شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

HANAA ALY

INTRODUCTION

Idiopathic immune thrombocytopenia (ITP) is a heterogeneous disorder with a diverse natural history and diverse pattern of treatment response ***(Kühne et al., 2011).***

It was previously known as idiopathic thrombocytopenic purpura and immune thrombocytopenic purpura, now ITP refers to "immune thrombocytopenia ***(Rodeghiero et al., 2009).***

It is developed secondary to the production of auto-antibodies against platelets leading to isolated thrombocytopenia, in the absence of other causes of thrombocytopenia such as drugs, infections, malignancy, or other autoimmune diseases The International Working Group (IWG) defines ITP as a platelet count less than 100×10^9/L in the absence of other secondary causes. In children, ITP typically presents in otherwise healthy patients, often resolving spontaneously or following therapy within 6–12 months of diagnosis. However, approximately 20%–25% of children with newly diagnosed ITP ultimately develop chronic disease, defined as thrombocytopenia lasting for >12 months ***(Neunert et al., 2011).***

Patients with ITP may bleed from any site particularly when the platelet count is below 10, 000/µl. The most common types of bleeding include epistaxis, oral bleeding, uterine bleeding (menorragia), and hematuria ***(Watts et al., 2004)***.

Intracranial hemorrhage (ICH) is the most devastating complication of ITP in children. Prevention of ICH is the primary goal of ITP treatment. However, the great majority of patients with ITP, even those with very low platelet counts, do not experience severe bleeding ***(Neunert et al., 2011).***

The features that predispose patients to develop ICH in addition to severe thrombocytopenia remain poorly defined. Potential risk factors include platelet counts below 10 to 20 × 10^9/L, non steroidal anti-inflammatory drugs (NSAIDs), head trauma, vasculitis associated with systemic lupus erythematosis (SLE), and cerebral arteriovenous malformations (AVMs) ***(Iyori et al., 2008).***

Hemorrhage in ITP patients may also be clinically silent (occult) and thus not readily determined by history and/or physical examination. Most descriptions of occult hemorrhage in ITP literature are case reports and focus on isolated bleeding in the GI or urinary tract ***(Dang et al., 2009).***

Brain microbleeds are a radiologic construct visualized through magnetic resonance imaging (MRI) that represent perivascular collections of hemosiderin-laden macrophages and are considered to be silent lesions resulting from previous petechial hemorrhages. These lesions are small (<5 mm in diameter) ***(Cordonnier et al., 2011).***

Aim of the Work

The aim of this study to investigate the frequency of occult (subclinical) intracranial hemorrhage (ICH) in Egyptian children with ITP as assessed by MRI brain and its relation to disease charctaristics and patients variables.

Chapter 1
IMMUNE THROMBOCYTOPENIA (ITP)

Definition:

ITP is a common autoimmune disease characterized by low platelet counts and an increased risk of bleeding ***(Donald et al., 2015).***

Individuals with ITP develop thrombocytopenia with a platelet count below the normal range generally defined as less than 100,000 cells/mm^3. They present with a sudden onset of cutaneous bleeding manifestations (bruising and/or a purpuric or petechial rash). Epistaxis is the presenting symptom in approximately 25% of children; haematuria occurs much less frequently. Bleeding after a previous surgery, tooth extraction or trauma ***(Veerle Labarque et al., 2014).***

Pathophysiology:

Total platelet mass in the body is regulated by the balance between production and clearance of platelets. In ITP, platelet mass shrinks as a result of accelerated platelet clearance, which is mainly due to autoantibody-mediated destruction by macrophages in spleen ***(Hirokazu et al., 2013).***

IgG autoantibodies bind to platelets causing their destruction. The antibodies bind to their target glycoprotein

molecules on the platelet surface by the variable portion (Fab) leaving the constant portion (Fc) exposed. The reticuloendothelial system (RES) phagocytic cells, namely monocytes/ macrophages express Fc ɣ receptors (FcɣR) on their surface which recognize and bind to the Fc portion of the antibodies on the platelet surface, thus leading to their rapid removal by phagocytosis. The spleen is very rich in Fc ɣ R-bearing phagocytic cells and is the main site for the destruction of the antibody-coated platelet ***(cooper et al., 2006)***

