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## ORIGINAL ARTICLE

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### HEMATOLOGICAL FINDINGS IN NOONAN SYNDROME

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BERTOLA DR et al. - Hematological findings in Noonan syndrome. *Rev. Hosp. Clín. Fac. Med. S. Paulo* 58(1):5-8, 2003.

**OBJECTIVE:** Noonan syndrome is a multiple congenital anomaly syndrome, and bleeding diathesis is considered part of the clinical findings. The purpose of this study was to determine the frequency of hemostatic abnormalities in a group of Noonan syndrome patients.

**METHOD:** We studied 30 patients with clinical diagnosis of Noonan syndrome regarding their hemostatic status consisting of bleeding time, prothrombin time, activated partial thromboplastin time and thrombin time tests, a platelet count, and a quantitative determination of factor XI.

**RESULTS:** An abnormal laboratory result was observed in 9 patients (30%). Although coagulation-factor deficiencies, especially factor XI deficiency, were the most common hematological findings, we also observed abnormalities of platelet count and function in our screening.

**CONCLUSIONS:** Hemostatic abnormalities are found with some frequency in Noonan syndrome patients (30% in our sample). Therefore, we emphasize the importance of a more extensive hematological investigation in these patients, especially prior to an invasive procedure, which is required with some frequency in this disorder.

**DESCRIPTORS:** Noonan syndrome. Hematological findings. Coagulation-factor XI deficiency.

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#### INTRODUCTION

Noonan syndrome (NS) is an autosomal dominant disorder comprising short stature, distinct craniofacial features, short or webbed neck, congenital heart disease, cryptorchidism in males, skeletal anomalies, and bleeding diathesis<sup>1</sup>.

The gene for NS was recently identified (PTPN11) in the long arm of chromosome 12. In a study of 22 patients affected by NS, 50% of them had a mutation in this specific gene, indicative of genetic heterogeneity in the disorder<sup>2</sup>.

Hematological findings in NS have

been described as early as the first reports of this condition, some of them with a life-threatening hemorrhage. Noonan (1968)<sup>3</sup> described an affected woman who had persistent thrombocytopenia. Several other descriptions of abnormal platelet count<sup>4,5</sup> and function<sup>6</sup> in this disorder followed. Deficiency of coagulation factors, especially factor XI<sup>7</sup>, is also considered part of the syndrome. Moreover, the asso-

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ciation of myeloproliferative disorder, mainly chronic myelomonocytic leukemia in childhood, and NS was not considered fortuitous<sup>8</sup>. The prevalence of reported hemostatic abnormalities in NS varies widely, ranging from 20%<sup>9</sup> to as high as 74%<sup>10</sup>. A study with a large cohort of 72 patients with NS by Sharland et al.<sup>11</sup> found a frequency of bleeding diathesis in 50%. Another study<sup>12</sup> found similar results (56%) in an evaluation of 18 patients. The most common abnormality in both studies was a factor XI deficiency.

Since NS has a variety of conditions that require surgical intervention,

a previous knowledge of the hemostatic status of these patients is essential for a better management of them.

We therefore screened 30 patients with a clinical diagnosis of NS for hemostatic abnormalities.

## METHODS

Patients with a possible diagnosis of NS were selected from our clinic. Twenty-six of these probands fulfilled the clinical criteria described by van der Burgt *et al.*<sup>13</sup> and were included in this study. Their first-degree relatives were also examined for a possible diagnosis of NS, and 5 of them were considered affected by this disorder. One of these relatives had died prior to this study, resulting in a total of 30 participant individuals. All the participating patients underwent a standardized questionnaire, including a detailed history of tendency to bleed, a complete physical examination, and a cardiac work-up, comprising an EKG and echocardiogram. A chromosome analysis was performed in all probands.

The hematological study consisted of a bleeding time (BT) test using the Ivy method, a prothrombin time (PT) test, an activated partial thromboplastin time (APTT) test, a thrombin time (TT) test, a platelet count, and a quantitative determination of factor XI. If any of these tests yielded abnormal results, it was followed by a more extensive work-up. Ingestion of medications that could interfere in the accuracy of the BT was avoided 2 weeks prior to the tests.

