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PATHOPHYSIOLOGY, INVESTIGATIONS, AND TREATMENT OF PATIENTS WITH IMMUNE THROMBOCYTOPENIC PURPURA

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AUTHORS' CONTRIBUTIONS

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Review Article

ABSTRACT

In otherwise healthy children or adults, immune thrombocytopenic purpura (ITP) has a low platelet count, usually less than 100,000, in the presence of common petechiae, bruises, or bleeding. It is explained that there is. ITP is most commonly found in children of all ages, not just adults. This activity describes the role of an inter-expert team in the evaluation and treatment of patients with immune thrombocytopenic purpura (ITP). The aim of this review article is to determine the etiology of immune thrombocytopenic purpura, formulate the patient's unique presentation with ITP, interpret general physical exam findings associated with ITP, and improve coordination of care among international team members. Outcomes will be discussed for patients with ITP.

Keywords: Hematoma; idiopathic thrombocytopenic purpura; petechiae; platelets.

1. INTRODUCTION

Immune thrombocytopenic purpura (ITP) is defined by the American Society of Hematology as isolated thrombocytopenia (platelet count 100,000/µl) with normal white blood cells and hemoglobin in the presence of a generalized purpuric rash. ITP was previously known as immune thrombocytopenic purpura or idiopathic thrombocytopenic purpura. Primary ITP is defined as ITP without a secondary etiology or underlying disease and is the subject of this article. ITP with an underlying cause or problem, such as B. ITP induced by drugs or systemic disease is called secondary ITP (eg, SLE, HIV, CVID, etc.). Primary ITP is divided into three stages based on the onset and persistence of symptoms. The term "newly diagnosed ITP" refers to ITP diagnosed in the last three months. Persistent ITP is defined as ITP that lasts 3 to 12 months after the initial diagnosis, while chronic ITP is defined as ITP that lasts more than 12 months after the initial diagnosis and does not resolve [1].

2. PATHOPHYSIOLOGY

ITP is caused by auto-antibodies, usually immunoglobulin G autoantibodies. ITP patients develop autoantibodies against platelet membrane

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proteins, particularly glycoprotein (GP) IIb / IIIa complex, GP Ib / IIa, and GP VI. Antibody-coated platelets are then rapidly eliminated by tissue macrophages, especially in the spleen, resulting in the formation of platelets with a shorter half-life. Platelet degradation is also prevented by these antibodies, leading to thrombocytopenia. On the other hand, T-cell mediated cytotoxicity has been suggested as an alternative method. In this way, cytotoxic T lymphocytes attack megakaryocytes in the bone marrow. The mechanism, however, is not well known [2].

Either way, there is always an exciting event that triggers platelet destruction. Infection or immunological changes are the two most common dynamic events. Infected ITP cases usually have a pre-existing viral or bacterial infection, which is the most common. Antibodies are produced in response to viral or bacterial antigens that cross-react with normal platelet antigens, a process called molecular mimicry. The most common viral infections are HIV, hepatitis C, cytomegalovirus and varicella zoster [3].

Autoimmune diseases that lead to a loss of peripheral tolerance and promote the generation of autoantibodies cause ITP with immunological alterations. Antiphospholipid syndrome, systemic lupus erythematosus, Evans syndrome, hematopoietic cell transplantation, chronic lymphocytic leukemia, common variable immunodeficiency, and autoimmune lymphoproliferative syndrome are the most common autoimmune diseases [4].

3. HISTORY AND PHYSICAL PRESENTATION

History: ITP is commonly seen in patients with a history of mucocutaneous hemorrhage, patellar rash and/or injury as this is a largely excluded diagnosis. Any secondary cause of thrombocytopenia, bleeding, or bruising in the history should be addressed. About 60% of children with ITP have had a viral illness in the past month. In older children, a slight increase in the incidence of ITP has been observed six weeks after receiving the measles, mumps, and rubella (MMR) vaccine, as well as varicella, hepatitis A, and tetanus-diphtheria-acellular pertussis vaccines. History of other secondary causes of thrombocytopenia should be investigated, as should any systemic symptoms (such as fever, weight loss, anorexia, night sweats, or bone pain), exposure to any drugs that may cause thrombocytopenia , History of individual bleeding. a family history.Bleeding or platelet disorders, recent infection, and any underlying condition such as rheumatological disease or liver disease. Signs of bleeding, bruising and petechiae should all be checked [5].

