Eur J Pediatr (1995) 154:949–952

ORIGINAL PAPER

B. Marino
M. G. Gagliardi
M. C. Digilio
B. Polletta
S. Grazioli
D. Agostino
A. Giannotti
B. Dallapiccola

Noonan syndrome: structural abnormalities of the mitral valve causing subaortic obstruction

Received: 14 December 1994
Accepted: 21 March 1995

B. Marino (✉) · M. G. Gagliardi
B. Polletta · S. Grazioli · D. Agostino
Paediatric Cardiology,
Bambino Gesù Hospital,
Piazza SantOnofrio, 4,
I-00165 Rome, Italy

M. C. Digilio · A. Giannotti
Department of Genetics,
Bambino Gesù Hospital, Rome, Italy

B. Dallapiccola
Uman Genetics,
"Tor Vergata" University, Rome, Italy

Abstract Among 41 consecutive children with classic Noonan syndrome, 27 patients (66%) presented cardiac anomalies. Eight patients (19.5%) had a congenital anomaly of the mitral valve consisting of 5 with partial atrioventricular canal defect and 3 with anomalous insertion of the mitral valve on the ventricular septum. Five patients (12%) presented with a significant left ventricular outflow tract obstruction caused by the anterior leaflet of the mitral valve: two cases with atrioventricular canal and three cases with isolated anomalous insertion of the mitral valve. Echocardiography is the best tool for the diagnosis. Cardiac defects of patients with Noonan syndrome may be explained on the basis of anomalies of the extracellular matrix involving cardiac valves including the mitral valve.

Conclusion In children with Noonan syndrome and left ventricular hypertrophy a careful echocardiographic assessment of the mitral valve should reveal those in whom the left ventricular outflow tract obstruction is anatomical in nature.

Key words Noonan syndrome · Congenital anomalies of the mitral valve · Atrioventricular canal defect

Introduction

The Noonan syndrome [1, 10] is a common genetic condition (incidence of 1/1000–1/2000) [4, 13] and, except for Down syndrome [12], the syndrome most frequently associated with congenital heart malformation.

Heart defects in Noonan syndrome consist of pulmonary stenosis (about 30% of cases) sometimes with dysplastic pulmonary valve, left ventricular hypertrophy (about 20% of cases), sometimes with hypertrophic cardiomyopathy, about 25% of cases atrial, or ventricular septal defect and others [4, 5, 8, 12–19, 22].

Until recently [7, 11, 20], the association with congenital malformation of the mitral valve has received little attention [8, 15].

Here we describe our results of the cardiological assessment of 41 patients with Noonan syndrome with particular reference to 8 children showing congenital anomalies of the mitral valve causing subaortic obstruction in 5 of them.

Patients and methods

Our study consisted of 41 consecutive children with classical Noonan phenotype (25 boys and 16 girls) observed in our hospital during the last 6 years. Their ages ranged from 8 months to 18 years (mean 8.6 years, median 9.7 years). All patients were referred for cardiological evaluation or genetic counselling. The diagnosis of Noonan syndrome was based on the presence of the classical phenotypic and facial features according to previously published criteria [1, 4, 10, 13]. Chromosomes were normal in all patients. The cardiac evaluation included chest X-ray, ECG and two-dimensional colour-Doppler echocardiography in all patients, and cardiac catheterization and angiocardiography in 20 cases.

The echocardiograms were performed with a Hewlett-Packard Sonos 1000 instrument with 5.0, 3.5 and 2.5 phased-array transducers. In each case a complete examination was performed with two-dimensional Doppler and colour flow techniques in subcostal,

Table 1 Twenty-seven cases with congenital heart disease

Diagnosis	N° of cases	%
Pulmonary valve stenosis	9	22
Pulmonary valve stenosis + atrial septal defect	3	7
Partial atrioventricular canal	5	12
Tetralogy of Fallot	3	7
Anomalous insertion of mitral valve	3	7
Hypertrophic obstructive cardiomyopathy	2	5
Others	2	5

apical, parasternal and suprasternal views. Chloral hydrate was used for sedation when necessary. Doppler peak instantaneous gradient through the right and left ventricular outflow tracts was calculated using the simplified Bernouilli equation.

Cardiac catheterization was performed in 6 children in order to dilate the pulmonary valve using a balloon and in 14 cases to confirm the diagnosis before surgical procedures. Various types of surgical procedures were performed in 17 patients.

Results

Cardiac anomalies (Table 1) were diagnosed in 27 patients (66%). Specifically, 12 children (29%) presented with pulmonary valve stenosis and 5 patients (12%) had a partial form of atrioventricular canal defect. In the latter group, two patients had a partial atrioventricular canal and subaortic obstruction due to anomalous insertion of the mitral valve into the left ventricular outflow tract [20].

