Hemostatic Abnormalities in Noonan Syndrome

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KEY WORDS
Noonan syndrome, coagulation, platelets, bleeding score

ABBREVIATIONS
ADP—adenosine diphosphate
aPTT—activated partial thromboplastin time
PT—prothrombin time
TRAP—thrombin receptor activating peptide

Dr Artoni designed the study, performed bleeding scores, and drafted the manuscript; Drs Selicorni, Cianci, and Cerutti recruited patients and helped with data analysis; Dr Passamonti designed the study and performed bleeding score and helped with data analysis; Ms Lecchi performed coagulation and platelet secretion tests; Dr Bucciarelli: designed the study and was in charge of methodology issues; Dr Gianniello helped with data analysis; Dr Martinelli coordinated the study and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Noonan syndrome is associated with a bleeding diathesis and abnormal coagulation tests.

WHAT THIS STUDY ADDS: Bleeding diathesis in Noonan syndrome was evaluated by using a validated bleeding score. For the first time, platelet function was fully investigated, and a significant prevalence of platelet abnormalities likely to contribute to the bleeding diathesis was found.

abstract

BACKGROUND: A bleeding diathesis is a common feature of Noonan syndrome, and various coagulation abnormalities have been reported. Platelet function has never been carefully investigated.

METHODS: The degree of bleeding diathesis in a cohort of patients with Noonan syndrome was evaluated by a validated bleeding score and investigated with coagulation and platelet function tests. If ratios of prothrombin time and/or activated partial thromboplastin time were prolonged, the activity of clotting factors was measured. Individuals with no history of bleeding formed the control group.

RESULTS: The study population included 39 patients and 28 controls. Bleeding score was $\geq$2 (ie, suggestive of a moderate bleeding diathesis) in 15 patients (38.5%) and $\geq$4 (ie, suggestive of a severe bleeding diathesis) in 7 (17.9%). Abnormal coagulation and/or platelet function tests were found in 14 patients with bleeding score $\geq$2 (93.3%) but also in 21 (87.5%) of those with bleeding score $<$2. The prothrombin time and activated partial thromboplastin time were prolonged in 18 patients (46%) and partial deficiency of factor VII, alone or in combination with the deficiency of other vitamin K–dependent factors, was the most frequent coagulation abnormality. Moreover, platelet aggregation and secretion were reduced in 29 of 35 patients (82.9%, $P < .01$ for all aggregating agents).

CONCLUSIONS: Nearly 40% of patients with the Noonan syndrome had a bleeding diathesis and $>$90% of them had platelet function and/or coagulation abnormalities. Results of these tests should be taken into account in the management of bleeding or invasive procedures in these patients. *Pediatrics* 2014;133:e1299–e1304

Noonan syndrome is a relatively common autosomal dominant inherited disorder with a prevalence of 1 case per 1000 to 2500 individuals and a complex phenotype characterized by facial dysmorphia, short stature, chest deformity, and heart and genital defects.[1] Diagnosis is made on the combination of variably expressed clinical features, genetic analysis, and differential diagnosis with Turner syndrome, Costello syndrome, and other rarer congenital diseases. Molecular studies showed abnormalities of various proteins in the Ras-mitogen-activated protein kinase (RAS-MAPK) pathway,[2] caused in the majority of cases by *PTPN11* gene mutations. Mutations of *SOS1*, *KRAS*, *RAS1*, or other genes[3,4] are also reported. The management of patients with Noonan syndrome requires a multidisciplinary approach because malformations and complications involving various organs (particularly heart, kidney, and stomach) can be present at birth or develop during childhood. The prognosis is variable, with ~25% of the patients dying of heart failure in the first year.[2] Indeed, cardiac surgery is frequently performed in these patients. A bleeding diathesis is often reported in patients with Noonan syndrome, although its degree of severity is currently unknown because of the lack of standardized methods of evaluation. A heterogeneous group of abnormalities of blood coagulation has been reported in up to 60% of patients, in particular, a prolonged activated partial thromboplastin time (aPTT) due to mild deficiencies of coagulation factors of the intrinsic pathway, such as factors XI, FVIII, and FXII, alone[5,6] or in combination.[7,8] A reduction of high molecular weight multimers of von Willebrand factor, compatible with the acquired von Willebrand syndrome due to congenital cardiac defects,[9] was recently reported in 15 patients.[10] However, whether these mild abnormalities (recently reviewed in Briggs and Dickerman[11]) may be responsible for the bleeding symptoms in patients with Noonan syndrome has not been elucidated. Furthermore, platelet function has never been investigated in depth, and a paucity of data, limited to a series of 19 patients[12] or single case reports,[13,14] is available. Finally, a standardized evaluation of the degree and severity of the bleeding diathesis has never been attempted in patients with Noonan syndrome. Within this context, our case-control study was aimed at investigating a cohort of patients with Noonan syndrome to identify coagulation and platelet function abnormalities, to correlate them with the severity of bleeding as assessed by a validated bleeding score, and to explore the potential of therapeutic options to prevent or control bleeding.

