Cardiomyopathy in Noonan's syndrome

Report of 3 cases¹

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Three patients with Noonan's syndrome associated with cardiomyopathy are described. The myopathy was obstructive in one patient and nonobstructive in two sibs.

Cardiovascular malformations in patients with a Turner's phenotype and a normal chromosomal karyotype (Noonan's syndrome) have been reported in several recent publications (Noonan and Ehmke, 1963; Chaves-Carballo and Hayles, 1966; Celemajer, Bowdler, and Cohen, 1968; Noonan, 1968). Congenital heart disease is present in 48 per cent (Smith, 1970) of the patients, the most common abnormality being valvar pulmonary stenosis (Chaves-Carballo and Hayles, 1966; Noonan, 1968). Supravalvar and pulmonary arterial branch stenosis (Nora and Sinha, 1968), atrial septal defect (Chaves-Carballo and Hayles, 1966; Noonan, 1968), and a persistent ductus arteriosus (Chaves-Carballo and Hayles, 1966; Noonan, 1968) are also frequently observed. Other infrequent cardiac lesions include aortic valvar stenosis (Chaves-Carballo and Hayles, 1966; Nora and Sinha, 1968), Ebstein's malformation (Wright, Summitt, and Ainger, 1968), ventricular septal defect (Chaves-Carballo and Hayles, 1966), tetralogy of Fallot (Chaves-Carballo and Hayles, 1966), truncus arteriosus (Warkany, 1971), and coarctation of the aorta (Chaves-Carballo and Hayles, 1966). Eccentric left ventricular hypertrophy has been recently described (Ehlers *et al.*, 1972) in familial and sporadic cases of Turner's phenotype with normal karyotype. This report extends these observations further and describes obstructive and nonobstructive hypertrophic cardiomyopathy in patients with Noonan's syndrome.

Case reports

Case 1

A 22-year-old white man was first seen for evaluation of

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short stature at the age of 8 years 11 months. On physical examination he had typical features of Turner's phenotype (Fig. a). There was a grade 2/6 systolic ejection murmur at the left sternal border. Chest x-rays showed mild cardiomegaly, and an electrocardiogram revealed left ventricular hypertrophy and ST and T wave changes. Findings at cardiac catheterization at 9 years 11 months, particularly the left ventricular angiogram and raised end-diastolic pressure in both ventricles without any other haemodynamic abnormalities, suggested the diagnosis of nonobstructive hypertrophic cardiomyopathy (Table). The patient did well for over 10 years but developed gross congestive cardiac failure at the age of 20 years 7 months. There was obvious cardiomegaly and the electrocardiogram showed biatrial and biventricular hypertrophy. After therapy with digoxin and diuretics there was considerable diminution in heart size and symptoms. A second cardiac catheterization performed after treatment showed no significant change in haemodynamics (Table). The patient's karyotype was 44,XY. He is, at present, moderately limited in activity.

Case 2

Sister of Case 1 was evaluated at the age of 12 years 5 months because of short stature, frequent respiratory infections, fatigue, and excessive perspiration. On examination she had typical features of the Turner phenotype (Fig. b). A buccal smear was chromatin positive. A chromosomal study was not performed.

Auscultation revealed a grade 2/6 systolic murmur at the apex. Chest x-ray showed moderate cardiac enlargement and an electrocardiogram revealed an indeterminate QRS axis, biatrial, and biventricular hypertrophy. Findings at cardiac catheterization were indicative of hypertrophic cardiomyopathy with very low cardiac output (Table). Congestive heart failure became more severe and she died one year later. At necropsy there was an infantile uterus, endometrium, and myometrium, and evidence of chronic congestive heart failure. The heart weighed 420 g with considerable hypertrophy of the left and right ventricle. The valves and coronary

TABLE *Cardiac catheterization data*

Case No.	Sex	Age at catheterization yr mth	Pressure (mmHg)						
			Right atrium (mean)	Right ventricle	Pulmonary artery	Pulmonary artery wedge (mean)	Left ventricle (apex)	Femoral artery	Cardiac index (l./min per m ²)
Case 1 486434	M	9:11	3	35/9-11	40/25 (33)	10-13	105/20-26	105/62 (80)	3.8
		20:07	5	42/7	36/24 (27)	14	120/13-16	120/82 (94)	3.6
Case 2 487671	F	12:05	13	58/18	60/22-32 (40)	28	96/27	132/80 (96)	1.9
Case 3 373231	M	11:04	8	28/8	28/16 (20)	16	230/15	100/60 (76)	3.4
		16:05	6	45/5-10	26/13 (17)	16	233/12-20	93/68 (82)	4.4
		17:05	3	47/8	28/12		187/13	108/73 (93)	3.4
		19:04	5.5	22/6-10	23/11 (18)	13	185/13-15	105/80 (95)	5.6

