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CONGENITAL QUALITATIVE PLATELET DISORDERS IN CHILDREN*

(Report on 60 patients)

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Prolonged bleeding time with a normal platelet count in a patient who has bleeding diathesis generally suggests some abnormality of the platelet function. Since the introduction of new methods in 1962 for studying platelet aggregation[1], an increasing number of patients with bleeding diathesis due to functional platelet disorders have been reported. Although congenital bleeding disorders in the pediatric age group are mostly due to plasma coagulation factor deficiencies, platelet abnormalities have been found in a small group of children as well. These types of congenital bleeding disorders have also been diagnosed in a striking number of children at the Hacettepe Children's Hospital.

The purpose of this paper is to report on 60 children with bleeding djsorders due to platelet dysfunction and to indicate the importance of this type of defect in the differential diagnosis of congenital bleeding diathesis.

Material and Methods

Sixty children with congenital bleeding problems due to qualitative platelet disorders without coagulation defects seen at Hacettepe Children's Hospital between 1974 and 1980 are the subject of this study. The ages of the patients at the time of diagnosis ranged from 7 months to 19 years with a mean of 6.7 years. There were 31 females and 29 males. None of the patients had taken aspirin or any other medications known to interfere with platelet function for one week prior to the study. The bleeding time was measured by the methods of Ivy et al[2]; platelet adhesiveness, clot retraction and the availability of platelet factor 3 (PF_3) were determined according to previously described methods[3,4].

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Venous blood samples were anticoagulated with 0.1 M sodium citrate in a ratio of 9 parts blood and 1 part citrate to study platelet aggregation. Platelet-rich plasma (PRP) was isolated from the blood at room temperature by centrifugation at 150 × g for 10 minutes. Platelet-poor plasma (PPP) was obtained by centrifugation of the remaining blood at 1200 × g for 15 minutes. Platelets were counted with phase contrast microscopy by the method of Brecher and Cronkite[5].

In all the aggregation studies, platelet counts in the PRP samples were adjusted to 350×10^9/l with autologous PPP.

Platelet aggregation was measured in a chrono-log aggregometer (Broomally, Pa, U.S.A.) and continuously recorded on a Model 702 Strip Chart Recorder by adenosine-5-diphosphate (ADP: Sigma Chemical Co.), epinephrine, collagen (bovine achilles tendon, Sigma Chemical Co.), and ristocetin (Lundbeck Co., Copenhagen, Denmark). ADP was dissolved in Tyrode's solution and epinephrine was diluted with saline to obtain a final concentration of 1.1×10^{-6} M and 2.5×10^{-6} M, respectively.

For the preparation of collagen suspension 2 gm dried material was suspended in 100 ml Tyrode's solution and homogenized in a blender for 10 minutes. The mixture was then centrifuged at 1200 × g for 15 minutes. The supernatant was removed and diluted with Tyrode's solution. Ristocetin was diluted with saline to obtain a final concentration of 2 mg/ml. Release and uptake of 14 C-serotonin was measured by the method described by Jerushalmy and Zucker[6]. In all patients prothrombin time (PT)[7] and partial thromboplastin time (PTT)[8] were also determined.

Results

Clinical and laboratory findings for the patients included in this study are given in Tables I and II.

During the 6-year period, 37 thrombasthenic children (Glanzmann's thrombasthenia) were diagnosed out of 60 children who had bleeding diathesis due to platelet disorders in whom PT, PTT and platelet counts were normal. None of the patients' platelets aggregated by ADP or epinephrine. Although 25% of these children's platelets gave a minimal response (5-10% aggregation) with collagen, the rest of the patients' platelets did not aggregate at all (Figure 1).

Hemorrhagic manifestations had started early in life with varying severity, in all the patients except a 13-year-old girl who came to the hospital because of menorrhagia. Most of the patients had purpura, ecchymoses, epistaxis and gingival hemorrhage occurring generally after minimal trauma. None of them showed visceral bleeding, and hemarthrosis was observed in only one patient. In 21 of the patients (57% of those studied) consanguinity existed between the parents.

