Noonan's cardiomyopathy: a non-hypertrophic variant

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Abstract
Objective—To describe the association of the Noonan's phenotype and a primary, familial non-hypertrophic cardiomyopathy with restrictive pathophysiology.
Design—Observational study.
Setting—Tertiary cardiac referral centre.
Patients—Affected family members.
Methods—Two generations of a single family were examined and a description of the clinical characteristics and electrocardiographic, echocardiographic, and haemodynamic data of those affected is given.
Results—Three family members have classic Noonan's phenotype and all have a non-dilated, non-hypertrophic cardiomyopathy. Inheritance is autosomal dominant but with variable penetrance. The electrocardiograms show increased left ventricular voltages in two patients. On echocardiography left ventricular wall and internal end diastolic dimensions are normal, and there is considerable bilateral atrial enlargement. Systolic function is moderately impaired in one patient and mildly impaired in another. Doppler echocardiography showed restrictive pathophysiology as an early end of left ventricular filling and considerable reversal of flow in the superior vena cava during atrial systole.
Conclusion—Hypertrophic cardiomyopathy is well described in Noonan's syndrome. This is the first report of a

non-hypertrophic cardiomyopathy with echocardiographic and haemodynamic features of restrictive pathophysiology.

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In 1967, four years after the original description of Noonan's syndrome in nine children with atypical pulmonary stenosis,¹ the first case of associated hypertrophic cardiomyopathy was described.² Subsequent screening by echocardiography has shown hypertrophic cardiomyopathy to be fairly common, occurring in about 25% of cases.^{3,4} We now report the association of Noonan's syndrome with a primary, familial, non-hypertrophic cardiomyopathy with echocardiographic and haemodynamic features of restrictive pathophysiology.

Patients and methods

Figure 1 shows the family tree. The proband and his two daughters have classical Turner's phenotype (webbed neck, pectus carinatum, cubitus valgus) and normal 46XY/XX karyotype, and thus fall within the clinical spectrum of Noonan's syndrome. All three have symptoms and signs of cardiomyopathy. All are of normal stature, two out of the three have been able to reproduce, and, although not formally assessed, all seem intellectually normal. The full blood count, routine biochemistry, plasma proteins, and serum iron and ferritin were normal. The proband's wife, brother, and son were examined. None had features of Noonan's syndrome, and their electrocardiograms and echocardiograms were normal. Other family members were not assessed but to our knowledge none are affected. The proband's father died of smoking related lung disease in his seventies. His mother is alive and well, but declined examination. Additional family members have not been contacted.

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Figure 1 Family tree.

Table 1 Electrocardiographic data

	Patient No		
	1	2	3
PR interval (ms)	200	280	160
QRS interval (ms)	120	120	80
Mean frontal QRS axis	90	*	60
P wave amplitude (mV)	0.3	0.4	0.2
QRS voltage (R ₅ + S ₂) (mV)	5.0	2.6	4.6

*Indeterminate.

Figure 2 Twelve lead electrocardiogram (patient 2) showing first degree heart block, non-specific intraventricular conduction delay, and indeterminate QRS axis. P waves are enlarged consistent with atrial overload. Unlike patients 1 and 3 left ventricular QRS amplitude is within normal limits.

CLINICAL PRESENTATION AND COURSE

Patient 1 (proband)

Patient 1, the proband, presented at the age of 35 years with atrial tachycardias, which were at first controlled medically. Five years later, aged 40, he underwent direct current His bundle ablation and implantation of a DDD pacemaker. Symptoms and signs of congestive heart failure first developed at the age of 43 and have been rapidly progressive. He is now 47 years old, in NYHA functional class IV, and taking diuretics and digoxin. He developed thyrotoxicosis when he was 41 and

received radioactive iodine. He is currently euthyroid. A mild non-specific distal skeletal myopathy was diagnosed when he was 45.

