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Hypertrophic Non-Obstructive Cardiomyopathy Caused by Disorder of the Myofiber Texture *

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Summary. A case of hypertrophic non-obstructive cardiomyopathy caused by a disorder of the myofiber texture was observed in a 10 year old boy. The heart weighed 390 g and showed concentric hypertrophy of the left and right ventricles as well as of the ventricular septum. Additional findings consisted in an abnormal septum membranaceum and a accessory tricuspid valve leaflet. Severe cardic hypertrophy was associated with prominent interstitial and subendocardial fibrosis, and pronounced intimal fibrosis of the intramural arteries. Electron microscopy revealed various degrees and stages of hypertrophy of the myocardial cells combined with severe degenerative changes. Additional changes of the sinus node and conduction system were responsible for a tachycardia-bradycardia syndrome, complete left bundle branch block and final total AV-block.

Introduction

The term cardiomyopathy has been recently redefined as a heart muscle disorder of unknown cause and not associated with systemic diseases (Abelmann, 1974). Cardiomyopathies can be classified on the basis of functional anatomy and clinical characteristics into three types: congestive, hypertrophic and obliterative. In the past, hypertrophic cardiomyopathy (HCM) used to be suspected only when left ventricular hypertrophy was associated with outflowtract obstruction, thus ignoring the fact that the latter is not an obligate feature of this disorder (Oakley, 1974). This attitude explains the great amount of publications related to idiopathic hypertrophic subaortic stenosis (IHSS), whereas the reports on cases of the non-obstructive type of hypertrophic cardiomyopathy are but a few. The lack of post mortem observation may, however, be attributed to the less typical course of the disease in non-obstructive HCM, with unexpected clinical deterioration and sudden death outside the hospital. The present report describes mainly the macroscopic and microscopic findings as well as the ultrastructural features in the heart of a child with non-obstructive hypertrophic cardiomyopathy.

Case Report

This white boy was born in 1963. He developed well until the age of five years, when he suddenly was overtaken by loss of consciousness associated with convulsions. At that time medical examination failed to reveal any sign of heart disease. Three months later two syncopal attacks occurred. An electrocardiogram, recorded for the first time in his life, depicted left ventricular hypertrophy and the chest x-ray disclosed cardiomegaly. The electroence-

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phalogram gave no indication of an underlying neurological disease. Digitalis therapy was started without much success. During the next two years frequent episodes of paroxysmal tachyarrhythmia and syncopal spells were noted, especially on exertion. In May 1970, the child was finaly admitted to a cardiological clinic. Catheterization[1] revealed slightly elevated right ventricular pressures, normal left ventricular systolic but high end-diastolic pressure values. No cardiac shunt could be detected. Angiocardiography with injection in the left ventricle indicated a considerable variation between end-diastolic and end-systolic volumes of the chamber, associated with increased thickness of the myocardium. A presumably muscular bulge, pertaining to the free wall, protruded into the cavity of the ventricle just below the left atrium. Although there was no systolic pressure gradient across the left ventricular outflow tract, the presence of IHSS was suspected. Digitalis was replaced by a β-adrenergic blocking therapy with 30 mg propanolol daily. During the next three years the child was free of symptoms except for exertional dyspnea. In October 1973, he experienced again a dramatic syncopal episode and was referred to our hospital.

On admission the boy appeared normally developed and well nourished. The heart beated rhythmically at a rate of 80/min, blood pressure was 100/70 mm Hg. Palpation revealed a precordial lift and a liver edge 4 cm below the right costal margin. On auscultation the heart sounds had normal intensity and no murmur could be detected. The electrocardiogram disclosed sinus rhythm, first degree atrioventricular block, complete left bundle branch block, and signs of left atrial hypertrophy; because of the bundle block the severity of ventricular hypertrophy could not be estimated properly. The type of rhythm disturbance that eventually precipitated a syncopal attack could be ascertained almost immediately by means of continuous electrocardiographic tape monitoring: During mild physical exercise a sudden burst of supraventricular tachycardia occurred, which ended abruptly in cardiac asystole and caused the patient's collapse. Sinus rhythm reappeared spontaneously after three seconds.

