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Bleeding Diathesis in Noonan Syndrome: A Common Association

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The Noonan syndrome (NS) is a multiple congenital anomalies (MCA) syndrome with well-known manifestations. Excessive bleeding has been described occasionally. We report on 19 patients with NS and a bleeding diathesis. Several different defects are identified in the coagulation and platelet systems occurring singly or in combination. Clinical expression is variable. It is concluded that bleeding diatheses occur in NS at a much higher frequency than previously suspected. Consideration is given to possible relationship to underlying metabolic defects which could explain the diverse nature of the bleeding diatheses and also play a role in the pathogenesis of NS. The variety of bleeding diatheses may also reflect heterogeneity within NS.

NS patients frequently undergo surgery with increased risk of bleeding. Appropriate evaluation and management is discussed. Evaluation of all NS patients and their families for bleeding disorders should provide important information about the frequency and type of bleeding diatheses which occur and perhaps help to clarify the etiology and pathogenesis of NS.

Key words: blood coagulation disorder, blood platelet disorder, Von Willebrand's disease, thrombocytopenia

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INTRODUCTION

The Noonan syndrome (NS) is a multiple congenital anomaly syndrome of short stature, webbed neck, facial anomalies, congenital heart defects and mental retardation that may occur on a sporadic basis or in a pattern consistent with autosomal dominant inheritance. Its pathogenesis is unknown and expression is variable. Etiologic heterogeneity seems likely. The NS has been the subject of a number of review articles [Allanson et al., 1985; Char et al., 1972; Collins and Turner, 1973; Duncan et al., 1981; Mendez and Opitz, 1985; Opitz, 1985].

A specific association between bleeding disorders and NS has been noted in a limited number of patients [Calvert, 1973; Char et al., 1972; Collins and Turner, 1973; de Haan et al., 1988; Festen, 1980; Hathaway, 1971; Humbert et al., 1970; Kitchens and Alexander, 1983; Komp, 1975]. These have most often been attributed to Factor XI deficiency and rarely to a platelet disorder. Our experience indicates that the frequency of a bleeding diathesis in NS is much higher than previously suggested and more diverse in nature.

Nineteen NS patients with clinical bleeding disorders and/or laboratory documentation of a bleeding diathesis are reported here. The bleeding abnormalities are of variable clinical severity and result from several different defects in the coagulation and platelet systems. In many cases the exact nature of the abnormality has not been identified.

The discussion considers the relationship of these diverse bleeding disorders to heterogeneity within NS, possible underlying metabolic disturbances and their role in morphogenesis, and clinical guidelines for patient management.

METHODS

Patients

All 19 patients were diagnosed as having NS on the basis of history and physical examination. Four patients (two pairs of mother and son) had a family history of NS and this was strongly suspected in an additional five patients. There were 12 males and 7 females. Age at time of initial evaluation for bleeding ranged from 1 year to 40 years. Coagulation studies were performed in order to evaluate clinical bleeding episodes or as part of a routine evaluation for NS. Eighteen patients had clinical evidence of a bleeding disorder based on physical examination or history but in many instances this was only elicited by specific questioning or examination. A bleeding disorder was unsuspected in one patient. Several patients appeared to have bleeding difficulties during early childhood which subsequently resolved. A family history of a bleeding disorder was elicited in seven patients and suspected in an additional patient. Patient 14 was reported previously during childhood by Humbert et al. [1970].

Bleeding Studies

Studies on all 19 patients included prothrombin time (PT), partial thromboplastin time (PTT), platelet count and bleeding time (BT) except for patients 2, 17 and 19 who did not have a BT. Recent aspirin exposure was excluded in all patients with BT determinations. Individual patients underwent additional specific testing as the clinical situation warranted and/or permitted. In several patients appropriate follow-up testing necessary to confirm an abnormality or to clarify the nature of the bleeding diathesis

was not possible because of unavailability or noncompliance. Bleeding studies were done in several different laboratories in which normal reference values varied. Interpretation of the results for each patient is based on the normal values used by the particular testing laboratory.

Additional Parameters

Patients were also evaluated for height, developmental delay/mental retardation, congenital heart defects, edema, hepatosplenomegaly, eye color and odor.