METHODS

Patients

Thirty-nine patients with Noonan syndrome regularly followed at the Pediatric Unit and 28 healthy individuals of similar age referred to the presurgery outpatient clinic with no history of bleeding were investigated. Inflammatory conditions were also excluded because they can raise some coagulation factors and thus affect coagulation tests. The history of bleeding was assessed in patients and controls using a validated bleeding score[15]: briefly a trained hematologist (AA or SMP) collected data on the severity of bleeding symptoms in the mucosal tracts (nasal, oral, gastrointestinal), organs (skin, uterus, brain), and joints. For each symptom, a score from −1 to 4 was assigned, and the total score (ie, the bleeding score) was calculated (Table 1). The bleeding score was considered indicative of a mild bleeding diathesis when $\geq$2 and of a moderate/severe bleeding diathesis when $\geq$4.[16] The questionnaire was administered to the study participants or their parents as appropriate, and clinical records were reviewed. Before venipuncture, the use of antiplatelet drugs in the previous week was carefully checked, and in such cases, blood sampling was postponed for at least 10 days to avoid interference with platelet function tests. Informed consent for the study was obtained from patients and control subjects or their parents, if patients were aged <18 years. The study was approved by the hospital institutional review board.

Laboratory Methods

Blood was collected in Vacutainer tubes containing 3.8% of sodium citrate as anticoagulant using a 23/25-G needle after $\geq$8 hours fasting from an antecubital vein minimizing stasis. Complete blood count was performed in Vacutainer tubes anticoagulated with ethylenediaminetetraacetic acid. For coagulation tests, blood was centrifuged at 3800 $\times$ *g* for 15 minutes to obtain platelet-free plasma for prothrombin time (PT) and aPTT testing (Instrument Laboratory, Milan, Italy). If either the PT or aPTT alone was prolonged, FVII or FVIII, FIX, FXI, and FXII levels were measured, respectively. If only PT was prolonged FVII was measured, and if only aPTT was prolonged FVIII, FIX, FXI and FXII were measured. Normal coagulation factor activity level is set by our laboratory at $\geq$70%, with the exception of FVIII, which is normal >50%. For platelet function tests blood, was centrifuged for 15 minutes at 190 $\times$ *g* to obtain platelet-rich plasma. The remaining blood was further centrifuged at 1100 $\times$ *g* to obtain platelet-poor plasma. Platelet aggregation studies were performed on a Chrono-Log lumi aggregometer (Mascia Brunelli, Milan, Italy): 450 μL of platelet-rich plasma were mixed with 50 μL of lucipherase and gently stirred at 1000 rpm at 37°C. After 30 seconds, an agonist (adenosine diphosphate [ADP] final

TABLE 1 Grades of Bleeding Severity Used by Tosetto et al[15] to Calculate Bleeding Score

