Preoperative Detailed Coagulation Tests Are Required in Patients With Noonan Syndrome

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Purpose: Patients with Noonan syndrome often require surgery at young ages. They are at high risk of perioperative bleeding from coagulation defects that might not have been detected by routine screening. These risks are rarely described in the oral and maxillofacial surgery (OMS) literature. The aim of this study was to evaluate the perioperative bleeding risks associated with Noonan syndrome and to propose preoperative guidelines.

Materials and Methods: This report describes a retrospective case series of patients with Noonan syndrome who underwent OMS procedures during a continuous observational period (2013 through 2016) in the authors' center. Clinical data, blood screening test results, and perioperative bleeding were analyzed.

Results: Five patients (age, 4 to 20 yr) with Noonan syndrome who underwent OMS procedures were included in this study. One patient presented a spontaneous bleeding tendency (epistaxis requiring cauterization). Blood screening showed clotting defects in 3 patients. One patient presented abnormal perioperative bleeding owing to a mild defect in factor XI.

Conclusion: Patients with Noonan syndrome must be referred to a hematologist for specific preoperative investigations and for adapted perioperative management.
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Noonan syndrome (NS) was initially described by Jacqueline Noonan[1] in 1963 as the association of heart malformations, pulmonary valve stenosis, short stature, hypertelorism, ptosis, undescended testes, skeletal malformations, and mild cognitive impairment. NS is an autosomal dominant disorder due in 50% of cases to a mutation in the *PTPN11* gene, implicated in the RAS and mitogen-activated protein kinase pathway.[2] The prevalence of NS varies from 1 in 2,500 to 1 in 1,000.[3] This condition is the second most common cause of congenital syndromic heart disease.[4] Since its initial description, several additional organ dysfunctions have been reported in NS, including vision and hearing defects, abnormal skin pigmentation, delayed puberty, digestive disorders causing failure to thrive, genital and kidney

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malformations, and lymphatic and hematologic abnormalities.[5] Furthermore, patients with NS have an increased risk of developing solid tumors, such as multiple giant cell lesions, embryonal rhabdomyosarcoma, neuroblastoma, genital and cutaneous tumors, and blood cancers.[5] Thus, patients with NS often require surgery at young ages and have a high risk of presenting perioperative complications, mostly from heart malformations and clotting disorders.

Various blood coagulation abnormalities affecting primary (platelet function) and secondary (coagulation) hemostasis have been reported in NS.[6] More precisely, coagulation abnormalities affect nearly 60% of patients with NS and mostly consist of mild combined deficiencies of several coagulation factors (V, VII, VIII, IX, X, and XI), causing a prolonged prothrombin time (PT) with or without a prolonged activated partial thromboplastin time (aPTT).[6-10] Defects affecting the von Willebrandt factor (vWF) also have been described.[11,12] Some of these coagulation defects might not be detected by routine screening and cause severe peri- and postoperative bleeding.

However, patients with NS are likely to undergo oral and maxillofacial surgery (OMS) procedures with a high risk of bleeding. In fact, in addition to the increased risk of developing multiple giant cell lesions of the maxilla and mandible, patients with NS have specific facial features that might indicate orthognathic surgery, such as a high-arched palate with an open bite, reduced maxillary and mandibular sagittal and transversal dimensions, and an increased facial height that becomes more obvious with age.[13-16] Although bleeding tendency is a common sign in NS,[17] the risk of excessive bleeding in this syndrome is poorly described in the OMS literature. To date, only Sugar et al[18] in 1994 highlighted the risks of abundant and life-threatening bleeding in a 22-year-old man with an indication for a Le Fort I osteotomy and a genioplasty.

The purpose of the present study was to evaluate the perioperative bleeding risks associated with NS and to propose preoperative guidelines based on a retrospective assessment of the 5 patients with NS who underwent surgery in the authors' unit.

Materials and Methods

STUDY DESIGN

To address the research purpose, the authors designed and implemented a retrospective case series. The study population was composed of all patients with NS presenting to the authors' center for evaluation and management of oral and maxillofacial conditions during a continuous observational period from 2013 through 2016. To be included into the study sample, patients had to present with confirmed NS and to undergo at least 1 OMS procedure.

The study was conducted according to the recommendation of the local ethics committee.

STUDY VARIABLES, DATA COLLECTION METHODS, AND DATA ANALYSES

Clinical data, including demographic and morphologic data, were collected retrospectively using medical records. Spontaneous bleeding tendency and perioperative bleeding were quantified and determined with a bleeding risk score[19] (Table 1).

