Measurement of Immunoglobulin A and Immunoglobulin M and their relation to treatment outcome of Immune Thrombocytopenic Purpura

Thesis

Submitted for partial fulfillment of Master Degree in Internal Medicine

Presented by

Aya Adel Mohamed Ahmed

M.B., B.Ch

Supervised by

Prof. Dr. Abdel Rahman Abdel Hamid Soliman

Professor of Internal Medicine and Clinical Hematology
Faculty of Medicine, Ain Shams University

Dr. Rania Abdel Moneem Radwan

Lecturer of Internal Medicine and Clinical Hematology
Faculty of Medicine, Ain Shams University

Dr. Haydi Sayed Mohamed

Lecturer of Internal Medicine and Clinical Hematology
Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2018

قياس الجلوبيولين المناعي (أ) والجلوبيولين المناعي (م) وعلاقتهما بنتائج العلاج من النقص المناعي للصفائح الدموية

رسالة

الماجستير في الأمراض الباطنة العامة توطئة للحصول علي درجة

مقدمة من

آية عادل محمد أحمد/الطبيبة

بكالوريوس الطب و الجراحة

تحت إشراف

أ.د/ عبدالرحمن عبد الحميد سليمان

أستاذ الأمراض الباطنة وأمراض الدم الإكلينيكية

كلية الطب- جامعة عين شمس

د/ رانيه عبد المنعم رضوان

مدرس الأمراض الباطنة وأمراض الدم الإكلينيكية

كلية الطب- جامعة عين شمس

د/ هايدي سيد محمد

مدرس الأمراض الباطنة وأمراض الدم الإكلينيكية

كلية الطب- جامعة عين شمس

كلية الطب

جامعة عين شمس

٢٠١٨

سورة البقرة الآية: ٣٢

First and foremost thanks to ALLAH, the Most Merciful.

I wish to express my deep appreciation and sincere gratitude to ***Prof. Dr. Abdel Rahman Abdel Hamid Soliman,*** *Professor of Internal Medicine and Clinical Hematology, Ain Shams University, for his close supervision, valuable instructions, continuous help, patience, advices and guidance. He has generously devoted much of his time and effort for planning and supervision of this study. It was a great honor to me to work under his direct supervision.*

I wish to express my great thanks and gratitude to ***Dr. Rania Abdel Moneem Radwan,*** *Lecturer of Internal Medicine and Clinical Hematology , Ain Shams University, for her kind supervision, indispensable advice and great help in this work.*

I wish to express my great thanks and gratitude to ***Dr. Haydi Sayed Mohamed,*** *Lecturer of Internal Medicine and Clinical Hematolog, Ain Shams University, for her kind supervision, indispensable advice and great help in this work.*

Last and not least, I want to thank all my family, my colleagues,, for their valuable help and support.

Finally I would present all my appreciations to my patients without them, this work could not have been completed.