Physical Exam: Most teens look healthier except for the petal rash, which does not heal under pressure. About two-thirds of people will experience bleeding, which can take the form of pituitary rash, phlegm bleeding, or even hemorrhage. Physical examination should focus on the symptoms of bleeding, especially mucus in the skin and mouth, as well as lymphadenopathy or hepatosplenomegaly, which may indicate secondary primary disease-causing ITP. On the skin, sticky bleeding appears as patchy, purulent or scratchy. It can also cause bleeding in the nasal passages (epistaxis), mouth and gum surfaces (bleeding gums), gastrointestinal tract, genitourinary system, or vaginal area. Conjunctivitis, or retinal hemorrhages, on the other hand, are rare in ITP [6].

4. COMPLICATIONS

Bleeding risk associated with low platelet count, especially if the platelet count is less than 20,000 / microL, is associated with higher ITP problems in children and adults. ITP causes bruising and petechiae in most patients. Mucosal bleeding, such as epistaxis or bleeding in the gums, may occur in patients with ITP. Patients with significant gastrointestinal bleeding may have hem-positive stool, hematuria or menorrhagia [7].

Intracranial hemorrhage is the most dangerous effect of ITP (ICH). The risk of ICH in newly diagnosed children is about 0.5%, slightly higher in children with chronic ITP, but still less than 1%. Most cases of ICH occur when the platelet count is less than 10,000 / mcL. Headaches, intermittent vomiting, altered mental status, seizures, focal neurological deficits and / or recent head trauma are all signs of ICH in children and adults [8].

If the patient has ICH, immediate testing, including neuroimaging and treatment, is required. Very low platelet counts (<10,000 / microL), head trauma, antiplatelet drug use, and severe bleeding are all risk factors for ICH. Nosebleeds last 5 to 15 minutes, and gastrointestinal bleeding and / or any other severe mucosal bleeding requiring hospitalization or blood transfusion is considered severe bleeding [9].

5. INVESTIGATIONS

5.1 Laboratory Studies

A complete blood cell count (CBC) count is the first step in diagnosing immunological thrombocytopenia (ITP). Isolated thrombocytopenia is a hallmark of ITP. Anemia and / or neutropenia may suggest other illnesses. The morphology of red blood cells (RBCs) and leukocytes on a peripheral blood smear is normal.

Platelets are normal in size, the number of large platelets varies. Some people with severe ITP may have megatherombocytes or stress platelets, which indicate the early release of megakaryocytic fragments into the bloodstream. Consider the problem of inherited platelets if most of the platelets are large, similar in size to RBCs, or if they do not have granules or are abnormal in color [10].

Pseudothrombocytopenia is evidenced by clumps of platelets in a peripheral smear obtained from EDTA-anticoagulated blood. If the platelet count is normal when tested on a blood sample anticoagulated with heparin or citrate, this type of pseudothrombocytopenia is diagnosed. A blood sample from patients with risk factors for HIV infection should be tested for HIV antibodies using an enzyme immunoassay. HIV test results may be negative in acute HIV retroviral syndrome. A polymerase chain reaction for HIV DNA is more reliable than an HIV test in this case [11].

Certain women may have chronic, relapsing multisystem disease with ambiguous and generalized signs or symptoms, such as: recurrent, numerous, painful, tender, or swollen joints. If the patient's thrombocytopenia becomes chronic and resistant to treatment, a negative antinuclear antibody (ANA) result may aid in the diagnosis of ITP [12].