RESULTS

A summary of all the pertinent bleeding studies is provided in Table I. Additional parameters which were evaluated in each patient are listed in Table II. A proposed classification regarding bleeding disorder was made in nine patients: I. factor XI deficiency (two patients), II. Presumptive Von Willebrand disease (vWD) (three patients), III. thrombocytopenia (one patient), IV. concomitant platelet and coagulation defects (three patients). Formal classification was not possible for the remaining ten patients but they were grouped into three general categories: V. platelet function defects; vWD excluded (three patients), VI. platelet function defects; vWD not excluded (two patients), VII. miscellaneous (five patients).

Factor XI Deficiency

Patient 1. A 29-year-old man with a vague history of easy bruising had prolonged bleeding following head trauma in a motor vehicle accident. The PTT was prolonged (37 sec) and factor XI levels were greatly decreased on two separate measurements (18%, 20%). He was not of Ashkenazi Jewish descent.

Patient 2. A 7-year-old girl had a history of chronic epistaxis, easy bruising and clinical evidence of ecchymoses. The PTT was prolonged (42 sec) and factor XI levels were greatly decreased (22%). She was not of Ashkenazi Jewish descent.

Presumptive Von Willebrand Disease

Patient 3. A 1-year-old girl was found to have a significant ecchymosis at the site of a sphygmomanometer cuff. BT (9.5 min) and PTT (45 sec) were prolonged. Factor VIII antigen level was borderline (44%).

Patient 4. A 3-year-old boy had no history of a bleeding diathesis but underwent routine screening as part of the evaluation for NS. BT (20 min) and PTT (43 sec, 47 sec) were prolonged. Ristocetin cofactor levels were normal but Factor VIII antigen was not measured.

Patient 5. A 14-year-old boy was reported to have easy bruising during early childhood which became infrequent during adolescence. PTT was prolonged (35 sec) and Factor VIII Antigen (36%) and Ristocetin cofactor (39%) were decreased. A BT was normal (7.5 min).

Thrombocytopenia

Patient 6. A 14-year-old boy had a history of easy bruising. BT was prolonged ($>$ 15 min) and platelet counts showed thrombocytopenia on two occasions (53,000, 72,000). Reevaluation at 15 years showed mild thrombocytopenia (132,000), normal

TABLE I. Bleeding Studies

Patient	(sec.) PT	(sec.) PTT	Factor levels (%) VIII	IX	XI	VIII Ag	Ris Co	(min.) BT	×1000 Plate ct.	Plate agg.	Misc.
1	n.a.	37↑	n.a.	n.a.	18↓ 20↓	n.a.	n.a.	N	N	N	
2	12.7↑	42↑	83	59	22↓	80	156	n.a.	232	n.a.	
3	11	45↑	71	n.a.	77	44 ~	82	9.5↑	N	n.a.	
4	11	43.5↑ 47↑	73	N	84	n.a.	N	20↑	344	N	XII 37%↓
5	12.5	35.4↑	68	n.a.	72	36↓	39↓	7.5	25↓	n.a.	XII 90%
6	12	39	n.a.	57	62	n.a.	n.a.	>15↑	53↓ 72↓	n.a.	
7	13.7	35	81	103	27↓	82	n.a.	10↑ 16↑	168	ABN	
8	N	53↑	55	69	54↓	75	78	13.5↑ 17.5↑	194	ABN	XIII 90%
9	N	52.5↑	72	69	48↓	72	120	8.5	169	ABN	XIII 56%
10	N	N	70	78	78	n.a.	68	>20↑	223	ABN	
11	10.7	36↑ 34↑ 32	127	120	188	93	87	12↑	250	ABN	
12	13↑ 12	41↑ 37.4	n.a.	n.a.	63	112	95	11.5↑	204	n.a.	
13	12	32	n.a.	n.a.	n.a.	n.a.	n.a.	15↑	374	n.a.	
14	11.2	30.6	n.a.	n.a.	n.a.	n.a.	n.a.	*↑ 8.5	180	ABN N	fibrgen 363
15	11	40	70	62	72	66	100	11↑	172	N	XII 63% XIII N
16	14	46↑ N	60	67	>75	n.a.	n.a.	6	N	N	XII 35%
17	N	N	n.a.	n.a.	>75	n.a.	n.a.	n.a.	N	ABN	XII 43%
18	12	30	n.a.	n.a.	n.a.	n.a.	n.a.	4.5	253	n.a.	
19	12	30.5	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	255	n.a.	

