100
Autoimmune Thrombocytopenic Purpura

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Abstract Immune thrombocytopenic purpura (ITP) is a common acquired autoimmune disorder characterized by a low platelet count caused by antibodies against platelet surface antigens, mostly glycoproteins IIb/IIIa and Ib/IX. ITP can be present as acute (mainly in children 1–7 years old) and chronic (mainly more than 10 years old). Platelet destruction is triggered by antibodies, but complement-mediated lysis and T-cell cytotoxicity could be involved. Disturbance in megakaryocytes maturation and platelet production, as well as apoptosis were also described. ITP is a diagnosis of exclusion. The diagnostic approach is based primarily on clinical history and physical examination. The first indication of ITP is reduction of platelet count without a change in other cell types. Detection of antiplatelet antibody supports an immune nature of the disease rather than contributing to ITP diagnosis. Treatment of ITP includes steroids, IV immunoglobulin, Rho(D)Ig, anti-CD20 antibody, splenectomy, immunosuppressive drugs, and thrombopoietin.

Keywords ITP · bleeding disorder · platelet antibodies

Definition

Immune (idiopathic) thrombocytopenic purpura (ITP) is a common acquired autoimmune disorder characterized by a low platelet count caused by antibodies against platelet surface antigens. The antiplatelet antibodies are mainly IgG, but IgA and IgM were also found. The epitopes against the antibodies are lying mostly in GPIIb/IIIa and GPIb/IX complexes, but antibodies against GPIa/IIa or GPIV were also described, and antibodies that react with multiple platelet antigens are common. The specific platelet antibodies considered causing accelerated platelet destruction. ITP can be classified based on the absence or presence of other diseases (primary or secondary), patient age (adults or children), and duration (acute or chronic). Considerable heterogeneity in ITP definition exists in the literature: platelet count thresholds ranged from 100 to 150 $\times$ 10^9/l; duration of thrombocytopenia (TP) before chronic disease is developed ranged from 6 weeks to 3–6 months. The presence of antiplatelet antibody in the plasma is not required for ITP definition. The consensus in definition of ITP is low platelet count, normal hemoglobin level and white blood cell count, no changes in blood smear (except TP), and the absence of other causes of TP.

Epidemiology

ITP is relatively common in children with estimated prevalence of 5:100,000 and somewhat lower in adults; an equal incidence in both males and females in the 1- to 7-year-old age patients with acute ITP is documented (Table 100.1). This is different from the adults who are more likely to have chronic ITP (1) with a female preponderance (1.7:1) (2). Women of age 20–40 years are afflicted most often and outnumber men by a ratio of 3:1 (3).

The trigger for ITP in children is assumed to be a viral infection (Epstein–Bar virus, cytomegalovirus, varicella, rubella, mumps, and parvovirus); most of the children recover within few weeks to 1 year, but about 15% of them remain chronically thrombocytopenic (4). Predisposing conditions in adults are infections such as human immunodeficiency virus, hepatitis C, and *Helicobacter*

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TABLE 100.1. Acute and chronic immune thrombocytopenic purpura (ITP).

	Acute	Chronic
Age (mostly)	1–7 years	>10 years
Lasting period	<3–6 months	>3–6 months
Sex	F:M = 1:1	F:M = 1.7:1
Incidence	After viral infection, vaccination, allergy	Primary or secondary
Association between platelet count and bleeding	Mild	Strong
Presence of IgM antiplatelet antibodies	Frequent	Rare
Need of therapy with platelet count	$<10 \times 10^8$/l	$<30 \times 10^8$/l
Preferential therapy	Anti-D, IVIg	Steroids, IVIg, splenectomy
Recovering	2 months	Years

pylori or presence of other diseases such as systemic lupus erythematosus (SLE) or cancer.

History

ITP was first described in the mid 16th century by Amatus Lusitanus as an exanthema in a disease called "flea-like without fever." Lazarus Riverius (1658) observed bleedings, which come out at the nose. A hundred years later, in 1735, Paul Gottlieb Werlhof reported a disease called "morbus maculosus hemorrhagicus." In 1808, Robert Willan described various types of purpura. Joseph Denys found in 1887 that purpura was associated with low platelet count. Name Kaznelson (1916) hypothesized that spleen was the site of platelet destruction and performed the first splenectomy in a TP patient. William Harrington (1951), who transfused plasma from ITP patients into normal volunteers, which was followed by a rapid fall in platelet counts, presented first evidence for humoral factors causing TP. The immune nature of the disease was suspected when Shulman in 1965 showed that the factor absorbed by platelets was present in the IgG-rich plasma fraction. Since the 1970 s, the identification of platelet antigens led to definition of specific platelet autoantibodies causing TP.