The results of a positive direct antiglobulin (Coombs) test in case of anemia and thrombocytopenia can help establish the diagnosis of Evans syndrome. The American Society of Hematology supports the evaluation of vaccine titers in children with ITP who have already received the first dose of MMR vaccination. If titers show complete immunity (as in 95% of young people), no additional MMR vaccine should be given. If the titers indicate that the child's immunity is inadequate, he should be given an MMR vaccine at the recommended age [13].

Some medical centers and mail-in referral laboratories offer specific antibodies to platelet antigen, platelet-related immunoglobulins, or other antibody platelet antibodies. Platelet antibody test results significantly depend on the laboratory used. A negative anti-platelet antibody test cannot rule out ITP as a diagnosis. According to the authors, this test is not recommended as part of routine testing. Antiplatelet antibodies are not needed to diagnose ITP [14].

According to studies from Italy, Japan and Korea, many people with ITP have Helicobacter pylori infection in the stomach, and elimination of H. pylori results in improved platelet count. However, in the United States and Spain, the prevalence of H. pylori infection is less pronounced in people with ITP, and eradication of H. pylori does not increase platelet count. As a result, routine testing for H. pylori infection in adults and children with ITP is not recommended [15].

According to a Taiwanese study, ITP may be an early hematologic manifestation of HIV infection. Patients with ITP were 6.47 times more likely to have HIV infection than patients without ITP, according to Lai et al., who recommended that patients with ITP be investigated for undiagnosed HIV infection [16].

5.2 Imaging Studies

Other possible causes of thrombocytopenia can be ruled out using non-invasive imaging studies such as computed tomography (CT) scanning and magnetic resonance imaging (MRI). However, it is not routinely evaluated in patients with immune thrombocytopenia (ITP). When medical history or physical indications indicate significant internal bleeding, a quick CT scan or MRI is recommended [17].

6. HISTOLOGIC FINDINGS

6.1 Bone Marrow Aspirate

Aspirate should have normal cell structure and shape of erythroid and myeloid progenitor. It is possible to increase the number of megakaryocytes. Megacariocytes may be large and immature due to increased peripheral platelet loss, although in many cases their shape is normal. Megacariocyte morphology must be carefully evaluated to rule out early myelodysplastic syndrome in elderly patients [18].

6.2 Bone Marrow Biopsy

Normal marrow cellularity should be visible in sections of a needle biopsy specimen or marrow clot, with no indication of hypoplasia or increased fibrosis [19].

6.3 Splenic Evaluation

There are no specific results in the spleen. The presence of extramedullary hematopoiesis in adults is uncommon and may indicate myeloid metaplasia. The spleen taken from individuals with immunological thrombocytopenia (ITP) should be thoroughly examined for evidence of primary splenic lymphoma, granuloma, or any other unrecognizable infectious disease [20].

6.4 Bone Marrow Examination

In patients with immune thrombocytopenia (ITP), bone marrow aspiration and biopsy showed normal or elevated megakaryocyte counts in the absence of other major abnormalities. The effectiveness of the bone marrow test in the diagnosis of ITP is unclear and further research is needed before clear criteria can be established [21].

Adult patients should follow the following recommendations: Examine the bone marrow of thrombocytopenic individuals over the age of 60 to rule out myelodysplastic syndromes or leukemia. Baseline pre-treatment bone marrow aspiration is beneficial for future reference in the treatment of corticosteroids. After 3-6 months of treatment, many individuals develop treatment-resistant chronic ITP and aggressively seek alternative diagnoses. Marrow aspirate was taken before any potential steroid-induced changes were beneficial. Before splenectomy, bone marrow aspiration and biopsy should be done to check for hypoplasia or fibrosis [22].

Bone marrow examination is not required for children and adolescents with typical ITP symptoms, or for children who fail treatment with intravenous immunoglobulin, according to the guidelines of the American Society of Hematology. According to the guidelines, bone marrow examination is not required for similar patients before starting corticosteroid therapy or undergoing splenectomy [23].