Results are normal unless indicated; ↑ prolonged, ↓ decreased, VIII Ag = factor VIII antigen, Ris Co = ristocetin cofactor, plate ct. = platelet count, plate agg. = platelet aggregation, n.a. = not available, N = normal, ABN = abnormal, fibrgen = fibrinogen, *prolonged but value unavailable; ~ = borderline data.

platelet associated immunoglobulin and no evidence of an immune etiology. Red and white blood cell counts were normal.

Concomitant Coagulation and Platelet Defects

Patient 7. A 16-year-old boy had a history of prolonged bleeding, chronic epistaxis and easy bruising. He developed a large hematoma following cardiac catheterization. BT was prolonged on two occasions (10 min, 16 min) and platelet aggregation studies were abnormal to collagen, ADP and epinephrine. Factor XI level was significantly decreased (27%).

Patient 8. A 15-year-old boy was evaluated for a history of easy bruising. Tonsillectomy at age 5 years was complicated by bleeding requiring tracheostomy. Dental extractions at 11 years were uncomplicated. BT was prolonged on two occasions (13.5, 17.5 min) and platelet aggregation studies were abnormal to collagen, epinephrine and ADP. PTT was prolonged (53 sec) and Factor XI was mildly decreased (54%). Studies of von Willebrand factor (vWf) were normal.

Patient 9. The mother of patient 8 was a 40-year-old woman with a history of bleeding. BT was at the upper limits of normal (8.5 sec) but platelet aggregation was abnormal to collagen, epinephrine and ADP. PTT was prolonged (52.5 sec) and factor XI was mildly decreased (48%). vWf levels were normal.

Platelet Function Defect; vWd Excluded

Patient 10. An 8-year-old boy was noted to have easy bruising despite two uncomplicated heart operations. BT was prolonged (> 20 min on two occasions) and platelet aggregation was abnormal for collagen but normal for epinephrine, ADP and ristocetin. A mild hemolytic process appeared to be present based on elevated reticulocyte count and decreased haptoglobin but this was not evaluated further.

Patient 11. A 10-year-old boy had a history of easy bruising and frequent ecchymoses. BT was prolonged (12 min) and platelet aggregation was abnormal to collagen and epinephrine but normal to ADP suggesting a defect in cyclo-oxygenase similar to that seen in aspirin induced effects. PTT was unexplainably prolonged in two measurements (38, 34 sec) but normal in a third study (32 sec). vWD was ruled out.

Patient 12. A 6-year-old boy had a history of prolonged bleeding and frequent easy bruising. BT was prolonged (11.5). PTT (41 sec) was slightly prolonged at initial testing but repeat PTT was normal (37 sec). Platelet function studies were never performed. vWD was ruled out.

Platelet Function Defect; vWd Not Excluded

Patient 13. A 3-year-old boy had prolonged bleeding after circumcision and a 3 × 3 cm ecchymosis at initial evaluation. BT was prolonged (15 min). Platelet count was normal but studies for platelet function and vWd were not done.

Patient 14. A 6-year-old girl had chronic epistaxis and ecchymoses noted since age 5. At age 6 years she had a prolonged BT, decreased platelet aggregation to collagen, decreased adhesiveness to glass beads and a normal platelet count. At age 14 she had severe operative hemorrhage during a repair of pterygium colli. At age 20 years she had prolonged bleeding following dental extraction. Other surgical procedures, including an open liver biopsy, were uncomplicated. She had frequent infections with leukopenia noted on several occasions. Repeat studies at 21 years showed

Results are normal unless indicated, ↑ prolonged, ↓ decreased. VIII Ag - Factor VIII antigen, Rist Co - ristocetin cofactor, plate ct - platelet count, plate agg. = platelet aggregation, n a. = not available, N = normal, AHN = abnormal, fibrgen - fibrogen, *prolonged but value unavailable, ~ = borderline data