Contents

List of Abbreviations

AMR ..... Ashwell-Morrell receptor

APCS..... Antigen presenting cells

ASH..... American society of hematology

Breg..... Regulatory B-cell

C..... Constant region

CDRs..... Complementarity determining regions

CH..... Constant heavy chain

CL ..... Constant light chain

CVID..... Common variable immunodeficiency

DCs ..... Dendritic cells

FcYR..... Fcy receptor

Foxp3 ..... Ranscription factor forkhead box protein 3

FRs ..... Framework regions

G6PD..... Glucose 6-phosphatase deficiency

GP ..... Platelet surface plycoprotein

HDD..... High dose dexamethasone

IBLS ITP bleeding scale

ICH..... Intracranial hemorrhage

IFN ..... Interferon

Ig ..... Immnunoglobulin

IL..... Nterlukein

ITP..... Idiopathic or immune thrombocytopenic purpura

IVIG ..... Intravenous immunoglobulin

IWG..... International ITP working group

JAK 2 ..... Janus kinase 2

MALT ..... Ucosal associated lymphoid tissue

mIgM..... Membrane bound IgM

MMF ..... Mycofenolate mofitel

Mrna..... Messenger ribonucleoutide analogue

OPSS`..... Overwhelming postsplenectomy sepsis

RNA ..... Ribonucleoutide analogue

sIgA..... Secretory IgA

sIgM ..... Ecreted IgM

STAT 3..... Signal transducer and activator of transcription 3

TGF ..... Tumor growth factor

Th ..... T helper

TPO ..... Thrombopoietin

TPO-RAs..... Thrombopoietin receptor agonist

Treg ..... Regulatory T cell

V..... Variable region

Vas ..... Vinca alkaloids

VH..... Variable heavy chain

VL ..... Variable light chain

VTE..... Venous thromboembolism

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Abstract

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenic purpura and autoimmune thrombocytopenic purpura, is defined as isolated thrombocytopenia with normal bone marrow and in the absence of other causes of thrombocytopenia. ITP has two distinct clinical syndromes, manifesting as an acute condition in children and a chronic condition in adults. ITP is primarily a disease of accelerated platelet destruction and impaired platelet production. Auto antibodies against platelet surface glycoproteins (GP), such as GPIIb/IIIa and GPIb/IX complexes, play major roles in both platelet destruction and impaired platelet production. Immune dysregulation, as represented by elevated or decreased serum immunoglobulin (Ig) levels, may increase disease severity as represented by failure to respond to treatment. These alterations in Ig levels may represent an inflammatory or activated immune state that makes the disease more difficult to control with specific treatment. Patient with common variable immunodeficiency (CVID) with low IgG, IgA, and/or IgM levels have 22% incidence of autoimmune disease, such as ITP, supporting the association of abnormal Ig levels with ITP.

Aim of the work: To measure the level of Immunoglobulin M (Ig M) and Immunoglobulin A (Ig A) and their relation to the treatment response in patients with immune thrombocytopenic purpura (ITP).

Methods: The study was conducted upon 60 ITP adult patients who were divided into 2 groups: group I were responder to the standard treatment (steroids), group II were non responder to the standard treatment. IgM and IgA were measured by Enzyme Linked Immunosorbent assay (ELISA).

Results: In this study the median level of IgA was high in non-responder compared to those who were responder to the treatment (group I) and the control group. Median level of IgM was low in non-responder compared to responder patients and to control group.

Conclusion: We concluded that statistically significant difference between responder and non-responder ITP patients as regard the level of IgM as the patients who had IgM level below the median were more resistant to steroid which is the standard treatment in ITP. On the other hand there was no significant difference in the level of IgA between responder and non-responder ITP patients.

Key word: Immunoglobulin M, Purpura, Immunoglobulin A

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP), also known as primary immune thrombocytopenic purpura and autoimmune thrombocytopenic purpura, is defined as isolated thrombocytopenia with normal bone marrow and in the absence of other causes of thrombocytopenia. ITP has two distinct clinical syndromes, manifesting as an acute condition in children and a chronic condition in adults ***(Salib et al., 2016).***

ITP is primarily a disease of accelerated platelet destruction and impaired platelet production. Auto antibodies against platelet surface glycoproteins (GP), such as GPIIb/IIIa and GPIb/IX complexes, play major roles in both platelet destruction and impaired platelet production ***(Noroozi et al., 2015).***

Acute ITP often follows an acute infection and has a spontaneous resolution within 2 months. Chronic ITP persists longer than 6 months without a specific cause ***(Neunert et al., 2011).***

The diagnosis of ITP is a process of exclusion. First, it has to be determined that there are no blood abnormalities other than a low platelet count, and no physical signs other than bleeding. Then, secondary causes (5–10 percent of suspected ITP cases) should be excluded. Such secondary causes include leukemia, medications (e.g., quinine, heparin), lupus erythematosus, cirrhosis, HIV, hepatitis C,

congenital causes, Antiphospholipid syndrome, von Willebrand factor deficiency and others ***(Najaoui et al., 2012)*.**

Although corticosteroids and splenectomy remain the main lines of ITP treatment, a new class of drugs, i.e., thrombopoietin receptor agonists (TPO-RAs) and rituximab, have substantially broadened the therapeutic options for refractory ITP patients. Moreover, the success of TPO-RAs in ITP patients shows that reduced platelet production caused by impaired megakaryocytopoiesis plays a greater role in ITP than previously recognized ***(Liu et al., 2011).***

Immune dysregulation, as represented by elevated or decreased serum immunoglobulin (Ig) levels, may increase disease severity as represented by failure to respond to treatment. These alterations in Ig levels may represent an inflammatory or activated immune state that makes the disease more difficult to control with specific treatment ***(Bussel et al., 2009)*.**

Certain patient populations with known immunologic disorders have an increased the risk of ITP; supporting the concept that immune dysregulation may contribute to the development of ITP ***(wang et al., 2005).***

Patient with common variable immunodeficiency (CVID) with low IgG, IgA, and/or IgM levels have 22% incidence of autoimmune disease, such as ITP, supporting

the association of abnormal Ig levels with ITP ***(Wang et al., 2005).***

IgA deficiency is also related to ITP in perhaps 1% to 2% of cases of ITP, but this may be primarily in those cases with concomitant IgG subclass deficiency ***(Schulze et al., 2011).***

Elevation in IgA may represent aberrations in mucosal immunity, leading to systemic autoimmune effects. The clear relation between Helicobacter pylori infection and immune thrombocytopenia suggests a possible association between mucosal inflammation and immune mediated destruction of platelets ***(Liebman et al., 2009).***