SPECIAL ARTICLE

QUALITATIVE PLATELET DISEASES

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Austin and Pepper [1] in 1913, Frank [2] in 1915 and Hess [3] in 1916 were the early reporters on purpura cases occurring with a normal number of thrombocytes.But these writers described their cases more or less within essential thrombopenia. Frank named these cases «pseudohemophilia hereditaria», emphasizing the fact that the disease was acquired from the family.

In 1918, Glanzmann [4] for the first time described thrombasthenia as a different disease from thrombopenia. The author postulated a hypothetic enzyme «retractozym» as the cause of retraction defect.

In 1926 Von Willebrand [5, 6] reported a new type of hemorrhagic diathesis in the Aaland Islands, and called this «hereditary pseudohemophilia». In all of the cases, the bleeding time was prolonged and retraction time normal. Jurgens, [7] using a capillary thrombometer, measured the time lapse in which thrombocytes unite to form platelet thrombus. While normally thrombus occurred in two or three minutes, in essential thrombopenia, thrombus occurred after 40 to 60 minutes. In 1925, Frank[8] and in 1927, his student Hartmann, [9] using the same device, observed that in other diseases, such as cirrhosis of the liver, although the number of thrombocytes was normal, the time required for the formation of a platelet thrombus was prolonged. Frank called this phenomenon (inability of platelets to unite to form a platelet thrombus) athrombia. He suggested that the lack of platelet plug in the puncture area is responsible for prolonged bleeding time.

Von Willebrand and Jürgens[10] studied the Aaland Island cases together in 1933 and introduced their study under the name of constitutional thrombopathy. In all of the cases examined, bleeding time was prolonged and the athrombia phenomenon was present.

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In 1941 Macfarland[11] stated that a capillary defect exists in these cases. In 1946, Estren, Medal, and Dameshek[12] described vascular pseudohemophilia.

Although Quick[13] and Brinkhaus[14] in 1947 showed the role of platelets in blood coagulation, the value of pathologic platelets in qualitative platelet diseases remained unclear until recent years. Bernard and Soulier in 1948,[15] Ekren[16] in 1951, and Sussman[17] in 1952 reported that in thrombopathy cases, the prothrombin consumption test was defective.

In 1953 the development of the thromboplastin generation test (TGT) by Biggs and Douglas[18] and Braunsteiner's[19] observation of defects in thrombasthenia cases when examined under electron microscope opened new areas for further investigation.

In 1954 Alatas and Ulutin,[20] using an electron microscope, confirmed Braunsteiner's findings of defects in pseudopod formation and in the hyalomere spreading and also that there was complete athrombia.

In 1954 Soulier and Larrieu,[21] Marx,[22] Soulier and Larrieu[23] again in 1955, Jürgens,[24] Braunsteiner[25] and other writers, recorded thrombocytic defects in thrombopathy cases by TGT. According to these authors the thromboplastic factor of thrombocytes (platelet factor 3) apparently decreased in thrombopathy. In 1956 Braunsteiner[26] showed that in thrombopathy cases platelet factor 3 is decreased but that the platelets are normal when examined by an electron microscope.

In 1956 Ulutin and Karaca[27, 28] observed a decrease of platelet factor 3 in five thrombopathy cases by TGT. However the same experimenters showed that the defects in the thrombocytes became normal when the platelets were incubated in distilled water. (The distilled water test is described by the authors.) In thrombopathy cases the defect in the platelets was functional, not quantitative. Based on these experiments the authors put forward the theory of «disintegration arrest and releasing defect.» In 1956 Frank, Ulutin and Karaca[29] described and named a new qualitative platelet discase: thrombasthenic thrombopathy. In 1957 Ulutin and Karaca[30] reported to the Turkish Medical Society the platelet osmotic resistance test and their observations in thrombopathy using this test. Both the test and its results were published, and new observations on the pathogenesis of thrombopathy were widely discussed.[31-34]

In 1958 Johnson, Monto and Caldwell[35] confirmed the authors' observations by showing that the decrease of platelet factor 3 in thrombopathy cases was in normal quantities after the fission of platelets by sonic oscillation. In the platelets of the same cases, by electron microscopy, Rebuck et al[30, 37] contrary to Braunsteiner, found pathologic findings. In 1958 Schulz and his colleagues[38, 39] working on thrombocyte sections, observed a defect in thrombopathy by electron microscopy.

Since 1954, my colleagues and I have been working on qualitative platelet diseases. For better understanding I will try to enumerate the diseases in this group. This classification will not be complete; better methods and new discoveries on platelet factors will reveal new types of the disease, but we can, for the time being classify the primary qualitative platelet diseases in two groups, isolated and associated as follows:

Qualitative Platelet Diseases

A. Isolated	*B. Associated*
1. Primary thrombopathy	1. Thrombasthenic hemophilia
2. Thrombasthenia	2. Thrombopathic hemophilia
3. Thrombasthenic thrombopathy	
4. Essential athrombia	

In the isolated group, the defect is seen only in the platelets. In the associated group the deficiency of AHG or PTC is added to the defect in the platelets.

