소아 면역성혈소판감소증의 진단적 접근

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Diagnostic Approach of Childhood Immune Thrombocytopenia

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Immune thrombocytopenia (ITP) is the most common cause of thrombocytopenia in children and can be defined as an autoimmune disorder of isolated thrombocytopenia without other causes of thrombocytopenia. This review will focus on the diagnostic approach of ITP, especially regarding the differential diagnosis. The practice of differential diagnosis has the goal of distinguishing primary ITP from secondary ITP and nonimmune thrombocytopenia requiring different treatments and showing different prognoses.

Key Words: Children, Diagnosis, Immune thrombocytopenia, Nonimmune thrombocytopenia, Secondary ITP

Introduction

Immune thrombocytopenia (ITP) is the most common cause of thrombocytopenia in children and can be defined as an autoimmune disorder of isolated thrombocytopenia without other causes or disorders causing thrombocytopenia. In thrombocytopenia, ITP is a default diagnosis [1-6].

The platelet threshold for the diagnosis of ITP has changed over the years. The ITP working group defined thrombocytopenia as a condition characterized by platelet count lower than 100,000 platelets per microliter [5,7]. The incidence of ITP is 4-9 cases out of 100,000 cases a year, and about half of the pediatric cases are occurring in children who used to be healthy [8,9].

This review will focus on the diagnostic approach of ITP, especially regarding the differential diagnosis. The practice of differential diagnosis has the goal of distinguishing primary ITP from secondary ITP and nonimmune thrombocytopenia requiring different treatments and showing different prognoses.
Platelet

The platelet is round and flat disk shape with a diameter of 1-2 micrometer in the stabilized state and change to function with irregular spherical shape giving out pseudopod in the activated state. Platelet is produced in the megakaryocytes of the bone marrow. It will survive for about 7-9 days and are removed from the reticuloendothelial system of spleen or liver. The main function is hemostatic action, and it is also involved in wound recovery and vascular remodeling. Traditionally, the normal range of platelet count has been 150,000-450,000/µL. Decreased platelets can lead to various degrees and types of hemorrhage, ranging from petechiae to severe hemorrhage, as well as delayed hemostasis [10-12].

In the case of hemostatic disorder, there is no ideal precise test for accurate diagnosis. With the patient’s medical history and physical examination, blood tests such as complete blood count (CBC), prothrombin time, activated partial thromboplastin time, peripheral blood, automated platelet function test (PFA-100) can be investigated at the bedside. When blood tests are performed in pediatric patients, a relatively large amount of blood is required, and some test results have limitations that are not valid from pediatric patients. Attention should be paid to interpretation in many cases such as accompanying infection condition, concomitant medication or blood collection inappropriately. In many cases, reexamination is necessary [4,13-15].

Classification

The categories of ITP can be classified according to etiology, disease evolution, refractoriness and age of onset. The terms, definitions and criteria of ITP were summarized in 2009 by international working group. ITP was used as the acronym for immune thrombocytopenia [4,5].

Etiologic classification is divided into primary ITP and secondary ITP. The primary ITP, classically defined “idiopathic,” is often seen in childhood after non-specific viral infections, Secondary ITP has a more complex etiology, as specific infections, drugs or vaccinations and immunologic abnormalities,

According to the evolution of disease, it is possible to identify three categories of ITP: newly diagnosed ITP; persistent ITP, still exists 3 months after diagnosis; and chronic ITP, lasting more than 12 months after diagnosis. In practice, acute ITP can be used as a concept against chronic ITP for convenience. Chronic ITP accounts for about 20% of the total cases of childhood ITP [16].

Refractory ITP is a condition of severe ITP which has considerable risk of bleeding requiring therapy after splenectomy or relapse after splenectomy. However, splenectomy should be delayed as long as possible expecting spontaneous remission and benign courses in children. Therefore, when non-splenectomized children with ITP do not respond to conventional medical therapy, the term “unresponsive to the specified therapy” would be used instead of “refractory” [5].