Two days later paroxysmal tachycardia recurred, precipitating unconsciousness, cyanosis and convulsions. From there on Verapamil was added to the β-blocking therapy with a final maintenance dose of 120 mg daily. The sinus rhythm remained undisturbed until one week later a complete atrio-ventricular block with a ventricular rate of 35 beats/min developed acutely, making intravenous cathether pacing mandatory. Pulmonary pressure at that time was 40/20 mg Hg. The drugs were suspected to have possibly caused the blockade, all the more as sinus rhythm returned eight hours after they were withdrawn. Another episode of tachycardia had to be dealt with on the third day and—now exculping the previous therapy—a second degree atrioventricular block reappeared, worsening into a state of complete dissociation within a week; the ensuing well known bradycardia motivated implantation of bipolar demand pacemaker with epicardial electrodes. During this surgical intervention a biopsy on the left ventricle was performed.

In the following two months the child did very well under a combined oral therapy with Verapamil, 80 mg daily, and digoxin. He could be brought progressively to perform physical work up to 10 kilopond meter, raising the heart rate to 110 beats/min. No more paroxysmal tachycardia was noticed and ventricular bradycardia interrupted the restored sinus rhythm only on occasion during the night sleep, thus triggering the pacemaker into action. The patient was discharged with the afore mentioned therapy, but kept under close observation. He continued to do reasonably well until death occurred suddenly at home four weeks later.

Necropsy Findings

At autopsy bland scars were found on the left thoracic wall at the implantation site of the pacemaker generator. The pericardial sack was obliterated by fibrous adhesions. Two pacemaker electrodes laid inserted into the anterior wall of the left ventricle. The heart was enlarged and weighed 390 g. The left ventricle had a globular configuration, its wall was extremely hypertrophic, measuring 1.5 cm in thickness below the mitral valve and 2 cm at the apex. There was severe hypertrophy and abnormal branching of the left ventricular trabeculae with slight endocardial fibrosis. A muscular bulge at the anterior upper border of

1 The results of this hemodynamic study were graciously put at our disposal by Dr. Wolf, head of the Department of Pediatric Cardiology at the University of Heidelberg.

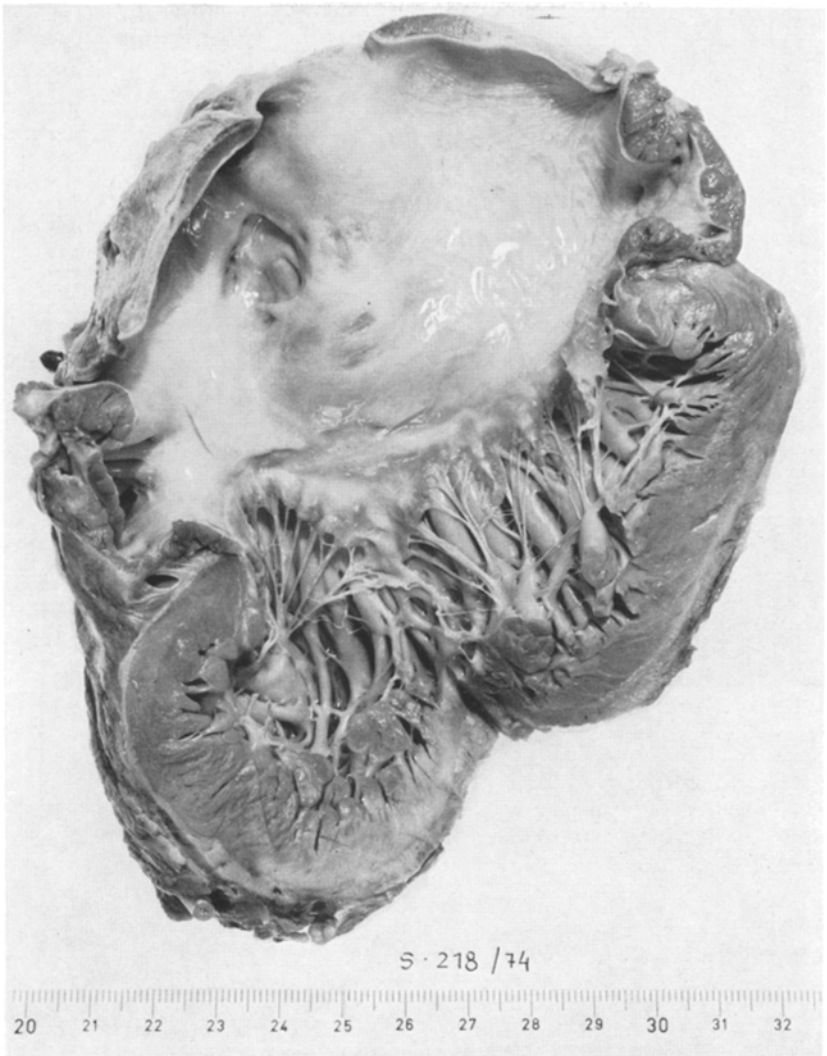

Fig. 1. Hypertrophic non-obstructive cardiomyopathy: Macroscopic appearance of the hypertrophic left ventricle with irregular branching of the trabecules and papillary muscles. Marked dilatation of the left atrium with fibrosis of the endocardium

