PRIMARY MYOCARDIAL DISEASE IN INFANCY: CLINICAL ASPECTS

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Primary myocardial disease is a clinical group of disorders with some features in common. Included in it are disorders in which the heart is mainly affected, with cardiomegaly and with suggestive or characteristic electrocardiographic changes; excluded from it are congenital cardiac malformations and known systemic disorders with only slight cardiac involvement. The inclusion of cases is rather arbitrary: thus, anomalous L. coronary artery is included, even though it is a congenital malformation, and glycogen storage disease of the heart, calcification of the coronary arteries and possibly virus myocarditis are included, even though extracardiac lesions occur and sometimes predominate. It is clear that the boundaries of the group will change, as more is learned of aetiology and pathology, but from the clinician's viewpoint the grouping is convenient and useful.

In a considerable proportion of published cases the diagnosis has been established only at autopsy. For this reason, and because primary myocardial disease is commonest in infancy, a broad clinical description of the group is presented, based on data from 27 infants (Table 1). Differential diagnosis of disorders within the group is discussed, particularly in relation to effective treatment.

The Present Series

All the patients were under 1 year of age when first seen. Thirteen were examined personally; records, investigations and autopsy specimens of the remainder were contributed by colleagues.

TABLE 1
27 INFANTS WITH PRIMARY MYOCARDIAL DISEASE

Myocardial Disease	Nos.
Glycogen storage disease of heart	1
Coronary artery calcification ..	1
Aberrant left coronary artery ..	4
Myocarditis ..	6
Endocardial fibroelastosis ..	15

Twenty-one of the 27 died, and in all these autopsy was carried out.

In the infant with *glycogen storage disease* of the heart the clinical diagnosis was made, and confirmed by muscle biopsy, at 3 months of age. Death occurred at 6 months. *Calcification of the coronary arteries* was found microscopically at autopsy in an infant, 3 months old, who died within a few hours of admission to hospital with acute bronchopneumonia. The mother's blood gave positive reactions to tests for toxoplasmosis. The diagnosis of *aberrant left coronary artery* was made in three of four cases during life; one of the patients survives, at the age of 2 years. Five of six infants with *myocarditis* died; the surviving one is alive and well at 2 years of age. Two presented with paroxysmal tachycardia; in one the diagnosis of primary myocardial disease (possibly endocardial fibroelastosis) had been made clinically; the remaining three died with acute heart failure before investigations could be carried out. Of the cases diagnosed as *endocardial fibroelastosis*, nine had been diagnosed in life; four of these survive and are now 2, 2, 3 and 8 years old respectively.

Clinical Picture

Family History. A family history of a similar disorder is sometimes obtained in children with glycogen storage disease of the heart or with endocardial fibroelastosis. In the present series two infants with endocardial fibroelastosis were cousins; the sibling of another probably died of the same disorder.

History. In most cases the description obtained was of a persistent or episodic disorder, usually of a few months' duration, beginning at 2 or 3 months of age or even, in a few, during the first weeks or days of life. There was a history of laboured breathing, wheeziness, 'chestiness' or lung 'infections', sometimes with slight cyanotic episodes.

Failure to thrive was common. A few infants had suffered from unexplained bouts of vomiting.

In about one-third of the cases there was no relevant previous history, and the first attack was acute and fulminating.

Examination. Three-quarters of all the cases were in heart failure when first examined. In these tachycardia and tachypnoea were observed, and in nearly all moist sounds were audible in the lungs and the liver was enlarged. Oedema and distension of the neck veins were uncommon. Slight, or occasionally marked, cyanosis was observed in half the infants with heart failure.

In all cases the heart was enlarged, whether in failure or not. The most useful method of detecting cardiac enlargement clinically was by palpation with a finger inserted under the xiphoid process.

In one-quarter of the cases a soft, systolic murmur was audible, usually along the left sternal border.

Investigations. In most cases radiograph of the chest was taken, and confirmed or revealed the cardiac enlargement. On radioscopy the left ventricle was sometimes seen to be predominantly enlarged, and cardiac pulsations were usually diminished.