Results

REPORT OF CASES

Case 1

A 17-year-old boy was referred to the authors' center for the management of a maxillary retrusion, and the authors decided on a Le Fort I osteotomy. He had been diagnosed with NS at birth and had a mutation in the *PTPN11* gene. In addition to maxillary retrusion, he presented hypertelorism, supernumerary teeth, low ears, cardiac defects including interauricular and interventricular communications, and a hypertrophic cardiomyopathy. In addition, he presented cutaneous papilloma and delayed growth with low insulin-like growth factor-1 (IGF1) levels requiring treatment with growth hormones. At 7 years of age, he underwent tooth extractions and otoplasty. No bleeding issues were reported during these procedures. Since that surgical procedure, he presented with several minor spontaneous episodes of epistaxis that were cauterized. To prevent severe peri- and postoperative complications during the Le Fort I osteotomy, detailed preoperative blood investigations were performed for the screening of coagulation defects. The patient had no spontaneous bleeding tendency. PT was normal but aPTT was prolonged. No deficiency in factors VIII, IX, and XI was detected. Platelet function analyzer was prolonged without platelet function abnormalities (Table 1). vWF level was slightly lower than normal; this was related in part to blood group O. To prevent excessive bleeding, vWF was administrated preoperatively. Surgery was uneventful except for minor epistaxis or mucosal bleeding that was controlled by bipolar coagulation and sutures.

Case 2

A 20-year-old woman was referred to the authors' center for impacted third molar teeth extractions and lingual frenectomy. She had been diagnosed with NS at birth owing to cardiac malformations (pulmonary artery stenosis and interauricular communication) and facial features (hypertelorism and low ears). She had a mutation in the *PTPN11* gene. She later

Table 1. BLEEDING SCORES AND COAGULATION TEST RESULTS FOR CASES 1 TO 5

	Case 1	Case 2	Case 3	Case 4	Case 5
Bleeding score[19]	3	0	0	0	0
PT (%)	88	84	72	100	100
KCT ratio (0.7-1.19)	1.24	1.13	1.23	1.02	1.65
PFA ADP (62-100 seconds)	122	ND	ND	ND	ND
PFA adrenalin (82-150 seconds)	173	ND	ND	ND	ND
vWF activity (50-150%)	45	ND	ND	ND	Normal
vWF Ag (50-150%)	55	ND	ND	ND	Normal
Fibrinogen	Normal	Normal	Normal	Normal	Normal
Platelet count	Normal	Normal	Normal	Normal	Normal
Factor VIII	Normal	ND	Normal	ND	Normal
Factor IX	Normal	ND	Normal	ND	Normal
Factor XI (60-168%)	Normal	ND	Normal	ND	58

Note: The authors recommend not testing factor XII, because factor XII deficiency does not cause excessive bleeding.

Abbreviations: ADP, adenosine diphosphate; Ag, antigen; KCT, kaolin clotting time; ND, not determined; PFA, platelet function analyzer; PT, prothrombin time; vWF, von Willebrandt factor.

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presented growth retardation and evolutive scoliosis. No spontaneous bleeding was reported. PT and aPTT were within normal ranges (Table 1). Cardiac surgery, impacted third molar teeth extractions, and lingual frenectomy were performed without any abnormal peri- and postoperative bleeding.

Case 3

A 12-year-old boy presented with progressive deformation of the lower jaw associated with tooth displacements. He had been diagnosed with NS owing to delayed growth with low IGF1 levels associated with heart defects (interauricular communication and pulmonary artery stenosis). A mutation in the *SOS1* gene was detected. Dental panoramic imaging and craniofacial computed tomogram showed osteolytic lesions of the lower jaw (Fig 1). Biopsy examination disclosed the presence of bilateral giant cell lesions of the mandible. Curettage of the lesions associated with teeth extractions was indicated. No spontaneous bleeding was reported. Preoperative hematologic screening did not show any coagulation defects, except for a prolonged kaolin clotting time (KCT) that was probably linked to factor XII deficiency. Because this deficiency does not increase the risk for abnormal bleeding, factor XII level was not determined (Table 1). No excessive bleeding occurred before and after the procedure.