the left ventricular wall, below the mitral valve projected into the left ventricular cavity. The left posterior papillary muscle was three-headed. The anterior papillary muscle was flattened and its broadened base was implanted just beneath the left ventricular outflow tract (Fig. 1). The mitral valve was bicuspidate and normal. The extremely dilated hypertrophic left atrium showed a thick diffuse endocardial fibrosis. Mild dilatation and marked hypertrophy were present in the right atrium and ventricle (Fig. 2). The right ventricular wall measured 5 mm in width. The tricuspid valve had three normal leaflets and an accessory leaflet inserted on the enlarged septum membranaceum. The aortic valve was normal. The leaflets of the pulmonary valve showed small fenestrations. The coronary arteries had a normal macroscopic appearance. Other autopsy findings included an enlarged thymus (110 g) and

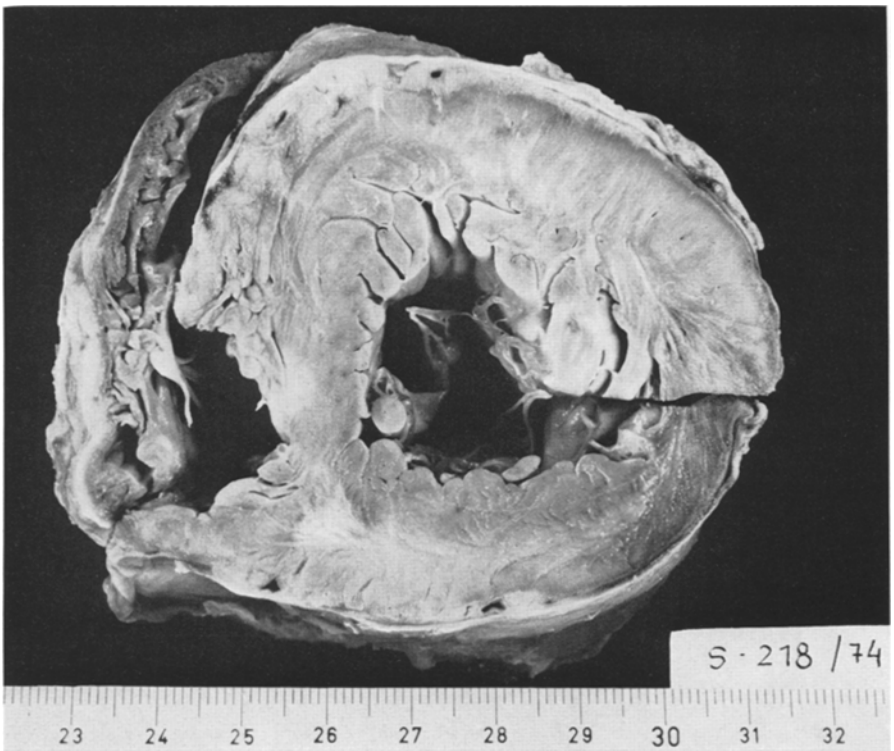

Fig. 2. Hypertrophic non-obstructive cardiomyopathy: Macroscopic cross section of the heart demonstrating concentric hypertrophy of the left ventricle and the ventricular septum. Moderate hypertrophy of the right ventricle. The white spots indicate areas of fibrosis

signs of chronic as well as acute congestion of the internal organs. Examination of the brain was not permitted.

Light Microscopic Findings

Several sections of the left ventricular wall, the ventricular septum and the right ventricle showed complete disorganization of the myocardial cells with abnormal branching of the hypertrophic myofibers (Fig. 3a). Most of the myocardial cells manifested severe hypertrophy with large polyploidic nuclei. There was considerable variation in the degree of interstitial fibrosis. The greatest amount of scar tissue was found in the subendocardial areas and within the thickened hypertrophic trabeculae and papillary muscles. Prominent intimal fibrosis of the arteries with narrowing of the lumina, and large infarctlike areas of scar tissue occurred particularly in some parts of the ventricular septum (Fig. 3b). Beneath the endocardium of the right ventricular septum, cross sections of transverse running arterial vessels could be observed. Sections through the right and left atrium disclosed hypertrophied but normally arranged muscle cells. Extensive endocardial fibrosis was present in the left atrium. An abnormal accessory tricuspid leaflet inserted on a thinned and enlarged septum membranaceum.

