Cardiac Findings in 31 Patients with Noonan's Syndrome

Débora Romeo Bertola, Chong Ae Kim, Sofia M. M. Sugayama, Lilian Maria José Albano, Jaqueline Wagenführ, Regina Lúcia Moysés, Claudette Hajaj Gonzalez

São Paulo, SP - Brazil

Objective *- To evaluate cardiac findings in 31 Noonan syndrome patients.*

Methods – *Thirty-one (18 males and 13 females)patients from 26 families affected with Noonan's syndrome were evaluated from the cardiac point of view with electrocardiography and echodopplercardiography.*

Results – *Twenty patients had some type of cardiac abnormality. The most frequent was pulmonary valve stenosis followed by hypertrophic myocardiopathy, commonly associated with valve defects. Upper deviation of the QRS axis was observed in 80% of these patients.*

Conclusion *- In view of the high frequency and diversity of cardiac abnormalities present in Noonan syndrome, cardiac evaluation with electrocardiography and echocardiography should be performed in all patients diagnostically suspected of having this disease.*

Keywords: Noonan syndrome, pulmonary valve stenosis, hypertrophic myocardiopathy .

Unidade de Genética do Instituto da Criança
Faculdade de Medicina da Universidade de São Paulo
Mailing address: Chong Ae Kim – Genética – InCor – Av. Dr. Enéas C. Aguiar, 647 – 05403-900 - São Paulo, SP

Noonan syndrome is a genetic disease of autosomal dominant inheritance, characterized by low stature, craniofacial dysmorphism, webbed neck, cardiac abnormalities, cryptorchism in male patients, skeletal anomalies, and hemorrhagic diathesis.

Noonan and Ehmke recognized the disease as a distinct entity in 1963 [1]; since then many cases have been described in the literature. Its incidence has been estimated at 1/1000 to 1/2500 live births [2], making it one of the most frequent syndromes associated with cardiac defects.

The most frequent cardiac abnormality in Noonan's syndrome is pulmonary valve stenosis, present in approximately 50% of the patients [3], followed by hypertrophic myocardiopathy occurring in 25% [4]. Both anomalies have peculiarities in Noonan's syndrome; in pulmonary valve stenosis, valves are often dysplasic, differing from the dome format and without the commissural fusion observed in nonsyndromic forms; hypertrophic myocardiopathy is frequently associated with cardiac defects, in particular, pulmonary valve stenosis. Although these cardiac findings are the most common ones [5], practically all other types of cardiac anomalies have been encountered in Noonan syndrome.

The electrocardiograms of affected patients commonly show an upper deviation of the QRS axis and deep S waves in the precordial derivations; these findings are not associated with a specific cardiac anomaly [5].

The gene responsible for Noonan syndrome has been mapped on the long arm of chromosome 12 [6], but in some families of affected patients, this connection was not observed, indicating the genetic heterogeneity of the disease.

Our objective was to study cardiac findings in individuals with Noonan's syndrome.

Methods

Thirty-one Noonan syndrome patients from 26 families were studied at the Clinical Genetics Unit of the Institute for Children of the Clinics Hospital of the Medical School of the University of São Paulo.

Noonan Syndrome diagnoses of these individuals; were based on the clinical criteria established by van der Burgt et al. [7]. Twenty-six proposed patients and their first-degree relatives (parents and siblings) were evaluated; recurrence of the disease was observed in five relatives. One of the chosen patients was an adopted child and another's father was not available for evaluation. Of the 29 remaining cases, 8 (28%) were familial and 21 (72%) sporadic. Eighteen patients were males and 13 were females, with ages ranging from 3 months to 41years (average 12 years) . One of the patients had already passed away at the time of the study; his data were obtained from medical files; photographs were used to analyze some of his craniofacial characteristics. The impossibility of detecting some of the craniofacial dysmorphisms in this patient is reflected in the total number of these findings shown (Table I).

The cardiac evaluation was based on a special physical examination, on the electrocardiogram, and on the echocardiogram.

Subjects affected with Noonan's syndrome were only included in the study after signing an informed consent, for themselves when adults, or by legal guardians when underage.

Results

The most commonly observed clinical findings in patients with Noonan's syndrome were: low stature, craniofacial dysmorphism, short or webbed, cardiac anomalies, sternal deformity, and the presence of pads at the tip of the fingers and toes (Table I).

Chromosome studies showed normal results for all patients.

Twenty (65%) of the patients had some form of echocardiographic abnormality (Table II).

Signs of right or left ventricular hypertrophy were present in 13 and 5 patients, respectively (Table III).

Upper deviation of the QRS axis was a rather common finding in 80% of these patients.

Discussion

Cardiac anomalies are common in Noonan syndrome and the major cause of morbidity and mortality in this disease.

In the present study, 65% of affected individuals had some form of cardiac abnormality. This frequency is higher than that estimated in other works (3,8), probably because the majority of our patients were sent by the Heart Institute and were known to have a cardiac anomaly, and also because a Genetic Unit of a tertiary hospital, in this case the Children's Institute, tends to receive only the more serious cases.

