Progressive familial heart block type I

Clinical and pathological observations

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Summary

Progressive familial heart block type I (PFHB-I) is an autosomal inherited disease. It was previously postulated that the disease is limited to the cardiac conduction tissue. The presentation of a patient with dilated cardiomyopathy focused on the possibility that this might be part of PFHB-I. This observation led to routine echocardiographic examination of patients with complete heart block, who belonged to PFHB-I families, and another 5 cases with signs of dilated cardiomyopathy were identified.

This is the first time, to our knowledge, that the histological picture of PFHB-I has been described.

From these case reports it is clear that in the presence of a dilated cardiomyopathy the prognosis in PFHB-I tends to be poor.

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Progressive familial heart block type I (PFHB-I), described by Brink and Torrington[1] during 1977, is an autosomal dominant inherited condition confined to a few family lines in South Africa, which originated from one ancestor. According to Torrington *et al.*[2] about 9 000 people could be carrying the affected gene. The condition is characterised by any of the following ECG findings: sinus bradycardia, right bundle-branch block, bifascicular block, second-degree atrioventricular block and complete heart block.

Brink and Torrington[1] and Van der Merwe *et al.*[3] postulated that the disease process is limited to the cardiac conduction tissue and therefore described it as a primary disease of the conduction system.

The pathogenesis of PFHB-I has as yet not been clarified. Although not fitting the histological picture, the degenerative hypothesis of Lev[4] is still the most widely accepted, but the mechanisms triggering the degenerative process are unknown. As far as we are aware, the histological aspects of this condition have not been described.

This communication describes the histological appearance of PFHB-I in 1 case and discusses congestive cardiomyopathy (5 cases) as a further clinical manifestation of the disease. These cases have not previously been reported.

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Case reports

Case 1

The patient belonged to a family suffering from PFHB-I. He was delivered by caesarean section due to fetal distress (slow heart rate). At birth he had severe non-immune hydrops fetalis with a third-degree heart block. A temporary pacemaker was inserted and 14 days later replaced with a programmable permanent pacemaker. At the age of 22 months the left ventricle began to dilate, although an ejection fraction of 61% was maintained. Four months later the child suffered a cerebrovascular accident and was readmitted in cardiac failure. An echocardiogram showed severe dilatation of the left ventricle (Table I)[5] with mural thrombi and a reduced ejection fraction of 33%. The diagnosis of a dilated cardiomyopathy was made. Ten days after admission the infant died as a result of another cerebral embolus.

Permission for autopsy was granted and the findings were as follows:

Histological examination of the cardiac conduction system included the sino-atrial node (by blocking the entire area of junction between the superior vena cava and the right atrial appendage, favouring the posterior portion), the atrioventricular node, and the bundle of His and the proximal portions of its right and left branches (by taking tissue blocks according to the techniques described by Hudson[6]). Serial sections were cut and every 7th section was stained with haematoxylin and eosin; every 12th section by Van Gieson's method for connective tissue, together with Verhoeff's stain for elastic tissue (Verhoeff-Van Gieson method).

Macroscopically, the heart was boot-shaped and bore epicardial adhesions near the apex in relation to pacemaker electrodes (Fig. 1). The visceral and parietal pericardium were linked together by adhesions over the inferior surface of the heart. The heart (180 g) showed generalised hypertrophy and dilatation in keeping with chronic volume overload. Multiple endocardial stasis thrombi (Fig. 2), some of which showed central liquefaction, were present at the left ventricular apex and on

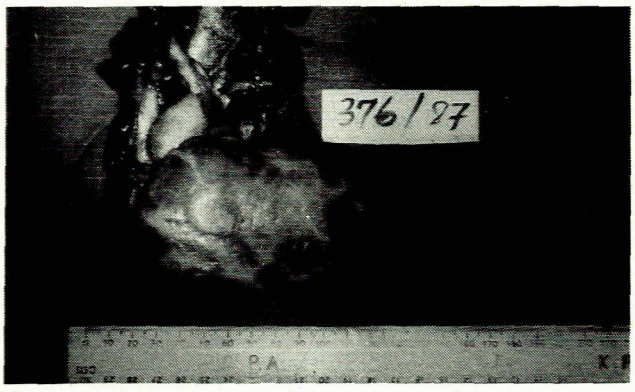

Fig. 1. Macroscopic appearance of the heart of patient 1. It is boot-shaped with apical adhesions in relation to the pacemaker electrodes.