TABLE II. Additional Parameters

Patient	Age	Sex	Clinical bleed	F/H NS	F/H B	Ht. %	CHD	MR	Edema	HS	Odor	Eye
1	29y	M	+	?	+	10	PVD	–	–	+	–	blue
2	7y	F	+	–	+	25	PS HOC?	+	+	–	+	blue-green
3	1y	F	+	?	–	3	HOC ASD TVD MVD	+	+	+	+	blue
4	3y	M	–	?	–	5	PVD	+	–	–	–	blue
5	14y	M	+	–	–	<3	ASD	+	? BW>97%	–	–	green
6	14y	M	+	–	–	3	PVD	+	–	+ liver	–	brown
7	16y	M	+	?	–	25	PVD	+	? BW>97%	–	–	brown
8	15y	M	+	+	+	<10	MVP	–	n.a.	–	–	blue
9	40y	F	+	+	+	<10	MVD	–	n.a.	–	–	blue
10	8y	M	+	–	–	<3	PVD ASD	–	–	+ spleen	–	n.a.

	[illegible]	[illegible]	+	+	+	<10	MVD	–	n.a.	–	–	blue
10	8y	M	+	–	–	<3	[illegible]VD ASD	–	–	+ spleen	–	n.a.
11	10y	M	+	?	–	<3	–	L.D.	+	–	–	green
12	6y	M	+	–	–	<3	PVD HOC	+	–	+	+	blue
13	3y	M	+	–	–	10	PS	+	? BW>97%	–	?	blue
14	21y	F	+	–	+	90	MVP	L.D.	+	+	+	blue
15	6y	M	+	–	+	10	innocent murmur	–	? BW>97%	+	–	brown
16	19y	M	+	+	+	10	PVD	–	–	–	–	green
17	39y	F	+	+	+	5	PVD	–	–	–	–	green
18	20y	F	+	–	–	<3	PVD MVD MVP	+	? BW>97%	–	–	brown
19	16y	F	+	–	–	<3	PVD MVD	L.D.	–	+	?	green

F/H (NS,B)=family history (Noonan syndrome, bleeding), CHD=congenital heart disease, MR=mental retardation, HS=hepatosplenomegaly, ?=possible but not confirmed, PVD=pulmonary valve dysplasia, TVD=tricuspid valve dysplasia, MVD=mitral valve dysplasia, PS=pulmonic stenosis, HOC=hypertrophic obstructive cardiomyopathy, ASD=atrial septal defect, L.D.=learning disability, MVP=mitral valve prolapse, BW=birth weight.

borderline normal BT (8.5 min), normal platelet count (180,000) and normal aggregation to collagen, ADP, epinephrine and ristocetin.

Miscellaneous

Patient 15. A 6-year-old boy had a history of prolonged bleeding following circumcision and a scrotal hematoma after orchidopexy. BT was prolonged (11 min) but platelet count and aggregation studies to collagen, ADP and epinephrine were all normal.

Patient 16. A 10-year-old boy had a history of easy bruising. PTT was prolonged (46 sec) but on repeat at 19 years was reported as normal. BT was normal. Platelet function and vWd studies were never performed.

Patient 17. The mother of patient 16 was a 39-year-old woman with a history of prolonged bleeding, menorrhagia and operative bleeding. PTT and Factor XI were normal but platelet aggregation studies were abnormal to collagen, ADP and epinephrine. Studies for vWd and BT were never done.

Patient 18. A 20-year-old woman had a history of chronic bruising and epistaxis until approximately 15 years old. Screening bleeding studies were normal.

Patient 19. A 16-year-old girl had a history of gum bleeding and two large ecchymoses at the time of initial evaluation. Screening bleeding studies were normal but BT was not done.

Additional Studies

Chromosomes. Eighteen patients had normal chromosomes. Patient 9 did not have a chromosome analysis.

Congenital heart defects. CHD was documented in 17/19 patients. Normal evaluations and/or innocent murmurs were found in the remaining two patients. The most common lesion was pulmonary valve dysplasia which occurred in 12 patients either as an isolated malformation or in the presence of additional lesions.