The production of antiplatelet autoantibodies was explained by the theory of molecular mimicary.An environmental antigen like those on infectious agents, resemble the host self-antigenic structure platelet glycoproteins stimulates B-cells to produce antibodies against the host own platelets. To do so B-cells require the help of CD4 positive T-cells. The role of helper T-cell in the pathogenesis of ITP has been established by many investigators in the recent years. These studies also suggested direct cytotoxic effect of T-cells on platelets in ITP ***(Osman et al., 2012).***

Abnormal T cells have been described in patients with ITP, including a higher T helper cell reactivity against platelets, a lower frequency of circulating $CD4^{+}CD25^{+}FoxP3^{+}$ Tregs and $CD4^{+}$ Th0, and Th1 activation patterns ***(Qiu et al., 2016)***

Most patients with ITP have detectible plasma and/or platelet-bound autoantibodies suggesting a non-antibody-

mediated mechanism of ITP. Related to this, cytotoxic $CD8^+$ T cells were found in the circulation of patients ***(Zhao et al., 2008).***

These $CD8^+$ T cells are able to directly lyse platelets in vitro and can accumulate in the bone marrow, where they are able to inhibit thrombopoiesis ***(Olsoon et al., 2008).***

Furthermore, compared with healthy individuals, $CD3^+$ T cells from patients with ITP have a lower rate of apoptosis and a higher clonal expansion rate, leading to abnormal cytokine secretion, including IL-2, INF-γ, and IL-10 which may be responsible for the lower $CD4^+CD25^+FoxP3^+$ Treg levels and function observed in patients with active disease ***(Ji et al., 2012).***

Tregs, via their critical functions in maintaining self-tolerance by interacting with APC and decreasing $CD19^+$ B cell and $CD8^+$ T cell responses, appear to be the key cell types that may be responsible for the initiation of ITP ***(Grataz et al., 2013).***

Epidemiology of childhood ITP:

Childhood ITP has an estimated incidence of 4.0-5.3 per 100,000 ***(Rodeghiero et al., 2009).***

ITP in children affects males and females equally, but in infancy, males are affected more frequently than females ***(Yong et al., 2010).***

Childhood ITP has an acute abrupt onset and is commonly preceded few weeks earlier by a viral illness or immunization, such as mumps, measles and rubella (MMR) vaccine ***(Hsieh et al., 2010).***

ITP resolves within 6 months in up to 85 % of children with or without drug treatment. However, 25% of children may continue to have symptomatic ITP ***(Nugent et al., 2006).***

Forms of ITP:

Acute ITP:

It refers to the development of isolated thrombocytopenia with a platelet count below the normal range (less than100, 000cells/mm^3 and meeting the diagnostic criteria. ITP that resolves most often in less than 3 months is termed acute ***(Rodeghiero et al., 2009).***

Persistent ITP:

Persistent ITP refers to patients between 3 to 12 months from diagnosis. This includes patients that do not reach spontaneous remission or do not maintain complete response off therapy ***(Rodeghiero et al., 2009)***.

Chronic ITP:

A small proportion (fewer than 20%) of children who present with what appears to be acute ITP will remain thrombocytopenic beyond 8–12 months and are considered chronic. Children with chronic ITP should be assessed for the presence of an associated illness, such as an underlying autoimmune disease including systemic lupus erythematosis, anti-phospholipid syndrome, common variable immune-deficiency, Human immunodeficiency virus (HIV), Crohn's disease, or B cell lymphoma ***(George et al., 2009).***

Diagnosis:

ITP commonly affects children between one and seven years of age. Childhood primary ITP usually runs a benign, self-limiting course, with or without treatment. Complete remission occurs within six months from diagnosis, commonly within 6–12 weeks, in the majority of children with the diagnosis of ITP. However, 20–30% of children will continue to have persistent low platelets count with bleeding symptoms beyond six months from diagnosis. The diagnosis of ITP in children is essentially one of exclusion. The child usually develops skin bruises, petechiae, or mucosal bleeding, who is otherwise healthy and having no lymphadenopathy or organomegally. Full blood count reveals isolated thrombocytopenia with normal hemoglobin (Hb) level, white

blood count(WBC)and normal peripheral blood smear ***(Nugent et al., 2006).***

The Page score, also known as the ITP Bleeding Scale (IBLS) assigns a bleeding severity score from 0 (no bleeding) to 2 (marked bleeding) at 9 anatomical sites by history (skin, oral, epistaxis, gastrointestinal, urinary, gynecologic, pulmonary, intracranial, and subconjunctival), and from 2 anatomical sites by physical examination (skin and oral) ***(Page et al., 2007).***