TABLE I. ECHOCARDIOGRAPHIC DIMENSIONS — CASE 1

Date	Age	LVED (mm)	LVES (mm)	EF (%)	Ao (mm)	LA (mm)	LA/Ao	IVS (mm)	LVPW (mm)	RVED (mm)	LVED/N (mm)
1 Aug 1985	**8 d**	**18**	**12**	**60**	**9**	**17**	**1:9**	**3**	**4**	**7**	**0,86**
8 Aug 1985	**16 d**	**23**	**16**	**55**	**9**	**13**	**1:4**	**2,5**	**3,5**	**6**	**1,1**
6 Mar 1986	**7,5 mo**	**28**	**18**	**63**	**15**	**18**	**1:2**	**4**	**4**	**6**	**1,08**
4 June 1987	**22 mo**	**43**	**29**	**61**	**18**	**26**	**1:4**	**5**	**5**	**8**	**1,39**
9 Sept 1987	**26 mo**	**52**	**43**	**33**	**21**	**23**	**1:1**	**4**	**4,5**	**8**	**1,68**

LVED = left ventricular end diastolic diameter; LVES = left ventricular end systolic diameter; EF = ejection fraction; Ao = aortic diameter; LA = left atrial diameter; IVS = ventricular septal diameter; LVPW = left ventricular posterior wall; RVED = right ventricular end diastolic diameter; LVED/N = left ventricular end diastolic normal values from Feigenbaum.[5]

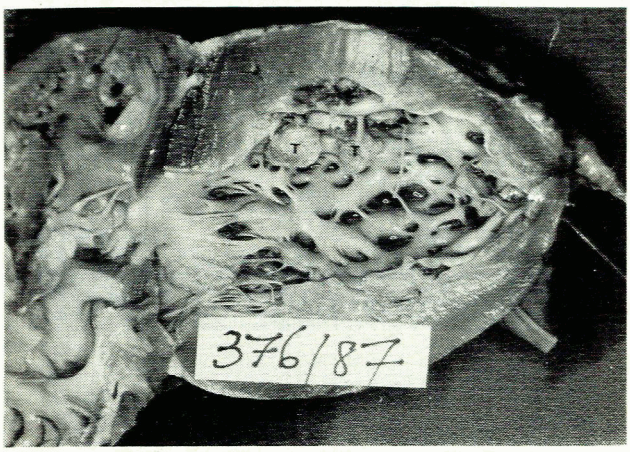

Fig. 2. A longitudinal section through the left ventricle showing generalised hypertrophy and dilatation with multiple endocardial stasis thrombi (T).

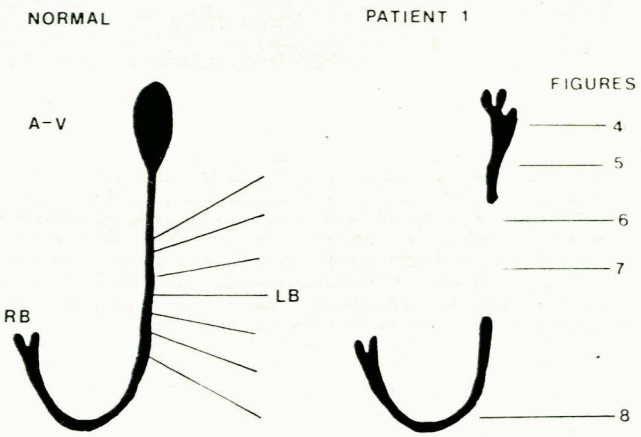

Fig. 3. Diagram of normal atrioventricular node and bundle of His (left) and the findings in patient 2 (right). The sites of the histological sections illustrated in Figs 4 - 8 are indicated in the diagram.

the inferior wall. The left ventricle showed diffuse endocardial sclerosis. No significant abnormality was detected in the great vessels, coronary arteries or heart valves. No septal defects were present and the ductus arteriosus and foramen ovale were both sealed. The visual appearance was reminiscent of a dilated cardiomyopathy.

Sections of the ventricular myocardium examined by microscope showed features of myocyte hypertrophy and scanty focal myocyte necrosis with a mononuclear cellular response consistent with myocyte damage of the type associated with catecholamine excess.[7,8] Only fibrous tissue was observed at the expected site of the sino-atrial node.

