Myocardial ultrastructural changes in Kugelberg-Welander syndrome¹

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Electron microscopical study of a biopsied specimen of myocardium from a patient with the Kugelberg-Welander syndrome revealed myocardial degeneration, including preferential loss of myosin filaments and abnormalities in the Z bands. Leptomeric fibrils were also observed in the cardiac muscle cell; there does not appear to be a previous report of the finding of such fibrils in human myocardium.

It has been reported that the heart can be involved in the Kugelberg-Welander (K-W) syndrome (Matsumoto *et al.*, 1971; Sterz *et al.*, 1971; Sugimura *et al.*, 1973), a spinal muscular atrophy described by Wohlfart *et al.* (1955), and Kugelberg and Welander (1956). Recently, we reported 2 cases of this syndrome with cardiomyopathy and reviewed the published reports (Tanaka *et al.*, 1976).

To our knowledge, there has not been any report of the fine structural changes of the myocardium in the K-W syndrome. In this communication, we describe the results of electron microscopical examination of myocardium from a patient with the K-W syndrome.

Case history

A 20-year-old man was referred in June 1974 to the Kagoshima University Hospital for investigation of muscular atrophy. He seemed to have been well until the age of 7 years, when he noticed progressive clumsiness in running. He first noticed difficulty in climbing stairs at the age of 17 years. One year before admission, he developed difficulty in getting up by himself. He had no symptoms of cardiac disorder. The family history and past history were not contributory. He did not drink alcohol. On admission, he was well developed. The pulse was 64/min and regular. The blood pressure was 102/42 mmHg. No murmur was audible. Neurological examination disclosed weakness and atrophy of the proximal muscles of the extremities. The gait was

waddling. The ankle jerks were slightly accentuated bilaterally.

Other deep tendon reflexes were not elicited. The sensory examination was normal. The electromyogram showed a neurogenic pattern. Muscle biopsy revealed mixed neurogenic and myogenic muscular atrophy. The nerve conduction velocity was normal. Blood picture, urinalysis, and blood chemistry were all within normal range. The chest x-ray film showed no cardiomegaly. The electrocardiogram was also normal. His bundle electrogram showed normal PA, AH, and HV intervals. Right cardiac catheterisation showed normal pressures. No shunt was seen.

METHODS

After informed consent was obtained, a Konno-Sakakibara catheter biptome (Konno and Sakakibara, 1963) was inserted into the right ventricle through the right saphenous vein, and endomyocardial biopsy was performed.

Histological sections of the biopsy specimen were stained with haematoxylin and eosin. For electron microscopical observation, the tissue was fixed in 3 per cent glutaraldehyde buffered with 0.1 M phosphate (pH 7.4) for 2 hours and postfixed in 2 per cent osmium tetroxide for 2 hours. After rapid dehydration with ethanol and propylene oxide, the tissue was embedded in Epon 812. A Porter-Blum ultramicrotome (Ivan Sorvall, Inc.) was used for cutting the blocks and the sections were stained on the grids with uranyl acetate and lead citrate. Electron micrographs were taken with a JEM 100B electron microscope.

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Fig. 1 Electron micrograph showing fine filaments and abnormality in the Z band. Many fine filaments are packed within the cytoplasm. Some of them are attached almost perpendicularly to the irregular Z-band-like material. The fine filaments are 60 to 80 Å in diameter. The Z-band-like material (ZM) is present in an irregular band and in a cylindrical mass. A few degenerated mitochondria are also present.

Results of morphological examinations

(A) LIGHT MICROSCOPICAL EXAMINATION

The specimen showed normal structure. No significant changes were observed in myocardial cells, the interstitial tissues, or in the endocardium.

(B) ELECTRON MICROSCOPICAL EXAMINATION

Degenerated myocytes were occasionally found among apparently normal myocytes. The degenerated myocytes contained many fine filaments, accumulations of Z-band-like material, a few abnormal mitochondria and some vesicles. The Z-band-like material was present in irregular bands or in cylindrical masses. A great many fine filaments were packed within the cytoplasm. Some of them were attached to the Z-band-like material almost perpendicularly. Thick filaments were very few or completely lost in these cells (Fig. 1). The fine filaments seemed to be actin filaments because of their perpendicular attachment to Z-band-like

material and because of their diameter (60 to 80 Å). A few mitochondria characterised by cristolysis or swelling were scattered within these myocytes. The incidence of these myocytes was about 1 or 2 out of 50 myocytes. An additional finding was the presence of leptomeric fibrils, which consisted of dense bands and fine filaments that were attached perpendicularly to each band and had a regular periodicity of about 220 mμ (Fig. 2). The leptomeric fibrils were seen in myocytes which showed degenerative changes, including degeneration of the mitochondria and irregularity of the Z bands.

Discussion

Seven cases of the K-W syndrome with cardiomyopathy have been reported. Histological studies of myocardium in this syndrome were reported in 2 patients. Sugimura *et al.* (1973) reported a 23-year-old woman who showed first degree atrio-ventricular block, atrial premature beats, and

Fig. 2 Electron micrograph showing leptomeric fibrils, which consist of dense bands (arrows) connected by fine filaments. They have a regular periodicity of about 220 m μ and seem to be connected to the sarcolemma (sectioned obliquely at S) on one side of the disorganised cell.

paroxysmal atrial tachycardia. Fibrosis of the right atrium was shown by endomyocardial biopsy. Using light microscopy we noted slight interstitial fibrosis in the myocardium from another patient, a 26-year-old man with K-W syndrome and cardiac changes (Tanaka *et al.*, 1976). The present study, the first report on electron microscopical findings of the myocardium in K-W syndrome, has revealed preferential loss of myosin filaments in some degenerated myocytes. Recently, Maron *et al.* (1975) reported on ultrastructural changes of cardiac muscle cells in patients with cardiac hypertrophy. They reviewed the published reports on myofibrillar changes. Preferential loss of myosin filaments has been reported in various abnormal cardiac cells. It has been observed in cardiac muscle cells in hypoxic rats (Dusek *et al.*, 1971), in the crista supraventricularis in patients with congenital heart disease (Jones *et al.*, 1975), and in the left ventricle in patients who had received daunorubicin therapy (Buja *et al.*, 1973; Buja and Ferrans, 1975). However, this finding has not previously been reported in the myocardium of patients with hereditary familial-

degenerative neuromyopathic diseases. We considered the preferential loss of myosin filaments found in this patient to be a degenerative change because other degenerative changes, including mitochondrial and Z band alterations, were also present in the myocytes.

Another finding seen in this patient was the presence of leptomeric fibrils. Leptomeric fibrils were discovered by Ruska and Edwards (1957) in the latissimus dorsi muscle of a young thrush in 1957. Since then, they have been found in myocardium as well as in the skeletal muscle of various mammals (Bogusch, 1975; Saetersdal and Myklebust, 1975). However, we have not found any previous report of leptomeric fibrils in human hearts. We also observed leptomeric fibrils in the myocardium of KK and yellow KK mice which were found to have myocardial degeneration (Nishi *et al.*). The function of the leptomeric fibrils is still controversial. The relation between the preferential loss of myosin filaments and the occurrence of leptomeric fibrils in our patient remains to be clarified.

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