On serial sections of the right atrium we found a small abnormal sinus node located almost within the atrial myocardium. The specialized fibers of this node showed some disorganization and slight interstitial fibrosis (Fig. 3c). The bundle of His was elongated, running on the top of the muscular ventricular septum. The branching portion showed moderate interstitial fibrosis. There was an almost complete fibrosis of the specialized myofibers of the middle portion of the left bundle branch. The right bundle branch showed no alteration.

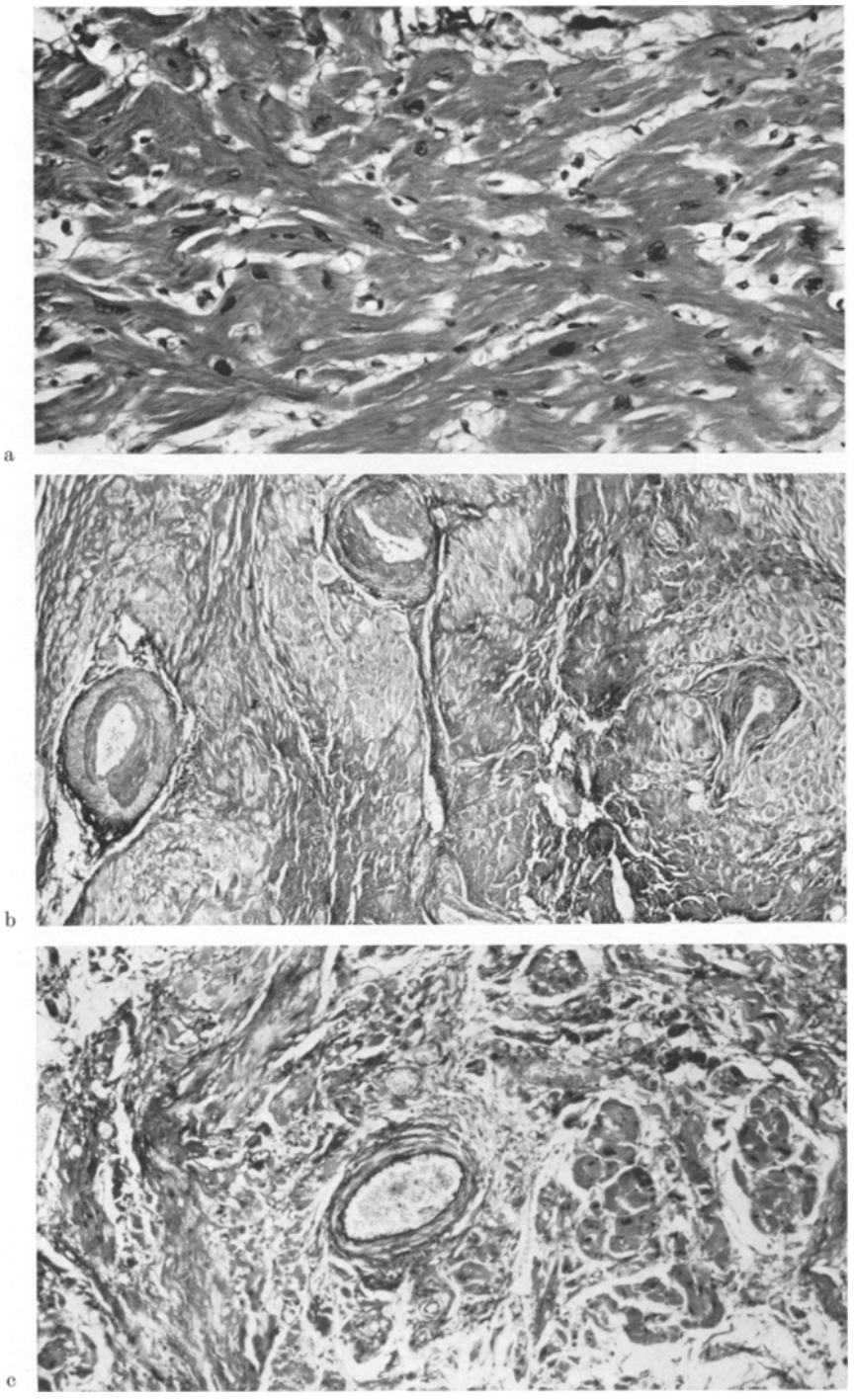

Fig. 3. (a) Ligth microscopy of the myocardium of the left ventricle with abnormal texture and branching of the hypertrophic myofibres, and large polyploidic nuclei. ×200. (b) Prominent intimal fibrosis of the intramural branches of the coronary arteries surrounded by post-infarct-like areas of scar tissue. ×32. (c) Abnormal sinus node with very small nodal artery and diffuse interstitial fibrosis. ×80