About 50% of the atrioventricular node appeared to be replaced by fibrous tissue (Figs 3 and 4) and the densely fibrosed central fibrous body (CFB) showed focal dystrophic calcification nearby. The proximal portion of the node was represented by widely scattered small islands of conducting tissue lying within the CFB. Serial sections revealed that these islands united to form a common island of nodal tissue, which appeared to show extensive depletion of myocytes at its periphery — the deficient area of nodal tissue was occupied by dense fibrous tissue.

The penetrating portion of the bundle of His contained abundant myocytes and was readily identifiable within the CFB (Fig. 5). Just below this, the main bundle abruptly vanished. No left bundle branches were seen. Serial sections of the fibrous atrioventricular junctions (Fig. 6) and of the membranous septum region (Fig. 7) failed to reveal conducting tissue. The distal portion of the right bundle branch was identified and appeared normal (Fig. 8).

Echocardiography

Echocardiography was performed on 193 patients belonging to PFHB families. Because patients with complete heart block were not subjected to special investigations in the initial study, only 5 patients with complete heart block belonging to PFHB families, who lived close to our hospital, were subjected to echocardiography after diagnosing a dilated cardiomyopathy in the index case. Four out of these 5 patients, in which known causes of dilated cardiomyopathy were excluded, presented with echocardiographic evidence of dilated cardiomyopathy.

Case 2

This patient was born on the 5 July 1986 with a complete heart block. She received a permanent pacemaker at the age of 3 months. At the age of 15 months the infant was referred to us with left heart failure. Echocardiography showed a dilated heart with an ejection fraction of 28%. This confirmed the clinical diagnosis of dilated cardiomyopathy. The baby died 3 months after discharge and an autopsy was not performed.

Case 3

This patient was born on 19 March 1957. He received a permanent pacemaker at the age of 27 years due to progression of a bifascular block to a complete heart block. The echocardiogram showed a dilated left ventricle with an ejection fraction of 51%, a definite deterioration of cardiac function when compared with the findings of previous echocardiograms (Table II).

