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Original Article

Evaluation of bleeding diathesis in patients with Noonan syndrome and comparison with thromboelastography (TEG) test results: A single-center experience

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ABSTRACT

Objective: Patients with Noonan syndrome (NS), who may need various surgical interventions throughout their lives, need to be evaluated carefully in the preoperative period due to the risk of bleeding diathesis. There is a limited number of studies evaluating bleeding diathesis in patients with NS. In this study, we aimed to determine the frequency of bleeding diathesis in patients with NS and to evaluate the place of thromboelastography (TEG) in determining the risk of bleeding.

Method: In our study, bleeding score and coagulation test results obtained from the files of 12 patients with NS were evaluated.

Results: The most frequently detected factor deficiency is vWF deficiency (41%), followed by platelet dysfunction (33%). Two cases with a bleeding score of 2 or above were detected, and in one of them, both platelet dysfunction (response to epinephrine in platelet aggregometer, 7%) and vWF deficiency (vWF Ag: 20%), and in the other case, mild Factor VII deficiency (17%) were detected. TEG results of nine patients were normal. TEG abnormality was detected in three patients and 2 of them had bleeding phenotype.

Conclusion: As a result, although laboratory examinations in patients with NS often yield values consistent with bleeding diathesis, bleeding event does not occur in most patients. We suggest that with the use of the TEG method, the risk of bleeding can be predicted and unnecessary treatments can be prevented.

Keywords: bleeding disorders, laboratory test abnormalities, Noonan syndrome, thromboelastography

INTRODUCTION

Noonan syndrome (NS) is a clinically and genetically heterogeneous disease that is frequently inherited as an autosomal dominant and rarely as an autosomal recessive. Its estimated prevalence is between 1/1000 and 1/2500.[1] The clinic of the disease may vary from mild to severe form.[2] Typical NS findings include facial findings, short stature, skeletal abnormalities, congenital heart defects, chest deformity, lymphatic dysplasia, cryptorchidism, developmental delay, and bleeding disorders.[3,4] *PTPN11* gene mutation, which causes activation of the RAS/mitogen-activated protein kinase (RAS-MAPK) pathway, is responsible for approximately 50% of patients.[5,6] In addition, *SOS1*, *RAF1*, *KRAS*, *MEK1*, *RIT1,* and *BRAF* gene mutations have also been associated with this RASopathy.[7,8]

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When NS was first described, its relationship with hematological disorders could not be clearly established.[9] It has been reported in some studies that there is an increase in the risk of bleeding disorders in the following years.[3,4] However, the frequency of bleeding diathesis varies significantly between studies, ranging from 20% to 92%.[4] Factor XI deficiency and platelet dysfunction are most frequently reported in NS.[3] Although factor deficiency was initially reported more frequently, platelet dysfunction was the most frequently detected hematological disorder, with a frequency of 83% in studies conducted in recent years.[10,11] Many patients with NS may be exposed to repeated surgical interventions in early childhood for cardiac pathologies, cryptorchidism, or lymphatic vessel abnormalities. Bleeding events have been reported to occur in 4.5-20% of these patients in the postoperative period.[12,13] Therefore, preoperative evaluation of hemostasis is crucial. On the other hand, although it is thought that normal findings in standard coagulation tests in these patients are not sufficient to exclude the risk of bleeding, no consensus has been established on the standard approach.[3] To our knowledge, thromboelastography (TEG) has not been used in the literature when determining the bleeding risk of NS cases. TEG is a very useful test for evaluating general hemostasis and predicting bleeding in cases of bleeding diseases. This study aimed to determine the frequency of bleeding diathesis in patients with NS and to evaluate the place of TEG in determining the risk of bleeding.

MATERIAL AND METHODS

Patients

We reviewed the file records of 12 patients who were referred to our pediatric hematology outpatient clinic with the diagnosis of Noonan syndrome between December 2010 and December 2020.