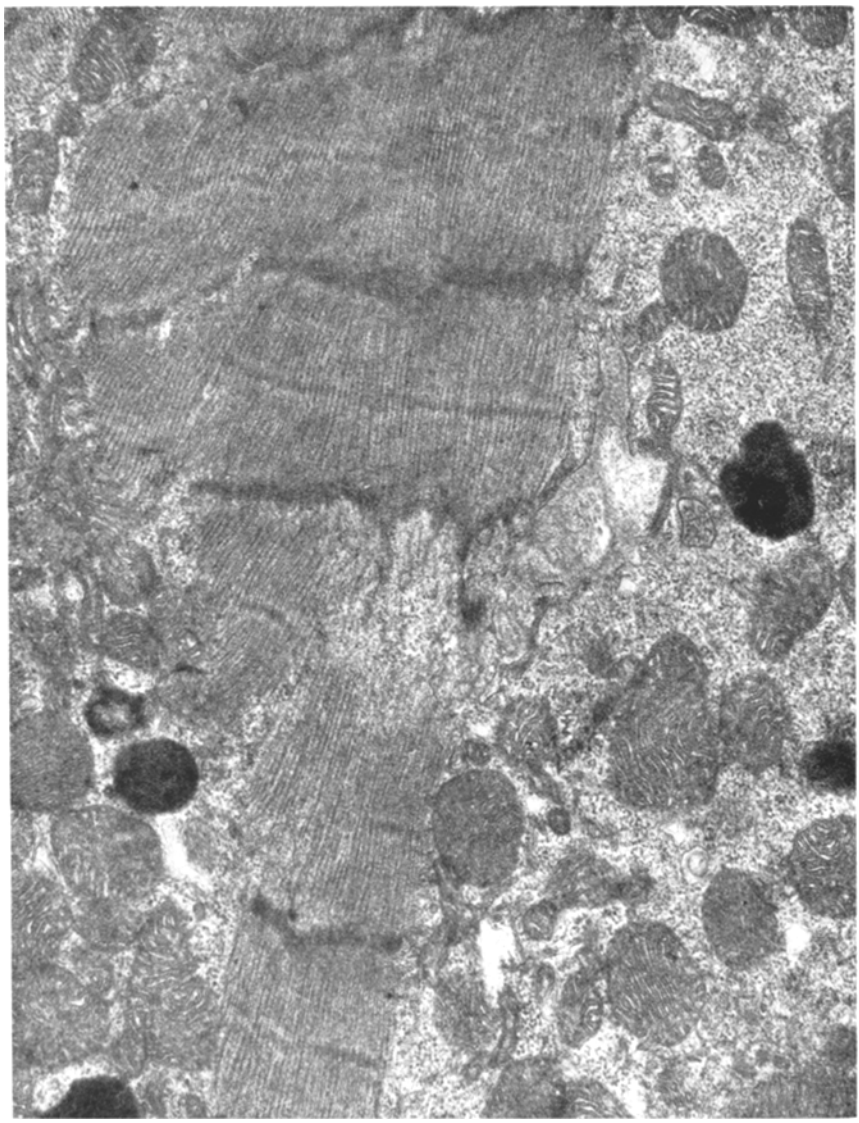

Fig. 4. Electron microscopy of myocardial biopsy specimen. Hypertrophied myofibrils with irregular z-bands. Small mitochondria within a ribosomes-rich sarcoplasm. ×16000

Electron Microscopy

Electron microscopy of small pieces of the left ventricular myocardium disclosed severely hypertrophied myocardial cells, surrounded by prominent interstitial fibrosis (Fig. 6). The widely different lengths of the sarcomeres were probably due to some contraction bands. Small mitochondria of irregular shape could be seen within large fields of sarcoplasm. Lamellae of rough endoplasmatic reticulum as well as increased amounts of ribosomes and glycogen granules, sometimes arranged in small clusters, were also present (Figs. 4, 5). In other areas numerous newly formed myofilaments were observed (Fig. 5). The ratio of mitochondria to