As a rule E.C.G. showed a left ventricular strain pattern (see below). Other investigations were carried out in some cases and included the following: Examination of the blood to exclude severe anaemia and leukaemia; blood culture when septicaemia was suspected; serological studies for coxsackie virus and toxoplasmosis; examination of the urine to exclude renal disease and medial arterial necrosis; serum transaminase estimations (in two cases of anomalous L. coronary artery, and two of endocardial fibroelastosis). In the cases included in this series such of these tests as were done were negative (unfortunately, toxoplasma investigations were not carried out in the infant with calcified coronary arteries, in whom they might have proved positive).

Diagnosis and Differential Diagnosis

The first stage in diagnosis is usually the detection of cardiac enlargement and, as a rule, suggestive E.C.G. changes in an infant with no significant cardiac murmur and little or no cyanosis (except possibly in a phase of severe heart failure).

The next stage is the exclusion of congenital malformations of the heart and great vessels, and of systemic disorders not principally affecting the heart. Table 2 groups conditions that may simulate primary myocardial disease, in older children as

TABLE 2
CONDITIONS EXCLUDED AT ALL AGES

I. Cardiac Disorders:	
<i>Congenital malformations of heart and great vessels</i>	
<i>Functional arrhythmias without demonstrable organic basis</i>	
<i>Tumours, e.g. rhabdomyoma, sarcoma, myxoma</i>	
II. Systemic Disorders:	
<i>Infectious</i>	
(a)	Bacterial, e.g. diphtheria, typhoid, pneumonia, septicaemia, bacterial endocarditis
(b)	Virus, e.g. poliomyelitis, influenza, measles, varicella, mumps, glandular fever
(c)	Parasitic and fungus, e.g. toxoplasmosis, histoplasmosis, trichiniasis, coccidiomycosis
<i>Mesenchymal</i>	
Rheumatic carditis, rheumatoid disease, disseminated lupus erythematosus and related diseases	
<i>Endocrine and Metabolic</i>	
Hyperthyroidism, cretinism, Cushing's disease, progeria, gargoylism, beri-beri	
<i>Haematological</i>	
Leukaemia, haemolytic anaemias, abnormal haemoglobins, severe iron deficiency	
<i>Neuromuscular</i>	
Friedreich's ataxia, progressive muscular dystrophy	
<i>Miscellaneous</i>	
Renal disease, hypertension (essential, endocrine, encephalitic, lead poisoning), arachnodactyly, carcinoid of intestine	

well as in infants. Exclusion can be attempted only as far as is practicable clinically, and is rarely complete even at autopsy.

When the presumptive diagnosis of primary myocardial disease has been made, the next step is differential diagnosis within the group. At the present time six entities are usually included. Table 3 summarizes the main distinguishing features

TABLE 3
PRIMARY MYOCARDIAL DISEASE: DIFFERENTIAL DIAGNOSIS

Disorder	Diagnostic Features
Group A: Glycogen storage disease of heart	Muscles flabby; large tongue usual; E.C.G.: exaggerated LV strain pattern; muscle biopsy shows excess glycogen
Aberrant L. coronary artery	'Anginal' attacks with feeding or crying;* radioscopy may show aneurismal L. ventricle; E.C.G.: deep Q in leads I and V ₅
Calcification of coronary arteries	Arterial calcification may be seen on radiograph
Medial necrosis of coronary arteries	Other congenital anomalies common; microscopic haematuria and other urinary abnormalities
Group B: Myocarditis	Congestive failure common; E.C.G. may show arrhythmias and low voltage
Endocardial fibroelastosis	Congestive failure common; E.C.G.: L. ventricular strain pattern usual

* Similar attacks have been observed occasionally in coarctation of the aorta and in endocardial fibroelastosis.

(a)

FIG. 1.—Endocardial fibroelastosis.

(a) Chest radiograph at 4 months of age. (b) E.C.G. standard leads. (The patient is alive and well at 2 years of age.)

(b)

in the clinical differential diagnosis; it also foreshadows a sub-division according to the likely response to treatment (see further).

Electrocardiographic Abnormalities. The E.C.G. changes warrant discussion because of their importance in diagnosis. It should be emphasized, however, that diagnosis cannot be made without clinical and other examinations, for E.C.G. changes similar to those of primary myocardial disease may occur in other disorders (see Table 2).

Endocardial Fibroelastosis. Primary endocardial fibroelastosis (not occurring in association with congenital malformations) illustrates the basic E.C.G. pattern of the group. This is an infantile left ventricular strain pattern (Fig. 1), usually most evident in the left precordial leads, though there is a considerable range of variations.

