



## Disorders of platelet function: evaluation and treatment

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■ Platelet function involves adhesion, aggregation, secretion, and elaboration of procoagulant activity. Compromise of any of these functions due to an inherited or acquired defect in primary hemostasis can result in bleeding diatheses. Acquired disorders are related to drugs, systemic disease, or hematologic disease. Although laboratory tests are available to evaluate platelet function, the history is of prime importance in the diagnostic workup. Plasmapheresis, dialysis, transfusion of normal platelets, administration of cryoprecipitate, and administration of corticosteroids are all acceptable treatment protocols in specific situations. The drug of choice for treating mild hemostatic abnormalities due to platelet function defects is desmopressin acetate, which may be administered by several routes, produces few, if any, side effects, and carries no risk of infectious disease transmission.

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**P**LATELETS ARE involved in primary hemostasis through the formation of a platelet plug; adherence of the platelet plug to the damaged vessel wall is maintained by blood coagulation. Consequently, disorders of platelet function and disorders of coagulation manifest as distinctive types of bleeding diatheses.

### PATIENT EVALUATION

Individuals with platelet defects have problems in primary hemostasis. Such patients will present with spontaneous petechiae and ecchymoses. Sudden ap-

pearance of bruises with no apparent trauma, bleeding from mucous membranes, menorrhagia, epistaxis, and bleeding from the gastrointestinal tract are all common manifestations of primary hemostatic abnormalities. Bleeding at a given site tends to be immediate and prolonged but not recurrent. For example, the inability of a patient with a platelet disorder to produce the initial hemostatic plug will result in prolonged bleeding after a tooth extraction. Once the bleeding has stopped, however, it is not likely to recur. Patients with platelet defects don't have bleeding into their joints, nor do they have retroperitoneal bleeding.

Patients with a coagulation defect, on the other hand, often present with deep spreading hematoma that develops over a period of several hours and is the result of an injury that may not be apparent. When a tooth is extracted, the individual with a coagulation defect will experience prolonged episodes of recurrent bleeding resulting from the inability to maintain the

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platelet plug in place. Hemarthrosis and retroperitoneal bleeding are also characteristics of coagulation defects.

Inherited platelet disorders are rare and generally are detected during childhood, especially if there is a positive family history. However, an inherited platelet disorder may cause no problems in the non-stressed patient. In contrast to inherited disorders, which are primary platelet diseases, an acquired platelet disorder generally appears during adulthood and is usually secondary to another disease.

A detailed history provides the best information regarding the clinical significance of a bleeding diathesis. Questioning patients about their tendency to bruise, excessive bleeding with dental work, and the need for transfusion with previous surgery can elicit information that is valuable for both diagnosis and prognosis. In addition, the patient history is key to the selection of appropriate laboratory studies.

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#### LABORATORY TESTS

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A variety of laboratory tests for the evaluation of platelet function are available. The bleeding time was once touted as the gold standard test of platelet function. Indeed, the bleeding time is useful in localizing a hemostatic abnormality,<sup>1</sup> but unfortunately it does not predict the risk for bleeding.<sup>2</sup> For example, in a Mayo Clinic study of 1,000 renal biopsies, there was no correlation between bleeding time and post-biopsy bleeding.<sup>3</sup>

The bleeding time depends to a certain extent on the platelet count, yet the bleeding time cannot be predicted from the platelet count, or vice versa.<sup>2</sup> As the platelet count decreases, the bleeding time tends to increase; thus, there is a general but non-linear correlation between platelet count and bleeding time. The relationship between the two tests, however, may be useful.<sup>4</sup> For example, if a patient has a longer bleeding time than one would expect from the platelet count, the presence of a condition that would hinder platelet function is suggested. Conversely, if the bleeding time is shorter than one would expect from the platelet count, one might suspect a diagnosis such as idiopathic thrombocytopenic purpura (ITP), in which platelets tend to be larger, more active, and more hemostatically effective. The presence of any one of a number of systemic diseases may also affect bleeding time.

Inasmuch as bleeding time depends on the technician performing the test, it is important that the technician not only be capable, but perform the test

frequently enough to achieve reproducible results. A bleeding time is done by applying a blood pressure cuff to the arm, inflating the cuff to a pressure of 40 mm Hg, using a template for making a standardized incision, blotting the blood from the wound every 30 seconds until the bleeding stops completely, and recording the time elapsed.<sup>5</sup>

It is important to consider the correlation between the hematocrit and the bleeding time, particularly in patients with uremia. Transfusion of red cells will almost always improve the bleeding time in uremic patients. Raising the hematocrit to 30 appears to maximize the improvement. Erythropoietin also has a beneficial effect in raising the hematocrit and decreasing the tendency to bleed.<sup>6</sup>

Of the *in vitro* tests of platelet function, the ristocetin agglutination test can confirm a diagnosis of von Willebrand's disease in a patient with prolonged partial thromboplastin time and prolonged bleeding time. Platelet aggregation can also be measured *in vitro*, but it does not correlate well with a patient's tendency to bleed.