Mental retardation. MR and/or developmental delay was present in nine patients. Learning disabilities were present in three other patients and one other had "immature" behavior.

Lymphedema. Congenital lymphedema was documented in four patients and strongly suspected in five additional patients because of the presence of high birth weight (> 97th centile) and pterygium colli.

Hepatosplenomegaly. This was identified in five patients. Apparently isolated splenomegaly was found in two patients.

Eye color. Twelve patients had striking light blue or green iris color typically seen in many NS patients. Three patients had deep blue color and three patients had light brown pigmentation.

Odor. An unusually pungent odor of urine and sweat was noted by the parents of five patients. One of these (patient 11) was previously reported to have trimethylaminuria [Humbert et al., 1970] and another patient was suspected to have this based upon description and dietary association but was not adequately evaluated. The other three patients were not evaluated for the odor.

Growth. Five patients had height below the 5th centile and an additional nine patients had height below the 10th centile. One patient had above-average height.

Family history. A family history of NS was present in patients 8/9 and 16/17 (mother and son) and considered a possibility in patients 1, 3, 4, 7, and 11 based on

physical examination and/or review of family photographs. A positive family history for a bleeding diathesis was present in seven patients but for most patients reported here, bleeding studies were not performed in relatives. Patient 1 gave a history of easy bruising in his maternal aunt and maternal grandfather. The mother of patient 2 had bruising as a child. Her current evaluation showed a prolonged BT (10.5 min), borderline Factor VIII antigen but normal PT, PTT, Factor VIIIc, Factor XI, ristocetin cofactor, platelet count and platelet aggregation studies suggestive of a mild vWD. Unfortunately, her daughter did not have a BT done. The mother of patient 12 had prolonged bleeding postpartum and with dental extractions. Patients 16 and 17 had a history of a bleeding diathesis and NS but inadequate studies were done to document a similarity of the bleeding disorder in the two. The maternal grandfather was diagnosed as having vWD. Overall, evidence for a family history positive for both NS and a bleeding diathesis was present in only two families (patients 8/9 and 16/17) and was suspected in an additional patient (no. 1).

LITERATURE REVIEW

de Haan et al. [1988] studied twelve patients with NS and found partial Factor XI deficiency in three of them. Two of these had a history of clinical bleeding. Two other patients with clinical bleeding problems had normal Factor XI levels.

Kitchens et al. [1983] reported on four patients with NS and partial deficiency of factor XI. All had prolonged PTT but no other coagulation studies were reported. Surgery complicated by hemorrhage occurred in all of the patients although this was attributed to factor XI deficiency in only two of them. The authors noted that most cases of factor XI deficiency occur in Ashkenazi Jews and none of the NS patients descended from this population. Factor XI assays and clinical bleeding episodes do not correlate consistently. However, homozygotes with levels $< 15\%$ may have more severe bleeding than heterozygotes with levels $> 15\%$.

Festen [1980] reported on four patients with NS who had post-operative hemorrhage following orchidopexy. One of the patients had a prolonged BT and abnormal platelet aggregation. Platelet counts and "other coagulation factors" were normal. One of the other patients had a prolonged BT but repeat studies were normal. The other two remaining patients had normal coagulation studies.

Komp [1975] studied "Car" factor, a defect in thromboplastin generation named for the family in which it was first identified. Two children with NS and this coagulation abnormality were reported. In addition, both patients had normal PTT and abnormal platelet aggregation in the presence of a normal BT. Specific factor XI assays were not done.

Humbert et al. [1970] originally reported our patient 11 when she was 6-years-old. Studies indicated a prolonged BT, decreased platelet aggregation to collagen, decreased platelet adhesiveness to glass beads and a normal platelet count.

Calvert [1973] reported on a 19-year-old man with NS and similar platelet findings. He had a long history of easy bruising since childhood and had post-operative hemorrhage following orchidopexy and tonsillectomy and prolonged bleeding after hand trauma. He had an abnormal euglobin-clot lysis time, decreased platelet adhesion to glass and "no other abnormality noted in a full investigation of bleeding and clotting."

