Glanzmann's thrombasthenia with mild von Willebrand's disease

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Abstract

A Saudi Arabian family is reported in which Glanzmann's thrombasthenia and von Willebrand's disease occurred simultaneously. The daughter presented with menorrhagia and gave a history of gastrointestinal bleeding and a strong family history of bleeding disorder. Full haematological investigations were performed on the proband, parents, and siblings, including complete blood count, bleeding time, prothrombin time, partial thromboplastin time, factor VIII:C, von Willebrand factor, ristocetin cofactor, platelet aggregometry, platelet glycoprotein Ib and IIb/IIIa and platelet antigen PLT-1 (Coulter Clone). The proband had Glanzmann's thrombasthenia, both parents had mild von Willebrand's disease and were carriers of Glanzmann's thrombasthenia. Three symptomatic brothers had both Glanzmann's thrombasthenia and von Willebrand's disease; two asymptomatic brothers had von Willebrand's disease only and one had completely normal results. Those family members with both diseases were more severely affected than those with just one disease.

In areas where consanguineous marriage is common, such as Saudi Arabia, multiple haemostatic abnormalities may occur, and investigation should not stop with the discovery of a single abnormality. The increased clinical severity of bleeding, including haemarthroses, in those patients having both congenital defects emphasises the importance of von Willebrand factor in glycoprotein Ib-mediated platelet adhesion.

(J Clin Pathol 1993;46:1134-1136)

Willebrand's disease is the commonest and most heterogeneous congenital haemostatic disorder, with variable severity, and arising from quantitative or qualitative deficiency of the adhesive glycoprotein, von Willebrand factor.

Case report and family history

A 14 year old girl was referred with a history of severe menorrhagia at menarche, requiring multiple blood transfusions. She had also required transfusion for gastrointestinal bleeding when she was 8 years old. She gave a history of bleeding after dental extraction, not severe enough to require blood transfusion. When first seen she was iron deficient, but not bleeding, having received hormonal treatment at the referring hospital to suppress menstruation.

The patient's parents are first cousins and have six sons and one daughter (the proband). The father, aged 43, had never experienced any bleeding abnormality but two of his brothers had died of severe bleeding after circumcision and another brother and a sister died of "oral bleeding" in childhood. The mother, aged 32, had heavy menstrual periods and experienced spontaneous bruises on the legs. When 15 years old, she had prolonged bleeding after tooth extraction, but no blood transfusion was required. She gave a history of prolonged postpartum haemorrhage when she delivered her daughter. The rest of her deliveries had been normal. She had no family history to suggest a familial bleeding diathesis. Three of the patient's brothers were symptomatic, all with spontaneous bruising, and two had haemarthroses of the knees and ankles. All had required blood transfusion during bleeding episodes, mainly epistaxis. The other three brothers were apparently normal.

Methods

Duplicate bleeding times were performed on separate occasions on all the family members using the Ivy method. Venous blood was obtained for duplicate haematological investigation, including complete count (CBC), prothrombin time (PT), and partial thromboplastin time (PTT) performed by standard methods. F VIII:C was assayed by a one stage technique using Universal Coagulation Reference Plasma (UCR) as a normal control (coefficient of variation (CV) 5.2%). Von Willebrand antigen (vWF:Ag) was measured

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Accepted for publication
1 June 1993

Glanzmann's thrombasthenia is a rare congenital disorder of platelet function associated with a prolonged bleeding time, a normal platelet count, abnormal clot retraction and absent macroscopic platelet aggregation in response to adenosine 5'-diphosphate and other platelet agonists.^{1,2} This has been reported as relatively common in four populations—namely, French gypsies, Iraqi Jews, Indian people and Jordanian Arabs,³ probably as a consequence of consanguineous marriage increasing the incidence of autosomal recessive traits and thereby the likelihood of symptomatic homozygous subjects. Von