Table (1): The immune thrombocytopenic purpura bleeding score assessment:

Site	Bleeding grade		
	0	**1**	**2**
Skin [physical examination (PE)]	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (PE)	None	1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	Multiple blood blisters and/or gum bleeding
Skin (Hx)	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (Hx)	None	1 blood blister or >5 petechiae and/or gum bleeding <5 min	Multiple blood blisters and/or gum bleeding >5 min
Epistaxis	None	Blood when blowing nose and/or epistaxis <5 min (per episode)	Bleeding >5 min (per episode)
Gastrointestinal (GI)	None	Occult blood	Gross blood
Urinary (U)	None	Microscopic (+ve dipstick)	Macroscopic
Gynecological (GYN)	None (normal period)	Spotting not at time of normal period	Bleeding >spotting not at time of period or very heavy period
Pulmonary	None	N/A	Yes
Intracranial haemorrhage	None	N/A	Yes
Subconjunctival haemorrhage	None	Yes	N/A

(Lemke et al., 2007)

Differential diagnosis:

The diagnosis of ITP in children is essentially one of exclusion. In order to differentiate ITP from other conditions, medical history should include type and severity of bleeding, systemic symptoms history of respiratory infections, medications, presence of bone pain and family history of bleeding disorders. Clinical examination should include observation for any dysmorphic features, especially skeletal anomalies, and the presence or absence of hepatosplenomegaly and or lymphadenopathy ***(British Society of Hematology, 2003).***

When the history and/or the clinical examination are atypical, the following conditions should be considered: in an infant, wiskott- Aldrich syndrome, Bernard-soulier syndrome and congenital thrombocytopenia should be taken in consideration, where as in an older child we should consider Von will brand disease type 11B, Aplastic anemia, Acute leukemia, Other autoimmune conditions like systemic lupus erythematosis (SLE), Antiphospholipid syndrome and common variable immune deficiency (CVID).If the young child is sick and febrile, the possibility of an infection should be considered especially meningococcal disease or HIV ***(Osman et al., 2012).***

Laboratory Studies:

The work up (ITP) starts with (CBC) and peripheral blood smear. They are essential to establish the diagnosis of ITP. CBC shows isolated thrombocytopenia with normal WBC and normal Hb levels. Anemia is present only if there is severe bleeding ***(Neunert et al., 2011).***

Bone marrow aspiration (BMA) is not required to establish the diagnosis of ITP and also is not necessary prior to steroid treatment in typical cases of ITP. However, BMA should be done if there is bone pain, lymphadenopathy, hepatosplenomegaly, anemia that is not explained by blood loss, or abnormally high or low WBC ***(Provan et al., 2010).***

Antiplatelet antibodies measurement does not assist in the diagnosis of ITP and therefore should not be routinely performed. Coagulation screening does not help in the diagnosis of ITP, and should be done only if infection or inherited bleeding disorders are considered. Test for Antinuclear Antibodies (ANA) could be performed in older children with ITP or those who have a chronic form of the disease. ANA testing is not required in children newly diagnosed with primary ITP. Immunoglobulin level should be done only if common variable immune deficiency (CVID) is suspected ***(Neunert et al., 2011).***

In children with ITP who have already received their first dose of measles-mumps-rubella (MMR) vaccine, the American

Society of Hematology recommends measuring vaccine titers. If the titers indicate full immunity (as is the case in up to 95% of children), then no further MMR vaccine should be given. If the titers indicate inadequate immunity, the child should receive further immunization with MMR vaccine at the recommended age ***(Neunert et al., 2011)***.

Many persons with ITP have Helicobacter pylori gastric infections and that eradication of H pylori results in increased platelet counts ***(Hwang et al., 2015).***

Presentation and clinical characteristics:

Disease onset was characterized and recorded as abrupt (duration of symptoms <14 days at presentation) or insidious (symptoms for ≥14 days at presentation ***(Edslev et al., 2007).***

Also recorded the incidence of bleeding manifestations; bleeding symptoms were classified as mild, moderate or severe. Mild symptoms were limited to bruises and petechiae in absence of mucosal bleeding. Moderate symptoms were defined as mucosal bleeding (such as epistaxis or gum bleeding) that did not require medical intervention. Severe symptoms included mucosal bleeding requiring immediate medical intervention (including blood transfusion), suspected or (ICH), and other life-threatening or fatal hemorrhage in any site ***(Roganovic et al., 2006).***