Idiopathic cardiomyopathy in infants

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Idiopathic cardiomyopathy in infants. Nine cases of cardiomyopathy in infants are described. The early age of occurrence suggests the possibility of an intra-uterine onset, and the finding of virus antibodies to a significant titre in 3 of the 4 mothers examined suggests intrauterine viral infection as a possible cause.

The degenerative changes which have previously been described in cardiac ganglia are confirmed, but they are also found in control material, and are believed to be associated with cardiac failure rather than be features attributable to virus infection.

There has been considerable interest in cardiomyopathy since Brigden in 1957 introduced the term to encompass a heterogeneous and ill-defined group of conditions, both familial and nonfamilial, of uncertain aetiology, but with the common factor of degenerative or inflammatory change in the cardiac muscle.

Cases have been described in both adults and infants. In adults, Elster, Horn, and Tuchman (1955) suggested that the myocardial lesions resulted from a combination of anoxia with ventricular hypertrophy and dilatation. Goodwin *et al.* (1961) reported cases associated with obstruction to blood flow in the heart. Sanders and Ritts (1965) regarded cardiomyopathy as an immunological response to infection, and Witham (1970) accepted that biochemical changes in the myocardial protein in the presence of a virus infection could diminish contractile efficiency. Of the nonfamilial cases reported in infants, the majority have been associated with coronary artery disease, fibroelastosis, or systemic disease, according to the review by Hudson (1965). Black-Schaffer (1957) suggested that the myocardial changes resulted from mechanical factors in association with a dilated ventricle. Zoltowska (1971) studied cardiomyopathy in infants who also had endocardial fibroelastosis. She showed degenerative changes in the nerve ganglia of the heart and considered these changes of aetiological significance.

It is apparent from these varying theories that there is at present no conclusive evidence as to the cause of nonfamilial cardiomyopathy, particularly

in infants. However, a viral origin has been suggested for endocardial fibroelastosis by Fruhling *et al.* (1962), and it appears possible that infantile cardiomyopathy without fibroelastosis may be of similar aetiology. The occurrence of cardiomyopathy during the first year of life, when the infant is believed to be protected by maternal antibodies, suggests that if a virus infection is implicated then it occurs either in the mother during pregnancy or in the first months after birth in the infant itself in subclinical form. In the present paper particular attention is directed to this hypothesis. Cases were, therefore, selected to include only those with myocardial lesions without endocardial fibrosis or other pathology, and where possible viral studies were made.

Material and methods

Nine infants who came to necropsy at the Duchess of York Hospital, Manchester, were studied. They were included in the series only if they showed gross cardiac enlargement at necropsy without congenital heart lesions, valvular or coronary artery disease, or fibroelastosis. Nor was there disease in any other organ which could be related to the cardiac enlargement. Thus the cause of death was considered to be a primary disorder of the myocardium of unknown origin.

Multiple blocks from both ventricles and atria were taken for the preparation of paraffin sections. They were stained by haematoxylin and eosin, van Gieson, periodic acid Schiff, phosphotungstic acid-haematoxylin, Verhoeff's elastic stain, and Gordon and Sweet's method for reticulin. Frozen sections were stained by Sudan IV and an immunofluorescent technique based on the method of Coons and Kaplan (1950) was used to investigate the presence of bound γ -globulin.

Necropsy tissues from 4 infants were subjected to virus culture. In 5 cases specimens of blood from the

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TABLE I
Summary of clinical findings

Case no.	Age	Sex	Duration of symptoms (dy)	Mode of death	Month of death	Mother's serology titres	Clinical diagnosis
1	5 wk	F	1	Sudden collapse	June	—	Sudden death
2	13 wk	F	1	Sudden collapse	November	—	Sudden death
3	2 wk	F	6	Circulatory failure	March	—	Myocarditis
4	14 wk	M	3	Circulatory failure	March	mumps 1 : 250 measles 1 : 250 influenza A 1 : 16 adenovirus 1 : 16 measles 1 : 100 mumps 1 : 40	Congenital heart disease
Sibs { 5	4 wk	M	2	Circulatory failure	December		Congenital heart disease
6	2½ wk	M	1	Respiratory infection	November		Bronchiolitis
7	9 mth	M	1	Sudden collapse	March		Sudden death
8	18 dy	M	10	Circulatory failure	September	influenza 1 : 16 adenovirus 1 : 16 rubella 1 : 160	Congenital heart disease
9	5 mth	F	2 mth	Circulatory failure	December		Congenital heart disease