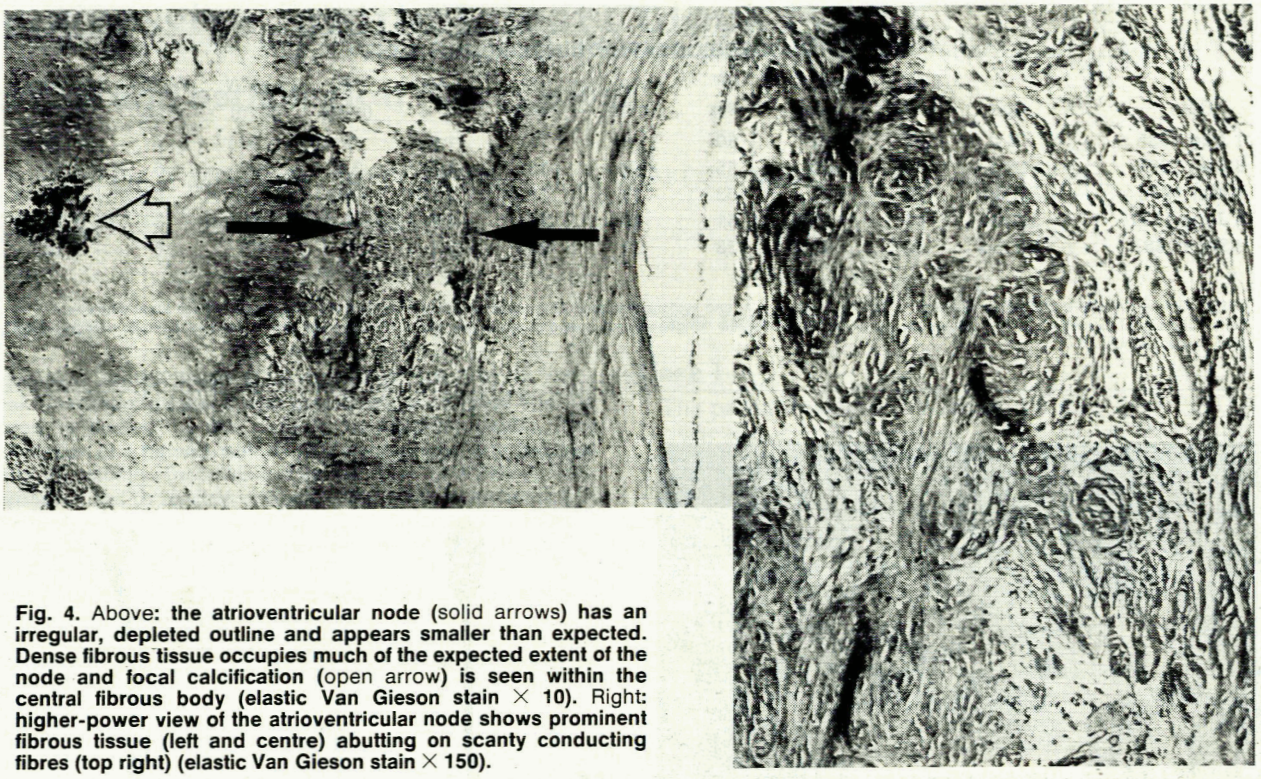

Fig. 4. Above: **the atrioventricular node** (solid arrows) **has an irregular, depleted outline and appears smaller than expected. Dense fibrous tissue occupies much of the expected extent of the node and focal calcification** (open arrow) **is seen within the central fibrous body (elastic Van Gieson stain × 10).** Right: **higher-power view of the atrioventricular node shows prominent fibrous tissue (left and centre) abutting on scanty conducting fibres (top right) (elastic Van Gieson stain × 150).**

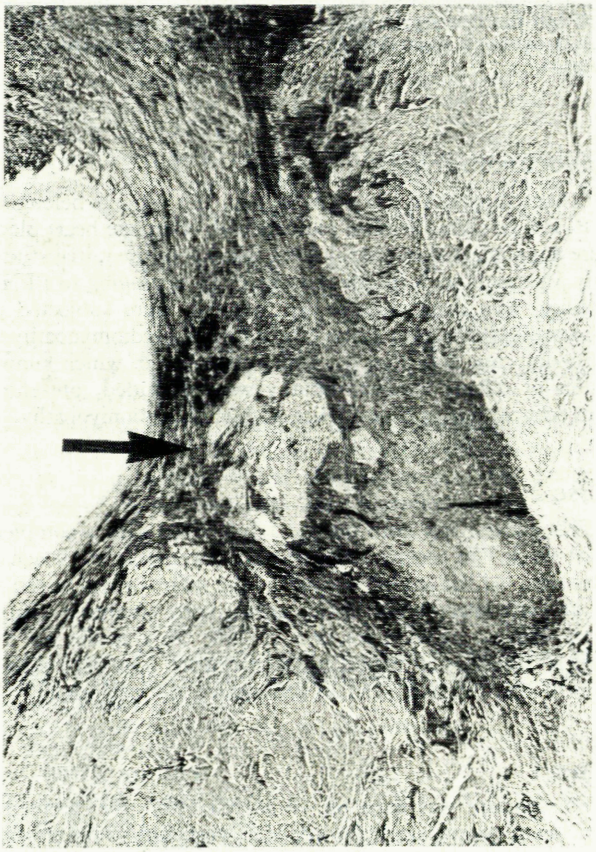

Fig. 5. Bundle of His (arrow) **penetrating the fibrous atrioventricular junction. Ventricular septum is below (elastic Van Gieson stain × 7).**

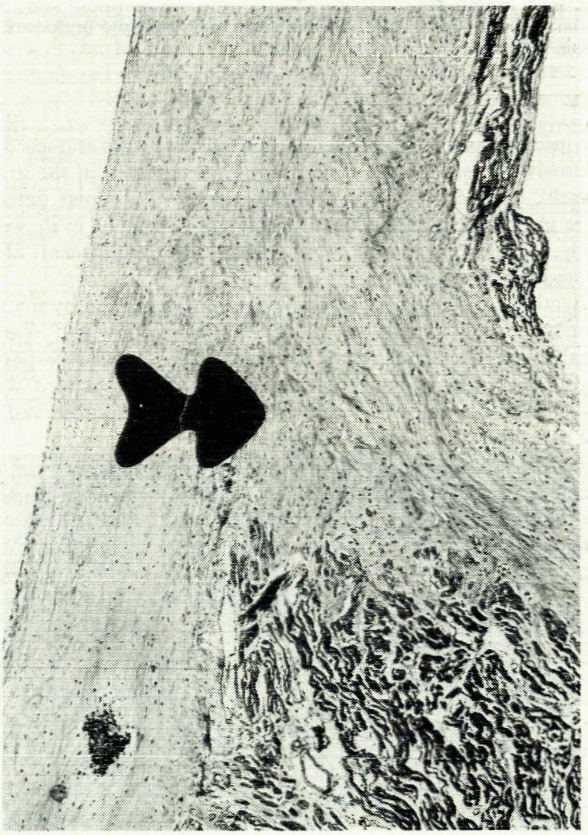

Fig. 6. Fibrous atrioventricular junction shows no conducting tissue at the expected site (arrow) **for the bundle of His (elastic Van Gieson stain × 20).**