The diagnosis of NS is made clinically according to the scoring system developed by van der Burgt.[14] This scoring system is divided into two subgroups, major and minor, according to the severity of the clinical findings. These findings include i) typical facial findings, ii) cardiac anomalies (pulmonary stenosis or hypertrophic cardiomyopathy), iii) short stature, iv) chest wall anomalies, v) family history, and vi) other (mental retardation, cryptorchidism, lymphatic dysplasia). According to this scoring system, the diagnosis is made if there are one major or two minor findings in addition to the major facies findings. In addition, if there are two major or three minor findings in addition to the minor facies findings, NS should be taken into account. Moreover, all patients in the study had PTPN11 mutation detected by the Next Generating Sequencing or Sanger sequencing method.

The pediatric bleeding score developed by Bowman et al.[15] (epistaxis, cutaneous, bleeding after minor injury, intraoral bleeding, gastrointestinal bleeding, bleeding after tooth extraction and pediatric-specific bleeding [post-circumcision, umbilical bleeding, cephalic hematoma, venous bleeding and macroscopic hematuria], post-surgical bleeding, central nervous system bleeding, menometrorrhagia, muscle hematoma, and scoring related to hemarthrosis) results were noted. A minimum of -3 and a maximum of 48 points can be obtained in the Pediatric Bleeding Score. A total score of 2 or above was considered significant in terms of bleeding tendency.

Laboratory methods

From the patient's file records, complete blood count, peripheral smear findings, prothrombin time (PT), activated prothrombin time (aPTT), fibrinogen level, platelet function analyzer (PFA-100), thrombin time, Factor V- VII- VIII- IX- X- XI - XII-XIII level, von Willebrand factor antigen level (vWf: Ag), von Willebrand factor ristocetin cofactor activity (vWf: Rcof), platelet aggregometer and TEG results were obtained. PT and aPTT values were evaluated according to age-appropriate normal ranges.[16] The PFA-100 result was considered normal if it was between 85–165 seconds for the Collagen/Epinephrine cartridge and 71–118 seconds for the Collagen/ adenosine diphosphate (ADP) cartridge.[17]

vWF: Ag and vWF: Rcof values below 30% were defined as vWF deficiency. If these values were 30-50%, which was considered the gray zone, it was accepted as vWF deficiency in the presence of bleeding clinic.[18] Factor V-VII-VIII-IX-X-XI-XII-XIII level was defined as factor deficiency if it was below 50%.

Haemoscope thromboelastograph analyzer (Haemoscope, USA) was used for TEG analyses. TEG is an in vitro test that provides information about clot formation, maximum clot thickness, and fibrinolysis. The R-value represents the time until the first evidence of a clot is detected. This time refers to the time from the beginning of the test to the point where the clot strength reaches 2 mm amplitude. Prolongation of the R time is associated with clotting factor deficiency, the presence of inhibitors, or the use of anticoagulants. K value means clot formation time and indicates the time it takes for the clot to reach an amplitude of 20 mm. It is related to both thrombin activity and fibrin formation. The angle formed between the tangent line drawn from the curve departing from the horizontal

axis and the horizontal axis (α angle) shows the speed at which the clot reaches maximum amplitude (MA). MA is affected by platelets and fibrinogen levels.[19] All TEG studies were performed with the CFMS LEPU 8800 device. R time was considered normal as 2-8 minutes, K time as 1-3 minutes, α angle as 55-78 degrees, and MA as 51-69 mm.[19]

Informed consent was obtained from all patients and their parents. The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. This study was approved by the University of Bakırçay Ethics Committee (decision number: 803).