mothers of the infants were examined for the presence of virus antibodies and for antiheart and antinuclear antibodies. Control material was obtained from the hearts of 11 children dying from congenital cardiac disease including valvular lesions but excluding myocardial involvement, and 6 children dying without cardiac abnormalities, all within the age range of 2 weeks to 10 months.

The *clinical findings* in the infants are summarized in Table I. It can be seen that the age of the patients ranged from 2 weeks to 9 months. 3 patients presented as cases of sudden death without apparent symptoms. Of the remainder, 4 had illnesses of less than 1 week's duration before death, while the other 2 had symptoms for 10 days and 2 months, respectively. Of the infants with symptoms, 5 died in circulatory failure and 1 had a respiratory infection. Of the 9 infants all but 1 died during the autumn or winter months between September and March.

The mothers of 5 of the infants, 2 of the children being sibs, were interviewed and questioned about their

health during the pregnancy. None had had a clinical infection during this period. They gave a history of uncomplicated pregnancies and were not taking any drugs. There was no history of inherited cardiac disease in any of the families.

Macroscopical appearances of the hearts. The striking feature in the hearts of all the cases was enlargement. This is shown in Table II which summarizes the pathological findings and in which the heart weight is expressed as a ratio of the body weight. It can be seen that the heart/body ratio ranges from 1 : 80 to 1 : 47, while in a control series of 50 infants under the age of 1 year without heart disease the range was found to be 1 : 200 to 1 : 104. The ventricles showed a greater degree of hypertrophy than that seen in the atria, but both ventricles and atria showed approximately equal dilatation. The dilatation of the ventricles produced a flattening of the apex of the heart giving it a globular appearance (Fig. 1). From Table II it can be seen that in 3 cases there was predominant enlargement on

TABLE II
Summary of pathological findings

Case no.	Age	Sex	Body weight (g)	Heart weight (g)	Heart/body ratio	Enlarged heart chambers				Necropsy tissue viral cultures	Pathological diagnosis
						LV	RV	LA	RA		
1	5 wk	F	4500	57	1 : 80	+	++	+	+		Bronchopneumonia; cardiomyopathy
2	13 wk	F	4840	68	1 : 71	++	++	+	+		Bronchopneumonia; cardiomyopathy
3	2 wk	F	4020	83	1 : 48	+	++			No growth	Cardiomyopathy
4	14 wk	M	4000	85	1 : 47	++	++			No growth	Cardiomyopathy
5	4 wk	M	2870	55	1 : 52	++	+			No growth	Cardiomyopathy
6	2½ wk	M	2400	41	1 : 58	++	++	+	+		Bronchopneumonia; cardiomyopathy; vestigial kidney
7	9 mth	M	6500	100	1 : 65	++	++			No growth	Bronchopneumonia; cardiomyopathy
8	18 dy	M	3080	46	1 : 66		++		++		Cardiomyopathy
9	5 mth	F	4000	60	1 : 66	++	+	+	+	No growth	Cardiomyopathy

FIG. 1.—Macroscopic appearance of the heart showing dilatation of the ventricles producing a globular outline.

the left side of the heart while in 2 cases the right side accounted for the main enlargement, and in the remaining 4 there was marked but approximately equal enlargement on both sides.

The myocardium was pale pink and in many cases

showed mottling due to the presence of lighter red or yellowish areas.

The endocardium was thin and translucent in all cases and no valvular lesions were present.

Microscopical appearances of the hearts. The myocardial fibres were irregularly swollen and distorted; they were widely separated from one another, sometimes with amorphous pinkish material between them. A few fibres were vacuolated and some were necrotic (Fig. 2 and 3). Adjacent to the necrotic areas surviving fibres showed loss of striation. There was a small amount of PAS-positive material in a halo around the nuclei of occasional fibres but there was no fibrosis, inflammatory cell infiltration, or fatty change. No bound γ -globulin was found using the immunofluorescent technique. Capillaries between the muscle bundles showed marked dilatation.