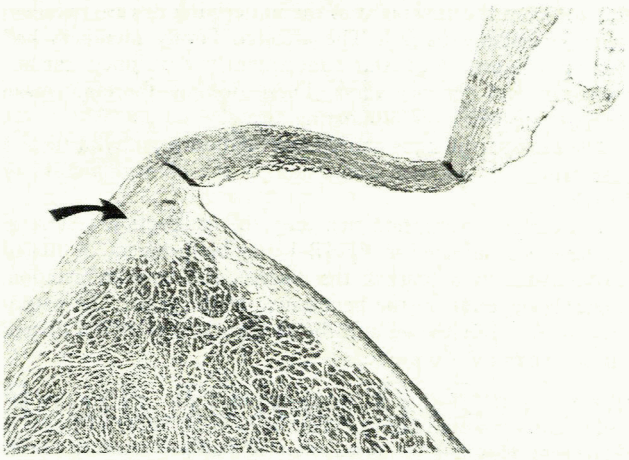

Fig. 7. Distal bundle of His is absent (arrow) from the inferior portion of the membranous septum (elastic Van Gieson stain × 5).

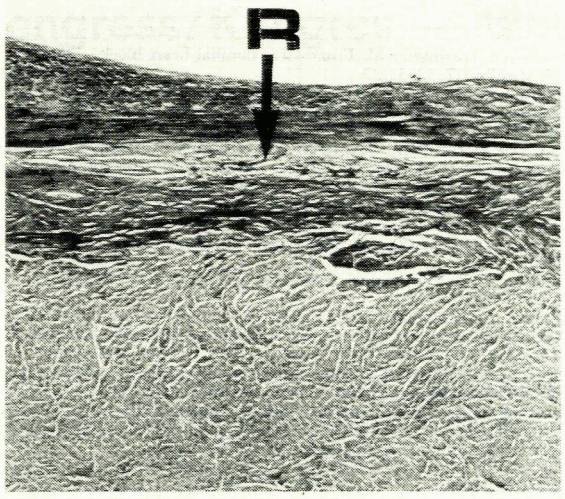

Fig. 8. Normal appearing distal right bundle branch (R) in a sub-endocardial position (elastic Van Gieson stain × 60).

Case 4

A 26-year-old woman had received an epicardially implanted permanent pacemaker at the age of 17 years. She had recently complained of fatigue, especially when exercising. On examination, she had a slightly displaced apex beat (5th intercostal space outside the mid-clavicular line). Echocardiography showed a slightly dilated left ventricle with an ejection fraction of 53% (Table II).

Case 5

The father of patient 4 received an epicardially implanted permanent pacemaker at the age of 44 years, after the development of complete heart block. At present he is asymptomatic. Echocardiography showed a slightly dilated left ventricle with an ejection fraction of 58%, a picture that resembles the early stages of dilated cardiomyopathy (Table II).

Discussion

Until now PFHB-I has been described as a disease affecting only the conduction tissue of the heart. The presentation of case 1 with a dilated cardiomyopathy raised the question of whether this condition was due to a viral infection or whether it was a more severe form of PFHB-I. The theory that the conduction tissue of the heart is specialised heart muscle, favours the latter suggestion.

Although there is no specific histological picture for dilated cardiomyopathy, the autopsy — the first to be performed on a patient with PFHB (case 1) — suggested the diagnosis of dilated cardiomyopathy and also showed that the atrioventricular node, the bundle of His, the left bundle branches and the sino-atrial node were replaced by fibrous tissue.

While dilatation of the cardiac chambers may result from volume overload associated with an unusually slow pulse, the insertion of a pacemaker at birth should have ameliorated this effect. This, together with the stasis thrombi within the heart, suggests that a dilated cardiomyopathy was indeed present. The focal necroses with mononuclear cellular response observed in the myocardium appeared to be related to catecholamine over-production due to brain death.[9] The latter interpretation is favoured over that of a chronic persistent myocarditis, but the latter possibility cannot be altogether excluded.