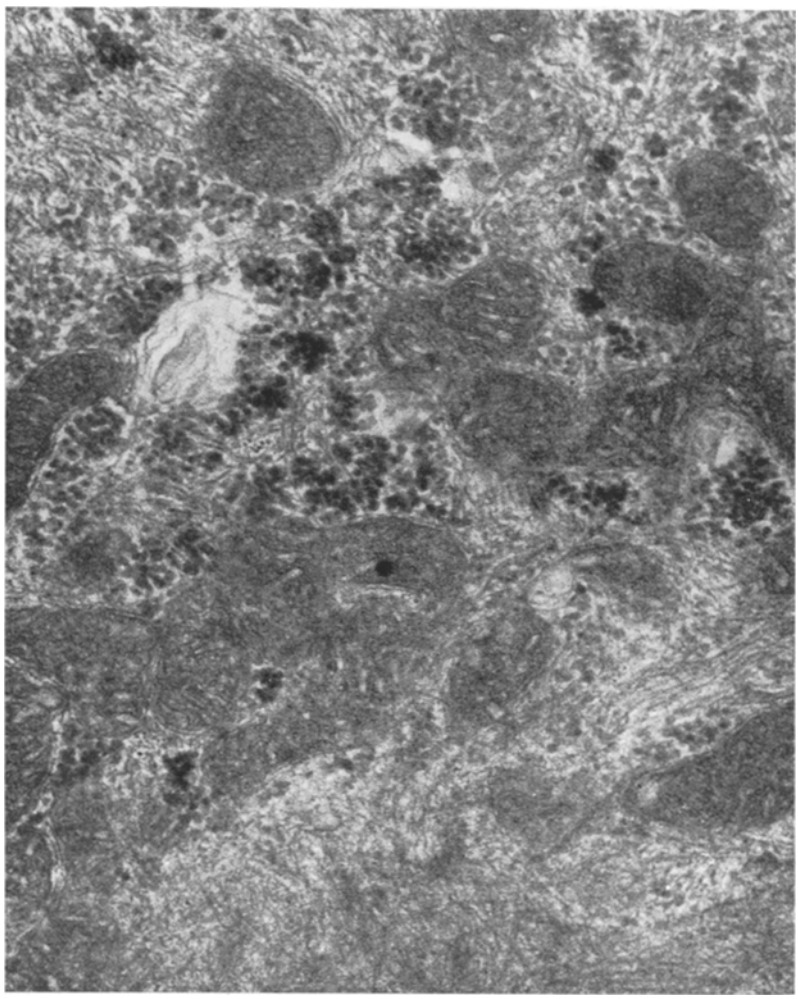

Fig. 5. Section of a myocardial cell with clusters of glycogen granules, irregular-shaped mitochondria and many new formed myofilaments. ×36000

myofibrils was decreased. Many areas showed degenerative changes with numerous myelin figures and lysosomic granules (Fig. 6). Some myocardial cells exhibited necrotic sequestrations.

Electron microscopy of an intercostal skeletal muscle biopsy revealed no abnormalities of the myofibers, except for a moderate enlargement of the endoplasmatic reticulum.

Comments

Recurrent syncopal episodes due either to bradycardia or paroxysmal tachycardia fit well in the so-called sick sinus syndrome. They do not explain, however, the whole array of conduction disturbances observed in this child. It is interesting to note that an initial diagnosis of IHSS was made at the age of seven years,