RESULTS

The average age of the 12 patients (6 girls, 6 boys) with NS included in the study is 6.4 years (range, 1.5-16 years). In 2 of the patients, the bleeding score was two or above. While platelet dysfunction (response to epinephrine in platelet aggregometer was 7%) and vWF deficiency (vWF Ag: 20%) were detected in one of them, mild Factor VII deficiency (17%) was detected in the other. PFA-100 values were high in six patients, and five of these cases had vWF factor deficiency or platelet dysfunction. Factor XI deficiency was not detected in any of the patients. Isolated type I vWF deficiency in 2 cases, both type I vWF deficiency and platelet dysfunction in 2 cases, both factor VII and type I vWF deficiency in 1 case, factor VII deficiency, factor X deficiency, and platelet dysfunction in 2 cases, isolated factor VII deficiency in 1 case, isolated platelet dysfunction in 1 case were detected. Bleeding diathesis was not detected in only 3 of 12 cases in terms of history and laboratory features. The most frequently detected factor deficiency was vWF deficiency (41%), followed by platelet dysfunction (33%). All factor deficiencies were mild factor deficiencies. Patient characteristics are shown in Table 1.

TEG results of nine patients were evaluated as normal. The first case (patient no:2) had a long K time and a decreased MA value. This patient with a high bleeding score had platelet dysfunction and vWF deficiency. The second case (patient no:4) with a high bleeding score had a prolonged R time and Factor VII deficiency. The third case (patient no: 7) had prolonged R time and vWF deficiency; however, the bleeding score of this patient was normal (Table 1).

Table 1. Bleeding score and laboratory results of the patients

Patient No	Bleeding Score	PFA-100	Platelet Count	PT	aPTT	Fibrinogen	Factor Levels	Platelet Aggregometer	Thromboelastogram
1	<2	col/epi:269-col/ADP:138	Normal	Normal	Normal	Normal	vWF Ag: %27	Normal	Normal
2	5	col/epi:219-col/ADP:106	Normal	Normal	Normal	Normal	vWF Ag: %20	Epinephrine response %7	Prolonged K-time, Decreased MA
3	<2	col/epi:171-col/ADP:98	Normal	Normal	Normal	Normal	Factor 7: %45	Normal	Normal
4	4	Normal	Normal	Normal	Normal	Normal	Factor 7: %17	Normal	Prolonged R-time
5	<2	Normal	Normal	Normal	Normal	Normal	Factor 7: %45 / vWF Ag: %3.6	ND	Normal
6	<2	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
7	<2	col/epi:237-col/ADP:96	Normal	Normal	Normal	ND	vWF Ag: %7	Epinephrine response %6.5 / ADP response %56	Prolonged R-time
8	<2	col/epi:276-col/ADP:117	Normal	Normal	Normal	Normal	Factor 7: %46 / Factor 10: %37.8	Epinephrine response %10	Normal
9	<2	Normal	Normal	Normal	Normal	Normal	Normal	Epinephrine response %14.7	Normal
10	<2	col/epi:188-col/ADP:116	Normal	Normal	Normal	Normal	Factor 8: %40 / vWF Ag: %44	ND	Normal
11	<2	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
12	<2	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal

ND: not done, PFA: platelet function analyzer, PT: prothrombin time, aPTT: activated partial thromboplastin time, vWF: von Willebrand factor, vWF Ag: von Willebrand factor antigen, ADP: Adenosine diphosphate

DISCUSSION

TEG was first described by Hellmut Hartert[20] in 1948, and its use in cardiac surgery and liver transplant surgery has become widespread over the years.[21] TEG is a very useful method to evaluate the entire coagulation process and predict the risk of bleeding. It is possible to quickly decide on treatment with the curve obtained in this method and to prevent unnecessary transfusions if TEG demonstrates the normal coagulation process in cases where abnormal results are detected in basic laboratory tests related to the coagulation process. To our knowledge, this is the largest study evaluating the usefulness of TEG in predicting bleeding in patients diagnosed with NS. In the study by Bruno et al.[22] a bleeding phenotype was identified in 5 of 12 NS cases evaluated for bleeding diathesis. Platelet dysfunction and at least one factor deficiency were detected in 4 out of 5 cases. In the same study, TEG results of 5 cases with bleeding phenotype and 4 cases without bleeding phenotype were reported as normal. Therefore, the authors suggested that it is not necessary to evaluate NS cases with TEG.[22] The 4 cases with bleeding diathesis in Bruno's study had platelet dysfunction, and the normal TEG in these patients may be since the standard activators in this test are not sensitive to platelet dysfunction (except Glanzman's thrombasthenia). In the study conducted by Barg et al., the bleeding status of 24 Noonan syndrome cases was evaluated with thrombin generation used to evaluate global hemostasis, and the parameters were found to be lower compared to the control group. However, no significant correlation was observed with the bleeding clinic.[23] In our study, TEG was found to be abnormal in 2 of the 2 cases with bleeding phenotype. However, in 1 case without bleeding phenotype, R time on TEG was prolonged. We showed that there were abnormalities in the TEG results of cases with high bleeding scores; however, the small number of patients we included made it difficult to generalize our results to NS patients. Studies involving a large patient population and TEG with platelet mapping (TEG-PM), which was developed to evaluate platelet functions in patients with NS, where platelet dysfunction is common, may be guiding.

