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Thrombocytopenic Syndromes Masquerading as Childhood Immune Thrombocytopenic Purpura

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Abstract

Immune thrombocytopenic purpura (ITP) is the most common cause of thrombocytopenia in children and adolescents. However, there are a number of other diagnoses that are often mistaken for ITP. A 10-year retrospective chart review was performed at the Children's Hospital of Alabama to characterize ITP. Initially, 492 patients who had the coded diagnosis of ITP (ICD 287.3) were identified. However, 83 (17%) of patients were found to have alternative diagnoses on chart review. Of the 83 patients, 13 patients (3%) represented coding errors or study classification errors. The 70 remaining patients (14%) had an alternative explanation for their thrombocytopenia, consisting of 31 different diagnoses. The most common diagnoses were familial thrombocytopenia (10%), systemic lupus erythematosus (9%), hypersplenism (9%), neonatal alloimmune thrombocytopenia (7%), Wiskott–Aldrich syndrome (7%), or systemic infection (6%). In total, 16 of the patients (23%) were ultimately diagnosed with one of a number of congenital syndromes with concurrent thrombocytopenia. Although this review confirms that most children with thrombocytopenia are diagnosed with ITP, 14% of the study population manifested other diagnoses. The clinician evaluating a child with thrombocytopenia must keep an open mind about the possible diagnosis and perform a comprehensive and thoughtful evaluation based on the clinical picture. ITP must be a diagnosis of exclusion as misdiagnosis in a child with thrombocytopenia may have a significant impact on morbidity and mortality.

Keywords

thrombocytopenia, autoimmune diseases, Fanconi anemia, congenital marrow failure syndromes, viral infections

Introduction

Immune thrombocytopenic purpura (ITP) is the most common cause of thrombocytopenia in children and adolescents.[1] The predominance of ITP as the etiology of thrombocytopenia in children leads clinicians to frequently assume the diagnosis in any child with isolated, moderate, or severe thrombocytopenia. However, ITP is a diagnosis of exclusion and the differential diagnosis of thrombocytopenia in children is broad and includes a significant number of serious, life-threatening, or life-altering illnesses.[2,3] Although the list of possible alternative etiologies of thrombocytopenia in children is known and described, the actual prevalence of these diagnoses in children evaluated for thrombocytopenia is not well characterized. Previously, we reported a 10-year experience with ITP in a large, tertiary care children's hospital.[4] We now present our experience from the same time period of children with illnesses mimicking or masquerading as ITP. We further suggest a clinical evaluation using history, physical examination and basic laboratory evaluations to identify children with thrombocytopenia of alternative causes.

Material and Methods

A 10-year retrospective chart review (1993-2003) was performed at the Children's Hospital of Alabama with the goal of characterizing ITP in children. Inclusion criteria included the ICD code for ITP (287.3). Using this criterion, 492 children, aged 1 to 18 years were identified for study. A total of 409 patients were confirmed with ITP and previously reported.[4] However, 83 (17%)

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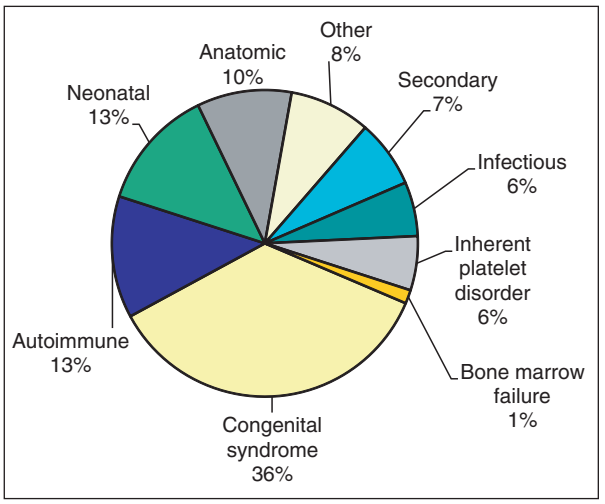

Figure 1. Categories of disorders masquerading as immune thrombocytopenia purpura

patients initially coded as ITP were found to have alternative diagnoses. Of the 83 patients, 13 patients represented coding errors or study classification errors. The 70 remaining patients had an alternative explanation for their thrombocytopenia, consisting of 31 different diagnoses. This 70 patient group is the basis of the present report.