Symptom	Score					
	−1	0	1	2	3	4
Epistaxis	—	No or trivial (<5)	>5 or >10′	Consultation only	Packing or cauterization or antifibrinolytic	Blood transf or replacement therapy or desmopressin
Cutaneous	—	No or trivial (<1 cm)	>1 cm and no trauma	Consultation only		
Bleeding minor wounds	—	No or trivial (<5)	>5 or >5′	Consultation only	Surgical hemostasis	Blond transf or replacement therapy or desmopressin
Oral cavity	—	No	Referred at least one	Consultation Only	Surgical hemostasis or Antifibrinolytic	Blood transf or replacement therapy or desmopressin
GI bleeding	—	No	Associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia	Spontaneous	Surgical hemostasis, Blood transf, replacement therapy, desmopressin, antifibrinolytic	
Tooth extraction	No bleeding in ≥2 extraction	None performed or no bleeding in 1 extraction	Referred in <25% of all procedures	Referred in >25% of all procedures, no intervention	Resuturing or packing	Blood transf or replacement therapy or desmopressin
Surgery	No bleeding in ≥2 surgeries	None performed or no bleeding in 1 surgery	Referred in <25% of all surgeries	Referred in >25% of all procedures, no intervention	Surgical hemostasis or antifibrinolytic	Blood transf or replacement therapy or desmopressin
Menorrhagia	—	No	Consultation only	Antifibrinolytics; pill use	D & C, iron therapy	Blond transf or replacement therapy or desmopressin or hysterectomy
Postpartum hemorrhage	No bleeding in ≥2 deliveries	No deliveries or no bleeding in 1 delivery	Consultation only	D & C, iron therapy, antifibrinolytics	Blood transf or replacement therapy or desmopressin	Hysterectomy

D & C, dilation and curettage; transf, transfusion.

concentration 4 μM, collagen 2 μg/mL, U46619 0.5 μM or thrombin receptor activating peptide [TRAP], 10 μM) was added and the aggregation/release reaction was followed for 3 additional minutes. A standard curve using fixed dose of adenosine triphosphate, added to platelet-poor plasma, was used to quantify secretion (expressed in nM/10^8 platelets).[17]

Statistical Analysis

Continuous variables are presented as median and range, and categorical variables as count and percentage. Comparisons between groups were made with the Student's *t* test for continuous variables and the Fisher's exact test for categorical variables. $P < .05$ was chosen as the cutoff for statistical significance. All analyses were performed with the statistical software SPSS (release 20, IBM SPSS Statistics for Windows, IBM Corporation, Armonk, NY).

RESULTS

Bleeding Symptoms

The general characteristics of the study population are represented in Table 2.

Fifteen patients (38.5%) had a bleeding score ≥2, which was ≥4 in 7 of these patients (17.9%). Bleeding symptoms were generally mild, the most frequent being easy bruising and epistaxis in 46% of patients (Table 3). Twenty patients had undergone 33 surgical interventions, 5 of which (2 cryptorchidism

TABLE 2 General Characteristics of the Study Population

	Patients With NS (*n* = 39)	Controls (*n* = 28)
Male/female	19/20	20/8
Age at diagnosis (y), median (range)	6 (0–14)	NA
Age at blood sampling (y), median (range)	10 (1–28)	13 (3–30)
Bleeding score, median (range)	2 (0–7)	0 (0–3)
NS gene mutations, *n* (%)		
PTNPN11	18 (46.2)	—
HRAS	4 (10.3)	—
BRAF	3 (7.8)	—
KRAS	2 (0.5)	—
RAF1	2 (0.5)	—
MEK1	1 (0.3)	—
MEK2	1 (0.3)	—
SOS1	1 (0.3)	—
Not found	7 (17.9)	—

NA, not applicable; NS, Noonan syndrome.

corrections, 1 tonsillectomy, 1 pulmonary valve stenosis, 1 duodenal biopsy) in 5 patients were complicated by excessive bleeding that had required blood transfusion in 2 cases. Four of these 5 patients had a bleeding score ≥4 (the remaining patient had a bleeding score of 2), and all had coagulation and/or platelet function abnormalities. Among the remaining 15 patients who had surgeries with no bleeding complications the bleeding score was ≥4 in 1 case only and ≥2 in 4 other cases (33%); 13 (87%) had coagulation and/or platelet function abnormalities. Among the 19 patients who did not undergo surgery, 2 had a bleeding score ≥4, and 4 had a bleeding score ≥2. Only 2 of them (with bleeding score of 2 and 0, respectively) had normal coagulation and platelet function tests. Table 4 shows the relationship between the bleeding score and coagulation and/or platelet function abnormalities, also in relation to surgical intervention. Overall, coagulation and/or platelet function abnormalities were found in 35 of 39 patients (89.7%, 6 coagulation, 17 platelet function, and 12 both abnormalities).