Clinical observations in the isolated group are identical, but they can be differentiated by laboratory investigations. The observations are given in order, beginning with primary thrombopathy from the isolated group.

Primary Thrombopathy *

In this type the primary defect is the lack of platelet factor 3 due to a releasing defect.

We have seen more than 40 cases of this type. It is seen equally in both sexes. Sixty per cent of the cases are hereditary and 40 per

* In literature this is known as Willebrand-Jürgens type of thrombopathy. In recent years the intimation of a lack of AHG in some cases of this type led us to associate different diseases with this name. Therefore we call primary thrombopathy only those in the isolated group accompanied by lack of platelet factor 3.

cent sporadic. As we saw more cases of this type, the percentage of sporadic cases seemed to increase. In hereditary cases, inheritance is simple dominant. In several other cases it shows a recessive character not related to sex.

The disease can be seen from birth through adulthood, although it is most common in children and young adults.

The clinical symptoms are: repeated epistaxis, easy bruising, ecchymosis, purpura, bleeding of the gums, nasopharyngeal bleeding, prolonged bleeding in ordinary cuts, excessive bleeding after tooth extraction, urogenital bleeding, gastrointestinal bleeding, hematemesis, and excessive bleeding following tonsilectomy. In two cases there was bleeding into the joints.

Primary thrombopathy and other congenital defects can be seen together. We observed combined primary thrombopathy cases allied with intraventricular septal defect, tetralogy of Fallot and Fröhlich's syndrome. Bleeding time in these cases was prolonged, but the time is not fixed. The number of platelet changes were between 200-400,000. In five cases we observed a mild thrombopenia and thrombopathy. This thrombopenic - thrombopathy will be discussed in a later section of this paper. In blood smears, platelets stood out separately, and when examined under a phase microscope the aggregation defect was seen in 53 per cent of the cases.

Thrombocytes in these cases show defects both in TGT and platelet factor 3 determination. The defect is functional. After treatment with a sonic oscillator, or after incubating the platelets in distilled water, the defect disappears.[27, 28, 35]

In 1957, we demonstrated, using the platelet osmotic resistance test, that platelets in primary thrombopathy cases show a strong resistance to hypotonic solutions.[30, 33]

In 1960 Nelken and his associates,[41] and in 1960 and 1962, Inceman and his colleagues[42, 43] confirmed our results by platelet osmotic resistance tests using the phase microscope. Examining the same type of platelets, Rebuck et al[36, 37] defined the differential count of platelets under an electron microscope. Normally most of the thrombocytes were in dendritic state. In the spread phase, a chromomere was thrown out of the cell in most of the thrombocytes and a vacuole remained. In thrombopathy the spread form and then the intermediate and dendritic phase were mostly seen. The viscous metamorphosis rate increased from the normal four per

cent to 43 per cent. Apart from this, contrary to normal form in spread state, chromomere was retained in most of the cells. These observations can be described as «disintegration arrest and granulomer retention».

Schulz[38] however showed that alpha granules containing platelet factor 3 are present in thrombopathy, although somewhat defective morphologically. On the other hand, gamma granules, tiny vesicles which unite to form intracellular endoplasmatic tubular systems, were not present in thrombopathy or were scattered and could not form an endoplasmatic tubular system.

Ulutin et al[10, 44] observed under an electron misroscope the morphological changes which occurred in platelets in the platelet osmotic resistance test. The following data was observed both normally and in thrombopathy. Platelets do not disintegrate in hypotonic solutions, and there is also no lysis in distilled water. It was found that cells which ordinarily keep their wholeness in a 0.10 per cent Nacl and distilled water solution are in spread form; and they give up their granules to the medium. Normal thrombocytes lost 82 per cent and thrombopathic thrombocytes lost 16 per cent of their granules to the medium. This 16 per cent is enough to correct the defect in the test. In normal platelets, the granules leave the membrane through certain points following a definite pattern, whereas in thrombopathy the granules show irregular scattering. Hypotonic solutions accelerate the releasing of granules to the medium.

These observations led us to the following explanation.[10, 45] The cause of the releasing defect, as we suggested, is a congenital defect of the endoplasmatic system. As a result of an ultrastructural defect, platelet factor 3 is not released and a thrombopathic defect occurs. More remains to be investigated in this subject although a few points have been proved experimentally.

Thrombasthenia

Thrombasthenia was first described by Glanzmann[1] in 1918. Braunsteiner et al, worked further on the subject in 1953. Laboratory observations on thrombasthenia differ from thrombopathy, although clinically the symptoms are the same. There are two basic defects in thrombasthenia : 1. Retraction defect, 2. Loss of hyalomere spreading and the inability of the thrombocytes to form pseudopods. Thrombocytes cannot come together to form islands and

cannot perform their functions in the center of the fibrin net. In the fibrin net there is no articulation formed by fibrin fibers in the platelet islands. The fibrin network is irregular, and intact thrombocytes can be seen in between. There is complete athrombia. The thrombocytes have platelet factor 3 in normal quantity and the prothrombin consumption test, TGT, and platelet factor 3 determination give normal results.