Results

Figure 1 demonstrates the broad categories of alternative diagnoses mimicking ITP in our series. Table 1 outlines the specific diagnoses by classification group. The most common diagnoses were familial thrombocytopenia (10%), systemic lupus erythematosus (9%), hypersplenism (9%), neonatal alloimmune thrombocytopenia (7%), and Wiskott–Aldrich syndrome (7%). In total, 16 of the patients (23%) were ultimately diagnosed with one of a number of congenital syndromes with concurrent thrombocytopenia. These included Wiskott–Aldrich syndrome, thrombocytopenia with absent radii (TAR) syndrome, Hermansky–Pudlak syndrome, Fanconi anemia, Klippel–Trenaunay–Weber syndrome, DiGeorge syndrome, and osteopetrosis. A total of 10 patients (14%) were diagnosed with a rheumatologic/autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis, Evans syndrome, and Crohn's disease). Four patients (6%) had an infectious etiology (cytomegalovirus [CMV], human immunodeficiency virus [HIV], gram negative septicemia). Six patients (9%) had disorders of impaired hematopoiesis or platelet segmentation (macrothrombocytopenia, May–Hegglin anomaly, amegakaryocytic thrombocytopenia, and aplastic anemia). There were 9 patients (13%) with neonatal alloimmune thrombocytopenia.

Table 1. Disorders Masquerading as Immune Thrombocytopenic Purpura[a]

Congenital
Familial thrombocytopenia (7)
Wiskott–Aldrich syndrome (5)
Thrombocytopenia with absent radii (4)
Hermansky–Pudlak syndrome (2)
Fanconi's anemia (2)
Klippel–Trenaunay–Weber syndrome
DiGeorge syndrome
Amegakaryocytic thrombocytopenia
Von Willebrand's—type II
Osteopetrosis
Autoimmune
Systemic lupus erythemetosus (6)
Rheumatoid arthritis (2)
Evans syndrome
Crohn's disease
Neonatal
Neonatal alloimmune thrombocytopenia (9)
Anatomic
Hypersplenism (6)
Kassabach–Merritt syndrome from hepatic hemangioma
Secondary
Portal vein thrombosis (2)
Liver failure
Disseminated intravascular coagulopathy
Infectious
Congenital cytomegalovirus (2)
HIV
Gram negative sepsis
Inherent platelet disorder
Macrothrombocytopenia (3)
May–Hegglin anomaly
Bone marrow failure
Aplastic anemia
Other
Thrombotic thrombocytopenic purpura (2)
EDTA-dependent pseudo-thrombocytopenia (2)
Lymphocyte hyperplasia
Posttransplant lymphoproliferative disorder

[a]Figures in parentheses denote number of patients.

Several diagnoses could fit multiple categories. Most children with thrombocytopenia masquerading as ITP in our series had significant congenital abnormalities of platelet production or hematopoiesis, serious autoimmune diseases, anatomic defects or important infections. In only rare cases was the diagnosis of limited clinical importance (EDTA-dependent pseudo-thrombocytopenia in only 2 cases).

Discussion

Immune thrombocytopenic purpura is the most common diagnosis associated with thrombocytopenia in children.[1,2]

The incidence of ITP is difficult to accurately define, but current estimates would predict between 1.9 and 6.4 per 100 000 children per year will be diagnosed with ITP.[5] Usually, the diagnosis of ITP is straightforward, but it is important for the clinician to remember that ITP is a diagnosis of exclusion and that there is no single confirmatory or pathognomonic test for ITP.

The "typical" case of ITP describes a school age child with sudden onset of bruising and petechiae, otherwise well appearing with no history of chronic illness, well grown, with normal complete blood count except for decreased platelet count and a benign physical examination with no organomegaly or other organ defects. In our retrospective review of 10 years of childhood ITP evaluated and treated in a pediatric tertiary care medical center, fully 86% of children initially diagnosed with ITP had that diagnosis confirmed on long-term follow-up. However, 14% (70 children) initially diagnosed with ITP were subsequently found to have other anomalies or illnesses responsible for their thrombocytopenia.

In most cases, clues from a comprehensive history, physical examination, or limited laboratory evaluation suggest alternative diagnoses and serve as important clues for the clinician evaluating a child or young person with thrombocytopenia.

A comprehensive and thoughtful history is an important component of the full evaluation of a child with thrombocytopenia (see Table 2). Age at presentation is an immediate clue since neonatal alloimmune thrombocytopenia and congenital infection would typically present early in life.[6] Autoimmune disorders are more frequent in the teenage years,[7] whereas congenital thrombocytopenias and similar disorders are typically diagnosed in early childhood.[8] The family history is not only most helpful in providing clues to familial forms for thrombocytopenias[9] but also proves useful in identifying several other inherited defects.