By age of onset, ITP can be divided into three categories: childhood-onset ITP, adolescents-onset ITP, and adult-onset ITP. ITP in young children is typically acute and self-remitting, and primary forms are the most common. ITP in adolescents shows a higher rate of chronicity and a greater percentage of secondary ITP [17,18].

Diagnosis

ITP is diagnosed by excluding other diseases presenting with thrombocytopenia through careful history consideration, physical examination, and laboratory evaluation [19,20],

1) Symptoms

The characteristic history is that a healthy child show sudden systemic petechiae or purpura without any trauma. Clinical findings are usually normal except petechiae and purpura. Immune thrombocytopenia may be asymptomatic, just checked by routine laboratory evaluations. In symptomatic cases, the number of platelets is very low (below 10,000/µL) and gum or mucous membranes bleeding is usually seen, and patients may also have nosebleeds, excessive menstruation, or intestinal bleeding. The most severe bleeding complication is intracranial hemorrhage (ICH)
Table 1. Diagnostic elements of ITP in children

| History taking                  | Present and past history of bleeding symptoms (petechiae to severe hemorrhage) |
|--------------------------------|--------------------------------------------------------------------------------|
|                                 | Systemic symptoms (fever, weight loss, etc.)                                   |
|                                 | Infection history (CMV, EBV, VZV, H. pylori, etc.)                             |
|                                 | Risk factors for HIV, Hepatitis B or C                                         |
|                                 | Drug (heparin, alcohol, quinidine, sulfonamides, aspirin) and herbal medicines history |
|                                 | Transfusion history                                                            |
|                                 | Autoimmune disease history (arthritis, skin rash, alopecia, venous thrombosis, etc.) |
|                                 | Family history                                                                 |
|                                 | Vaccination history (MMR, Hepatitis A, Hepatitis B, Influenza, DTaP, Varicella, Pneumococcus, etc.) |
|                                 | Alcohol history<sup>a</sup>                                                     |
|                                 | Pregnancy status<sup>a</sup>                                                    |
|                                 | Comorbid conditions (GI/CNS/GU disease, etc.)<sup>a</sup>                      |
| Physical examination            | Bleeding sign                                                                  |
|                                 | Lymphadenopathy/hepatomegaly/splenomegaly                                       |
|                                 | Symptoms of infection (HIV, other viral infection, etc.)                         |
|                                 | Symptoms of autoimmune disease (arthritis, goiter, nephritis, vasculitis, etc.) |
|                                 | Skeletal anomalies (inherited/congenital thrombocytopenia, etc.)                |
|                                 | Symptoms of thrombosis<sup>a</sup>                                              |
| Laboratory test                 | Complete blood count (including re-test with citrate bottle)                   |
|                                 | Reticulocyte count                                                             |
|                                 | Peripheral blood smear                                                         |
|                                 | Coagulation and platelet function screening test                               |
|                                 | Immunoglobulin level                                                           |
|                                 | Autoimmune profile                                                            |
|                                 | Direct antiglobulin test                                                        |
|                                 | HIV, hepatitis B and hepatitis C screening                                      |
|                                 | Blood type                                                                     |
|                                 | Bone marrow examination (in selected case)<sup>a</sup>                          |
|                                 | H. pylori (in selected case)<sup>a</sup>                                        |
| Test of potential utility       | Glycoprotein-specific antibody                                                  |
|                                 | Antiphospholipid syndrome screening                                             |
|                                 | Antithyroid antibodies and thyroid function test                               |
|                                 | Viral PCR for parvovirus and CMV                                               |
|                                 | Pregnancy test (in women of childbearing potential)<sup>a</sup>                 |
| Test of unproven benefit        | Antinuclear antibodies (in suspecting autoimmune disease)<sup>a</sup>          |
|                                 | Thrombopoietin                                                                 |
|                                 | Reticulated platelets                                                           |
|                                 | Platelet-associated immunoglobulin G                                          |
|                                 | Bleeding time                                                                  |
|                                 | Platelet survival study                                                        |
|                                 | Serum complement                                                               |

<sup>a</sup>Adapted from Provan et al. [26] and George et al. [28].