The cells of the large ganglia showed degenerative changes: they were swollen and vacuolated and in many the nuclei were pyknotic or karyolytic (Fig. 4).

Examination of the hearts of the control group with nonmyopathic heart disease showed no abnormality in the myocardium, but in 10 of the 11 hearts there were abnormalities in the ganglia similar to those in the cases of cardiomyopathy.

There was no abnormality in the hearts of the control group dying of noncardiac disease.

Virus and serological studies. In 6 cases necropsy specimens of throat swabs, liver, spleen, kidney, and intestinal contents were cultured but no virus was isolated.

The serum of the mothers of 5 of the infants, 2 of the children being sibs, was examined for virus antibodies. In 1 case there were rubella antibodies to a titre of 1:160. The mother of the 2 sibs had measles and

FIG. 2.—Myocardium showing separation and distortion of fibres. (H. and E. $\times 120$.)

FIG. 3.—Myocardium showing the irregular outline of the fibres, some with loss of nuclei. (H. and E. $\times 300$.)

mumps V and S antibodies each at a titre of 1 : 250, and influenza and adenovirus antibodies each at a titre of 1 : 16. One mother had a measles antibody titre of 1 : 100 and mumps V and S antibodies each at a titre of 1 : 40, and in the fourth mother there were influenza and adenovirus antibody titres each at 1 : 16.

No antiheart or antinuclear antibodies were detected in the mothers' serum.

Discussion

Three main features for consideration emerge from this study.

First is the strikingly early age at which established myocardial damage may be present, for the youngest infant in the series died only 2 weeks after birth. This strongly suggests that cardiomyopathy may be of intrauterine onset. If a virus infection is responsible there is no direct evidence, for cultures of tissues were negative. It could, however, be postulated that the myocardial damage is caused by a complex immune mechanism resulting from virus or virus antibody crossing the placenta. It is, of course, not necessary to assume that all

FIG. 4.—Ganglion cells containing vacuoles and showing degeneration and loss of nuclei. (H. and E. $\times 350$.)

infections start *in utero*. In infants dying with cardiomyopathy after several months of life the virus infection may have occurred after birth, maternal antibodies being sufficient to suppress clinical symptoms but insufficient to prevent damage to the infant's myocardium. The terminal illness in most cases was short with cardiac failure as a predominant feature. In some of the infants a superimposed respiratory infection may have been the trigger mechanism precipitating failure in the already damaged heart. This possibility would be supported by the fact that in this admittedly small series 8 of the infants died in the autumn or winter months when such infections are prevalent.

The second point of interest is the finding of virus antibodies to a significant titre in the sera of 3 of the 4 mothers in whom this examination could be made. It is widely accepted that rubella virus will produce cardiac lesions, though at present there is no general acceptance that the viruses of measles or mumps have a damaging effect on myocardium. The findings do, however, favour the theory of viral implication possibly by an immunological mechanism as suggested in the previous paragraph.

The third point concerns degenerative changes in the cardiac ganglia. Zoltowska was impressed with their significance as indicative of damage by virus infection. Comparable changes were present in the ganglia in all our cases of cardiomyopathy. We, however, consider that histologically the changes in the ganglia appear of more recent origin than those in the cardiac muscle itself. Moreover, the ganglia in the control group of infants dying in heart failure from noncardiomyopathic causes show precisely similar changes. We therefore believe that the degeneration in the cardiac ganglia is not due to virus infection, but is a nonspecific change probably related to terminal anoxia in

association with cardiac failure. This view is supported by the absence of any abnormalities in the ganglia of our further control group of 6 infants dying not in heart failure. Despite this, we feel that the overall evidence from our study favours a viral cause for nonfamilial infant cardiomyopathy.

We consider that viral studies on infant tissues and maternal serum should be carried out in all instances where necropsy shows gross cardiac enlargement without anatomical or other obvious cause.

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