Familial right ventricular dysplasia with biventricular involvement and inflammatory infiltration

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Abstract

The aetiology of right ventricular dysplasia/cardiomyopathy is presently unknown. A genetic background has been suggested, but myocarditis may play a part in its pathogenesis. Two familial cases of right ventricular dysplasia, one of whom had also a diagnosis of myocarditis, are reported. Both patients presented with ventricular arrhythmias. The father subsequently had a “flu-like” syndrome, heart failure, and biventricular dysfunction; “active” myocarditis was found at endomyocardial biopsy. Then the patient died suddenly. The daughter developed progressive biventricular dysfunction; then she was resuscitated from a cardiac arrest, and subsequently died suddenly. In both patients necropsy showed severe right ventricular atrophy and fibroadipose substitution, associated with biventricular fibrosis. Inflammatory infiltration was also present in the first patient. This study shows the association of right ventricular dysplasia and myocarditis in the same family. These cases may represent a link between inherited and acquired (“inflammatory”) forms of the disease.

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The aetiology of arrhythmogenic right ventricular dysplasia/cardiomyopathy remains

unclear.¹ In fact, although a familial occurrence has been reported and a genetic pattern suggested,² non-familial forms are relatively frequent. Moreover inflammatory infiltrates were described in biopsies of some of these patients,³⁻⁶ suggesting an inflammatory mechanism in the pathogenesis of the disease.⁴ We describe two familial cases, father and daughter, affected by this disease. Both initially presented with apparently idiopathic ventricular arrhythmias. The father had left ventricular dysfunction and congestive heart failure. At endomyocardial biopsy active myocarditis was diagnosed. The daughter, during follow up, developed right ventricular dysfunction with subsequent left ventricular involvement. Both patients died suddenly. In both postmortem examination disclosed an extensive fibroadipose substitution of the right ventricular myocardium compatible with right ventricular dysplasia, associated with diffuse inflammatory infiltrates in the father. The possible links between familial disease, inflammation, and pathological changes in the pathogenesis of the disease are discussed.

Case reports

CASE 1
The first patient was first evaluated when he was 28 year old because of ventricular arrhythmias. The electrocardiogram showed a first degree atrioventricular block, left anterior hemiblock, and T wave inversion from V1 to V3 with frequent multiform ventricular extrasystoles. He subsequently developed an advanced atrioventricular block and was treated with permanent pacemaker and amiodarone.

Table 1 Echocardiographic and haemodynamic data

	Case 1			Case 2		
	1981	1984	1986	1984	1985	1988
M mode echo:						
LVEDD/LVESD (cm)	5.4/3.0	6.1*/5*	6.4*/5*	4.2/2.5	4.4/3.3	5.2/4.3
SF (%)	44	18*	22*	40	25*	17*
RVEDD (cm)	1.2	2.4	2.1	2.1	3.3*	3.2*
Cross sectional echo:						
RVEDA/RVESA (cm ²)		23/15	26/18	23/16	25/20	35*/28*
RV SFA (%)		35*	31*	29*	20*	21*
LV EDV/LV ESV (ml)		114/85		43/18	45/26	69/42
LV EF (%)		26*		58	41*	39*
Haemodynamics:						
LV pressure (mm Hg)	135, 0/5	100, 0/10		120, 0/10		
LVEDV (ml/m ²)	63	101*		82		
LV EF (%)	61	38*		58		
RV pressure (mm Hg)	22, 0/2	23, 0/2		17, 1/3		
CI (l/min/m ²)	2.6	3.2		4		
MPWP (mm Hg)	6	9		7		

*Abnormal data.
LV, left ventricle; RV, right ventricle; EDD, end diastolic diameter; ESD, end systolic diameter; SF, shortening fraction; EDA, end diastolic area; ESA, end systolic area; SFA, shortening fraction of areas; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; CI, cardiac index; MPWP, mean pulmonary wedge pressure.

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Figure 1 Case 1: endomyocardial biopsy sample from the right ventricle showing lymphocytic active myocarditis. Note the inflammatory infiltrates adjacent to the necrotic myocytes and the increase of the interstitial connective tissue. (Haematoxylin and eosin, magnification $\times 50$).

