
NOONAN SYNDROME: A CLINICAL AND GENETIC STUDY OF 31 PATIENTS

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SUMMARY: Noonan syndrome is a multiple congenital anomaly syndrome, inherited in an autosomal dominant pattern. We studied 31 patients (18 males and 13 females) affected by this disorder regarding their clinical and genetic characteristics. The most frequent clinical findings were short stature (71%); craniofacial dysmorphisms, especially hypertelorism, ptosis, downslanting of the palpebral fissures; short or webbed neck (87%); cardiac anomalies (65%), and fetal pads in fingers and toes (70%). After studying the probands' first-degree relatives, we made the diagnosis of Noonan syndrome in more than one family member in three families. Therefore, the majority of our cases were sporadic.

DESCRIPTORS: Noonan syndrome. Valvar pulmonary stenosis. Autosomal dominant. Proband.

Noonan syndrome (NS), described in 1963 by Noonan and Ehmke¹, is characterized by short stature, dysmorphic craniofacial features, short or webbed neck, congenital heart disease, cryptorchidism in the males, skeletal anomalies and bleeding diathesis.

Its incidence is not well characterized, but is estimated at 1/1000 to 1/2500², which makes this disorder one of most common syndromes associated with congenital heart disease.

The majority of the cases are sporadic, but familial transmission has been well documented^{3,4}, consistent with an autosomal dominant pattern of inheritance. There is a preponderance of maternal transmission, which is attributed to the cryptorchidism in the males and consequent infertility.

The gene responsible for NS was mapped to the long arm of chromosome 12^{5,6}, but some families have no linkage to this region, indicating genetic heterogeneity in this disorder⁵.

We were interested in studying the clinical and genetic aspects of this syndrome due to its frequency and its wide phenotypic spectrum.

METHODS

We identified 31 patients affected by NS, derived from 26 families.

The ascertained proband and his first-degree relatives underwent a standardized questionnaire and physical examination. They were classified as affected by this disorder based on the clinical criteria described by van der Burgt et al.⁵, 1994. For those individuals classified as affected, a complete cardiac work-up, comprising EKG and echocardiogram, an abdominal ultrasound, column and wrist X-rays, ophthalmological examination, and coagu-

lation studies were performed. These latter consisted of a bleeding time (BT) by the Ivy method, a prothrombin time, an activated partial thromboplastin time, a thrombin time, a platelet count, and a coagulation assay for factor XI. If any of these studies yielded abnormal results, it was followed by a more extensive work-up. Karyotyping was done in all probands.

The patients were included in this study only after a written consent was obtained.

RESULTS

Thirty-one patients (18 males and 13 females) were included in this study. Their ages ranged from 3 months to 41 years (mean 12 years). Twelve probands (46%) were white, 10 were mulatto (38%), 3 were black (12%), and 1 was oriental (4%).

The mean age of the diagnosis in the probands was 6 years and 9 months.

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PRENATAL AND BIRTH DATA

Complications during pregnancy were observed in 11 gestations out of 30 (36%); one patient was adopted and there was no record of that period. The most frequent complications were premature contractions and vaginal bleeding (20%) and polyhydramnios (10%).

The majority of the patients were born at term (90%), by cesarean section (50%).

Birth weight was known in 27 babies born at term, with a mean of 3365 g for the females and 3445 g for the males. Length was known in 22 patients with a mean of 48.05 cm for the females and 48.5 cm for the males.

Some anomalies of NS, such as congenital heart defect and lymphedema were observed in 23% and 13% of the patients, respectively, in the neonatal period.

The stay in the nursery ranged from 1 to 30 days (mean 7 days).

CLINICAL FINDINGS (Table 1)

CARDIAC FINDINGS

Twenty patients (65%) had congenital heart defects (Table 2).

A superior deviation of the QRS axis was frequently found in the EKG (52%), not associated with a specific heart defect. Signs of right ventricular hypertrophy were present in 13 patients and left ventricular hypertrophy in 5.

HEMATOLOGICAL EVALUATION

Six patients showed a tendency to bleed, usually mild, characterized by hematomas, epistaxes, and a prolonged bleeding time.

The coagulation assays in these patients revealed anomalies in nine of them (Table 3).

Table 1 - Clinical findings in 31 patients with NS.