Children with abnormal hematological findings such as immature cells or persistent neutropenia on a peripheral smear should have their bone marrow examined. On peripheral smears, many children with acute ITP show an increase in the number of normal or abnormal cells, indicating a recent viral illness. When normal treatment fails after six months, bone marrow aspiration is recommended [24].

7. DIFFERENTIAL DIAGNOSIS

Thrombocytopenia has a wide range of differential diagnoses, including but not limited to: systemic symptoms (fever, joint pain, or weight loss), hepatosplenomegaly, lymphadenopathy, leukocytosis, and significant anemia (HG10) leukemia. All clinical and laboratory findings. Particularly acute lymphocytic leukemia (ALL). Epstein-Barr virus, CMV, hepatitis C and HIV-1 are all active infections. Anemia, jaundice, elevated reticulocyte count, sporocytes and polychromasia are all clinical and laboratory findings of autoimmune hemolytic anemia (AIHA). Thrombocytopenia may be a current symptom of systemic autoimmune disease such as systemic lupus erythematosus (SLE) or autoimmune lymphoproliferative syndrome (ALPS) [25].

In the sequence of recurrent infections, some immunodeficiency syndromes, especially the common variable immunodeficiency (CVID), appear with thrombocytopenia. In a man with eczema, small platelet size, hemorrhagic platelet count, family history, and no response to ITP treatment, Wiskot-Aldrich syndrome should be considered. People with thrombocytopenia, hypocalcemia and cardiac abnormalities should be considered for Di-George syndrome. Heparin, quinidine, phenytoin, sulfonamides, valproate, and vancomycin are just some of the drugs that can cause thrombocytopenia. Thrombocytopenia can occur with bone marrow failure, as seen in aplastic anemia. Hemolytic uremic syndrome (HUS) is characterized by a recent history of hemolytic anemia, thrombocytopenia, and severe kidney injury, as well as gastrointestinal symptoms [26].

Severe microangiopathic hemolytic anemia, thrombocytopenia, and neurologic symptoms characterize thrombotic thrombocytopenic purpura (TTP) (ie, confusion, drowsiness, or headache). Thrombocytopenia associated with hemorrhage and thrombosis with end-organ damage due to sepsis, trauma, or cancer is a symptom of disseminated intravascular coagulation (DIC) [27].

8. TREATMENT

8.1 Initial Management

If a child's platelet count is less than 30,000 / microliter, they should be kept away from activities that put them at risk of bleeding from trauma. These activities include, but are not limited to, contact and collision sports (such as soccer, boxing, lacrosse, and hockey) and any other activity that carries a risk of head injury (such as baseball, soccer, skiing, Or gymnastics). Antiplatelet drugs such as aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in both children and adults. Patients with a platelet count below 20,000 / μL should avoid anticoagulants such as heparin, enoxaparin, and warfarin [28].

8.2 First-Line Therapies

According to the 2019 guidelines of the American Society of Hematology, children with no or mild bleeding (eg wounds) can be monitored for bleeding regardless of platelet count. This includes repeated laboratory tests to check platelet counts under the supervision of a pediatric hematologist. Fifty to

seventy percent of children recover without intervention within three to six months of initial treatment. Prednisolone 2–4 mg / kg / day (maximum 120 mg daily) is recommended for 5–7 days for children with non-fatal bleeding and / or poor health. Intravenous immunoglobulin (IVIG) or anti-D-immunoglobulin may be given to children when corticosteroids are contraindicated or not selected [29].

The 2019 American Society of Hematology guidelines suggest that adults with a platelet count greater than 30 x 10 / L who are asymptomatic and have mild sputum bleeding should be seen without treatment. Frequent laboratory tests under the supervision of a hematologist are required to monitor platelet levels. Adults with a platelet count of less than 30 x 10 / L and minimal bleeding should be treated with corticosteroids for six weeks. Adults with a platelet count of less than 20 x 10 / L who are asymptomatic and have minimal mucus bleeding should also be hospitalized for short-term corticosteroid therapy. Prednisone (0.5-2 mg / kg / day) or dexamethasone (40 mg / kg / day) are corticosteroids recommended based on the instructions [30].