Coagulation Tests

In 21 patients, PT and aPTT were normal, whereas in 18 patients and 4 controls (P = .008), 1 or both tests was prolonged (Table 5). All the patients with a prolonged PT and a normal aPTT had partial FVII deficiency, alone or in combination with other coagulation factor deficiencies. In 3 patients with FVII deficiency, the administration of a single sublingual vitamin K dose (5–10 mg) was followed by the normalization of both the PT and FVII. The aPTT was prolonged in 10 patients (3 of whom had also a prolonged PT) mainly due to FXII deficiency. Among controls, 1 had prolonged PT due to partial FVII deficiency, 2 had prolonged aPTT due to partial FXII deficiency, and 1 had both tests prolonged because of FX deficiency (38%). Fibrinogen activity was normal in all patients and controls.

TABLE 3 Bleeding Symptoms Reported by Patients With Noonan Syndrome

Type of Bleeding	*n* (%)
Easy bruising	11/39 (28.2)
Epistaxis	7/39 (17.9)
Gum bleeding	6/39 (15.4)
Postsurgical bleeding/total interventions	5/33 (15.2)
Bleeding from minor wounds	5/39 (12.8)

TABLE 4 Relationship Between the Bleeding Score and Coagulation and/or Platelet Function Abnormalities, According to Surgical Intervention

	Coagulation and/or Platelet Abnormalities	
	Yes (*n* = 35)	No (*n* = 4)
Bleeding score ≥2	14 (35.9)[a]	1 (2.6)[b]
Bleeding score <2	21 (53.8)[a]	3 (7.8)
Surgery yes, *n*	18	2
Bleeding score ≥2	9 (45)[a]	0
Bleeding score <2	9 (45)	2 (10)
Surgery no, *n*	17	2
Bleeding score ≥2	5 (26.3)	1 (5.3)[b]
Bleeding score <2	12 (63.2)[a]	1 (5.3)

Values are number (percentages).
[a] Platelet function tests not performed in 2 patients.
[b] Platelet function tests not performed in 1 patient.

Platelet Aggregation Tests

Platelet aggregation/secretion tests were performed in 35 patients and 28 controls. All had a normal platelet count (median 228 000 platelets/μL; range 132 000–350 000). Twenty-nine patients and 7 controls (P < .0001) had platelet aggregation or secretion to ≥1 aggregating agent lower than the fifth percentile of the values obtained in the control group (Table 5). The percentage of platelet aggregation was significantly lower in patients than controls with all the aggregating agents (P < .01 for all aggregating agents; Fig 1). Platelet secretion was also significantly lower in patients than controls, but only after stimuli such as collagen and U46619 (P < .01) and not with ADP or TRAP as aggregating agents (Fig 2). Overall, 35 patients and 11 controls

TABLE 5 Results of the Coagulation Tests, Type of Coagulation Factor Deficiency and Abnormal Platelet Function Tests in Patients and Controls