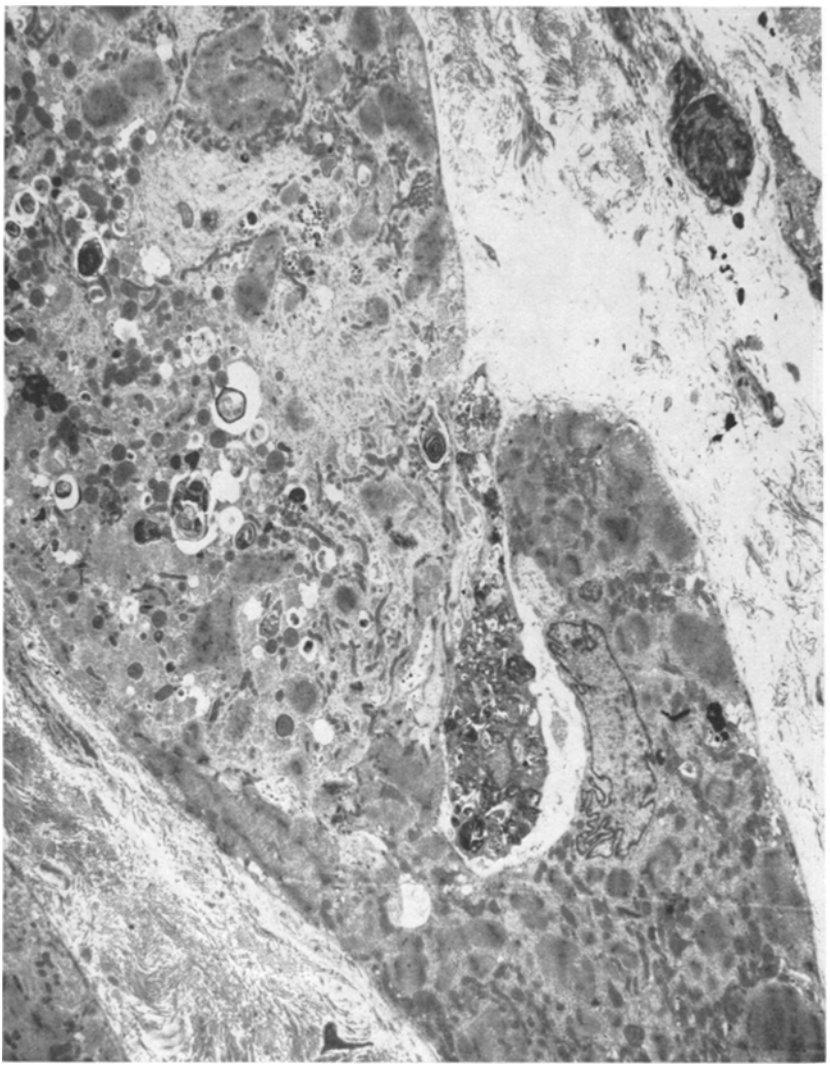

Fig. 6. Degenerated myocardial cells with numerous myelin figures and lysosomic granules as well as focal sequestration of necrotic material. The cells are surrounded by marked interstitial fibrosis. ×3200

based on the projection of a muscular bulge of the left ventricular wall below the left atrium as revealed by the angiocardiogram, although the pressure curves showed no systolic gradient across the left ventricular outflow tract. A glycogen storage disease was excluded by liver biopsy. Electron microscopy of myocardial biopsic material from the left ventricle disclosed hypertrophy and severe interstitial fibrosis as well as several degenerative changes suggesting a very poor prognosis for this child who effectively died three months later.

At autopsy the major gross anatomical feature was a symmetrical concentric hypertrophy of the left ventricle. The thickness of the ventricular septum was almost the same as that of the left ventricular free wall, an observation which led to the final diagnosis of non-obstructive hypertrophic cardiomyopathy. The trabeculae and papillary muscles of the left ventricle showed marked hypertrophy and an abnormal arrangement. The muscular bulge suggested by the angiocardiography was actually found at the anterior upper border of the left ventricle below the left atrium. Similar findings were described by Oakley (1974) and should be considered in the differential diagnosis of hypertrophic cardiomyopathies. This unusual form of cardiomyopathy revealed additional abnormalities including an accessory tricuspid valve leaflet, an enlarged septum membranaceum as well as an abnormal subendocardial course of the perforating septal branches of the left anterior descending coronary artery.

The most characteristic abnormality observed by light microscopy was the disorganization in the arrangement of muscle cells in the ventricular septum as well as in the right and left ventricle and also partially in the right atrium. The abnormal myocardial cells with a three dimensional branching of their myofibrils will contract in an asynergic way, resulting in a smaller resultant force vector than if the cells were oriented in parallel (Ferrans *et al.*, 1972; Knieriem, 1972). This frustrating work load will stimulate hypertrophy of the myocardial cell. An additional characteristic was the arrangement of these myocardial cells in "whorls" of muscle bundles (van Noorden *et al.*, 1971) and irregular trabeculae. Severe cardiac hypertrophy was associated with prominent interstitial fibrosis and subendocardial scarring as a sign of coronary insufficiency. This was supported by pronounced intimal fibrosis of the intramural arterial vessels particularly within the ventricular septum. The thickening of the vascular layers may be caused by an adaptive reaction of the coronary arteries to increased vascular wall tension (Vlodaver and Neufeld, 1967).