8.3 Second-line Therapies

Children with non-life-threatening mucosal bleeding and/or decreased health-related quality of life who do not respond to first-line treatments or who have chronic ITP should first try a receptor agonist of thrombopoietin (eltrombopag or romiplostim), according to the 2019 American Society of Hematology Guidelines. If a thrombopoietin receptor agonist does not work after some time, rituximab should be given as the next treatment option. Splenectomy is often reserved for children with severe thrombocytopenia and bleeding symptoms who require numerous drug treatments and should be postponed as long as possible due to the high risk of spontaneous remission and asplenic sepsis. The current suggestion for splenectomy in children is to wait at least 12 months after diagnosis and until the child is older than five years [31].

According to the 2019 Guidelines of the American Society of Hematology, adults with ITP who have corticosteroid dependence or corticosteroid refractory for more than 3 months or are considered chronic ITP should receive second-line treatment. These include thrombopoietin receptor agonists (eltrombopag, romiplostim, or ava thrombopog), rituximab, and splenectomy. Second-line treatments are selected based on ITP duration, number of hospital stays, comorbidities, and patient preferences. Thrombopoietin receptor agonists are the treatment of choice for patients who desire a long-term response and do not want surgery. Rituximab is the best treatment for patients who do not want to take the drug for a long time or who do not want to have surgery. Splenectomy should be considered for patients who desire a long-term response, but should be postponed after the first year of diagnosis as it may be in remission within the first year [32].

In 2018, the FDA authorized fostamatinib, a spleen tyrosine kinase (Syk) inhibitor, as a therapy option for individuals with refractory illness to second-line medications. Danazol or immunosuppressive medicines such as azathioprine, cyclosporine, and mycophenolate are also possibilities for second-line treatment [33].

9. PROGNOSIS

Despite treatment, most children with ITP recover within three to six months of initial manifestation. According to studies, between ten and twenty percent of children with ITP develop chronic ITP, which is defined as thrombocytopenia lasting more than twelve months after diagnosis. Older age at diagnosis, less severe thrombocytopenia at initial diagnosis, slower development of symptoms, absence of prior infection or vaccination prior to diagnosis of ITP, and absence of mucosal bleeding in the time of presentation are risk factors for chronic ITP. In children with chronic ITP, spontaneous remission occurs in about half of cases after years of treatment, with many cases occurring within the first two years, but others up to five years after diagnosis [34].

Chronic ITP in children under the age of ten is more likely to go into remission than in older children. Children who die with ITP die primarily from complications related to catastrophic bleeding, particularly cerebral hemorrhage. The majority of mortality and morbidity in children with chronic ITP is caused by the long-term effects of immunosuppressive treatments, mainly infections [35].

With one or more treatments, most adults achieve a stable platelet count. Spontaneous remission occurs in about 10% of people and usually occurs within the first 6 months. One-third to two-thirds of people without spontaneous remission achieve stable platelet counts with first-line treatment. The remaining adults with ITP develop refractory disease and require additional second-line treatment or, in the worst case, splenectomy. The overall risk of developing systemic lupus erythematosus or chronic lymphocytic leukemia is recorded when the first ITP is generated by an

autoimmune mechanism and then an adult develops systemic lupus erythematosus or chronic lymphocytic leukemia [36].

Adult mortality from ITP is only slightly higher than the age-matched group and is mostly owing to bleeding problems, as it is in children. The majority of ITP patients die of causes unrelated to the disease rather than complications from the disease or therapy [37].

10. EPIDEMIOLOGY

Annual incidence in children is estimated at between 1 and 6.4 per 100,000. According to researchers, the annual incidence of pediatricians is higher, because the reported cases are based on symptomatic ITP, which requires hospitalization rather than the overall incidence of ITP. Children can appear at any age, although the prevalence is highest between the ages of 2 and 5, with a second increase during adolescence. From infancy to infancy, men have a slight advantage over women. However, women outnumber men in their youth (ie, between the ages of 18 and 45), due to increased estrogen levels, which may lead to spontaneous immunity in these patients. With increasing incidence in spring and early summer, seasonal changes have also been observed in adolescents, corresponding to viral infections. Annual incidence rates in adults are estimated at between 1 and 6 per 100,000. However, since ITP is more chronic in adults, the prevalence rate is approximately 12 cases per 100,000. In adults, peak incidence occurs at age 60, however, incidence increases with age. The frequency is the same for men and women over 60 years of age [38].