Pathogenesis

The pathogenesis of ITP is accelerated platelet destruction as a result of antiplatelet antibodies. Interaction of autoantibodies with platelet surface antigens leads to platelets clearance by the reticuloendothelial system, mostly by the spleen, via Fcγ receptors, or to platelet destruction by complement-mediated lysis. The T-cell cytotoxicity is not excluded. Disturbance in megakaryocytes maturation and platelet production was also described (5). Electron microscopic studies showed that 50–75% megakaryocytes in ITP had extensive damage, with abnormalities of the membrane system. Other studies showed extensive apoptosis and an increased proportion of megakarycytes with activated caspase-3 (6). In some cases, thrombopoietin level was found to be inappropriately low in patients with ITP, and plasma of patients with ITP suppressed in vitro production or maturation of megakaryocytes and platelet production. Although antibodies appear to mediate these effects, other mechanisms as altering the cytokine milieu of the bone marrow may alternatively be the cause. Transforming growth factor (TGF)-β1 secreted by T cells is a potent inhibitor of megakaryocyte maturation and its level inversely correlates with disease activity. Recently, a role of platelet apoptosis in the pathogenesis of ITP was suggested; accelerated platelet apoptosis in response to anti-GPIIb antibody was demonstrated in a murine model of ITP (7).

The trigger for the autoantibody production is not clear. In acute childhood ITP, molecular mimicry has been proposed as the pathogenetic mechanism, although only few reports showed cross-reactivity between viral antibodies and platelets (e.g., varicella zoster). In chronic adults' ITP, molecular mimicry was suggested for *H. pylori* and GPIIIa, but in most cases the antibodies are directed against "cryptic" epitopes or neoantigens that become visible to the immune system. Recent studies show that apoptotic cells cause exposure of hidden antigens to the immune system by redistribution of intracellular autoantigens into cell surface blebs or by generating neoantigens. Existence of "cryptic" antigen could be explained also by increased expression of HLA-DR and CD40-ligand by platelets of ITP patients. In summary, the pathogenesis of ITP is associated with different immune defects triggered by external events cooperating with genetic factors and environment.

Clinical Manifestations

ITP in adults usually has an insidious onset and is presented as a chronic disorder. In contrast, ITP in children at an age 1–7 years follows viral or another illness and typically is presented as an acute disorder. Children older than 10 years may be more likely to have a chronic course. Symptoms of ITP are variable and range from mild bruising and mucosal bleeding to massive hemorrhage. Local abnormalities in different systems may increase the risk of bleeding. Generally, bleedings are associated with reduction of platelet count below 30×10^9/l. Children with severe TP (below 10×10^9/l) suffer from mild hemorrhage, and only few of them have serious symptoms including intracranial hemorrhage. During normal pregnancy, within the third trimester, platelet count tends to fall,

usually with no bleeding risk to mother or infant. However, ITP in pregnant women is dangerous to infants due to transmission of antibodies across the placenta causing fetal or neonatal TP and hemorrhage. This type of neonatal TP must be distinguished from alloimmune TP, in which mothers become sensitive to platelet membrane antigens present on fetal platelets.

Diagnostic criteria

ITP presents as primary (idiopathic) or secondary disorder. The latter is associated with lymphoma, leukemia, HIV infection, hepatitis C, myelodysplastic syndrome, and other disorders. In children, a preceding illness, mostly viral infection or other immunogenic factors, such as allergic reaction, insect bite, or vaccination, may be a trigger for development of ITP. The diagnostic approach for ITP is based primarily on clinical history and physical examination (8, 9). ITP is a diagnosis of exclusion. First of all, the physician should distinguish the type of bleeding due to primary (platelet-type) or secondary (coagulation-type) hemostasis disorder. Pseudo-TP and other pathologies, such as microangiopathic drug-induced TP, and those associated with bone marrow failure should be ruled out. In young children (within a few weeks of birth), a possibility of congenital disorders, such as Wiskott Aldrich syndrome and Bernard–Soulier syndrome, should be considered. In older children, aplastic anaemia and acute leukaemia must not be missed.

The first indication of ITP is reduction of platelet count without a change in other cell types, found on a routine blood count. The blood film serves also to exclude other abnormalities. If atypical findings are present, additional investigations are desired to perform.