EBV, Epstein-Barr virus; CNS, central nervous system; CMV, cytomegalovirus; DTaP, a vaccine for diphtheria, pertussis, and tetanus; GI, gastrointestinal; GU, genitourinary; HIV, human immunodeficiency virus; MMR, measles-mumps-rubella combined vaccine; PCR, polymerase chain reaction; VZV, varicella zoster virus.

<sup>a</sup>Test in selected cases.
2) Laboratory

In CBC, it is observed as isolated thrombocytopenia. At the beginning of the invention, patients had moderate to severe thrombocytopenia, usually less than 20,000/µL. The mean platelet volume and platelet distribution width may tend to increase from accelerated turnover of platelets. Hemoglobin, leukocyte count, and leukocyte differential count should be normal, but anemia can occur when there are severe nosebleeds or menorrhagia. In PT and aPTT, they are within normal range. In PFA-100 or bleeding Time, it is extended beyond the normal range due to thrombocytopenia [14,23,25].

Bone marrow examination is usually performed prior to therapy (e.g., administration of thrombopoietin-receptor agonists [TPO-RAs]), to ensure that bone marrow is normal. However, according to the recent guidelines, bone marrow examination is not necessary in children with typical ITP or even after failure to intravenous immunoglobulin therapy [4,19]. Regarding anti-platelet antibody and anti-nuclear antibody, they are not helpful for either exclusion or confirmation of the diagnosis of ITP and not necessary in children with suspected ITP [4,19,26-28].

Table 1 shows the diagnostic elements of ITP in children.

### Table 2. Causes of secondary ITP and nonimmune thrombocytopenia in children

| Secondary ITP                       | Causes                                                                 |
|-------------------------------------|------------------------------------------------------------------------|
| Infection                           | CMV, EBV, VZV, HBV, HCV, HIV, parvovirus                              |
|                                     | H. pylori, tuberculosis                                                |
| Therapy with certain drugs          | Drug (NSAIDS, antibiotics, antivirals, etc.) and Herbal medication     |
|                                     | Vaccination (MMR, Hepatitis A, Hepatitis B, Influenza, DTaP, Varicella, Pneumococcus, etc.) |
|                                     | Transfusion                                                            |
| Autoimmune                          | Autoimmune thrombocytopenia (Evans syndrome, etc.)                    |
|                                     | Antiphospholipid syndrome                                              |
|                                     | Systemic lupus erythematosus                                           |
|                                     | Sjogren’s syndrome                                                    |
|                                     | Autoimmune lymphoproliferative syndrome                               |
|                                     | Autoimmune thyroiditis (Hashimoto’s diseases, etc.)                   |
| Immunodeficiency                    | Common variable immune deficiency                                      |
|                                     | IgA deficiency                                                        |
|                                     | DiGeorge’s syndrome                                                   |
|                                     | Wiskott-Aldrich syndrome                                              |
| Others                              | Neonatal alloimmune thrombocytopenia                                  |
| Nonimmune thrombocytopenia          | Congenital agemakaryocytic thrombocytopenia (CAMT)                    |
|                                     | Thrombocytopenia-absent radius (TAR) syndrome                          |
|                                     | May-Hegglin anomaly                                                   |
|                                     | Wiskott-Aldrich syndrome (X-linked)                                    |
| Bone marrow failure syndrome        | Fanconi anemia, Myelodysplastic syndrome                              |
| Lisosomal storage disorders         | Gaucher’s disease                                                      |
|                                     | Niemann-Pick’s disease                                                 |
| Platelet-type von Willebrand disease| Bernard-Soulier syndrome, Velocardiofacial syndrome                   |
| Chromosome 22q syndrome             | Hypersplenism                                                          |
| Others                              | Bone marrow transplantation, chemotherapy                              |
|                                     | Disseminated intravascular coagulation                                |
|                                     | Thrombotic microangiopathy                                             |

Adapted from Neunert et al. [4] and Consolini et al. [17].

EBV, Epstein-Barr virus; CMV, cytomegalovirus; DTaP, a vaccine for diphtheria, pertussis, and tetanus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; MMR, measles-mumps-rubella combined vaccine; VZV, varicella zoster virus.
1) Pseudothrombocytopenia

In cases of clotting occurs as a result of inappropriate management during the blood test process or as a result of difficult blood sampling or in cases of technical problems and lack of blood collection volume.