Cardiomyopathies are often associated with conduction abnormalities (Ferris, 1973; Davies, 1971; Knieriem, 1974). In the present case the predominant arrhythmia has been a brady-tachycardia syndrome combined with total atrioventricular block. Histological examination revealed marked interstitial fibrosis of the abnormally located sinus node. The almost complete fibrosis of the left bundle branch was responsible for the complete left bundle branch block which preceded total atrioventricular block in this child. The sudden death in this child may have been due to asystole following a recurrent episode of paroxysmal tachycardia. Another possibility may be the loss of atrial contraction following atrial arrhythmia in the presence of increased inflow resistance to ventricular filling (Goodwin, 1970).

Electron microscopic investigations of myocardial biopsies have been performed in different forms of idiopathic cardiomyopathies. The major findings consisted in various degrees of hypertrophy of the myocardial cell with irregular myofibrils, changing amounts of mitochondria, increased number of ribosomes and glycogen particles as well as the formation of new filaments (Meessen and Poche, 1967; Meessen, 1971; Ferrans *et al.*, 1972). Van Noorden, Olsen and Pearse (1971) suggested that these various ultrastructural changes may be in general non-specific signs of extreme hypertrophy due to diverse causes. Doerr (1971,

1972, 1974) has demonstrated cases of cardiomyopathies with mitochondriosis and discussed the difficulties of excluding changes of the myocardium after chronic myocarditis. According to Ferrans *et al.* (1972) hypertrophic obstructive cardiomyopathy reveals a focal characteristic disorganization and abnormal architecture of the hypertrophied myofibers, which we could confirm in surgically resected muscle of the left outflow tract (Meessen and Poche, 1967; Knieriem, 1972).

In the present case the abnormal architecture was not only confined to one focal area, but was distributed throughout both ventricular walls and the ventricular septum, even in some areas of the right atrium. It seems reasonable to conclude that the abnormal architecture of muscle cells is apparently the basic disorder in this case of non-obstructive cardiomyopathy. Our observations suggest that this abnormality is probably congenital as this is the case in hypertrophic obstructive cardiomyopathy (Ferrans *et al.*, 1972). The associated cardiac anomalies, described in this paper also support this hypothesis.

References

Abelmann, W. H.: The cardiomyopathies. In: E. Braunwald (ed.), The myocardium: Failure and infarction. New York: HP Publishing Co 1974

Davies, M. J.: Pathology of conducting system of the heart. London: Butterworths, 1971

Doerr, W.: Morphologie der Myokarditis. Verh. dtsch. Ges. inn. Med. **77**, 301–335 (1971)

Doerr, W.: Plötzlicher Herztod — Morphologische Aspekte. Verh. dtsch. Ges. inn. Med. **78**, 944–969 (1972)

Doerr, W.: Herz und Gefäße. In: W. Doerr, Organpathologie, Bd. I. Stuttgart: Thieme 1974

Ferrans, V. J., Morrow, A. G., Roberts, W. C.: Myocardial ultrastructure in idiopathic hypertrophic subaortic stenosis. Circulation **45**, 769–792 (1972)

Ferris, J. A.: The atrioventricular node in hypertrophic obstructive cardiomyopathy. Beitr. Path. **148**, 296–303 (1973)

Goodwin, J. F.: Congestive and hypertrophic cardiomyopathies: a decade of study. Lancet **1970I**, 731–738

Knieriem, H.-J.: Morphologische Grundlagen der Herzhypertrophie. Verh. dtsch. Ges. Kreisl.-Forsch. **38**, 1–21 (1972)

Knieriem, H.-J., Finke, E.: Morphologie und Ätiologie des totalen A. V.-Blocks. München-Berlin-Wien: Urban & Schwarzenberg 1974

Meessen, H.: The structural basis of myocardial hypertrophy. Brit. Heart J. **33**, Suppl. 94 (1971)

Meessen, H., Poche, R.: Beiträge zur pathologischen Anatomie der Fallot'schen Fehler und zur idiopathischen Herzhypertrophie. Anglo-Germ. Med. Rev. **4**, 73–87 (1967)

Oakley, C. M.: Clinical definitions and classification of cardiomyopathies. Postgrad. med. J. **48**, 703–713 (1972)

Oakley, C. M.: Clinical recognition of the cardiomyopathies. Circulat. Res. 34—35, Suppl. **II**, 152–167 (1974)

Van Noorden, S., Olsen, E. G., Pearse, A. G.: Hypertrophic obstructive cardiomyopathy: A histological, histochemical and ultrastructural study of biopsy material. Cardiovasc. Res. **5**, 118–131 (1971)

Vlodaver, Z., Neufeld, H. N.: Musculoelastic layers in coronary arteries. Vasc. Dis. **4**, 136 (1967)

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