CLINICAL FINDINGS	Nº (%)
GENERAL	
Short stature	22/31 (71%)
Delayed bone age	12/22 (55%)
CRANIOFACIAL FEATURES	
Hypertelorism	16/30 (53%)
Ptosis	15/31 (48%)
Downslanting palpebral fissures	14/31 (45%)
Epicanthi	12/31 (39%)
Proptosis	4/30 (13%)
Fundus anomalies (eyes)	2/24 (8%)
Anterior segment anomalies (eyes)	3/12 (25%)
High arched palate	13/30 (43%)
Dental malocclusion	11/30 (37%)
Low-set ears	6/31 (19%)
Thick helix	8/31 (26%)
NECK	
Short or webbed neck	27/31 (87%)
Low posterior hair line	14/30 (47%)
THORAX	
<i>Pectus cariantum</i> and/or <i>excavatum</i>	16/31 (52%)
Cardiac anomalies	20/31 (65%)
ABDOMEN	
Hepatomegaly and/or splenomegaly	4/30 (13%)
Renal anomalies	2/30 (7%)
GENTALIA	
Cryptorchidism	7/18 (39%)
LIMBS	
Fetal pads in fingers and toes	21/30 (70%)
Wide and short nails	16/30 (53%)
<i>Cubitus valgus</i>	6/30 (20%)
COLUMN	
Vertebral anomalies	8/30 (27%)

Table 2 - Congenital heart defects observed in 31 patients with NS.

CARDIAC ANOMALIES	N (%)
• VPS and/or SVPS	10/23 (43%)
• VPS/ASD	3/23 (13%)
• VPS/MVP	1/23 (4%)
• VPS/HCM	3/23 (13%)
• HCM	4/23 (17%)
• VSD	1/23 (4%)
• Valvar aortic thickened	1/23 (4%)

VPS and/or SVPS = Valvar pulmonary stenosis/supravalvar pulmonary stenosis
 VPS/ASD = Valvar pulmonary stenosis/atrial septal defect
 VPS/MVP = Valvar pulmonary stenosis/mitral valve prolapse
 VPS/HCM = Valvar pulmonary stenosis/hypertrophic cardiomyopathy
 HCM = Hypertrophic cardiomyopathy
 VSD = Ventricular septal defect

GENETIC ASPECTS

We examined all first-degree relatives of the probands, personally (68%) or by photographs (32%), except for

two: one patient was adopted and the father of another child was not available. In the remaining 24 families, three (12.5%) had more than one affected person.

Table 3 - Hematological findings in 31 patients with NS.

HEMATOLOGICAL FINDINGS	Nº (%)
• Thrombocytopenia	2/10 (20%)
• Deficient platelet aggregation	1/10 (10%)
• Increased BT	1/10 (10%)
• Isolated FXI deficiency	1/10 (10%)
• Combined FXI deficiency	2/10 (20%)
• Isolated FXII deficiency	1/10 (10%)
• Combined FXII deficiency	1/10 (10%)
• Isolated FVIII deficiency	1/10 (10%)

Karyotype was normal in every proband.

DISCUSSION

NS is considered a frequent autosomal dominant disorder and its wide phenotypic spectrum led these patients to the attention of different clinicians, such as, endocrinologists, ophthalmologists, cardiologists, pediatricians, and hematologists. A better understanding of this heterogeneous syndrome allows a more accurate management of these patients.

Prenatal history is usually unremarkable, but sometimes polyhydramnios can be detected by fetal ultrasound. Sharland et al. (1992) ⁷ observed this anomaly in 43 of 130 pregnancies of fetuses affected by NS. It was also observed in our study, but in just 10% of pregnancies, probably due to the lack of ultrasound performed in the mothers of our patients.

Short stature is proportional and post-natal. These patients have a normal birth weight and length. Their growth decreases by three months of age and remains consistently below the 5th percentile. ⁸ The bone age has usually a two-year delay. In our study, 71% of our patients were three SD below the mean for height, and 55% of them showed a delayed bone age.

The most frequent craniofacial features observed in this study include hypertelorism, ptosis, downslanting of the palpebral fissures, high arched

palate and dental malocclusion. Lee et al. ⁹ (1992) found ocular anomalies in 95% of 58 patients with NS. The most common were hypertelorism, refractive errors, and anterior segment changes, especially prominent corneal nerves. This latter was diagnosed in three of our patients.