In this study, the normal values for the hematological tests are as follows: BT: up to 7 minutes in children until 10 years of age and 10 minutes above that age; Platelet count: 150000-400000/mm<sup>3</sup>; PT (R): 1-1.20 (patient PT/pool of controls PT); APTT (R): 0.76-1.16 (patient APTT/pool of controls APTT);

Coagulation factors VIIIc and IX: 60%-160%;

Coagulation factors XI, XII, and ristocetin cofactor: 50%-150%;

Von Willebrand factor: 60%-150%.

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

## RESULTS

Thirty patients (17 males and 13 females) were included in this study. Ages ranged from 3 months to 41 years (mean 12 years and 4 months). Twelve probands (46%) were white, 10 were mulatto (38%), 3 were black (12%), and 1 was oriental (4%).

The main clinical findings of the affected NS patients are summarized in Table 1.

**Table 1** - Clinical findings in 30 patients with Noonan syndrome.

CLINICAL FINDINGS	Nº (%)
Short stature	21/30 (70%)
Hypertelorism	16/30 (53%)
Ptosis	15/30 (50%)
Downslanting of the palpebral fissures	14/30 (47%)
High arched palate	13/30 (43%)
Dental malocclusion	11/30 (37%)
Short or webbed neck	26/30 (87%)
Cardiac anomaly	19/30 (64%)
Cryptorchidism	7/17 <sup>1</sup> (41%)

(1) Number of affected males

The most frequent cardiac anomaly observed in this group of patients was pulmonary stenosis (14 individuals), followed by hypertrophic cardiomyopathy in 3 patients. One individual had aortic stenosis, and another one had ventricular septal defect (VSD).

All probands had a normal karyotype.

Nine patients (30%) reported a tendency to bleed, characterized by easy bruising, mild nose bleeding, and prolonged local bleeding after a simple cut and dental extraction. A surgical

procedure had been performed in 15 patients (50%); some of them had more than one surgical procedure. These included primarily heart surgery and/or cardiac catheterization (6 patients), an orchidopexia (5) and an ENT surgery - tonsillectomy (3). The other surgical procedures included a herniorrhaphy and correction of the ptosis of the palpebral fissures and a craniectomy in one patient due to an ophthalmic artery aneurysm. Only 2 of the patients who had an open-heart surgery bled profusely, requiring blood transfusion. In one of them, the bleeding was attributed more to the procedure itself, since re-operation stopped the bleeding. In the other patient, we could not recover details of the procedure.

An abnormal hemostatic profile was obtained in 9 patients (30%) (Table 2). Coagulation-factor deficiencies were observed in 5 individuals (isolated factor XI deficiency in 1 patient and combined in another 2; isolated factor XII deficiency in 1 patient and combined in another patient, and factor VIII deficiency in 1 patient). One individual with a combined deficiency of factor XII and IX also had a platelet aggregation defect. Isolated low platelet count and an increasing BT were also found.

## DISCUSSION

NS is a well recognized genetic disorder, and although its incidence is not accurately known, it is estimated at 1/1000 to 1/2500<sup>14</sup>, making this disorder one of the most common syndromes associated with congenital heart disease.

Due to its broad phenotypic spectrum, NS caught the attention of different clinicians. Studies in these patients have been performed in attempt to better understand this heterogeneous disorder.

**Table 2** - Hematological findings in 30 patients with Noonan syndrome.

HEMATOLOGICAL FINDINGS	Nº (%)	BLEEDING TENDENCY	SURGICAL PROCEDURE
Low platelet count	1/30 (3%)	-	-
Increased BT	1/30 (3%)	Easy bruising	-
Increased APTT	1/30 (3%)	Easy bruising	-
Isolated factor XI deficiency	1/30 (3%)	-	Cardiac catheterization
Combined factor XI deficiency (VIII, IX, and ristocetin cofactor)	2/30 (7%)	P1. Prolonged bleeding (dental extraction)	P1. Cardiac surgery and cryptorchidism P2. Cryptorchidism and ptosis
Isolated factor XII deficiency	1/30 (3%)	-	Pyloric hypertrophy
Combined factor XII deficiency (IX) and deficient platelet aggregation w/ increased BT	1/30 (3%)	-	Umbilical hernia
Isolated factor VIII deficiency	1/30 (3%)	-	-
TOTAL	9/30 (30%)		

P1: patient 1; P2: patient 2

Several reports have emphasized the importance of the hematological aspects in NS, which include abnormal platelet count and function, as well as deficiency of various coagulation factors.