TABLE II. ECHOCARDIOGRAPHY FINDINGS IN SURVIVORS

Parameter	Case 3	Case 4	Case 5	Normal range	Normal mean
LVED (mm)	**64**	**53**	**60**	**35-57**	**47**
LVES (mm)	**46**	**39**	**41**	**—**	**—**
EF (%)	**52**	**53**	**58**	**64-83**	**74**
SF (%)	**27**	**28**	**31**	**28-44**	**36**
LVET (ms)	**260**	**289**	**262**	**265-325**	**294**
VcF (circ/s)	**0,7**	**0,8**	**0,8**	**1,02-1,94**	**1,3**
IVSd (mm)	**8,4**	**8,3**	**5,6**	**6-11**	**9**
IVSs (mm)	**11**	**10,8**	**7,5**	**—**	**—**
% SEPT TH	**31**	**30**	**33**	**18-53**	**35**
LVPWd (mm)	**8,4**	**7,5**	**5,6**	**6-11**	**9**
LVPWs (mm)	**11**	**10**	**7,5**	**—**	**—**
% LVPW TH	**31**	**30**	**33**	**39-82**	**60**
RVED (mm)	**23**	**13**	**10**	**7-23**	**15**
MV-EPSS (mm)	**15**	**16,6**	**13**		**< 5 for normality**

LVED = left ventricular end diastolic diameter; LVES = left ventricular end systolic diameter; EF = ejection fraction; SF = shortening fraction; LVET = left ventricular ejection time; VcF = velocity of circumferential fibre shortening; IVSd = inter-ventricular septum (diastole); IVSs = inter-ventricular septum (systole); % SEPT TH = percentage septal thickening; LVPWd = left ventricular posterior wall (diastole); LVPWs = left ventricular posterior wall (systole); % LVPW TH = percentage left ventricular posterior wall thickening; RVED = right ventricular end diastolic diameter; MV-EPSS = mitral valve E-point septal separation.

In the light of these findings, patients who had already received permanent pacemakers due to the existence of complete heart block were also subjected to echocardiography. Patients 2, 3, 4 and 5 so discovered also showed signs of a dilated cardiomyopathy. Measurement of the ejection fraction, shortening fraction, velocity of circumferential fibre shortening, septal thickening %, and left ventricular posterior wall thickening showed that all 3 survivors were below the normal mean, indicating a reduction in function. These parameters, together with the left ventricular end-diastolic diameter and mitral valve E-point septal separation, are clearly indicative of early congestive cardiomyopathy (Table II). There were no signs of thrombi or focal areas of dysfunction. It is interesting that all 5 cases received their pacemakers after developing complete heart block and that the pacemakers were fixed with epicardial electrodes. From these facts, it can be concluded that these patients were more severely affected than the other members of the PFHB families who may only have isolated, less serious ECG findings.

The autopsy demonstration of significant replacement of the conduction system by fibrous tissue provides a good explanation for the clinical and ECG findings described by Brink and Torrington[1] and Van der Merwe *et al.*[3] The pathology of the conduction tissue in case 1 was similar to that described in other cases of congenital complete heart block[10] and fits the group 3a patients described by Carter *et al.*,[11] in whom fibrous interruption between the AV node and the bundle of His was noted. Connective tissue disease, particularly systemic lupus erythematosus, has been noted in the mothers of some neonates with congenital heart block.[12] In all our cases immunological screening was negative for systemic lupus erythematosus. It is clear that this unique familial condition does not fit any of the present hypotheses of complete heart block, including Lev's disease.

Patients with PFHB present with various ECG abnormalities depending on which portion of the conduction tissue has been replaced by fibrous tissue. Why the disease is only progressive in some is unknown. A possible explanation for this phenomenon may be attributed to a difference in gene penetrance.

The association of conduction abnormalities with dilated cardiomyopathy is rare and such an association is more commonly found in hypertrophic cardiomyopathy. However, this does not affect the observations in our families. We looked at the problem from the viewpoint of the affected family members and not from the viewpoint of the underlying disease manifestation (cardiomyopathy). The affected family members had complete heart block and subsequently developed cardiomyopathy and not vice versa. These findings therefore make PFHB-I an even more fascinating disease.

The presence of signs of a dilated cardiomyopathy in these 5 cases adds yet another dimension to the clinical picture of PFHB-I.

The earlier assumption that only the conduction system of the heart was affected in PFHB-I may be incorrect. A dilated cardiomyopathy as part of the disease, and its manifestation, probably depends on the penetrance of the gene. The pathogenesis is still unknown and the prognosis is poor if a dilated cardiomyopathy is present.

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