Cardiac abnormalities are common findings in NS, and they are the principal concern in this disorder. In our study, 65% of the patients had a congenital heart defect. This frequency is higher than the 50% estimated in this syndrome ¹⁰, and it is probably due to the preferential referral of our patients from a cardiac clinic.

The most frequent heart defect observed in our study was pulmonary stenosis (PS), present in 17 patients out of 20 with cardiac anomalies (85%). The prevalence of this heart defect in NS is well described in the literature ^{7,11}. It was an isolated finding in nine instances (53%) and when associated with another cardiac anomaly, the most common were atrial septal defect (ASD) and hypertrophic cardiomyopathy (HCM) (three cases each).

The second most common cardiac anomaly in NS is the HCM ⁷, also observed in our study. Unlike the non-syndromic HCM, in NS it is frequently associated with a heart defect, especially PS ¹². Here, four out of our five patients with HCM had associated pulmonary, aortic, or tricuspid valves involved.

Other congenital heart defects observed in our study were a ventri-

cular septal defect (VSD) and valvar aortic thickened in one patient each. Noonan ¹³ (1994) stated that virtually every type of heart defect has been described in this disorder.

The EKG showed a superior deviation of the QRS axis in 16 patients (80%), observed in cases with valvar pulmonary stenosis (VPS), supravalvar pulmonary stenosis (SVPS), HCM and VSD. Superior deviation of the QRS axis was not found in patients without cardiac anomalies. This finding is a helpful tool in the diagnosis of a NS patient ¹⁴.

The cardiac involvement in these patients is a frequent finding and has peculiarities when compared to non-syndromic heart anomalies. Also, these patients frequently have a chest deformity with *pectus carinatum* superiorly and *excavatum* inferiorly ¹⁵, which interferes with cardiac auscultation. Therefore, a complete cardiac work-up should be performed in every patient with a suspected diagnosis of NS, with EKG and echocardiogram.

Genital anomalies are frequent in the males, especially the cryptorchidism, considered responsible for the infertility observed in this group of patients. Cryptorchidism was observed in seven (39%) of our male patients and was bilateral in six of them.

Vertebral anomalies were discovered in 27% of our patients. They were not prominent clinically and were mainly spina bifida occulta, scoliosis, and kyphosis.

Hematological anomalies in NS involve platelets (number and function) and coagulation factors, especially factor XI deficiency ¹⁶. In our study, factor XI deficiency was also the most common, isolated or associated with other deficient factors, such as, factor XII, VIII, IX, and ristocetin cofactor. There was a poor correlation between the bleeding history and the coagulation assays findings ¹⁶. In our study, nine patients had anomalies in the

coagulation assays, but only two of them had a history of bleeding.

NS is both clinically and genetically complex. It is considered an autosomal dominant disorder with variable expression and incomplete penetrance. Molecular studies have confirmed that it is a heterogeneous disorder.

In our study, the majority of the cases were sporadic. Familial instances were observed in only three families. The characterization of familial and sporadic cases is essential for adequate genetic counseling, requiring a careful physical examination of all first-degree relatives¹⁷. The recurrence risk for the children of an affected person is 50%

and is less than 1% for normal parents of a child affected by this disorder.

The identification of a marker, by molecular techniques, would help in the diagnosis and genetic counseling of a NS patient. At present, diagnosis relies primarily on clinical observations.

RESUMO

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A síndrome de Noonan é uma patologia de múltiplas anomalias congênitas, herdada em um padrão de herança autossômico dominante. Estudamos 31 pacientes (18 do sexo mas-

culino e 13 do sexo feminino) afetados por essa síndrome quanto aos aspectos clínicos e genéticos. As características clínicas mais freqüentemente observadas foram a baixa estatura (71%); os dismorfismos craniofaciais, principalmente o hipertelorismo, a ptose e a inclinação ínfero-lateral das fendas palpebrais; o pescoço curto ou alado (87%); as anomalias cardíacas (65%) e a presença de coxins nas pontas dos

dedos das mãos e pés (70%). Após estudarmos os parentes de primeiro grau dos probandos, fizemos o diagnóstico da Síndrome de Noonan em um deles em três famílias. Portanto, a maioria dos nossos casos foram esporádicos.

DESCRITORES: Síndrome de Noonan. Estenose pulmonar valvar. Autossômica dominante. Probando.

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