A

B

Figure 2 Postmortem findings in case 1. (A) The free wall of the left ventricle is thin (particularly at the apex) and infiltrated by adipose tissue (yellow appearance). A bulge is evident at the median third of the interventricular septum (arrow). The walls of the right ventricle are very thin and extensively infiltrated by adipose tissue. The transillumination method clearly shows the absence of myocardium in the anterior wall of both ventricles. LV, left ventricle; RV, right ventricle. (B) Histological specimen of the right ventricle, periapical region. A focus of lymphocytic myocarditis is evident in an area of fatty myocardial infiltration. (Haematoxylin and eosin, magnification $\times 50$).

Physical examination, chest x rays, M mode echocardiogram, and cardiac catheterisation were normal (table).

Three years later he had a "flu-like" syndrome and was admitted with severe heart failure.

Echocardiography showed biventricular dysfunction and biatrial enlargement (table).

Endomyocardial biopsy from the right ventricle showed "active" myocarditis according to the Dallas criteria⁷ (fig 1).

The patient improved clinically after a treatment with prednisone, azathioprine, digoxin, and diuretics. However, biventricular dysfunction persisted and subsequent biopsies showed marked interstitial and subendocardial fibrosis. Seven months later the patient was resuscitated from an out of hospital cardiac arrest. Heart failure recurred and he died suddenly at the age of 35.

At postmortem examination all four chambers were dilated. The anterior and lateral walls of the left ventricle in the middle and apical portions and the right ventricular walls were thinned and replaced by fibrous and adipose tissue. In some areas of the anterior wall the myocardium was completely absent and a transillumination was evident (fig 2A). There was an aneurysm in the middle third of the interventricular septum and areas of fatty infiltration. Microscopically, multifocal areas of inflammatory infiltration were present in both ventricles, associated with severe adipose substitution and moderate fibrosis (fig 2B).

CASE 2

The daughter of the first patient was first seen when she was 12 because of complex ventricular arrhythmias.

The ECG showed negative T waves from V1 to V4 and frequent polymorphic ventricular extrasystoles. Non-sustained ventricular tachycardia was documented during Holter monitoring and during an effort test. An echocardiogram showed an apical hypokinesis of the right ventricle, with a normal left ventricle (table). Intracardiac pressures and left ventricular function were normal at cardiac catheterisation. Endomyocardial biopsy from the right ventricle showed only a mild atrophy of the myocytes with mild fibrosis and inflammatory infiltration. The patient was subsequently treated with amiodarone.

An echocardiogram performed one year later (1985) showed a worsening of right ventricular function and the appearance of septal hypokinesis and a mild decrease in left ventricular ejection fraction (table).

Three years later, while playing volleyball, she had a cardiac arrest caused by ventricular fibrillation. She was resuscitated with no neurological sequelae. A new echocardiogram showed a severe right ventricular dysfunction with multiple akinetic wall bulges and a further deterioration of left ventricular function with diffuse hypokinesis but without significant dilatation (table); there was also an akinetic bulge at mid septal level (fig 3).

The patient had a slowly progressive increase in dyspnoea and peripheral oedema

Figure 3 Case 2: cross sectional echocardiography. Left frame: Parasternal short axis at the level of the papillary muscles in systole. The left ventricle (LV) shows akinesia and localised thinning at the level of the anterior portion of the interventricular septum (arrow). The right ventricle (RV) is dilated. Right frame: Apical four chamber view in systole. The right ventricle (RV) is severely dilated with multiple akinetic wall bulges (B); RA, right atrium; LA, left atrium.

and was found dead at home at the age of 18, six years after the initial evaluation.

At necropsy there were severe degenerative changes caused by the long interval (three days) between death and the examination. The right ventricle was markedly dilated, with severe wall thinning and extensive fibrous and adipose substitution. The left ventricle was moderately enlarged and showed a localised wall thinning at the apex and a small septal aneurysm.

Microscopically, multifocal areas of atrophied myofibres, severe fibrosis, and moderate adipose substitution were present in both ventricles.

Discussion

Right ventricular dysplasia is an idiopathic heart muscle disorder, characterised by fatty or fibrofatty replacement of right ventricular myocardium.¹ The aetiology of the disease is still unknown, but, in many cases, it appears to be an inherited disorder with familial incidence.^{2,8} Recently Rampazzo *et al*⁹ localised the gene involved in the genesis of the disease on chromosome 14q23-q24. However, others suggested that right ventricular dysplasia may be at least in some cases the consequence of a previous myocarditis.^{4,5,10-13}

In fact inflammatory infiltrates are not uncommon in histological specimens from these patients.