A bleeding diathesis has been considered part of NS, but its prevalence varies widely. The largest study<sup>11</sup> estimated its frequency in 50%. In our study, an abnormal laboratory screen was observed in 30% of our patients, which is a significant finding.

The most frequent hematological abnormality described in NS is a factor XI deficiency<sup>11</sup>. It is interesting to note that congenital deficiency of factor XI was described originally in persons of Jewish ethnicity, where the homozygous state could present a severe form of the disease<sup>7</sup>. In our study, factor XI deficiency was also the most common hematological finding (33%), and none of our patients were of Jewish ethnicity. The background of the patients studied had been emphasized in other papers, prompting the conclusion that there is an association between this hematological abnormality and NS.

It is known that there is a poor correlation between the tendency to bleed and the level of circulating factor XI<sup>12</sup>. In our study, only 1 patient who showed a mild deficiency of factor XI (41%), reported prolonged bleeding after a dental extraction, but had normal clotting in 2 surgical procedures (correction of his heart defect and cryptorchidism). The other 2 patients denied any bleeding tendency. One of them had a cardiac catheterization, and the other had correction of the cryptorchidism and palpebral ptosis without bleeding problems. Both also had a mild deficiency of factor XI (37% and 40%).

The factor XII deficiency (31% and 32%), observed in 2 of our patients, did not lead to a bleeding problem, as expected. One of these patients, who complained only of easy bruising, also had a factor IX (49%) deficiency, as well as a platelet function abnormality (hypoaggregation to ADP and adrenalin). He underwent a correction of an umbilical hernia without abnormal bleeding.

Another patient, who also complained of easy bruising, had a pro-

longed bleeding time and a platelet hypoaggregation to ristocetin. The rest of the tests were repeatedly normal, and a diagnosis of von Willebrand disease could not be established.

The multiplicity of unrelated types of bleeding abnormalities and the variability of their expression in NS are difficult to attribute to a single gene defect<sup>15</sup>. It is possible that the gene responsible for NS somehow interacts with the regulation of other genes involved in the coagulation pathway. This could explain the great variety of the hematological abnormalities seen in this disorder.

Although the hematological findings in NS are complex and the correlation between the clinical findings and the circulating levels of some coagulation factors is not always precise, all clinicians should be aware of this problem and be prompted to conduct a more extensive hematological work-up in these patients. Prior knowledge of a hemostatic abnormality in case of an invasive procedure could be assuring of a better management if bleeding occurs.

## RESUMO

BERTOLA DR e col. - Achados hematológicos na síndrome de Noonan. **Rev. Hosp. Clín. Fac. Med. S. Paulo** 58(1):5-8, 2003.

**OBJETIVO:** A síndrome de Noonan é uma patologia de múltiplas anomalias congênicas e, dentre os achados clínicos, a diátese hemorrágica está incluída. O propósito deste estudo é determinar a frequência de anormalidades hemostáticas nos pacientes afetados.

**MÉTODO:** Nós estudamos 30 pacientes afetados pela síndrome quan-

to aos aspectos hematológicos que consistiu de tempo de sangramento, tempo de protrombina, tempo de tromboplastina parcial ativada, tempo de trombina, contagem de plaquetas e dosagem do fator de coagulação XI.

**RESULTADOS:** Um resultado laboratorial anormal foi observado em 9 desses pacientes (30%). Apesar dos achados mais comuns terem sido as deficiências dos fatores de coagulação, especialmente do fator XI, também observamos anormalidades no número e na função plaquetária.

**CONCLUSÕES:** Anormalidades

hemostáticas são observadas com certa frequência em pacientes com síndrome de Noonan (30% em nossa amostra). Enfatizamos, portanto, a importância de uma investigação hematológica mais detalhada nesses pacientes, especialmente antes da realização de um procedimento invasivo, o qual é requerido com certa frequência na síndrome.

**DESCRITORES:** Síndrome de Noonan. Achados hematológicos. Deficiência do fator XI de coagulação.

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