In the study by Bertola et al.[24] abnormal laboratory findings related to coagulation were reported in 9 of 30 patients (30%). Factor deficiency was identified in five cases, thrombocytopenia in 1 case, and platelet dysfunction in 1 case. Factor XI deficiency was most commonly reported (3 in 9 cases), and mild deficiency was detected in those with factor XI deficiency.[24] In the study of Sharland et al.[25] it was reported that 65% of 72 NS cases had a history of bleeding, and 50% had factor deficiency (most commonly Factor XI deficiency). However, later studies reported that platelet dysfunction was more common in patients with NS.[4,23,26] Ruiz-Llobet et al.[26] reported platelet dysfunction in 15 of 22 children (68%) with NS. Moreover, it has also been reported that platelet transfusion was performed in 2 of 14 cases (one with blepharoplasty and the other with kidney biopsy) due to bleeding events during or after surgical intervention. In the study of Artoni et al.[4] it was found that 38.5% of the 39 patients with NS included had a bleeding score of 2 or more (approximately half of these cases had a bleeding score of 4 or more). In addition, factor deficiency or platelet function abnormality was reported to be detected in 93.7% of those with bleeding diathesis and 87.5% of those without bleeding diathesis.[4] In the same study, factor deficiency was identified in 46% of the patients (most commonly Factor VII deficiency), and platelet dysfunction was identified in 83%.[4] In the systematic review of Nugent et al.[3] a total of 428 NS patients from 31 studies were included, and it was reported that 43% of the patients had a bleeding history and 195 (46%) had a specific bleeding disorder. It has been reported that 78% of these patients have a single factor deficiency, and the most common deficiency is Factor XI (81 patients). In the current study, unlike the literature, vWF deficiency was the most common (41%), followed by platelet dysfunction (33%). This may be related to the small number of patients.

Our study has some limitations that should be acknowledged. This study is a single-center retrospective study, and this may have caused bias in case selection. Since mutations in the same gene were detected in all patients, genotype-phenotype correlation was not investigated. Additionally, the relatively small number of patients included made it difficult to draw clear conclusions about the results.

As a result, abnormalities in coagulation-related laboratory results were detected in 9 of 12 patients in this study. However, only two patients had a bleeding score of 2 or higher. Two of the patients with abnormal TEG results had a history of bleeding. NS patients, who require surgical intervention more frequently throughout their lives than the normal population, should be evaluated carefully in terms of bleeding risk. Although abnormalities compatible with bleeding diathesis are frequently detected in laboratory examinations in patients with NS, bleeding may not occur. TEG testing may be a useful test in predicting bleeding and preventing unnecessary treatments. Further studies are needed to standardize TEG, one of the preoperative tests, in these patients.

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Ethical approval

This study was approved by the Ethics Committee of Bakırçay University in İzmir, Turkey, in accordance with the Declaration of Helsinki. All of the children and/or their parents gave their written informed consent before the study (date/number: 21.12.2022/803).

Author contribution

Medical Practices: SOA, SG, YO, THK; Concept: SOA, THK; Design: SOA, NT, IOA, THK; Data Collection or Processing: SOA, ME; Analysis or Interpretation: SOA, SG, YO, THK; Literature Search: SOA; Writing: SOA. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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