Fontaine *et al*⁵ in a review of 27 patients with right ventricular dysplasia found inflammatory infiltrates in eight, whereas Thiene *et al*¹⁴ classified the disease, from a pathological point of view, into lipomatous and fibrolipomatous. Because they found that the fibrolipomatous pattern was frequently associated with inflammatory infiltrates, necrotic myocytes,

fibrosis, and aneurysms, they regarded this form as the possible expression of a chronic myocarditis, in which infectious and/or immunological factors could have a pathogenetic role. These observations are supported by the experimental study by Matsumori and Kawai¹⁵ who found that BALB/c mice infected with Coxsackie virus B3 developed selective right ventricular myocarditis with myocardial cell destruction, followed by acute mononuclear cell infiltration and later right ventricular aneurysms. Moreover, the case described by Zolezzi *et al*¹⁶ can be regarded a clinical example of myocarditis with predominant right ventricular involvement. Zolezzi *et al* interpreted the right ventricular abnormalities as being secondary to myocarditis, whereas others^{17,18} thought that the inflammatory infiltrates were a reaction to a damaged myocardium.

Familial cases are difficult to explain in this context. Familial cases of myocarditis have seldom been described,^{11,12,18} though sometimes they were associated with right ventricular dysplasia.^{11,12} A genetic predisposition and susceptibility to infections, or a familial cardiomyopathy with superimposed inflammation can be hypothesised. O'Connell *et al*¹⁸ found a deficiency of suppressor lymphocyte function in a patient with familial myocarditis. In this case the inherited factor could be a deficiency in immunoregulation and host response.

In this report we describe two patients (father and daughter) who died suddenly when young. The familial association, the relatively rapid clinical deterioration, the malignant ventricular arrhythmias with aborted sudden death and the pathological findings suggest that they both had the same disease. The daughter had symptoms and echocardiographic findings compatible with right ventricular dysplasia and left ventricular

involvement was confirmed at postmortem examination, whereas the father had a progressive severe left ventricular failure. Endomyocardial biopsy and postmortem examination showed the presence of inflammatory infiltrates and myocyte necrosis indicative of myocarditis, associated with adipose infiltration of both ventricles and of the interventricular septum.

Interestingly, the clinical findings and course of this case are very similar to those of the patient reported recently by Hofmann *et al.*¹³: in both patients the clinical presentation was characterised by apparently idiopathic heart block and ventricular tachycardia; then heart failure appeared, associated with biventricular dysfunction and diagnosis of myocarditis at endomyocardial biopsy. Subsequently, both patients had an aborted sudden death caused by ventricular arrhythmias, and pathological findings (at surgery or necropsy) were compatible with right ventricular dysplasia. Another interesting case of an association between ventricular tachycardia, "active" myocarditis, and fibrofatty infiltration of right ventricular outflow tract was reported by Imakita *et al.*¹⁰ Their patient, however, did not have typical clinical features of right ventricular dysplasia, apart from ventricular tachycardia with left bundle branch block morphology.

There are two explanations for the clinical course and pathological findings in our first case: (a) an arrhythmogenic pre-existing inherited pathology involving both ventricles with superimposed later myocarditis ("association of two pathologies") and (b) a myocarditis, in a genetically predisposed subject, causing necrosis of the myocytes and fibrofatty substitution.

Our patients were unusual in several respects. Both patients showed a severe left ventricular involvement, particularly case 1. Right ventricular dysplasia with left ventricular involvement is not uncommon,⁶ but typically it causes only mild or moderate depression of ejection fraction or regional wall motion abnormalities: severe left ventricular involvement is rare. A septal aneurysm was seen in both patients at echocardiography during follow up (fig 3), and confirmed at necropsy (fig 2A). There are reports of ventricular aneurysms being caused by viral myocarditis,¹⁹ and also of a fibrolipomatous pattern of right ventricular dysplasia.¹⁴ Finally, both our patients showed rapid development of severe biventricular dysfunction, heart failure, and sudden death. Right ventricular dysplasia is usually slowly progressive.²⁰

We found a form of cardiomyopathy with left and right ventricular involvement in two

members of the same family. There was a severe loss of myocardium in the right ventricle, which was replaced by adipose and fibrous tissue. These anatomical changes and the clinical presentation of the disease are compatible with right ventricular dysplasia. One of our patients also had severe inflammation. These cases may represent a link between the inherited and the acquired ("inflammatory") form of right ventricular dysplasia.

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