Characteristically, the S-T level is depressed or elevated. The T wave tends to be small, isoelectric or inverted, especially in leads I, V_5 and V_6 with a horizontal heart or in leads II, III, V_5 and V_6 with a vertical heart. In addition, there is usually a tall upright QRS, indicative of ventricular hypertrophy, and often exaggeration of P waves which suggests auricular enlargement.

The diagnosis of endocardial fibroelastosis is made by exclusion, if the basic E.C.G. pattern occurs with cardiomegaly and there are no specific

features to indicate other disorders. In some cases of isolated myocarditis, however, the E.C.G. pattern may be indistinguishable from that of endocardial fibroelastosis; the two disorders may occur together (as in one fatal case in the present series). It is important to bear in mind also that with endocardial fibroelastosis, particularly the acute, fulminating cases, the E.C.G. pattern may be atypical; while in more chronic cases the typical pattern may take time to develop. Thus, in one case in the present series minimal E.C.G. changes, originally of doubtful significance, became characteristic of fibroelastosis three months later.

In infants having digitalis the E.C.G. pattern of fibroelastosis may be mimicked in the absence of this disorder, or distorted if it is present.

In glycogen storage disease of the heart, the E.C.G.

FIG. 2.—Glycogen storage disease of heart.

(a) Chest radiograph at 3 months of age. (b) E.C.G. standard leads. (c) E.C.G. lead V_5 .

changes may be so grossly exaggerated as to be diagnostic. A typical example is shown in Fig. 2 (in which the voltages were reduced by one-third to permit recording), which bears a remarkably close similarity to the E.C.G.s of the few published cases.

In most cases of *aberrant left coronary artery* the E.C.G. pattern is characteristic (Keith, 1959) and is similar to that of anterior myocardial infarction in the adult. A typical tracing (Fig. 3) shows a deep Q wave, most marked in leads I and V_5 , together with S-T elevation and T wave inversion. In lead III S-T is depressed and T upright.

In *myocarditis* the left ventricular strain pattern may also be seen, though the changes are inconstant and often minimal. Voltages may be low and variable and T waves flattened. Prolongation of the P-R interval, or some other conduction disturbance, is much commoner than in other forms of primary myocardial disease. In some cases arrhythmia is the predominant feature, clinically and electrocardiographically. Thus, two cases in the present series were originally diagnosed as paroxysmal supra-ventricular tachycardia; in the fatal case the region of the sino-auricular node was the site of a haemorrhage (Apley, Corner and Gibson, 1955).

In *medial necrosis* and in *calcification of coronary arteries* the E.C.G. changes may be those of left ventricular strain, but are not specific (Rosenbaum,

Nadas and Neuhauser, 1953), and differential diagnosis depends on other investigations.

Prognosis

From the point of view of prognosis, the primary myocardial disorders may be divided into two groups (Table 3).

Group A. The individual anomalies in this group are rare, but may be diagnosable in life (Table 3), unless investigations cannot be carried out because of the rapid course of the illness. In this group there is at present no effective treatment. Occasionally, however, an infant with aberrant L.

(a)

FIG. 3.—Anomalous left coronary artery.
 (a) Chest radiograph at 2 months of age. (b) E.C.G. standard leads.
 (c) E.C.G. lead V₅.

(c)

(b)

coronary artery does survive into adult life.* Two of the cases in the present series were operated on, and various operations to correct the anomaly have been suggested (Apley, Horton and Wilson, 1957), but so far without success.

Group B. In the second and commoner group the prognosis is much better, but depends to a large extent on treatment. In this group, as compared

with the first, congestive cardiac failure is a prominent feature. It seems possible that it is the effective treatment of the congestive failure that permits eventual recovery from the underlying disease.

When endocardial fibroelastosis is diagnosed, and the child recovers, doubts as to the diagnosis may be entertained. If a heart with severe, isolated endocardial fibroelastosis is examined after death it is difficult to believe that recovery in severe cases could ever be possible; yet infants with clinical and other findings indistinguishable from those of the fatal cases can and do recover. It could be assumed that the milder cases alone recover, but there is no conclusive evidence to support this. Alternatively, it may be that those who recover were, in fact, suffering not from endocardial fibroelastosis,

* It has been stated that early death is inevitable if symptoms occur in infancy (Keith, 1959), but I have recently seen a girl aged 12 (a patient of Dr. F. W. Brimblecombe), with the criteria of anomalous L. coronary artery, who was markedly breathless in infancy.

but from myocarditis or from some other clinically indistinguishable disorder. These doubts cannot at present be resolved; but since digitalis therapy may prove effective in this group of disorders it should be prescribed, even if the diagnosis of endocardial fibroelastosis is accepted with reservations.