11. DISCUSSION

ITP patients face a variety of difficulties. ITP is a diverse disease with high morbidity, including bleeding, but not limited enough. Despite the availability of numerous drugs with different modes of action, the treatment of ITP can be uncertain due to differences in its underlying pathobiology and natural history. ITP patients face a variety of physical and mental barriers when trying to control their platelet count, manage treatment side effects, and counter the risk of recurrence [39].

Despite recent advances in the management of ITP, some areas still need more research. We need a short, validated tool that reveals clinically important patient reporting results and can be easily integrated into routine ITP clinical care. The effects of medications on fatigue and HRQoL should be assessed using these tools. In addition, more research is needed on the potentially harmful effects of corticosteroids on patients' lives [40].

Patients say it is important for them to maintain a healthy platelet count, but most ITP medications do not work. Therefore, it is important to identify the limitations of existing treatments and evaluate new technologies. Given the recent guidelines recommending shorter corticosteroid periods, first-line medication with the ability to improve rapid response and long-term remission will ultimately improve HRQoL and be desirable. There is currently insufficient evidence to support rituximab or TPO-RAs as a first-line treatment for ITP; However, more information about costs, effects on HRQoL, long-term remission and safety can help advance the management and integration of these drugs [41].

Primary immune thrombocytopenia (ITP) is an autoimmune disease that causes isolated thrombocytopenia due to increased platelet destruction and reduced platelet production. Corticosteroids, intravenous immunoglobulin, and anti-D immunoglobulin are first-line drugs. Splenectomy, rituximab, and thrombopoietin receptor agonists, as well as a number of other immunosuppressive drugs, and experimental therapy are options for patients who are resistant to these therapies, who become corticosteroid-dependent, or who relapse after corticosteroid treatment. . Despite recent advances in ITP management, some areas still require more research. Although evaluation of patient-reported ITP outcomes is important to understand and guide treatment, these indicators are not routinely tested in the clinical setting [42].

As a result, corticosteroids are first-line treatments for both children and adults, but there is no evidence to improve the quality of life or other patient outcomes in either case. Long-term courses of corticosteroids, whether children or adults, can significantly affect a patient's quality of life due to sleep disorders, weight gain, and mental health issues. In adults, additional treatment may be needed to deal with excessive bleeding, but for most patients, the results are temporary. As a result, it is important to identify the limitations of existing medications and review modern approaches such as the likelihood of a reaction and the amount of effect on the patient's most distressing symptoms, and the treatment developed based on the risk of side effects or Complications [43].

Finally, a validated screening approach that identifies clinically relevant patient-reported findings will help patients and clinicians in routine clinical practice, proper monitoring of patient health beyond the management of ITP test results and physical

symptoms. The purpose of this descriptive review is to examine the management of patients with newly diagnosed and refractory ITP by focusing on the limitations of existing drugs from a patient perspective [44].

12. CONCLUSION

Clinically severe ITP can occur in both children and adults, making it a common diagnosis among pediatric and adult healthcare professionals. While the pediatrician or general practitioner may be the first to notice the initial rash with hematologic abnormalities, effective diagnosis and treatment requires collaboration with a multidisciplinary team of hematologists, pathologists, and nurses knowledgeable about ITP. Treatment regimens can include information about the diagnosis of ITP, the risk of bleeding associated with the disease, and effective therapy. Many patients and caregivers need to be educated on how to avoid certain sports and activities that are associated with an increased risk of bleeding, as well as how to avoid certain medications, such as aspirin and NSAIDs, that can further lower platelet counts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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