FIG. Photograph of two sibs (a and b) and a sporadic case (c) of Noonan's syndrome associated with hypertrophic cardiomyopathy. Features of Noonan's syndrome include short stature, webbed neck, cubitus valgus, widely spaced and hypoplastic nipples, pectus deformity, and low set ears.

arteries were normal. Microscopical examination of the left ventricle showed myocardial hypertrophy with scattered areas of fibrosis which were most prominent in the subendocardial layer.

Several family members of the probandi (Cases 1 and 2) were examined but not karyotyped. All members except the father were normal. The father was short statured (163 cm) but was without other stigmata of Noonan's syndrome. His chest x-ray showed cardiomegaly and an electrocardiogram indicated conspicuous left ventricular hypertrophy. A clinical diagnosis of cardiomyopathy was made. He did not consent to have cardiac catheterization.

Case 3

A white man, 20 years 6 months of age, with typical features of Turner's phenotype (Fig. c) was first evaluated at 2 months of age because of a seizure. He had no cardio-respiratory symptoms until 13 years of age when he began to complain of chest pain, decreasing exercise tolerance, dizziness, and dyspnoea on exertion. The chest x-ray showed moderate cardiomegaly and an electrocardiogram revealed a superior axis in the frontal plane, and hypertrophy of the left ventricle and atrium. The diagnosis of obstructive hypertrophic cardiomyopathy (idiopathic hypertrophic subaortic stenosis) and mitral regurgitation was confirmed at cardiac catheterization and angiography (Table). Right ventricular outflow obstruction was subsequently also noted. At age 16 years and 6 months, after the second catheterization, treatment with oral propranolol was started because of recurrent chest pain and dizzy spells. There was some improvement in his symptoms and a reduction in the left ventricular outflow gradient (Table). When last examined, he had mild to moderate exercise tolerance. The patient's karyotype was 44,XY, and there was no clinical evidence of cardiomyopathy in other family members.

Discussion

Classical Turner's syndrome is characterized by short stature, webbing of the neck, cubitus valgus, and sexual infantilism in phenotypic females with sex chromosome monosomy (45:XO). The incidence of cardiovascular malformations in XO Turner's syndrome is 44 per cent (Rainier-Pope *et al.*, 1964). The most common cardiac abnormality is coarctation of the aorta. There is another group of patients, both male and female, with phenotypic features similar to those of Turner's syndrome but without a chromosomal abnormality. Many of these subjects also have skeletal anomalies, mental retardation, hypertelorism, and congenital heart disease. To the paediatrician or paediatric cardiologist this group is better known as Noonan's syndrome (Noonan and Ehmke, 1963). Right-sided cardiac malformations (Noonan and Ehmke 1963; Chaves-Carballo and Hayles, 1966; Celermajer *et al.*, 1968; Noonan, 1968) are frequently present, particularly pulmonary valvar

and branch stenosis. Abnormalities of the left heart are uncommon (Ehlers *et al.*, 1972). The cases presented in this report are of interest because they clearly document for the first time the occurrence of symptomatic obstructive (idiopathic hypertrophic subaortic stenosis), and familial nonobstructive hypertrophic cardiomyopathy in patients with Noonan's syndrome. The cardiovascular findings noted do not differ significantly from other cases with isolated or familial cardiomyopathy. The association of cardiomyopathy with Noonan's syndrome may be coincidental. However, the development of heart disease in only those sibs (Case 1 and 2) with the stigmata of the syndrome, and the increased incidence of other cardiovascular hypertrophy in this condition all suggest a closer relation between these two entities.

The patients reported by Ehlers *et al.* (1972) were asymptomatic but had angiocardiographic evidence of abnormal left ventricular septal hypertrophy, usually associated with the electrocardiogram finding of a superiorly oriented A QRS. Our patients in addition to the angiographic changes were symptomatic, two having developed congestive heart failure and one severe left ventricular outflow obstruction. One may therefore postulate that a spectrum of left ventricular myopathy probably occurs in Noonan's syndrome, with some patients having only angiographic or electrocardiographic abnormalities and others the clinical manifestations and haemodynamic changes of severe obstructive or nonobstructive cardiomyopathy.

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