Patient 2 (daughter)

Patient 2, a daughter, presented when 2 years old with congestive heart failure that was slowly progressive. She is now 21, in NYHA class III, and has a raised jugular venous pressure and ascites. She attended a normal school until the age of 16, but has never been employed and is supported by her mother. Hypothyroidism was diagnosed when she was

Figure 3 M mode echocardiogram through the mitral valve (patient 3). This shows early closure of the mitral leaflets and abbreviated left ventricular cavity enlargement.

Figure 4 Cross sectional echocardiogram (patient 3) in the apical four chamber view showing normal ventricular cavity size and bilateral atrial enlargement.

19, and she is currently taking thyroxine replacement, as well as digoxin and diuretics.

Patient 3 (daughter)

Patient 3, the younger of the two sisters, remained asymptomatic until she was 18. She then reported palpitation although no arrhythmias have been documented on repeated electrocardiographic monitoring. One year later she has unlimited exercise tolerance, is on no medication, married, working full time, and is currently pregnant.

Table 2 Echocardiographic features

	<i>Patient No</i>			<i>Normal values</i>
	<i>1</i>	<i>2</i>	<i>3</i>	
M mode and cross sectional echocardiography:				
Left ventricular				
End diastolic diameter (cm)	5.0	5.0	4.6	3.9–5.6
End systolic diameter (cm)	4.2	3.8	3.0	2.0–3.8
Septal thickness (cm)	1.0	0.8	1.0	0.7–1.2
Posterior wall thickness (cm)	1.0	0.8	0.9	0.7–1.0
Fractional shortening (%)	16	24	35	30–45
Left atrial diameter (cm)	5.6	6.0	5.5	2.5–4.1
Doppler echocardiography:				
Rhythm	DDD	AF	SR	—
Heart rate (beats/min)	65	130	70	—
Isovolumic relaxation time (ms)	100	100	120	60–120
Mitral deceleration time (ms)	90	60	80	150–300
E wave V max (m/s)	0.7	0.9	1.1	—
A wave V max (m/s)	0.2	—	0	—

AF, atrial fibrillation; SR, sinus rhythm.

INVESTIGATIONS

Electrocardiography

Table 1 shows details of the pre-ablation electrocardiogram in patient 1 and the electrocardiograms in patients 2 and 3. All show a non-specific intraventricular conduction delay resembling incomplete right bundle branch block (fig 2). The PR interval is at the upper limit of normal in patient 1 and prolonged in patient 2. The inferior P waves are peaked in patients 1 and 2. Left ventricular voltages are increased in patients 1 and 3 but not in patient 2, and the T waves are upright in all.

ECHOCARDIOGRAPHY

All studies show normal cardiac valves (table 2). Each shows bilateral atrial enlargement and normal ventricular end diastolic internal dimensions and wall thickness (fig 3 and 4). The ventricles seem morphologically normal, and in particular there is no localised apical hypertrophy. Left ventricular fractional shortening is normal in patient 3 (35%), mildly reduced in patient 2 (24%), and severely reduced in patient 1 (16%). In all left ventricular cavity expansion ends early in diastole as assessed by eye (fig 4), and a restrictive left ventricular filling pattern on Doppler echocardiography is indicated by short transmitral deceleration times (range 60–100 ms) and low or absent A wave velocities (fig 5). The velocities across the mitral valve show little variability throughout the respiratory cycle. The left ventricular isovolumic relaxation times are normal (range 100 to 120 ms). Forward flow in the superior vena cava is, however, predominantly systolic, which is not typical of a restrictive pathophysiology (fig 5). Although there is considerable reversal during atrial systole there is no consistent respiratory variability. Despite high pulmonary artery pressures measured by cardiac catheterisation in patient 1 there is virtually no tricuspid regurgitation on colour flow mapping.

Cardiac catheterisation

A left and right heart study was performed in patient 1. Pulmonary artery pressure was 70/35 mm Hg, mean pulmonary capillary wedge pressure 35 mm Hg, right ventricular end diastolic pressure 20 mm Hg and right atrial pressure 25 mm Hg. Left ventricular filling showed a dip and plateau pattern (fig 6).