In this cases, the results are reported to thrombocytopenia even though the patient’s platelet count is normal. If there is no symptom of bleeding, review the patients and carry out retest. In some patients, EDTA-dependent platelet clumping can occur, so the peripheral blood smear should be checked for clumping and retest using citrate tube instead of EDTA tube should be conducted [16,29,30].

2) Infections

Thrombocytopenia may occur secondary to infection with viruses such as infectious mononucleosis (CMV, EBV, VZV), hepatitis virus (HCV), HIV, or H. pylori infection. In this case, treatment and prognostic course may follow the causative infection, usually with chronic course through different mechanisms [16,31-35].

3) Drugs

Thrombocytopenia may associated with therapeutic medicines (some antibiotics, some anticonvulsants, etc.) or alternative medicines (such as vitamins, nutritional supplements, herbs, etc.) taken in the past month. It is often not recognized, developing recurrent unexplained thrombocytopenia. It can be diagnosed when thrombocytopenia develops repeatedly associated with a specific medicine and exhibits complete recovery after cessation of the same drug. Heparin-induced thrombocytopenia is possible to observe in childhood but rarely [36-40].

4) Autoimmune disease

Thrombocytopenia of chronic course can be seen in various systemic autoimmune disease such as systemic lupus erythematosus (SLE), Sjogren’s syndrome, Evans syndrome (autoimmune hemolytic anemia and thrombocytopenia), anti-phospholipid antibody syndrome (APS), autoimmune lymphoproliferative syndrome (ALPS), and autoimmune thyroiditis. In adolescent patients, antinuclear antibody (ANA) tests are more likely to be positive. When accompanied by anemia, coombs test should be screened for Evans syndrome [41-46].

5) Immunodeficiency

Some immunodeficiency such as common variable immunodeficiency (CVID), selective IgA deficiency, and DiGeorge’s syndrome may have immune thrombocytopenia as manifestations [16,23,47,48].

6) Genetic/congenital thrombocytopenia

Congenital thrombocytopenia, such as congenital amegakaryocytic thrombocytopenia (CMT), thrombocytopenia-absent radius (TAR) syndrome, May-Hegglin anomaly, often misdiagnosed as ITP and commonly present with altered platelet size. Wiskott–Aldrich syndrome usually comprehends the association of thrombocytopenia with small platelets, eczema, and frequent infections. In acute leukemia, inherited bone marrow failure syndrome such as Fanconi anemia, thrombocytopenia can occurs but associated with other cytopenias, Lysosomal storage disorders, such as Gaucher’s and Niemann-Pick’s disease, may present thrombocytopenia at clinical onset, usually combined with splenomegaly. Platelet-type von Willebrand disease or chromosome 22q syndrome such as Bernard-Soulier syndrome or velocardiofacial syndrome may present thrombocytopenia associated symptoms [25,49-57].

7) Age-associated considerations

In neonatal age, common form of ITP is the alloimmune due to the production of maternal antibodies directed against neonatal platelet alloantigens. In adolescent females, the possibility of ITP secondary to pregnancy should be considered [58,59].

In vaccination periods, providing protective immune responses, vaccines may promote autoimmune diseases, such as ITP. Vaccine-associated autoimmunity can be caused either by antigen-mediated immune mechanisms or by vaccine constituents or adjuvants. However, most vaccine-associated ITP is mild and well-responsive to therapy. In contrast, because infections may trigger ITP causing severe consequences, it would be thoughtful to vaccinate children
with previous history of ITP [36,60,61].

Table 2 lists the possible causes of secondary ITP and non-immune thrombocytopenia in childhood and adolescence.

## Conclusion

Over the past several decades, the diagnosis and management of ITP has evolved. This report focused on the diagnosis of ITP. As differential diagnosis is important in practicing ITP disease, physicians should keep in mind the importance of distinguishing whether it is primary ITP or secondary ITP or nonimmune thrombocytopenia.

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