mitochondrial enzymes (Walter 1981). In some mitochondriopathies the metabolic disturbances are defined (Walter 1981; Tassin and Brucher 1982). In Leigh's disease, a mitochondriopathy has been discussed as causative factor (Crosby and Chou 1974; Egger et al. 1982) but mitochondrial changes in the cells of the central nervous system have seldom been described (Vuia 1975; Walter 1981). However, some authors suggest that ragged-red fibres are typical of Leigh's disease (Crosby and Chou 1974; Willems et al. 1977; Walter 1981), and discuss the possibility of a mitochondrial cytopathy with varying expressivity. From the pathogenetic point of view Leigh's disease may be compared with the Kearns-Sayre-Syndrome, in which abnormal mitochondria with paracristalline inclusions in the CNS, skeletal muscles, liver and myocardium are known to occur (Bastiaensen et al. 1972; Olson et al. 1972). Further mitochondrial myoencephalopathies are found in Alper's disease, Zellweger-syndrome, Reye-syndrome and Kinky-hair-syndrome (Walter 1981).

In our case we failed to show comparable mitochondrial changes or paracristalline inclusions in skeletal muscles, liver, small intestine or the CNS (Seitz et al. 1984). In Leigh's disease several investigations have revealed disturbances of oxidative phosphorylation possibly leading to latent hypoxia in myocardial cells by enzymatic deficiency or inhibition. The numerical increase in mitochondria can be considered as a cellular attempt to compensate for enzymatic deficiencies (Walter 1981; Tassin and Brucher 1982; Schmitt 1982) but it should be remembered that mitochondriosis is a non-specific phenomenon in degenerate hypertrophic myocardial cells (Maron et al. 1975).

The marked reduction of contractile myofibrils might be interpreted as a result of disturbed protein-synthesis as cellular metabolism is inadequated for synthesis. Askanas et al. (1978) found a disturbance of mitochondrial protein-synthesis and growth in muscle cell cultures of patients with ophthalmoplegia. Hence even storage diseases (glycogenosis; Fabry's disease) are associated with a numerical reduction of myofibrils and thus a pure spatial problem might be of additional importance, leading to diminished myofibrillar mass. A mitochondrial enzyme defect of myocardial cells in our case could not be demonstrated.

Apart from the mitochondriopathy, a myocardial fibre disarray including abnormal branching was evident in the heart. Such fibre disarrays appear in normal hearts and under various pathological conditions (Becker and Caruso 1982). They are considered to be typical but not pathognomonic of hearts with idiopathic hypertrophic cardiomyopathy (HOCM and HNCM) (Maron and Roberts 1979). In hypertrophic cardiomyopathy mitochondriosis of the myocytes can be seen (Ferrans et al. 1972) but we have never seen changes of this extent before in our myocardial biopsies. We cannot exclude the co-existance of a mitochondriopathy and a hypertrophic cardiomyopathy without a cause- and effect relation in our patient. In hypertrophic cardiomyopathy the hypertrophy and fibre disarray appears to be

a genetically determined feature of the abnormal myocardial cells. It is not known whether contractile behaviour is changed to such a degree that focal disarrangement will develop or be intensified. The observation of abnormally ramified muscle fibres in the septum, on the margins of the left ventricular wall of normal hearts or in the periphery of myocardial scars suggests the influence of mechanical forces, causing uncommon angles between adjacent myocytes. These mechanical forces may play only a minor part; Hübner and Grantzow (1983) observed a heart with a similar mitochondriopathy and no muscle fibre disarray.

Our observation shows that infantile hypertrophic cardiomyopathy may exhibit a mitochondrial cardiomyopathy. This differential diagnosis can be confirmed by a skeletal muscle biopsy, but ultimately a myocardial biopsy might be unavoidable.

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