Case 4

A 4-year-old boy was referred to the authors' center for multiple decidual decayed teeth extractions. The diagnosis of NS was suspected at birth because of the presence of cardiac defects (interventricular communication and pulmonary artery stenosis), cryptorchidism, and typical facial features (hypertelorism, low implanted ears). Genetic studies are ongoing. He presented growth retardation treated with growth hormone. He underwent cardiac surgery at 18 months of age and tonsil adenoidectomy and amygdalectomy at 3 years. No spontaneous bleeding was reported. PT and aPTT were within normal ranges (Table 1). Teeth extractions (4 decidual second molars) were performed without abnormal bleeding.

Case 5

A 16-year-old boy was referred to the authors' center for the management of giant cell lesions of the maxilla and mandible. The diagnosis of NS was suspected in utero because of the presence of hydramnios and cardiac defects. At birth, typical craniofacial features of NS were noted (hypertelorism, ptosis, low implanted ears, and bifid uvula) in addition to undescended testes and pectus carinatum. A mutation in the *SOS1* gene was detected. At 2 months of age, he presented chylothorax owing to lymphatic malformations. He also presented feeding issues that required enteral feeding and delayed growth from low IGF1 levels. He later received testosterone supplementation because of delayed puberty. No spontaneous bleeding was reported.

The giant cell lesions, affecting the right maxilla and mandible bilaterally, were treated by intralesional injections of triamcinolone. The patient was later managed in another center for the extractions of multiple odontomas and of impacted maxillary third molars. The preoperative blood screening showed a slightly prolonged KCT. No additional coagulation tests were performed. Continuous and diffuse perioperative bleeding occurred during teeth extractions and