An isolated congenital anomaly of the mitral valve (excluding cases with atrioventricular canal) was diagnosed in 3 children (7.5%). In all of them, the defect consisted of an anomalous insertion of the mitral valve on the ventricular septum [6, 9, 21] causing obstruction of the left ventricular outflow tract (Fig. 1). In one of these patients there was an associated coarctation of the aorta. In all, 5 patients showed subaortic obstruction due to an anomalous insertion of the anterior leaflet on the muscular ventricular septum. Of these five children two had also a dysplastic pulmonary valve without significant pressure gradient. Subaortic Doppler peak instantaneous gradients and peak-to-peak gradients at cardiac catheterization in these patients are listed in Table 2.

Four of the five patients were submitted for surgery: one for aortic coartectomy, one for a left-ventricle-to-aorta conduit implantation (and after 2 years to mitral valve replacement to relieve left ventricular outflow tract obstruction) and two for correction of partial atrioventricular canal and relief of subaortic obstruction (Table 2).

In all patients that underwent surgery, echocardiography was able to precisely demonstrate the type of subaortic obstruction.

All patients survived the surgical procedures except one who died 6 months after aortic coartaction. The last three patients underwent surgery are in good conditions in a medium follow up of 16 months.

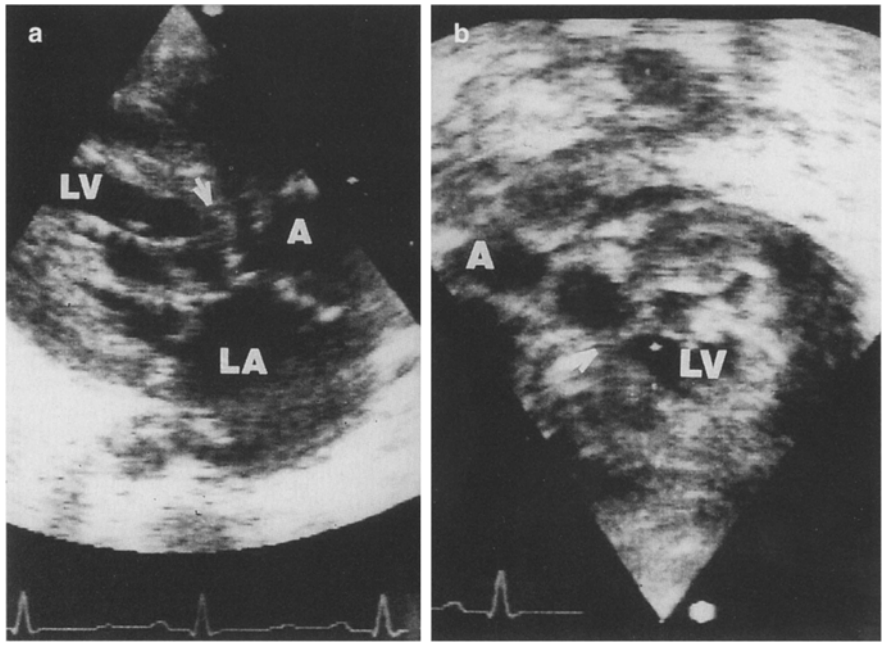

Fig. 1 Two-dimensional echocardiography in long-axis parasternal view (**a**) and subcostal view (**b**) in a case with anomalous insertion of the mitral valve (case1, Table 2). Note the insertion of the anterior leaflet of the mitral valve *(arrow)* on the ventricular septum crossing the left ventricular outflow tract and causing subaortic stenosis. (*A* aorta, *LA* left atrium, *LV* left ventricle)

Table 2

Diagnosis	Age	Subaortic gradient		Surgical treatment
		Echo	Cath	
Anomalous insertion of mitral valve + aortic coarctation	8 days	80 mmHg	–	Aortic coarctectomy
Anomalous insertion of mitral valve	15 months	50 mmHg	–	
Anomalous insertion of mitral valve	12 months	55 mmHg	50 mmHg	Interposition left ventricle – aorta conduit
Partial atrioventricular canal defect + subaortic obstruction	4 years	55 mmHg	45 mmHg	Correction of partial atrioventricular canal defect + relief of subaortic obstruction
Partial atrioventricular canal defect + subaortic obstruction	9 years	70 mmHg	55 mmHg	Correction of partial atrioventricular canal defect + relief of subaortic obstruction

Discussion

Congenital anomalies of the mitral valve in patients with Noonan syndrome have been reported only in connection with partial or complete atrioventricular canal defects [12, 20]

However, isolated anomalous insertion of the mitral valve on ventricular septum, a rare cardiac defect causing subaortic stenosis [6, 9, 21], has never been described in the literature on Noonan syndrome [1, 4, 5, 7, 8, 10–20, 22].

A recent paper described four infants with Noonan syndrome and "polyvalvular disease" including dysplasia of the leaflets of the mitral valve with short cords and nodular myxomatous tissue [11]. One of the these patients had accessory leaflet tissue of the mitral valve [11] but none presented with a subaortic obstruction due to anomaolous insertion of the mitral valve as observed in our patients [7].

Moreover, histological examination indicating myocardial maldevelopment [2, 3] suggests that cardiac defects in this syndrome may be due to anomalies of the extracellular matrix.