Discussion

Noonan's syndrome is an autosomal dominant syndrome with variable penetrance characterised by a Turner's phenotype but with a normal karyotype. Up to 60% of cases have cardiovascular abnormalities, the commonest of which is hypertrophic cardiomyopathy.⁵ The family in this report has a non-hypertrophic cardiomyopathy with many features consistent with restrictive pathophysiology. To our knowledge this is the first report of a non-hypertrophic cardiomyopathy in Noonan's syndrome.

Two family members are severely affected. The presentation with symptoms of car-

Figure 5 Pulsed Doppler recordings (patient 1) with simultaneous electrocardiograms, phonocardiograms, and respiratory trace. Top: transmitral diastolic flow with abbreviated left ventricular filling and small A wave. Unlike pericardial constriction there is little variability of flow with respiration. Bottom: flow in the superior vena cava recorded with pulsed Doppler with the probe in the right supraclavicular fossa. Normally there is both systolic and diastolic orthograde flow with minor flow reversal (above the line) after atrial systole, usually in expiration. In this patient, orthograde flow is almost exclusively systolic and flow reversal after atrial systole is more obvious than normal. I, inspiration; E, expiration.

diomyopathy was in middle age in one and from birth in the other. The only other affected family member is mildly symptomatic in her late teens. The electrocardiograms show a non-specific intraventricular conduction delay in all and left ventricular hypertrophy by voltage criteria in two out of the three. There is first degree heart block in one. M Mode and cross sectional echocardiography show non-dilated, non-hypertrophied ventricles, and enlarged left atria most characteristic of restrictive cardiomyopathy, and consistent

Figure 6 Left ventricular pressure trace (patient 1) showing dip and plateau filling pattern characteristic of restriction.

with this, Doppler echocardiography shows an abbreviated left ventricular diastolic filling and reduced or absent flow during atrial systole. The considerable flow reversal in the superior vena cava during atrial systole is also typical of restrictive filling, although atypically forward flow is predominantly in ventricular systole.⁶ Cardiac catheterisation was performed in patient 1, which showed high filling pressures and the characteristic early filling pattern of restriction.

Although restrictive filling patterns are commonly seen in patients with left ventricular hypertrophy and more rarely in dilated cardiomyopathy where filling pressures are high, a restrictive cardiomyopathy is much less common.⁷ This may be due to amyloidosis, or less commonly haemochromatosis, glycogen storage diseases, scleroderma, sarcoidosis, endocardial fibroelastosis, or endomyocardial fibrosis.⁸ Sporadic or familial primary restrictive cardiomyopathy is rare, and has not been described in association with Noonan's syndrome.⁹⁻¹¹

In the present cases we did not perform myocardial biopsy to exclude secondary causes of restriction as it was thought that this was unlikely to contribute to further management. The clinical picture in patient 1 is complicated by direct current His bundle ablation that may in part account for the rapid deterioration and considerably impaired systolic function. Moreover the interpretation of venous flow patterns is complicated by dual chamber pacing in this patient. Similar echocardiographic and electrocardiographic features are, however, found in his two daughters. The history of thyroid disease is unlikely to be relevant, and none of the cases had taken drugs with cardiotoxic effects.

Hypertrophic cardiomyopathy without hypertrophy has been described.¹² In one family this was a postmortem diagnosis in patients who died suddenly and were found to have

morphologically normal hearts but myocardial disarray characteristic of hypertrophic cardiomyopathy. In another family the echocardiograms in affected members showed non-hypertrophied ventricles and features consistent with restrictive cardiomyopathy. Postmortem histological examination in one of these showed myocardial disarray. Hypertrophic cardiomyopathy has a broad morphological and pathophysiological spectrum. Hypertrophy is well known in Noonan's syndrome and has been shown to occur with myocardial disarray.¹³ It is possible that the family described in this report represent the non-hypertrophic end of the same spectrum.

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