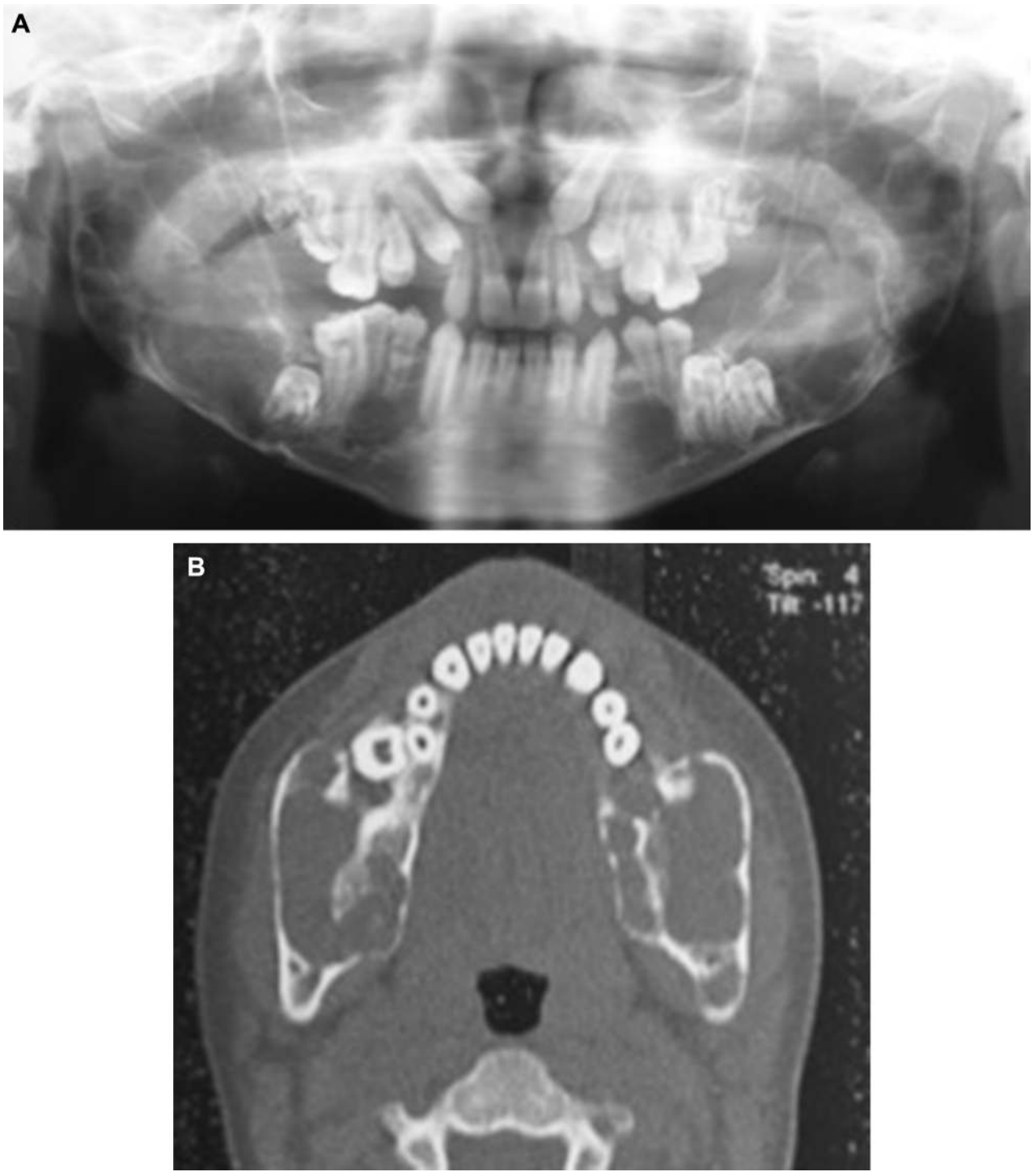

FIGURE 1. Case 3. Preoperative dental panoramic *A*, radiograph and *B*, computed tomogram showing medullar osteolysis and displacement of the outer and inner cortical layers by giant cell lesions of the mandible.

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the surgeon decided to interrupt the surgery and delay the extraction of the impacted maxillary third molars. The detailed postoperative blood screening showed a prolonged KCT and mild factor XI deficiency (58%; normal, 60 to 168%; Table 1).

Discussion

The aim of this study was to highlight the risk of perioperative bleeding in NS in a series of 5 patients who underwent OMS procedures. Although bleeding