The release of <sup>14</sup>C-serotonin, platelet factor 4 (PF 4), and beta-thromboglobulin ( $\beta$ -TG), substances found in platelet granules, is an indicator of platelet secretion. Abnormal secretion of these substances is often quite sensitive to the presence of drugs and the disease status, but again may not predict bleeding.

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#### INHERITED PLATELET FUNCTION DISORDERS

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Platelet function involves adhesion, aggregation, secretion, and elaboration of procoagulant activity. The compromise of any of these functions due to an inherited platelet defect can result in bleeding diatheses.<sup>7</sup>

Platelet adhesion to damaged blood vessels requires the presence of a multimeric protein called von Willebrand factor. Deficiency of either von Willebrand factor itself or the larger von Willebrand factor multimers results in von Willebrand's disease.

The glycoprotein Ib-IX complex, present on the platelet surface, binds the von Willebrand factor, and its absence produces a severe but rare bleeding diathesis (Bernard-Soulier syndrome).<sup>7</sup>

Platelet aggregation requires fibrinogen binding to the platelet surface. The glycoprotein IIb-IIIa complex provides a fibrinogen-binding site that is essential for platelet aggregation. Individuals born without sufficient numbers of functional platelet IIb-IIIa complexes have Glanzmann's thrombasthenia, a rare autosomal-

recessive disease.<sup>8</sup> Platelet secretion includes the release of delta (or dense) granules containing serotonin, adenosine diphosphate (ADP), and adenosine triphosphate (ATP), and alpha granules containing von Willebrand factor, fibrinogen, albumin, immunoglobulin-gamma (IgG), and many other proteins found in plasma, in addition to platelet-specific proteins such as PF 4,  $\beta$ -TG, platelet-derived growth factor, and thrombospondin.<sup>9</sup> Absence of alpha granules produces a mild bleeding disorder known as "gray platelet" syndrome.<sup>7</sup> The absence of dense granules is also associated with bleeding, increased bruising (usually), epistaxis, menorrhagia, and excessive surgical blood loss, and is referred to as "storage pool" disease.<sup>9</sup>

Elaboration of procoagulant activity is an important platelet function. Platelets provide the lipid surface for the generation of thrombin and factor Xa and thereby localize the production of a fibrin clot at the site of a vascular injury. A single patient with a platelet procoagulant disorder but symptoms resembling those of a coagulation disorder has been reported.<sup>10</sup> Although inherited platelet disorders can produce excessive bleeding, they are rare.

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#### ACQUIRED DISORDERS

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Acquired disorders of platelet function, unlike the inherited types, are very common.<sup>11</sup> They include not only disorders of adhesion, aggregation, and secretion, but global disorders in which all aspects of platelet function are abnormal. Acquired disorders of platelet function may be caused by drugs, systemic disease, or hematologic disorders.

#### Drug-related disorders

Inhibition of platelet function by drugs occurs frequently. Aspirin, one of the most-used drugs, inhibits platelet function by irreversibly inactivating cyclo-oxygenase, an enzyme in the platelet. This renders the platelets incapable of producing prostaglandins (particularly thromboxane A<sub>2</sub>) and, as a consequence, unable to secrete ADP and serotonin. The disorder of platelet secretion caused by aspirin is not particularly important in otherwise healthy individuals.<sup>11</sup> In association with another problem of the hemostatic system, however, inhibition of this aspect of platelet function can result in excessive bleeding. A mild hemophiliac, for instance, can act like a more severe hemophiliac if given aspirin. Likewise, aspirin may induce a bleeding diathesis in a thrombocytopenic

chemotherapy patient.

Nonsteroidal anti-inflammatory drugs (NSAIDs) also inhibit cyclo-oxygenase, but their clinical significance is even less than that of aspirin. Whereas aspirin can prolong the bleeding time, this is rarely seen in patients given NSAIDs.<sup>11</sup> Unlike aspirin, which inhibits cyclo-oxygenase for the life span of the platelet, the NSAID effect disappears once the drug is removed.

Although the beta-lactam antibiotics (penicillins and cephalosporins) are potent inhibitors of *in vitro* platelet function, their clinical effect is not significant. Patients who have taken high doses of these drugs—for example, individuals with acute endocarditis—will show a prolongation of the bleeding time that usually begins several days after the drug is started and may persist for several days after the drug is stopped. However, hemorrhage is not a problem.<sup>11</sup> Moreover, patients with leukemia who are receiving high doses of broad-spectrum antibiotics rarely have bleeding problems unless they have associated thrombocytopenia. In addition, this bleeding is usually corrected by the administration of platelets. The *in vitro* platelet abnormality induced by antibiotics is probably due to their interaction with the platelet surface and the resultant inability of platelet agonists to interact with receptors.

Finally, some food additives, garlic, and certain fungi found in Chinese food produce substances that can inhibit platelet function. Clinically, however, their effect is not important.