Perhaps the most important component of the history in evaluation of children with thrombocytopenia is the past medical history and thorough review of systems. Is there a history of bleeding in a child with a severe thrombocytopenia noted on routine laboratory screening? If the answer is no, pseudo-thrombocytopenia should be considered.[10] A history of deep tissue or joint bleeding is unusual for routine forms of thrombocytopenia such as ITP and should prompt consideration of other disorders including Von Willebrand's disease or consumptive coagulopathy. Recurrent infections suggest an immune deficiency (Wiskott–Aldrich syndrome, DiGeorge syndrome, leukemia).[11] A history of recurrent fractures, vision or hearing loss should prompt evaluation for osteopetrosis.[12] Structural defects of the extremities or other congenital anomalies are clues to marrow failure syndromes such as Fanconi anemia or TAR syndrome.[13] A critical point to consider is how well grown the child is. Many children with Fanconi anemia go undiagnosed despite

Table 2. Historical Features in Evaluation of Thrombocytopenia

Age at presentation
Neonate
Neonatal alloimmune thrombocytopenia
Congenital infection
Infant
Wiskott–Aldrich syndrome (if male)
Familial thrombocytopenia
Congenital amegakaryocytic thrombocytopenia
Other congenital syndromes
Teenager
Autoimmune
Family history
Thrombocytopenia
Familial thrombocytopenia
Bleeding disorders, females with hysterectomies
Von Willebrand's
Infant with previous siblings with neonatal thrombocytopenia
Neonatal alloimmune thrombocytopenia
Rheumatologic disorders
Rheumatoid arthritis
Lupus
Males with eczema, frequent infections
Wiskott–Aldrich syndrome
Past medical history or review of systems
Bleeding history
Is there a real bleeding history? (EDTA-dependent pseudo-thrombocytopenia)
Joint bleeds (Hermansky–Pudlak syndrome)
Heavy menses (Von Willebrand's disease)
Infections
Wiskott–Aldrich syndrome
DiGeorge syndrome
Frequent fractures (osteopetrosis)
Rash/eczema (Wiskott–Aldrich syndrome)
Congenital anomalies
Absent radii (TAR)
Thumb anomalies (Fanconi anemia)
Difficulty with vision/hearing
Osteopetrosis
History of poor growth/delayed development
Fanconi anemia
History of organ transplantation (PTLD)
History of chronic illness (Crohn's, liver disease)
Systemic symptoms (SLE, RA)
Fever
Rash
Joint pain/inflammation
Bloody diarrhea (Crohn's, Wiskott–Aldrich)

Abbreviations: TAR, thrombocytopenia with absent radii; PTLD, lymphoproliferative disorder; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

Table 3. Physical Examination in Evaluation of Thrombocytopenia

Bruising/petechiae
Physical anomalies/dysmorphic features
Abnormal facies (DiGeorge, Fanconi)
Absent radii (TAR)
Thumb anomalies (Fanconi)
Skin abnormalities
Hyperpigmentation (Fanconi)
Hypopigmentation (Hermansky–Pudlak syndrome)
Malar rash (SLE)
Port wine stain (Klippel–Trenaunay–Weber syndrome)
Eczema (Wiskott–Aldrich)
Skin hemangiomas (Kassabach–Merritt)
Splenomegaly (hypersplenism)
Hepatomegaly (liver disease)
Abdominal distension/other mass noted (hemangioma)
Varicosities or other vascular malformations ± underlying soft tissue/bony hypertrophy (Klippel–Trenaunay–Weber)
Growth delay/short stature (Fanconi anemia)
Acute neurologic abnormalities (TTP)
Heart murmur (DiGeorge)
Toxic/ill appearing
Sepsis
TTP
DIC

Abbreviations: TAR, thrombocytopenia with absent radii; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura; DIC, disseminated intravascular coagulation.

chronic thrombocytopenia and poor growth. A child with apparent, chronic ITP with growth parameters below the 5% for age should suggest a diagnosis of Fanconi anemia.[14] Finally, systemic symptoms to include fever, rash, joint swelling, and pain are unusual in ITP and require consideration of other illnesses, including leukemia, autoimmune disorders, or infection. Bone pain in particular is a warning sign for possible acute leukemia.