A cardiac murmur was heard in 12 (60%) of the neonates with cardiac problems, allowing for a precocious, adequate follow-up.

In agreement with literature reports, the most frequent cardiac anomaly was pulmonary stenosis, found in 70% of

Table I – Clinical findings in 31 Noonan syndrome patients

Clinical finding	Nº (%)
General	
Low stature	22/31 (71%)
Delayed bone age	12/22 (55%)
Craniofacial characteristic	
Hypertelorism	16/30 (53%)
Palpebral ptosis	15/31 (48%)
Infero-lateral slanting of the palpebral slits	14/31 (45%)
Epicanthus	12/31 (39%)
Proptosis	4/30 (13%)
High palate	13/30 (43%)
Poor dental occlusion	11/30 (37%)
Low-implanted ears	6/31 (19%)
Upper helix thickening	8/31 (26%)
Neck	
Short or webbed	27/31 (87%)
Low hair implantation in nape	14/30 (47%)
Thorax	
Pectus carinatum and/or *excavatus*	16/31 (52%)
Cardiac anomalies	20/31 (65%)
Genitalia	
Cryptorchism	7/18 [2] (39%)
Members	
Pads at the tip of the fingers and toes	21/30 (70%)
Broad and short nails	16/30 (53%)
Cubitus vulgus	6/30 (20%)
Hematological anomalies	
Factor XI, XII and/or VIII deficiencies	5/30 (17%)
Platelet anomalies	3/30 (10%)

(1)Two standard deviations below average; (2) total number of male patients.

Table II - Cardiac anomalies observed in Noonan syndrome patients

Cardiac anomalies	Nº	%
PVS and/or SVPS	10	50%
EPV/MVP	3	15%
ASD	1	5%
HM	4	20%
VSD	1	5%
Aortic valve thickening	1	5%
Total	20	100%

PVS– pulmonary valve stenosis; SVPS- supravalvar pulmonary stenosis; MVP- mitral valve prolapse; HM- hypertrophic myocardiopathy; ASD- atrial septal defect; VSD- ventricular septal defect.

Table III – Electrocardiographic findings in Noonan syndrome patients

Findings	Nº	%
RVO	12	57%
LVO	5	24%
RAO	1	5%
RBB	2	9%
Sinus bradycardia	1	5%
Total	21	100%

RSO- right ventricle overload; LVO- left ventricle overload; RAO- right atrium overload; RBB- right branch block.

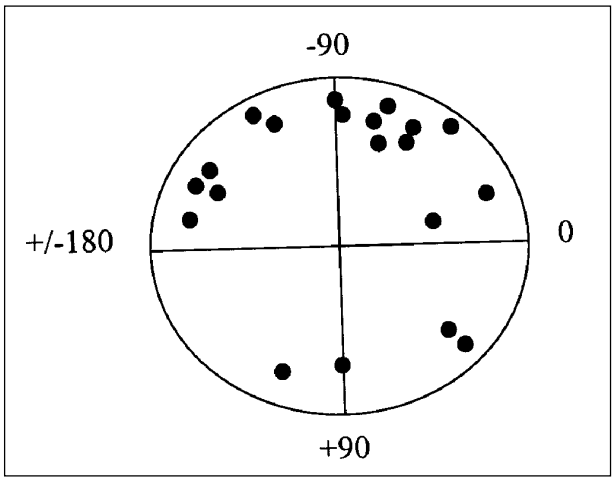

Fig. 1 - QRS axes in patients with cardiac anomalies.

the patients with cardiac problems. The pressure gradient between the right ventricle and the pulmonary arterial trunk varied between 23 and 121mmHg in these patients. Three (21%) had a pressor gradient above 60mmHg characterizing important pulmonary stenosis, 4 (29%) slight stenosis (pressor gradient between 20 and 40mmHg), and 7 (50%) moderate pulmonary stenosis. The most common associated anomalies were interarterial communication and hypertrophic myocardiopathy. Char et al. [9], studying 45 cases of Noonan' syndrome, observed interarterial communication to be the most frequent cardiac defect associated with pulmonary stenosis.

Echocardiographic findings showed a dysplasic pulmonary valve in 4 (24%) of our cases of pulmonary valve stenosis. Burch et al. [4], in an echocardiographic study of 119 Noonan syndrome patients, diagnosed dysplasic valves in 8 (27%) of 30 of these patients- who also had pulmonary stenosis.

Despite the presence of pulmonary valve dysplasia in one third of the patients, the majority of them had no evidence of dysplasia on echocardiography; this observation should be considered in the therapy of these individuals.