Coagulation and Platelet Function Tests	Patients With Noonan Syndrome	Controls
Abnormal PT and/or aPTT, *n* (%)	18 (46.2%)	4 (14.3)
Only PT prolonged, *n* (%)	8 (20.5)	1 (3.6)
Deficient factor, *n* (% of activity in each patient)[a]		
VII	5 (32, 36, 42, 50, 58)	1 (41)
VII+X	2 (28/61, 53/63)	
VII +X+V	1 (59/52/59)	
Only aPTT prolonged, *n* (%)	7 (17.9)	2 (7.1)
Deficient factor, *n* (% of activity in each patient)		
XII	3 (53, 57, 65)	2 (35;45)
XI	1 (65)	—
IX	1 (67)	—
VIII	1 (48)	—
None (lupus anticoagulant)	1 (–)	—
Prolonged PT and aPTT, *n* (%)	3 (7.7)	1 (3.6)
Deficient factor, *n* (% of activity in each patient)		
X	—	1 (38)
VII+X	1 (40/57)	—
VII+X+V	1 (59/52/59)	—
IX+X+V	1 (62/53/44)	—
Abnormal platelet function tests, *n* (%)	29 (82.9)[b]	7 (25)[c]
Coagulation or platelet function abnormalities, *n* (%)	35 (89.7)	11 (39.3)
Coagulation and platelet function abnormalities, *n* (%)	12 (34.3)	0

[a] For each coagulation factor, activity is normal for values ≥70%, but for factor VIII, it is normal for values ≥50%.
[b] Platelet function tests were performed in 35 patients and all controls.
[c] Platelet aggregation or secretion below the fifth percentile of the distribution of values among controls to ≥1 aggregating agent.

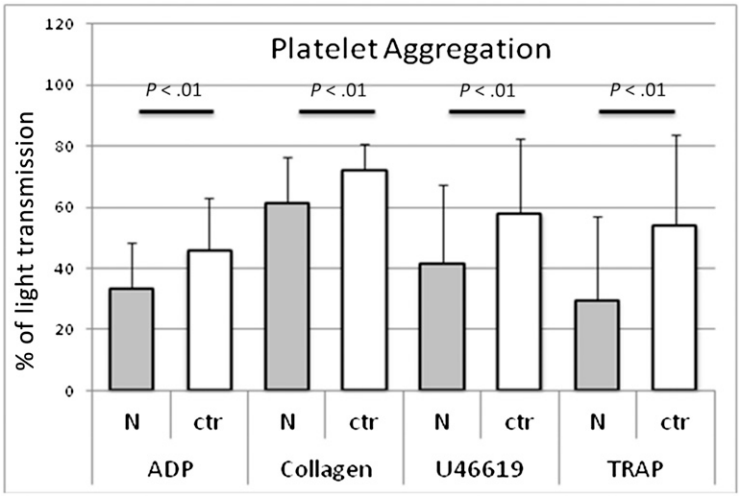

FIGURE 1
Percentage of platelet aggregation to ADP, collagen, U46619, or TRAP in patients with Noonan syndrome (N, solid bars) and controls (ctr, open bars). Vertical lines above bars indicate 1 SD.

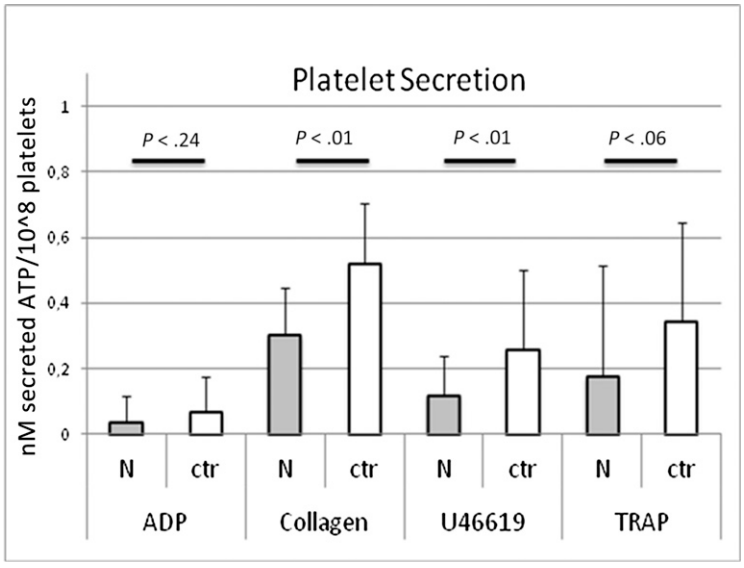

FIGURE 2
Mean platelet ATP secretion (nM/10^8 platelets) after aggregation with ADP, collagen, U46619, or TRAP in patients with the Noonan syndrome (N, solid bars) and controls (ctr, open bars). Vertical lines above bars indicate 1 SD.