Our results suggest that anomalous insertion of the mitral valve, alone [7] or together with an atrioventricular canal defect [20] should be included in the spectrum of congenital cardiac anomalies associated with Noonan syndrome. In patients with Noonan syndrome and left ventricular hypertrophy, careful echocardiographic assessment of the mitral valve should reveal those in whom the left ventricular outflow tract obstruction is anatomical in nature.

Moreover, the association of subaortic obstruction with a partial atrioventricular canal defect (in two of four patients) suggests the need of an accurate phenotype analysis and assessment of left ventricular outflow tract in all cases of atrioventricular canal defect without Down syndrome [6, 9, 20].

References

1. Allanson JE (1987) Noonan syndrome. J Med Genet 24: 9–13
2. Amman G, Sherman FS (1992) Myocardial dysgenesis with persistent sinusoids in a neonate with Noonan's phenotype. Pediatr Pathol 12: 83–92
3. Burch M, Mann JM, Sharland M, Shinebourne EA, Parton MA, McKenna WJ (1992) Myocardial disarray in Noonan syndrome. Br Heart J 68: 586–588
4. Burch M, Sharland M, Shinebourne E, Smith G, Patton M, McKenna W (1993) Cardiologic abnormalities in Noonan syndrome: phenotypic diagnosis and echocardiographic assessment of 118 patients. J Am Coll Cardiol 22/4: 1189–1192
5. Calermajer JM, Bowdler JD, Cohen DH (1968) Pulmonary stenosis in patients with the Turner phenotype in the male. Am J Dis Child 116: 351–358
6. De Biase L, Di Ciommo V, Ballerini L, Marcelletti C, Bevilacqua M, Marino B (1986) Prevalence of left-sided obstructive lesions in patients with A-V canal without Down syndrome. J Thorac Cardiovasc Surg 91: 467–468
7. Gagliardi MG, Polletta B, Digilio C, formigari R, Santoro G, Giannotti A, Marino B (1994) Anomalie strutturali della valvola mitrale nei pazienti con sindrome di Noonan G. Ital Cardiol 24/2: 32
8. Hirsch HD, Gelband H, Garcia O, Gottlieb S, Tamer DM (1975) Rapidly progressive obstructive cardiomyopathy in infants with Noonan syndrome. Circulation 52: 1161–1165
9. Marino B, Vairo U, Corno A, Nava S, Guccione P, Calabrò R, Marcelletti C (1990) Atrio-ventricular canal in Down syndrome. Prevalence of associated cardiac malformations compared with patients without Down syndrome. Am J Dis Child 144: 1120–1122
10. Mendez HMM, Opitz JM (1985) Noonan syndrome: a review. Am J Med Genet 21: 493–506

11. Narayanswami S, Kitchiner D, Smith A (1994) Spectrum of valvar abnormalities in Noonan's syndrome. A pathologic study. Cardiol Young 4: 62–66
12. Noonan JA (1968) Hypertelorism with Turner phenotype. A new syndrome with associated congenital heart disease. Am J Dis Child 116: 373–380
13. Noonan JA, Ehmke DA (1963) Associated non-cardiac malformations in children with congenital heart disease. J Pediatr 63: 468–470
14. Nora JJ, Torres FG, Sinha AK, McNamara DG (1970) Characteristc cardiovascular anomalies of XO Turner syndrome, XX and XY phenotype, and XO/XX Turner mosaic. Am J Cardiol 25: 639–641
15. Nora JJ, Nora A, Sinha AK, Spangler RD, Lubs HA (1974) The Ullrich-Noonan syndrome (Turner phentoype). Am J Dis Child 127: 48–55
16. Nora JJ, Lortscher RH, Spangler RD (1975) Echocardiographic studies of left ventricular disease in Ullrich-Noonan syndrome. Am J Dis Child 129: 1417–1420
17. Phornphutkul C, Rosenthal A, Nadas AS (1973) Cardiomyopathy in Noonan syndrome. Br Heart J 35: 99–102
18. Sharland M, Morgan M, Smith G, Burch M, Patton M (1993) Genetic counselling in Noonan syndrome. Am J Med Genet 45: 437–440
19. Siggers DC, Polani PE (1972) Congenital heart disease in male and female subjects with somatic features of Turner's syndrome and normal sex chromosome (Ullrich's and related syndromes). Br Heart J 34: 41–46
20. Starr A, Hovaguimian H (1994) Surgical repair of subaortic stenosis in atrioventricular canal defects. J Thorac Cardiovasc Surg 108/2: 373–376
21. Vairo U, Marino B, Pasquini L, Gagliardi MG, Formigari R, De Zorzi A, Di Donato R, Marcelletti C (1992) Anomala inserzione della mitrale. Una rara forma di ostruzione sottoaortica nell'infanzia. Cardiologia 37/3: 227–233
22. Van Der Hauwaert LG, Fryns JP, Dumoulin M, Logghe N (1978) Cardiovascular malformations in Turner's and Noonan's syndrome. Br Heart J 40: 500–509