Hathaway [1971] reported on a 14-year-old girl with "Turner phenotype," valvular pulmonic stenosis and normal chromosomes (his case no. 16). She had frequent ecchymoses and occasional epistaxis. Bleeding time was prolonged (> 15 min) and platelet aggregation, adhesion and release were abnormal. Platelet count and PTT were normal.

Char et al. [1972] reported on a 30-year-old man with NS and thrombocytopenia (platelet count 60,000). Bone marrow aspiration showed megakaryocytopenia. Hematocrit was elevated due to cyanotic congenital heart disease and WBC and PTT were normal. Clinical bleeding problems were not reported.

Noonan [1968] reported on a 16-year-old girl with persistent thrombocytopenia.

In a review of NS, Collins et al. [1973] reported on a 5-year-old girl with recurrent severe viral infections and amegakaryocytic thrombocytopenia. Her birth weight was > 97th centile.

Cremers and ter Haar [1974] reported a patient with prolonged BT and PTT and deficiency of Factor VIII.

Feldman et al. [1976] reported on a 5 1/2-year-old girl with "Turner phenotype" and normal chromosomes. She had congenital lymphedema of hands and feet. Recurrent and severe infections occurred during childhood. Anemia was present until age 5. Bone marrow biopsy at 4 years showed decreased erythroid and myeloid precursors and normal numbers of megakaryocytes. Repeat studies at 5 1/2 years showed significant improvement but still abnormal levels.

Krishnan et al. [1978] reported on a 13-year-old girl with "Turner phenotype" and normal chromosomes with congenital hypoplastic anemia noted at age 2 months. Thrombocytopenia and leukopenia only occurred after therapy for acute myelocytic anemia at age 13 years.

DISCUSSION

Our 19 patients and the literature reports indicate an association between bleeding diatheses and NS beyond what could be expected by coincidence. The incidence is difficult to assess from these studies because undoubtedly there is biased ascertainment of NS patients with bleeding problems and failure to study NS patients without bleeding. The inherent difficulties in achieving accurate laboratory evaluation of bleeding disorders compounds the problem. Also, a number of the patients had incomplete evaluations. However, from our experience it is estimated that some type of bleeding abnormality occurs in as many as 1/3 of all NS patients. As documented earlier, these occur as several different types of bleeding diatheses. Furthermore, there is variable expression ranging from severe surgical hemorrhage to clinically mild but detectable bruising to a relatively mild bleeding history and even to abnormalities limited to laboratory tests with no obvious clinical expression. Some patients show a tendency to "outgrow" their bleeding problem, i.e. the frequency and severity lessens with advancing age, especially after childhood. This was also described in two patients reported by de Haan et al. [1988]. This parallels other frequent observations in NS such as resolution of congenital lymphedema and some forms of congenital heart defects and evolution of the overall phenotype with advancing age [Allanson et al., 1985].

The distinction made between the various types of bleeding diatheses in NS as set forth in the Results section is, in some cases, arbitrary and perhaps a consequence of incomplete evaluation. For example, patient 12 has the same laboratory abnormalities that were found in patient 11 but he did not undergo platelet function testing. It

is very possible that if this were done the patients would have demonstrated identical results and permitted a more accurate classification. However, it is clear that abnormalities in factor XI, vWd factor, platelet function and platelet number occur singly or in combination in the group of patients as a whole.

Patients with an apparently complex bleeding diathesis as in patient 11, with a platelet function defect and prolonged PTT, or patient 7 with a platelet function defect and factor XI deficiency, are difficult to explain on the basis of a single defect in the coagulation system. Patients with acyantoic congenital heart defects (particularly valvular lesions) may have prolonged BTs either associated with platelet aggregation defects [Buerling-Harbury and Galvan, 1978] or acquired vWd [Gill et al., 1986]. However, the association of isolated coagulation factor deficiencies (e.g. factor XI) is rarely seen in these patients. Interestingly, this association was inconsistent among the patients in this report, as many of the patients without valvular disease had the types of bleeding abnormalities which are associated with valvular disease and patients with valvular disease often had other types of bleeding abnormalities.