($P < .0001$) had coagulation or platelet function abnormalities, whereas 12 patients and no controls ($P = .0001$) had both (Table 5).

DISCUSSION

In this case-control study, a cohort of patients with Noonan syndrome was extensively investigated to identify hemostatic abnormalities leading to a bleeding diathesis, which is a common feature of this syndrome. We found that bleeding symptoms, when analyzed through a validated questionnaire and a resulting bleeding score, were present in nearly half of the patients, being generally mild and mostly represented by cutaneous or mucosal bleeding. However, 5 patients reported excessive postsurgical bleeding, which required blood transfusion in a 2-year-old boy who underwent a pulmonary valve stenosis intervention and in a 5-year-old boy who developed a duodenal hematoma after endoscopic biopsy. Both patients had abnormal coagulation and/or platelet function tests.

In our patients, the prevalence of coagulation and/or platelet abnormalities was high not only in those with a bleeding diathesis but also in those without (93.7% vs 87.5%). In addition, bleeding episodes were not only related to surgical interventions (15.2%) but were also spontaneous in a relevant proportion of patients (31.6%). PT and/or aPTT were prolonged in ~50% of patients due to various coagulation factor deficiencies. The most frequent abnormality was deficiency of the vitamin K–dependent FVII, perhaps because of insufficient dietary intake or reduced intestinal adsorption of this vitamin.[1] The oral administration of vitamin K resulted in the normalization of both FVII levels and PT.

Coagulation factor deficiencies, found in 46% of patients, were always mild and thus unlikely to explain the increased risk of spontaneous bleeding. The latter was more likely associated with platelet function abnormalities and indeed were found in 83% of patients. The most severe platelet function abnormalities, low aggregation and secretion in response to collagen, were found in 34% and 43% of patients, respectively. It should be pointed out that platelet function tests were performed with concentrations of aggregating agents able to cause a strong and sustained platelet aggregation in normal adults. Patients with Noonan syndrome had reduced platelet aggregation with all the agonists tested, suggesting an association among Noonan syndrome, a platelet function defect, and the bleeding tendency of these patients.

Some of our findings deserve a critical discussion. The bleeding score was based on a validated questionnaire on patients with bleeding symptoms and

was less frequently abnormal than hemostasis tests. There are two possible reasons for this discrepancy. First, the questionnaire is sensitive to abnormalities of primary hemostasis (ie, platelet function) but not to those of secondary hemostasis (ie, coagulation). Second, it was previously validated[15] in an adult population to discriminate patients to be studied for primary hemostasis defects. Although these can be considered as limitations of the study, it should be pointed out that children have had a limited exposure to bleeding risk situations because of their relatively short life, and therefore it is likely that even low bleeding scores are able to detect a significant bleeding diathesis.[18] In addition, our data are in agreement with those stemming from a cohort of 79 adults with a bleeding diathesis and 21 controls in which platelet function abnormalities were identified by laboratory methods in only 50% of those with a high bleeding score.[19] Finally, in a large cohort of adults investigated in our center for a suspected abnormality of primary hemostasis, no correlation between platelet function abnormalities and the bleeding score was observed.[20]

CONCLUSIONS

Twenty percent of patients with the Noonan syndrome had a history of severe bleeding diathesis and another 20% of moderate bleeding diathesis. Bleeding episodes occurred not only during surgical interventions but also spontaneously. Laboratory investigation revealed coagulation and mainly platelet function abnormalities in 90% of patients. We recommend conducting coagulation and platelet function tests in patients with Noonan syndrome. In case of bleeding episodes or surgical interventions in patients with platelet function abnormalities, we recommend administration of vitamin K in patients with low levels of FVII and prolonged PT, general hemostatic agents such as tranexamic acid and desmopressin, and, in the most severe cases, platelet transfusion.

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