Despite many studies have been undertaken regarding definitive search for platelet autoantibodies, this issue still remains a diagnostic challenge. Measurement of platelet-associated IgG by fluorescence flow cytometry is sensitive but lacks specificity. Assay of serum-containing antibodies, especially when a pool of normal platelets is used for antibodies binding, has a higher specificity but lacks sufficient sensitivity. Measuring autoantibodies against specific platelet targets, including glycoproteins (GP) IIb/IIIa, Ib/IX, IV, and Ia/IIa, is promising but still possess low sensitivity. Among them, the anti-GP IIb/IIIa antibodies are the most common. Currently, monoclonal antibody immobilization of platelet antigen (MAIPA) and radioactive immunobead assays are used. But such assays are available in a limited number of platelet laboratories. Even when the specific antibodies are assayed, they can be demonstrated in only 60–65% of ITP patients. The causes of "absent" specific antiplatelet antibody may be the presence of antibody against other platelet surface proteins, presence of anti-idiotype antibodies, T-cell-mediated platelet destruction, immunosuppressive therapy, or methodological detection problems. Hence, to date, detection of antiplatelet antibody supports an immune nature of the disease rather than contributing to ITP diagnosis. However, in the case that the third-line treatment is considered, the determination of anti-platelet antibodies may be of use.

Bone marrow examination for the diagnosis of ITP is not recommended providing that thorough clinical history and physical examination are undertaken and that the blood count and smear show no abnormalities apart from TP. Bone marrow analysis is recommended to perform in patients who are older than 60 years, or have atypical findings, or poor response to first line treatment, or in whom splenectomy is being considered. In children, bone marrow examination should be reserved for those having atypical clinical and laboratory features (10). It is performed usually before steroid therapy is given.

Special assays such as thrombopoietin level and the presence of reticulated (young) platelets may be informative, but they are restricted to limited number of laboratories. Based on the role of *H. pylori* in initiating ITP, it is worthwhile to detect the microorganism, at least in patients who are refractory to the common therapy.

Prediction

In patients with TP whose peripheral blood film revealed only low platelet count, several laboratory findings allow prediction of ITP and discrimination from other disorders: increased platelet-associated and serum anti-platelet antibodies, finding of platelet antibody-producing B cells, elevated percentage of reticulated platelets, and normal or slightly increased plasma thrombopoietin level. Three or more of these signs were found at presentation in 96% patients later diagnosed as ITP (11).

Therapy

Treatment of ITP should be considered on the basis of platelet count, bleeding severity, and general clinical status (12). The requirement for treatment is tailored to the individual patient. In adults, therapy is not indicated in those patients having platelet count greater than 30×10^9/l or without signs of bleeding. If there is a need for maintenance therapy, platelet count of more than 30×10^9/l must be achieved.

Children with acute ITP and mild clinical disease may be managed with supportive advice, but platelet count should be monitored until resolution of clinical symptoms. The asymptomatic pregnant women with ITP and platelet count higher than 20×10^9/l do not require treatment until delivery is imminent. Platelet count of 50×10^9/l is regarded safety for both vaginal delivery and Caesarian section (8).

The treatment of ITP aimed to interfere with antibody-mediated platelet destruction, to inhibit the function of macrophage Fcλ receptors and antibody production by B cells. The first-line therapy includes corticosteroids and intravenous immunoglobulin (IVIg). About two-thirds of patients respond well to corticosteroids, but the drug should be stopped in non-responding patients after 4 weeks of therapy. In about 75% patients, IVIg therapy is followed by rapid elevation of platelet count that lasts about 3–4 weeks. The mechanism of action of IVIg involves blockade of Fc receptors on macrophages, immune suppression, and possibly the presence of anti-idiotype antibodies in the pooled human Ig. It is the decision of the physician not to treat ITP, treat with one of these two drugs or with the combination of drugs, and to define the duration of the treatment.

Splenectomy belongs to the second-line therapy, and in two-thirds of patients significant increase of platelet count occurs, which is often sustained without additional therapy. Patients failing to respond to the first- and second-line therapies can be treated with interferon-α, anti-CD20 antibody (rituximab), Rho(D) immunoglobulin (for Rhesus-positive patients), or cytotoxic drugs modulating or inhibiting B-cell antibody production and T-cell cytotoxicity. Repeated protein A immunoadsorption alone or in combination with corticosteroids is effective in patients with refractory ITP. Thrombopoietin or nonimmunogenic thrombopoietic peptides represent a new strategy for treatment of ITP patients who are refractory to second- and third-line therapies.

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