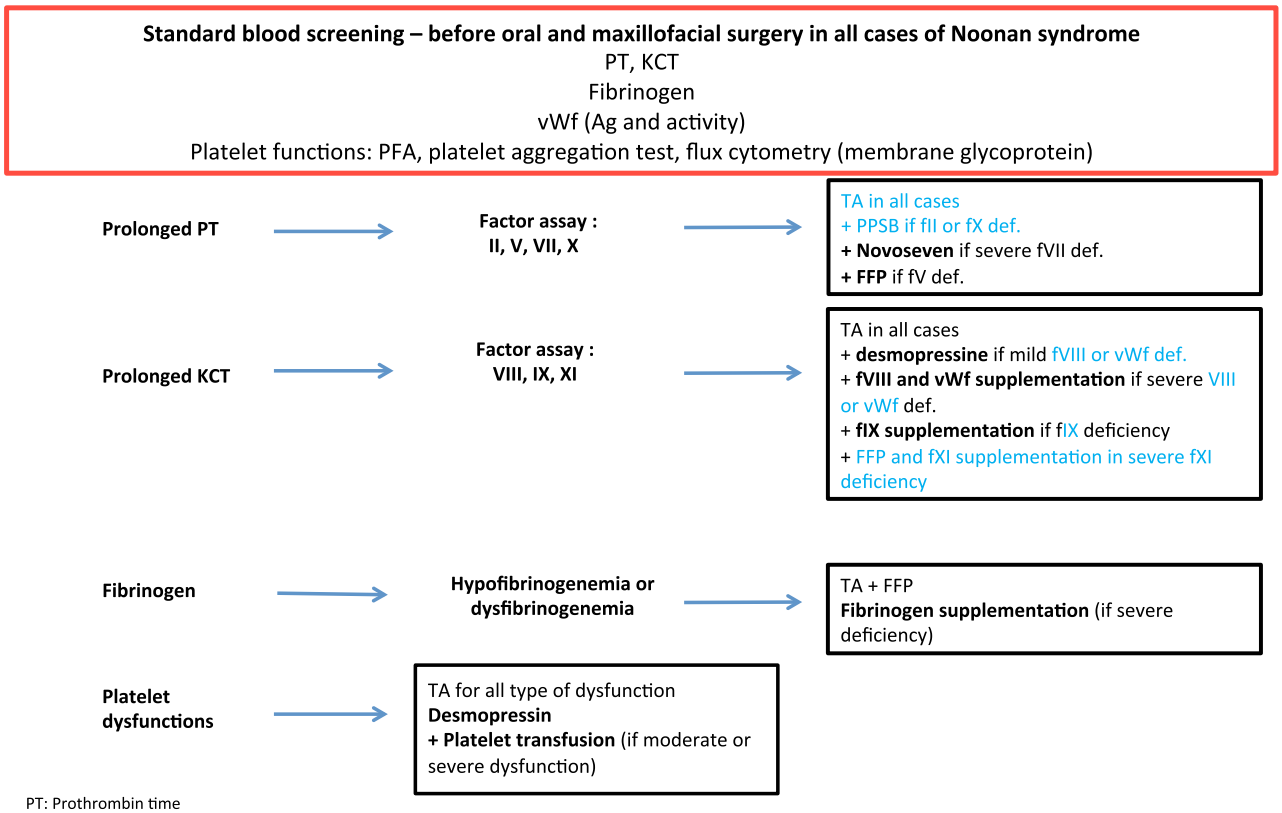

FIGURE 2. Preoperative guidelines for the management of coagulation defects and platelet abnormalities in Noonan syndrome. Ag, antigen; vWF, von Willebrandt factor.

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tendency was reported in only 1 patient, the coagulation blood screening showed abnormal values in 3 patients. Of these 3 patients (cases 1, 3, and 5), only 2 (cases 1 and 5) were at risk of perioperative bleeding.

In case 1, a mild vWF deficiency was detected. Although the deficiency in vWF was mild, vWF was administrated because of the presence of a hypertrophic cardiomyopathy that contraindicated the use of desmopressin. In fact, desmopressin can induce perioperative blood pressure variations, which can lead to congestive heart failure from restrictive diastolic dysfunction, which is a characteristic of hypertrophic cardiomyopathy.[20]

In case 5, the severe perioperative bleeding episode could have been linked to the mild factor XI deficiency. In fact, there is no correlation between the degree of factor XI deficiency and the risk for a severe bleeding episode.[21] Because factor XI is implicated in fibrinolysis,[21] the authors recommend the administration of tranexamic acid pre- and perioperatively. In case 5, surgery had to be interrupted because of abnormal perioperative bleeding.

The present report highlights that complete blood cell screening should be performed in all patients with NS before OMS procedures, even if no history of abnormal bleeding (spontaneous or during invasive procedures) has been reported.

Moreover, as reported by Sugar et al,[18] the authors found that even mild clotting factor deficiencies can lead to severe bleeding during surgical procedures, in particular in case of mild factor XI deficiency. In a recent case-and-control study, 40% of a series of 39 patients with NS had a severe or moderate bleeding tendency (Tosetto bleeding score, ≥ 4 or ≥ 2).[6,19] In the same series, spontaneous bleeding occurred in nearly half the patients with NS and was generally explained by functional platelet abnormalities, reported in 83% of patients, rather than by deficiencies in coagulation factors.[6] Interestingly, coagulation and platelet abnormalities were present in 87.5% of patients with NS

without a reported bleeding tendency,[6] showing that even if patients with NS do not report abnormal bleeding episodes, they are strongly predisposed to excessive perioperative bleeding. In addition, platelet dysfunctions are detected by standard laboratory methods in only 50% of patients with high bleeding scores.[6,22] Because functional platelet abnormalities might be responsible not only for spontaneous bleeding but also for excessive perioperative bleeding, Artoni et al[6] recommended performing coagulation and platelet function tests in all patients with NS. In accord with Artoni et al,[6] the authors recommend performing complete coagulation screening tests preoperatively in patients with NS and administering general hemostatic agents (tranexamic acid and desmopressin), vitamin K for factor VII deficiency and prolonged PT, and, in the most severe cases, platelet transfusion for bleeding episodes or surgical procedures. In addition, for mild vWF deficiency, the authors recommend desmopressin injections to increase levels of factor VIII and vWF.[23] For severe vWF deficiencies, administration of vWF is indicated.[23] The authors' specific preoperative guidelines for the management of coagulation defects and platelet function abnormalities in patients at risk of abnormal bleeding are presented in Figure 2. Because factor XII deficiency does not cause abnormal bleeding, the authors do not recommend testing this factor.

Although this report carries the intrinsic limitations of all retrospective case studies, the conclusions are in line with those of previous findings and should be considered in the management of this rare condition, for which the prospective validation of treatment protocols is unlikely because of its low prevalence.[6,10-12,17,18]

Because patients with NS can have platelet abnormalities and defects in coagulation factors and there is no strong correlation between coagulation abnormalities and the risk for excessive perioperative bleeding, all patients with NS should be informed that they have a risk of abnormal bleeding during maxillofacial surgical procedures. Although the investigations show no coagulation defects, there is still a potential bleeding risk, as for all surgical procedures. Thus, all patients with NS should be referred to a hematologist for specific preoperative investigations and for adapted perioperative management.