TABLE I

Some Clinical Data on Patients with Qualitative Platelet Disorders

Type of disease	No. of patients	Age range	Sex	Age at onset of hemorrhagic manifestations	Incidence of consanguinity (%)	Bleeding history in the family (%)
Glanzmann's thrombasthenia	37	9 mo - 13 y	19 F, 18 M	1 mo - 2.5 y*	57	28
Thrombopathia	11	7 mo - 13 y	6 F, 5 M	2 mo - 2.5 y	51	36
Bernard-Soulier syndrome	9	11 mo - 16 y	5 F, 4 M	11 mo - 16 y	88	86
Hermansky-Pudlak syndrome	3	8 y - 19 y	1 F, 2 M	7 mo - 7 y	0	66

* With one exception (13 years at age of onset).

TABLE II

Laboratory Data of Patients

	Bleeding time (N: 4-7 min)	Platelet adhesiveness (N: 48-75%)	Clot retraction (N: 43-77%)	PF_3	^{14}C-serotonin•• Uptake (N: 70-90%)	^{14}C-serotonin•• Release (N: 30-80%)
Glanzmann's thrombasthenia	N (3) Abn (37)•	Abn (37)	N (3) Abn (34)	N (2) Abn (35)	—	—
Thrombopathia	N (4) Abn (7)	N (7) Abn (4)	N (5) Abn (6)	N (3) Abn (8)	83-100-51	0-0.5- 4
Bernard-Soulier syndrome	N (6) Abn (9)	Abn (9)	N (6) Abn (3)	Abn (9)	37- 51-67	1.5-8.5-17
Hermansky-Pudlak syndrome	N (1) Abn (2)	Abn	N (1) Abn (2)	N (3)	81- 63-67	2.8-0.6- 0

N = Normal; Abn = Abnormal.

• = Numbers in parentheses indicate the number of patients.

•• = Studied in three patients.

In 11 patients qualitative platelet disorder was shown to be due to release defect (thrombopathia), which is characterized by abnormalities of second phase aggregation (Figure 1). The incidence of consanguinity between the parents was 51%.

Bernard-Soulier syndrome (giant platelet syndrome) was diagnosed in 9 patients, three of whom had thrombocytopenia. In all the patients, platelet aggregation studies were compatible with the impaired release mechanism. Platelet ^{14}C-serotonin release was evaluated in only 3 patients and found to be decreased. Most of these patients had minor bleeding episodes such as ecchymosis. However, in two cases severe epistaxis and menstrual bleeding were observed. Four patients were siblings from two different families. The consanguinity between parents was found to be 88%.

Three albino patients with bleeding diathesis were diagnosed as having Hermansky-Pudlak syndrome. Their platelets also showed release defects with abnormalities of second phase aggregation. Although easy bruising was the main complaint, severe hemorrhagic manifestations were not documented in any case. In this group two patients were siblings, and no consanguinity was found between the parents.

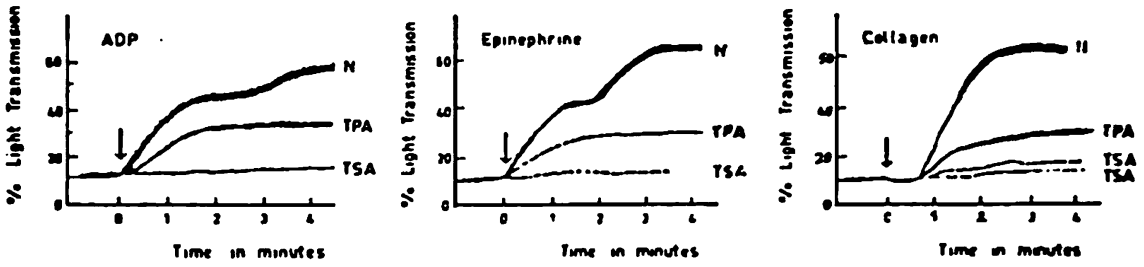

Figure 1

ADP, epinephrine and collagen-induced platelet response of citrated PRP from normal (N) children and patients with Glanzmann's thrombasthenia (TSA) and thrombopathia (TPA).

Discussion

Hemorrhagic disorders due to platelet dysfunction, both congenital and acquired, have previously been reported in children[9,10].