As discussed earlier, in most cases there is no evidence for a family history of NS or a bleeding diathesis. However, family studies are lacking in most of the cases. Only five patients have direct evidence for or suggestion of cosegregation of NS and the bleeding diathesis. However, it is impossible to draw conclusions from this in light of the variable expression of both NS and bleeding diatheses and the lack of adequate family investigations.

No correlation can be made between the presence or particular type of bleeding diathesis and the various parameters listed in Table II. The various abnormalities occur with reasonable frequency as expected for NS.

Speculation about the basic defect present in some of these bleeding diatheses and a possible relationship to metabolic disturbances or cell surface interactions can be made. This might explain how seemingly unrelated bleeding diatheses can occur in the NS population and within individual patients on the basis of a single defect.

For example, the patients with a pungent odor or documented trimethylaminuria might have their origin in an inborn error of metabolism. Higgins et al. [1972] studied patient 14 and determined that her decreased ability to oxidize trimethylamine to trimethylamine-oxide was due to a higher Km for the microsomal mixed function oxidase responsible for this reaction. The authors also suggested the possibility of a common mechanism between this and the hematologic manifestations.

The patients previously described with "Car" factor deficiency [Komp, 1975] have a pattern of platelet aggregation defects mimicking aspirin-induced effects. This would point to an abnormality in prostaglandin synthesis, possibly at the level of cyclo-oxygenase mediated conversion of arachidonic acid to cyclic endoperoxides. This is precisely the type of defect suggested in patient 11 and possibly patient 7. Defects in prostaglandin synthesis or action could conceivably create far-reaching effects beyond platelet function, including morphogenesis. For example, alteration of embryonic/fetal cardiac blood flow has been shown to be one factor in producing some types of congenital heart defects, including some of those found in NS [Clark, 1984].

Reynolds et al. [1986] presented six patients with some NS-like manifestations and strikingly "coarse features." Bleeding problems were not mentioned. Extensive metabolic studies were normal. They suggested the name cardio-facio-cutaneous (CFC) syndrome to distinguish these patients from NS. Screening these patients for bleeding disorders would be most interesting in light of their phenotypic overlap with NS.

Pickering et al. [1981] have provided concrete evidence for a bridge between bleeding disorders and malformation syndromes by demonstrating a high prevalence of mitral valve prolapse in patients with vWD. They hypothesize that this association represents an underlying mesenchymal dysplasia. This might explain the association of bleeding and congenital heart defects in NS, in addition to some of the other frequent findings such as myopathic appearance and ligamentous laxity.

Factor XI deficiency is rare in the non-Ashkenazi population. It is also one of the coagulation proteins which has not been mapped on the human genome. Heterozygotes have clinical bleeding episodes and can be identified in the laboratory. The unusual but repeated occurrence of factor XI deficiency in some NS patients suggests that the two conditions are not coincidental and may be cosegregating. Therefore, linkage studies and DNA analysis of these families might provide a key to understanding the basic defect in NS and a means of diagnosing affected individuals.

Many patients with NS undergo one or more operations including herniorraphy, orchidopexy, open heart surgery, cardiac catheterization, dental extraction and revisions of ptosis, pterygium colli and lymphatic vessel anomalies. A bleeding diathesis increases the risk for intraoperative or postoperative hemorrhage. It appears that in general this is not severe, but individual cases have had serious complications. Physicians involved in the care of patients with NS should be aware of this association and pay particular attention to historical and clinical evidence of abnormal bleeding. Any patient with NS should undergo adequate screening for a bleeding diathesis at an early age and certainly preoperatively. An appropriate evaluation should include PT, PTT, BT and platelet count. If any abnormalities appear on this initial screen subsequent testing should include the appropriate specialized evaluations including platelet function tests, vWd factors and individual coagulation factor levels including factor XI. It is also prudent for these patients to avoid the use of aspirin or aspirin-containing products.

Identification of a bleeding diathesis in a patient with the provisional diagnosis of NS can also be a diagnostic aid since bleeding disorders are not frequently associated with those conditions included in the differential diagnosis of NS. Identification and evaluation of these patients, including family studies, will enable a better assessment of the scope and frequency of bleeding disorders in NS. Hopefully, this will help to elucidate the mechanisms underlying both problems.

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