Writing of endocardial fibroelastosis, Keith and his co-authors (Keith, Rowe and Vlad, 1958), state: 'The prognosis more or less depends on recognition and digitalis therapy.' Most of Keith's cases survived, while his untreated or inadequately treated cases died. In Nadas's (1957) series nearly half survived, almost all with digitalis therapy. In the present series four cases diagnosed as endocardial fibroelastosis and one diagnosed as myocarditis survived; but a high proportion of the cases that succumbed were seen for the first time only when moribund. In two fatal cases recovery might have been possible: in one digitalis was discontinued soon after heart failure had been corrected, and in the other it was discontinued in error after three months.

The prognosis depends not only on early, adequate and prolonged digitalis therapy, but also on other factors. Thus, the fulminating case may die within a few hours of the onset of symptoms, despite treatment; the mortality rate varies with the proportion of fulminating cases seen, and in the present series this was higher than the 25% described by Dennis, Hansen and Corpening (1953). A relapse after an initially good response to treatment is ominous. It is generally agreed that the mortality rate is higher if symptoms and signs of the illness occur in the first weeks or months of life, as compared with the end of the first year or later.

In those infants in Group B who survive recovery is apparently complete. Cardiac function seems to be unaffected, the size of the heart gradually returns to normal, and the abnormalities in the E.C.G. disappear. The return to normal according to the present series, however, takes place over a period of years rather than months.

Treatment

Under this heading the disorders in Group B alone are considered here. Diagnosis should, if possible, be established before the patient is *in extremis*, to give treatment its best chance. The essential of treatment is digitalization, and oxygen and antibiotics are usually given in addition. The infant's distress may be alleviated if the head and shoulders are propped up and maintained in this position. Morphine, diuretics, a low salt diet and steroids have also been given in some cases, but it is difficult to decide how much they help.

In the treated cases in the present series digoxin was used. The oral digitalizing dose for infants is between 0.04 and 0.06 mg. per lb. body weight; half the dose is given at once and the remainder in divided doses over the first 24 hours. If the patient is gravely ill an initial dose may be given parenterally, and should be half the calculated oral dose. The daily maintenance dose, given orally, is about one-quarter of the digitalizing dose. These figures are only guides: in children, as in adults, digitalization is an individual matter and the optimal dose for each patient can be determined only by careful observation. The digitalizing dose may be repeated if a good response has not occurred and there is no evidence of toxicity. In infants the only common clinical evidence of overdosage is vomiting, though coupled beats occasionally occur. A satisfactory response is judged not on E.C.G. changes but clinically, by slowing of the pulse, occasionally by disappearance of a gallop rhythm, and by improvement in the infant's general condition. The patient looks better, the respiration rate and raised temperature fall, the size of the liver decreases, and moist sounds in the lungs disappear.

In endocardial fibroelastosis there may be a critical level for the dosage of digitalis. A little above the optimal level for the individual, vomiting may occur; a little below it, signs of cardiac failure persist. Since the weight of an infant increases so rapidly, the amount of digitalis may need to be increased proportionately in long-continued treatment. If the infant acquires an infection, or if heart failure recurs, the dose of digitalis should be increased promptly.

Experience suggests that it is advisable to continue giving digitalis long after the acute illness has subsided. It seems a wise precaution to continue with digitalis for a year, then to reduce the dose before eventually omitting treatment. If a relapse or deterioration occurs at any time digitalis should be given for at least a year afterwards.

Conclusion

Primary myocardial disease is less rare than has been believed. The diagnosis can be made more frequently in practice if the clinical picture is familiar, if cardiomegaly is carefully sought, and if the value of electrocardiography in infancy is appreciated. The clinician's task is important, despite the gaps in our knowledge of aetiology and pathology, for on diagnosis depends what may prove to be life-saving treatment.

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Addendum

Since the above report was written, 12 cases of anomalous left coronary artery have been reported from the Johns Hopkins Hospital (Sabiston, Pelargonio and Taussig, 1960). After ligation of the anomalous artery, together with de-epilicardiazation, three cases have survived (one to the age of 4 years).

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