Table 1 Haemostatic studies

Family members	Age (years)	Bleeding (2-10 m) *	PTT (26-38 s) *	FVIII:C (0.5-2 µ/ml) *	VWF:Ag (0.5-1 µ/ml) *	RiCoF (0.5-1 µ/ml) *	Platelet PLT-1	Platelet Gp Ib	Platelet Gp IIb/IIIa complex	Clot retraction	Diagnosis
Propositus	14	>15	32	2.10	0.81	1.07					Type I Glanzmann's thrombasthenia
		>15	33	1.68	0.75	1.11	1%	73%	Absent	Absent	
		>15	30	1.63	0.74	1.31					
Father	43	4.5	29	0.93	0.63	0.44					Von Willebrand's disease
		6	28	1.39	0.73	1.31			39%	ND	GT carrier
		5.5	28	1.34	0.49	0.62	101%	118%			Von Willebrand's disease
Mother	32	14.5	27	0.70	0.37	0.34					GT carrier
		6.5	31	0.97	0.40	1.10			47%	ND	Von Willebrand's disease
		7	30	1.01	0.40	0.53	99%	89%			GT carrier
Brother (1)	13	5	37	0.74	0.25	0.75	ND	ND	ND	ND	Von Willebrand's disease
		>15	34	0.81	0.45	0.23					
Brother (2)	19	>15	35	1.50	0.49	1.18					Type I Glanzmann's thrombasthenia and von Willebrand's disease
		>15	33	1.03	0.33	0.55	5%	55%	5%	Absent	
Brother (3)	8	>15	38	1.46	0.52	1.07	1%	85%	Absent	Absent	Type I Glanzmann's thrombasthenia and von Willebrand's disease
		14	34	0.71	0.43	0.53					
Brother (4)	7	8	32	1.81	0.75	1.46	ND	ND	ND	ND	Normal
		5	32	1.00	0.62	1.53					
Brother (5)	6	11	34	2.28	0.65	1.39	ND	ND	ND	ND	Von Willebrand's disease
		5.5	33	0.63	0.42	0.83					
Brother (6)	3	>15	33	1.81	0.48	1.05			11%		Type II Glanzmann's thrombasthenia and von Willebrand's disease. Possibly BSS heterozygote
		>15	30	1.81	0.36	0.71	8%	24%		Reduced	

*Normal range.

by Laurell Rocket immunoelectrophoresis⁴ with UCR as a normal control (CV 7.12%), and an abnormal control from Biodata was also used. Ristocetin cofactor (RiCoF) was measured using lyophilised platelets,⁵ UCR being the normal control (CV 5.58%), with the abnormal control being from Biodata. Platelet aggregometry of platelet rich plasma (PRP)⁶ was performed using adenosine diphosphate (ADP) 1 µmol/ml and 2 µmol/ml, arachidonic acid 2.5 µg/ml, collagen 2 mg/ml and 4 mg/ml, and ristocetin 1 mg/ml and 1.5 mg/ml. The platelet antigen PLT-1 (Coulter Clone) and glycoproteins Ib and IIb/IIIa complex were studied by flow cytometry (EPICS, Coulter).

Results

A summary of the haemostatic investigations is given in tables 1 and 2. The propositus and brothers (2) and (3) have type I Glanzmann's thrombasthenia. Brother (6) seems to have a less severe form, type II, and in addition to have reduced glycoprotein Ib, but blood platelet morphology was normal, and his

platelets responded to ristocetin (1.5 mg/ml) in a manner similar to that of his siblings. No other family member had reduced glycoprotein Ib concentrations. Pending extended family studies, therefore, it cannot be excluded that the brother (6) is a Bernard-Soulier heterozygote in addition to the other inherited anomalies.

Discussion

The occurrence of both Glanzmann's thrombasthenia and von Willebrand's disease in a single family in which the parents are first cousins indicates that both parents carry the thrombasthenia gene. Four of their seven children have this disease, and in addition they both carry an abnormal von Willebrand's gene which is mild in expression and has been transmitted to some of their sons. Being carriers for both diseases has allowed the expression of either disease in some offspring or the simultaneous expression of both in others, reflecting the increased chance of coinheritance of rare disorders in populations where consanguineous marriage