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References

1. Noonan JA: Hypertelorism with Turner phenotype. Am J Dis Child 116:373, 1968
2. Tartaglia M, Kalidas K, Shaw A, et al: PTPN11 mutations in Noonan syndrome: Molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. Am J Hum Genet 70:1555, 2002
3. Mendez HMM, Opitz JM, Reynolds JF: Noonan syndrome: A review. Am J Med Genet 21:493, 1985
4. Marino B, Digilio MC, Toscano A, et al: Congenital heart diseases in children with Noonan syndrome: An expanded cardiac spectrum with high prevalence of atrioventricular canal. J Pediatr 135:703, 1999
5. Roberts AE, Allanson JE, Tartaglia M, et al: Noonan syndrome. Lancet 381:333, 2013
6. Artoni A, Selicorni A, Passamonti SM, et al: Hemostatic abnormalities in Noonan syndrome. Pediatrics 133:e1299, 2014
7. Bertola DR, Carneiro JDA, D'Amico ÉA, et al: Genetics clinic unit of the Children's Institute, University of São Paulo: Hematological findings in Noonan syndrome. Rev Hosp Clin 58:5, 2003
8. de Haan M, vd Kamp JJ, Briët E, et al: Noonan syndrome: Partial factor XI deficiency. Am J Med Genet 29:277, 1988
9. Massarano AA, Wood A, Tait RC, et al: Noonan syndrome: Coagulation and clinical aspects. Acta Paediatr 85:1181, 2010
10. Sharland M: Coagulation-factor deficiencies and abnormal bleeding in Noonan's syndrome. Lancet 339:19, 1992
11. Gill JC, Wilson AD, Endres-Brooks J, et al: Loss of the largest von Willebrand factor multimers from the plasma of patients with congenital cardiac defects. Blood 67:758, 1986
12. Wiegand G, Hofbeck M, Zenker M, et al: Bleeding diathesis in Noonan syndrome: Is acquired von Willebrand syndrome the clue? Thromb Res 130:e251, 2012
13. Emral ME, Akcam MO: Noonan syndrome: A case report. J Oral Sci 51:301, 2009
14. Horowitz SL, Morishima A: Palatal abnormalities in the syndrome of gonadal dysgenesis and its variants and in Noonan's syndrome. Oral Surg Oral Med Oral Pathol 38:839, 1974
15. Okada M, Sasaki N, Kaihara Y, et al: Oral findings in Noonan syndrome: Report of a case. J Oral Sci 45:117, 2003
16. Allanson JE: Objective studies of the face of Noonan, cardiofacio-cutaneous, and Costello syndromes: A comparison of three disorders of the Ras/MAPK signaling pathway. Am J Med Genet A 170:2570, 2016
17. Witt DR, McGillivray BC, Allanson JE, et al: Bleeding diathesis in Noonan syndrome: A common association. Am J Med Genet 31: 305, 1988
18. Sugar AW, Ezsias A, Bloom AL, et al: Orthognathic surgery in a patient with Noonan's syndrome. J Oral Maxillofac Surg 52: 421, 1994
19. Tosetto A, Rodeghiero F, Castaman G, et al: A quantitative analysis of bleeding symptoms in type 1 von Willebrand disease: Results from a multicenter European study (MCMDM-1 VWD). J Thromb Haemost 4:766, 2006
20. Mckenzie IM, Weintraub RG: Cardiomyopathies, *in* Lake CL, Booker PD (eds): Pediatric Cardiac Anesthesia (ed 4). Philadelphia, PA, Lipincott Williams and Williams, 2005, pp 530–536
21. Lowe GC, Lordkipanidzé M, Watson SP, on behalf of the UK GAPP Study Group. Utility of the ISTH bleeding assessment tool in predicting platelet defects in participants with suspected inherited platelet function disorders. J Thromb Haemost 11: 1663, 2013
22. James P, Salomon O, Mikovic D, et al: Rare bleeding disorders—Bleeding assessment tools, laboratory aspects and phenotype and therapy of FXI deficiency. Haemophilia 20:71, 2014
23. Veyradier A, Fressinaud E, Goudemand J, et al: [Willebrand disease]. Hematologie 17:278, 2011 [in French]