Percutaneous dilatation with a balloon catheter, the treatment of choice in cases of moderate and serious pulmonary stenosis, is rarely effective when the valve is dysplasic [5]. Ishizawa et al. [10], who performed this procedure in 4 Noonan syndrome patients with dysplasic pulmonary valves, obtained good results in two of them. The authors postulated that valvuloplasty should be performed as an initial procedure in patients with Noonan syndrome and pulmonary stenosis, even when evidence of valve dysplasia is found. In our study, three patients, one with serious, two with moderate pulmonary stenosis, respectively, who underwent valvuloplasty, had a significant reduction in the pressor gradient of those with moderate stenosis. It is important to point out that none of these three patients had signs of valve dysplasia on the echocardiogram. Four patients with Noonan syndrome underwent surgical correction of pulmonary stenosis (commissurotomy, pulmonary valvuloplasty, myectomy, and amplification of the right ventricle's outlet by insertion of a bovine pericardium graft), of these two had a pressor gradient above 110mmHg, one had moderate pulmonary stenosis, and in one, no reduction ~~of~~ in the pressor gradient was observed following valvuloplasty.

The second most common cardiac anomaly of Noonan's syndrome is hypertrophic myocardiopathy, also observed in our study. Differently from the non-syndrome form, Noonan syndrome hypertrophic myocardiopathies are frequently associated with a valve anomaly, mainly pulmonary stenosis. Four of our patients with hypertrophic myocardiopathy also had involvement of pulmonary, aortic, or mitral valves.

Interventricular communication and aortic valve thickening were other cardiac findings diagnosed with echocardiography in our study.

The electrocardiogram showed an upper deviation of the QRS axis in 16 (60%) patients with cardiac abnormalities. This was observed in cases of pulmonary valve stenosis, supravalvar pulmonary stenosis, hypertrophic myocardiopathy, and interventricular communication. However, it was not found in patients affected by Noonan's syndrome without cardiac anomalies. Neither was there a direct correlation between the degree of obstruction of the right ventricle's outlet and axis deviation. The physiopathology of this symptom is not fully known, but appears to involve not only counterclockwise rotation of the heart, but also a disturbance in the conduction system of affected patients [11]. This electrocardiographic finding may aid in the diagnosis of Noonan syndrome.

Cardiac involvement is rather frequent in Noonan syndrome patients, with peculiarities when compared with nonsyndromic cases. Affected individuals often have thoracic deformities, with *pectus carinatum* upwards, and *excavatum* downwards; both deformities are capable of interfering with cardiac auscultation. A detailed cardiac evaluation, including electrocardiographic and echocardiographic examinations, is recommended for every patient with a diagnostic suspicion of Noonan syndrome.

This is a relatively frequent autosomal dominant inherited genic disease; the wide spectrum of its clinical manifestations or phenotype variability calls for the services of various specialists including pediatricians, endocrinologists, ophthalmologists, cardiologists, and hematologists. A better understanding of this heterogeneous syndrome may lead to more adequate follow-up and treatment of affected patients.

References

1. Noonan JA, Ehmke DA. Associated noncardiac malformations in children with congenital heart disease. J Pediatr 1963; 63: 468-70.
2. Nora JJ, Nora AH, Sinha AK, Spangler RD, Lubs HA. The Ullrich-Noonan syndrome (Turner phenotype). Am J Dis Child 1974; 127: 48-55.
3. Allanson JE - Noonan syndrome. J Med Genet 1987; 24: 9-13.
4. Burch M, Sharland M, Shinebourne E, Smith G, Patton M, McKenna W. Cardiologic abnormalities in Noonan syndrome: phenotypic diagnosis and echocardiographic assessment of 118 patients. J Am Coll Cardiol 1993; 22: 1189-92.
5. Noonan J, O'Connor W. Noonan syndrome: a clinical description emphasizing the cardiac findings. Acta Pediatr Jpn 1996; 38: 76-83.
6. Jamieson CR, van der Burgt I, Brady AF, et al. Mapping a gene for Noonan syndrome to the long arm of chromosome 12. Nature Genet 1994; 8: 357-60.
7. van der Burgt I, Berends E, Lommen E, et al. Clinical and molecular studies in a large dutch family with Noonan syndrome. Am J Med Genet 1994; 53: 187-91.
8. Mendez HMM, Opitz JM. Noonan Syndrome: a review. Am J Med Genet 1985; 21: 493-506.
9. Char F, Rodriguez-Fernandez HL, Scott CI, Borgaonkar DS, Bell BB, Rowe RD. The Noonan syndrome – a clinical study of forty-five cases. BD: OAS 1972; VIII: 110-8.
10. Ishizawa A, Oho SI, Dodo H, Katori T, Homma SI. Cardiovascular abnormalities in Noonan syndrome: the clinical findings and treatments. Acta Pediatr Jpn 1996; 38: 84-90.
11. Armengol AJ, Brohet CR, Intermans JP, Vliers A. Le ventricule gauche dans le syndrome de Noonan. Aspects électro-vecto-écho et angio-cardiographiques. Arch Mal Coeur 1987; 4: 445-53.