Table 2 Platelet aggregation studies

Aggregating agents	ADP (µmol/ml)		Collagen (µg/ml)		Arachidonic acid (mg/ml)	Ristocetin (mg/ml)	
Dose	1	2	2	4	2.5	1	1.5
Propositus	Absent	Absent	Absent	Absent	Absent	Normal	Normal
Father	Absent	Absent	Absent	Absent	Absent	Normal	Normal
Mother	Normal	Normal	Normal	Normal	Normal	Normal	Normal
	Absent	Primary wave	Normal	Normal	Normal	Normal	Normal
Brother (1)	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Brother (2)	Absent	Absent	Absent	Absent	Absent	Present*	Present*
Brother (3)	Absent	Absent	Absent	Absent	Absent	Present*	Present*
Brother (4)	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Brother (5)	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Brother (6)	Absent	Absent	Absent	Absent	Absent	Present*	Present*

*Abnormal wave with the phenomenon of aggregation and disaggregation.

is an accepted custom, as in Saudi Arabia. We have found no similar published description of such an occurrence.

Sporadic cases of Glanzmann's thrombasthenia have been reported from all over the world, but the disease seems to be relatively common in four populations—namely, French gypsies, Iraqi Jews, Indian people and Jordanian people. Therefore, although Glanzmann's thrombasthenia is typically a rare disorder, it can be almost as common as haemophilia and von Willebrand's disease in regions where consanguinity is common.

Many thrombasthenic women were initially diagnosed because of severe bleeding at menarche.² The female propositus in this family had gastrointestinal bleeding when she was 8 years old, but she was not investigated fully until she had menorrhagia at menarche. The prevalence of haemarthrosis in this family is high, two of the brothers experiencing joint pain and swelling: both have Glanzmann's thrombasthenia type I and mild von Willebrand's disease. The third brother, affected by both diseases (with type II thrombasthenia), has not yet developed joint pathology at age 3. The propositus was the only member who has thrombasthenia type I alone and did not give any history of joint swelling or pain. Therefore, we conclude that members expressing both diseases, thrombasthenia type I and mild von Willebrand's disease, are more severely affected than those who have one disease.

Von Willebrand factor is important as an adhesion molecule in the mechanism of platelet aggregation through its interaction with glycoprotein IIb/IIIa complex, independently of fibrinogen.⁷ It is also involved in progressive adhesion of platelets to sub-endothelium at high shear rate through its binding to glycoprotein IIb/IIIa—also independently of fibrinogen.⁸ The platelets of patients with severe Glanzmann's thrombasthenia may form a monolayer on subendothelial tissue in a perfusion system.⁹ Von Willebrand factor mediates initial platelet adhesion to subendothelium through interaction with glycoprotein Ib.¹⁰ In this kindred with Glanzmann's thrombasthenia the character and severity of the clinical haemostatic defect was apparently much more severe in those patients with severely reduced glycoprotein IIb/IIIa and von Willebrand's disease of mild degree. This confirms the critical role of von Willebrand factor in the mediation of platelet adhesion via the glycoprotein Ib mechanism.

Assays of platelet glycoproteins Ib and IIb/IIIa are considered useful not only in diagnosing Glanzmann's thrombasthenia and

Bernard-Soulier syndrome, but also in detecting the carrier states of these disorders. We found that PLT-1 antigen, a platelet-megakaryocyte antigen of undetermined molecular weight, was severely reduced in the patients with Glanzmann's thrombasthenia of both types, but was expressed in normal quantities in those with the carrier state. This observation implies a structural dependence on the presence of at least some glycoprotein IIb/IIIa.

Pending further investigations, it is premature to draw finer conclusions from the reduced glycoprotein Ib concentration in brother (6). Studies of the extended family will be required to confirm the possibility of the Bernard-Soulier gene also being present in this kindred.

There were no cases of double inheritance of the von Willebrand's gene, with consequent severe disease, in this family. The mother has not reported any miscarriages, but regularly has heavy menstrual periods, and it is possible that a severely affected fetus may not be viable.

Our experience with this family underlines the importance of careful studies in patients in Saudi Arabia, and their relatives, to exclude unusual combinations of congenital haemostatic disorders, which might require specially designed approaches to management.

We are grateful to Dr El-Hadi M Abbas for referring the index case, to Mrs Fatmata Dawo for laboratory assistance, and to Ms Janet Lontoc and Ms MC Musngi for typing the manuscript.

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