Like a complete history, a careful physical examination will provide important clues to alternative diagnoses when evaluating a child with thrombocytopenia (see Table 3). The first step is to evaluate for signs of platelet-type bleeding (petechiae, purpura, mucous membrane lesions). The absence of bleeding in a child with apparent severe thrombocytopenia should raise a red flag. In addition, deep seated bleeding into joints or muscles is uncommon in routine childhood ITP and should also result in consideration of alternative diagnoses. Dysmorphic features and abnormalities of the thumb or forearm should suggest syndromes such as TAR or Fanconi anemia.[8] Skin abnormalities, including hyperpigmentation (Fanconi anemia), hypopigmentation (Hermansky–Pudlak syndrome[15]), malar rash in lupus,[16] port wine stain in Klippel–Trenauny–Weber syndrome,[17] eczema in Wiskott–Aldrich syndrome,[11] and large hemangiomas in Kassabach–Merritt syndrome[18] all offer important clues. Organomegaly is unusual in ITP and could suggest hypersplenism, liver disease, or malignancy. As stated above, growth delay is a key clue to Fanconi anema. Neurologic defects could suggest an alternative diagnosis such as thrombotic thrombocytopenic purpura[19] or serve as a marker of a central nervous system hemorrhage, a rare but serious complication of ITP.[20] Ill-appearing children with thrombocytopenia should prompt consideration of bacterial or viral sepsis and/or consumptive coagulopathy.[21] Typically, routine childhood cases of ITP are well appearing with diffuse petechiae and purpura.

In most cases of apparent childhood ITP, the necessary laboratory evaluation to confirm the clinical suspicion and rule out other etiologies is quite limited (see Table 4). The most important laboratory evaluation consists of a complete blood count to screen for anemia or abnormalities of the white blood cell count or white blood differential count. Although anemia can occur in cases of ITP with significant bleeding, the presence of anemia or white blood cell abnormalities should raise caution and prompt further evaluation.[22] Many hematologists would also recommend close evaluation of the blood smear by experienced pathologists or hematologists to exclude blood cell abnormalities that provide clues to other diagnoses (see Table 4). The clinician should carefully evaluate morphology comments provided with automated or manual blood counts to search for concerning features. In most children with apparent ITP, no further laboratory evaluation is necessary for diagnosis, although some laboratory tests may help in selection of available therapy options (eg, knowledge of the blood type for possible use of WinRho D as therapy). Depending on the details of the history and physical exam and the level of suspicion of alternative diagnoses, a wide array of other diagnostic laboratory tests are available and may prove helpful (see Table 4). Routine bone marrow evaluation of suspected cases of ITP rarely changes the clinical course or diagnosis and is no longer routinely recommended.[5,23]

Although our review confirms that most children with thrombocytopenia are diagnosed with ITP, fully 14% of our population in a tertiary care medical center manifested other diagnoses. The clinician evaluating a child with thrombocytopenia must keep an open mind about the possible diagnosis and perform a comprehensive evaluation to include careful physical examination, complete blood count with differential, review of the peripheral blood smear to evaluate for platelet size, morphology, and leukocyte inclusions and other directed laboratory studies based on the clinical picture. ITP must be a diagnosis of exclusion as misdiagnosis of ITP in a child with

Table 4. Laboratory Studies in Evaluation of Thrombocytopenia

CBC
Are other counts affected?
Review of smear
Size/number of platelets
Small → Wiskott–Aldrich
Large → giant platelet syndrome
Clumps → EDTA-dependent pseudo-thrombocytopenia
Neutrophil inclusions → May–Hegglin
Signs of hemolysis
TTP
Evans syndrome
Reticulocyte count
Elevated → hemolysis
Decreased → decreased red cell production
PT/PTT
Abnormal → Von Willebrand's, sepsis, and consumptive coagulopathy
Bone marrow aspirate
Amegakaryocytic thrombocytopenia
Aplastic anemia
Chemistries
Hypercalcemia → DiGeorge
Increase in BUN/creatinine → TTP
Liver function tests
Immunoglobulins
Wiskott-Aldrich with low IgM
Lymphocyte markers/functional testing
Wiskott–Aldrich
Rheumatologic markers
ANA, anti-dsDNA, RF
Genetic testing
Wiskott–Aldrich
Viral titers (CMV, HIV)
X-rays/scans/ultrasound
Increased bone density (osteopetrosis)
Hemangioma (Kassabach–Merritt)
Splenomegaly (hypersplenism)
Portal vein thrombosis

Abbreviations: CBC, complete blood count; TTP, TTP, thrombotic thrombocytopenic purpura; PT, prothrombin time; PTT, partial thromboplastin time; BUN, blood urea nitrogen; ANA, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA; RF, rheumatoid factor; CMV, cytomegalovirus.

thrombocytopenia may have a significant impact on morbidity and mortality.

Authors' Note

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Declaration of Conflicting Interests

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