In recent years there have been advances in understanding the pathogenesis of this disease. Bettex-Galland and Lüscher[46, 47, 48] extracted thrombasthenin from the platelets, which is a retractile protein resembling myosine. The retraction of thrombasthenin may occur when ATP, glucose, Ca++ and Mg++ are present in certain concentration. In this system thrombasthenin works as an ATP-ase. Several experimenters[49-55] have shown the presence of glycolytic mechanisms in platelets.

Gross and colleagues[53, 56, 57] showed that in thrombasthenia cases, glyceraldehyde phosphate dehydrogenase (GAPDH) and pyruvate kinase (PK) enzymes decrease considerably in platelets, and as a result ATP is decreased. Because of this, the high energy necessary for retraction did not occur. Larrieu et al[58] described a type of thrombasthenia in which GAPDH and ATP were normal and the defect was corrected with the addition of ATP and Mg.++ According to present observations thrombasthenia, which is a hereditary disease, is caused by at least three separate defects: 1. congenital deficiency of thrombasthenin; 2. lack of GAPDH and PK; 3. the type described by Larrieu and her associates.

Thrombasthenic Thrombopathy

Both thrombopathic and thrombasthenic defects are found together in this type, which was described by Frank, Ulutin and Karaca[59] in 1956. Lack of platelet factor 3 is seen in platelets due to releasing defect. Thrombocytes are resistant to hypotonic solutions. Retraction is defective and complete athrombia is present. Under an electron microscope the defect is found in pseudopod formation and in hyalomere spreading as in the cases of thrombocytoasthenia.

Essential Athrombia

Two cases of essential athrombia first described by Inceman[60] in 1955, have been reported. The pure athrombia defect is present

TABLE 1

ISOLATED QUALITATIVE PLATELET DISEASES

	Primary Thrombopathy	Thrombasthenia	Thrombasthenic Thrombopathy	Essential Athrombia
Bleeding Time	Prolonged	Prolonged	Prolonged	Prolonged
Coagulation Time	Normal	Normal	Normal	Normal
Clot Retraction	Normal	Pathologic	Pathologic	Normal
Prothrombin Time	Normal	Normal	Normal	Normal
Lacet	+ to 4 +	+ to 4 +	+ to 4 +	+ to 4 +
Prothrombin Consumption Time	Pathologic 70 %	Normal	Pathologic	Normal
Platelet TGT	Pathologic	Normal	Pathologic	Normal
Athrombia Phenomenon	Pathologic 53 %	Pathologic	Pathologic	Pathologic
Electron Microscope Findings	Disintegration arrest and granulomer retention	Defective pseudopod formation and no hyalomere spreading	Defective pseudopod formation and no hyalomere spreading	—

and the aggregation and adhesion ability of the thrombocytes is completely defective. Platelet factor 3 is normal. There is no retraction defect and viscous metamorphosis is normal.

When the patients' platelets were suspended in NaCl solution, the defect disappeared. This original observation of Inceman[60] is confirmed by Braunsteiner[25] and Hellem.[62] In his studies Hellem suggested that a factor R, released from erythrocytes was responsible for the platelet adhesion. In 1961 Gaarder and Laland[63] reported ADP's role in platelet adhesion. This is accepted by many authors. Inceman[64] also proved that platelet adhesion to glass and fibrin was of a different character.

Associated Qualitative Platelet Diseases

In 1953 Alexander and Goldstein[65] reported cases where deficiency of AHG and prolonged bleeding time were seen together. Several patients of both sexes were recorded as having this syndrome. Similar observations were reported in patients examined in the Aaland Islands, with the conclusion that they had vascular defects, combined with a deficiency of AHG.

Nilsson et al[66, 67] in 1957 raised the AHG level by injecting human plasma fraction 1-0 into subjects with this type defect, thus making the bleeding time normal. The authors claimed that a lack of vascular factor was responsible for this condition, and several articles were published subsequently confirming this observation. In our studies on the cases of prolonged bleeding time with AHG deficiency, we found thrombasthenic and thrombopathic defects in the platelets.[68 - 72] The cases we examined were thrombasthenic hemophilia, and thrombopathic hemophilia.

Paykoç and Erişirgil[73] made a similar observation in a case where prolonged bleeding time was seen together with a lack of PTC. We call this whole group athrombia hemophilica.

In thrombasthenic hemophilia, defects were seen in pseudopod formation and in hyalomere spreading of the platelets, whereas in thrombopathic hemophilia platelet factor 3 deficiency is due to a releasing defect.

In the literature this whole group is collected under the name of Von Willebrand syndrome.

On the basis of our observations we classify Von Willebrand syndrome as follows:[74]

Von Willebrand Syndrome
(Lack of AHG or PTC associated with prolonged bleeding time).

1. Platelet defect (Athrombia hemophilica)
   a. Thrombasthenic type (Thrombasthenic hemophilia)
   b. Thrombopathic type (Thrombopathic hemophilia)
2. Capillary defect (Vascular hemophilia)
3. Lack of «vascular» factor
4. Combinations of all of the types

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