In most of the patients, congenital disorders are rarely diagnosed in childhood, except in cases of surgical intervention. However, during a 6-year period we diagnosed 60 cases of qualitative platelet disorders out of 344 children with congenital coagulation defects. In our series, after hemophilia A, qualitative platelet diseases were the most common inherited hemorrhagic disorders. Among those thrombasthenia was seen most frequently. This disorder was described by Glanz-

mann in 1918[11]. Although the exact cause of Glanzmann's disease is unknown, recent findings strongly suggest a deficiency of specific membrane proteins (glycoprotein IIb and IIIa)[12,13]. Bleeding was usually observed early in life in our patients, with extreme variability in severity. The variability of some of the laboratory results and the range of severity of bleeding clearly suggest that thrombasthenia is not a homogeneous disorder[9,14,15]. Basically confirming the results of Chediak et al[16] and Malmsten et al[17], our study indicated that thrombasthenic platelets have different metabolic activities (unpublished data). The incidence of consanguinity between the parents of thrombasthenic children was found to be 57%, which was higher than the rates reported previously[9].

One of the qualitative platelet disorders rarely diagnosed in the pediatric age group is thrombopathia. These diseases are also heterogeneous and characterized by a defect in release mechanism. The first phase of aggregation of platelets by ADP and epinephrine may be decreased or normal. Second phase aggregation is abnormal. Collagen-induced aggregation was also abnormal in all our cases (Figure 1). Eleven of our patients had this type of platelet disorder. In this heterogeneous group of patients it is difficult to distinguish on the basis of the clinical and platelet aggregation studies whether these patients have primary secretion defect or storage-pool disease. Although we were not able to study platelet adenine nucleotides which are stored in dense granules, defective ^{14}C-serotonin release indicated that at least 3 of our patients (those we were able to study) might have a storage-pool defect. The normal uptake of ^{14}C-serotonin in our patients could be explained with a specific platelet membrane receptor for its uptake[18]. Since bleeding problems are very mild and prolonged bleeding can be detected only after surgical intervention, these types of defects are generally diagnosed in adulthood. If parents were more alert to the ecchymoses of their children, the diagnosis could be made in early life. The youngest of our patients was a 7-month-old boy. Most of these children were brought to us with the fear of leukemia.

Giant platelet syndrome was diagnosed in 9 patients. This is a rare autosomal recessive hereditary disease first described by Bernard and Soulier in 1948[19]. This syndrome is characterized by giant platelets, impaired subendothelial adhesion and ristocetin-induced aggregation. However, some cases might have a storage-pool defect as seen in our patients. Thrombocytopenia, which can be observed in this syndrome, was found in 3, one of whom had a normal platelet count at times. Although the exact mechanism of thrombocytopenia is unknown, platelet survival was found to be decreased, which was thought to be due to membrane defect[20]. The incidence of consanguinity between parents was found to be very high (88%). This group of patients will be reported in detail.

Three albino patients, two of them siblings, had Hermansky-Pudlak syndrome. This syndrome was described by Hermansky and Pudlak in 1959 in two albinos with

prolonged bleeding time[21]. Platelet aggregation studies of our patients indicate the storage-pool defect which is characteristic of this disease[17,22,23]. In our series these patients were diagnosed at a later age than the others with qualitative platelet disorders. The bleeding episodes were mild and did not require blood transfusions.

In summary, bleeding time is the most important screening test in the differential diagnosis of congenital qualitative platelet disorders. However, normal or slightly prolonged bleeding time may be observed, especially in patients with release defects. Therefore, when bleeding diathesis is suspected, detailed platelet functions should be studied to establish the diagnosis. As far as we know this report covers the largest series of children to date with congenital bleeding disorders due to platelet dysfunction. This may be related to the high incidence of consanguineous marriages in Turkey[24].

Summary

Qualitative platelet disorders were shown to be the second most frequent cause of congenital bleeding diathesis, after hemophilia A, diagnosed at Hacettepe Children's Hospital, Ankara, between 1974 and 1980. During this period, 60 new children with congenital qualitative platelet disorders who were seen because of mild, moderate or (rarely) severe hemorrhagic diathesis were evaluated. Thirty-seven of them were shown to have thrombasthenia, 11 thrombopathia, 9 Bernard-Soulier syndrome, and 3 Hermansky-Pudlak syndrome. The high incidence of qualitative platelet disorders in Turkey is most likely related to the high frequency of consanguineous marriages, especially in small villages.

As a result of this study, we would like to emphasize the importance of considering congenital platelet disorders in the differential diagnosis of congenital bleeding diathesis when prothrombin and partial thromboplastin times are normal.

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