#### Effects of systemic disease

Chronic renal disease, chronic liver disease, and disseminated intravascular coagulation are among the systemic conditions associated with abnormal platelet function. Chronic renal disease is the prototype of a systemic disease that causes defects in platelet function. Studies of patients with uremia reveal that a large number have abnormal platelet function. Furthermore, abnormalities exist in all aspects of platelet function—aggregation, adhesion, metabolism of prostaglandins, and generation of procoagulant activity. In uremia, platelet function abnormalities are associated with prolonged bleeding time. However, while the severity of the renal disease appears to correlate with the increased bleeding time, it does not correlate with the risk of bleeding.<sup>2</sup> Intensive dialysis usually corrects the bleeding time in uremic patients, suggesting that the defects in platelet function are caused by dialyzable components.

In liver disease, hemostasis is impaired in several ways. Vitamin K-dependent clotting factors are not produced. Associated hypersplenism may decrease the platelet count: abnormalities of fibrinogen, elevated fibrinogen degradation products, and the effects of uninhibited plasmin may impair platelet function. In disseminated intravascular coagulation, abnormal platelet function may result from interaction of the fibrin degradation products with the platelet surface and the subsequent impairment of the IIb-IIIa-fibrinogen interaction.

Patients who have undergone cardiopulmonary bypass surgery have abnormal platelet function believed to be due to interaction of the platelets with the bypass machine.<sup>11</sup> Administration of platelets to patients who bleed after their heparinization has been reversed is a common procedure and usually corrects the problem.

### Hematologic conditions

Chronic myeloproliferative diseases, leukemia, and myelodysplasia are hematologic diseases associated with abnormal platelet function.<sup>11</sup> In these diseases, platelets are intrinsically abnormal. Abnormal platelet function is also seen in plasma cell dyscrasias such as multiple myeloma, due to the presence of paraproteins that can inhibit all aspects of platelet function. When bleeding occurs in a patient with a plasma cell dyscrasia and is not due to thrombocytopenia, it often responds to removal of the paraproteins by plasmapheresis. Platelet function tests also normalize, but whether these *in vitro* abnormalities are responsible for the bleeding is not always clear. Patients with paraproteins also have other *in vitro* clotting abnormalities, such as low levels of factor VIII and factor IX. The presence of these abnormalities does not appear to correlate with bleeding. On the other hand, the factor most likely responsible for bleeding in these patients is hyperviscosity.

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### TREATMENT

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When a patient is bleeding because of a platelet function abnormality, various treatment modalities are available, including the transfusion of normal platelets. Transfusion, however, carries the risk of transmitting an infectious agent such as the human immunodeficiency virus (HIV) or hepatitis viruses.

Cryoprecipitate, which supplies factor VIII to correct bleeding in hemophiliacs, will also stop bleeding

and shorten the bleeding time in patients with uremia and storage pool disease.<sup>12</sup> However, administration of cryoprecipitate risks the transmission of infectious diseases, as well.

In patients with platelet function abnormalities not due to aspirin, giving corticosteroids (eg, prednisone 20 to 30 mg daily for several days prior to surgery) will reduce the bleeding time and has been reported to prevent excessive bleeding.<sup>13</sup> Although the mechanism is not clear, the beneficial effect of corticosteroids is believed to be due to their effect on the integrity of endothelium. This effect on the endothelium may also be responsible for the observation that petechiae tend to disappear quickly in patients with ITP who are given steroids, even though their platelet count doesn't rise. In some patients with platelet disorders, particularly those with uremia, conjugated estrogens will stop bleeding and shorten the bleeding time.

Desmopressin acetate has become the treatment of choice for correction of platelet function disorders. Administration of desmopressin increases the plasma concentration of factor VIII, von Willebrand factor, and plasminogen activator. Currently, the beneficial effect of desmopressin on hemostasis is thought to be due to its ability to release von Willebrand factor from endothelial cell storage sites.<sup>14</sup>

Although usually given intravenously at a dose of 0.3 to 0.4  $\mu\text{g}/\text{kg}$  infused over 15 minutes, desmopressin can also be administered subcutaneously and intranasally. Its effect persists for approximately 4 to 6 hours. Because stores of von Willebrand factor in the endothelial cells are eventually depleted, patients who are given repeated doses of desmopressin may develop tachyphylaxis. Thus, desmopressin therapy may be successful initially, but ineffective when administered a third or fourth time.

Of course, desmopressin therapy carries no risk of transmitting HIV or hepatitis viruses. In addition, desmopressin has the benefit of producing only mild side effects, if any. For patients who experience adverse effects, mild facial flushing, transient headache, a slight increase in heart rate, or a decrease in blood pressure are the common symptoms. Isolated reports of hyponatremia in children and thrombosis in elderly patients suggest caution when administering desmopressin in these patient populations. Nevertheless, desmopressin appears to be the treatment of choice for mild hemostatic abnormalities due to platelet function defects.

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