Predictors of Outcome in Pediatric Immune Thrombocytopenic Purpura: Relation to Thrombopoietin Levels

Thesis

Submitted for Partial Fulfillment of M. Sc. Degree

In Pediatrics

By

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2018

Acknowledgment

First and foremost, I feel always indebted to GOD, the Most Kind and Most Merciful.

I'd like to express my respectful thanks and profound gratitude to ***Prof. Dr. Amira Abdel Moneim Adly,*** *Professor of Pediatrics - Faculty of Medicine- Ain Shams University for her keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to ***Dr. Fatma Soliman Elsayed Ebeid,*** *Assistant Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I wish to introduce my deep respect and thanks to ***Prof.Dr.Eman Abdel Rahman Ismail,*** *Consultant of Clinical Pathology, Faculty of Medicine, Ain Shams University, for her kindness, supervision, great help, active participation, guidance and cooperation in this work.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Gina Gergis Abd Elsayed

List of Contents

List of Tables

List of Tables (Cont...)

List of Tables (Cont...)

List of Figures

List of Figures (Cont...)

List of Figures (Cont...)

List of Abbreviations

Abb.	Full term
Anti-dsDNA	*Anti double stranded DNA*
ASH	*American society of hematology*
BMI SDS	*Body mass index standard deviation score*
c-Mpl	*Myeloproliferative leukemia protein*
CMV	*Cytomegalovirus*
CR	*Complete response*
CVID	*Combined variable immunodeficiency*
ELISA	*enzyme –linked immunosorbent assay*
FDA	*Food and Drug Administration*
HBV	*Hepatitis B virus*
HCV	*Hepatitis C virus*
HIV	*Human immunodeficiency virus*
HSC	*hematopoietic stem cell*
ICH	*Intracranial hemorrhage*
ITP	*Immune thrombocytopenia*
IVIG	*Intravenous immunoglobulins*
IWG	*International Working Group*
MKs	*Megakaryocytes*
MF	*Myelofibrosis*
MAIPA	*Monoclonal antibody-specific immobilization of platelet antigen*
MPV	*mean platelet volume*
NSAIDS	*Non steroidal antiinfammatory drugs*
R	*Response*
TPO	*Thrombopoietin*
TPO-RA	*Thrombopoietin receptor analogues*
VNN1	*Vanin-1*

Abstract

Background: Immune thrombocytopenia (ITP) is one of the most common bleeding disorders in children. It is not easy to predict the course of the disease at the time of initial diagnosis. Measurement of thrombopoietin levels may help distinguish between various causes of thrombocytopenia and predict treatment response to thrombopoietin receptor agonists. Some studies investigated predictors of outcome in ITP but these were retrospective studies and to our knowledge, no prospective studies in children with ITP. **Aim:** This prospective study aimed to investigate the clinical features of immune thrombocytopenia in children and adolescents and predictors of outcome including the diagnostic potential of thrombopoietin levels as well as role in predicting response to therapy. **Methods:** Seventy pediatric patients with ITP; 25 were newly diagnosed patients, 45 had chronic ITP. They were compared with 20 age- and sex-matched healthy controls. Patients were studied stressing on bleeding manifestations, organomegaly/lymphadenopathy and therapy. Bleeding score was calculated to each patient according to the ITP Bleeding Scale (IBLS). Complete blood count was done serum levels of thrombopoietin were assessed by enzyme linked immunosorbent assay. The 25 patients with newly diagnosed ITP were followed-up for 3 months. The response after each line of treatment was recorded. **Results:** The incidence of epistaxis and bleeding with hypotension were higher in chronic ITP patients than newly diagnosed ITP patients. Initial platelets count at diagnosis was significantly higher in chronic ITP than newly diagnosed ITP patients. Age of onset > 5 years as well as the incidence of no recovery after 4 weeks of diagnosis and menorrhagia was significantly higher in active ITP patients than those in complete remission. It was found that 9 out of 25 (36.0%) patients had persistent ITP after 3 months follow-up and all were in active condition compared with those who entered in remission. Comparison between newly diagnosed patients who entered in complete remission and who became persistent after 3 months follow-up showed that age of onset > 5 years old was associated with progression to persistent ITP. Intake of IVIG was more frequent among newly diagnosed ITP patients who entered in complete remission although the difference did not reach a significant level. Initial platelet count at diagnosis was significantly higher in persistent ITP than those who had remission while platelets count 4 weeks after diagnosis was significantly lower. As regards thrombopoietin levels, no significant difference was found between all

ITP patients and controls or between newly diagnosed and chronic ITP patients. High thrombopoietin levels have been noticed among those in active ITP. Thrombopoietin levels were significantly higher among patients with persistent ITP than those who had complete remission. Thrombopoietin level was significantly different in relation to initial response where highest levels were found among patients who had no response. ITP patients who experienced loss of response (relapse) had higher thrombopoietin levels. Thrombopoietin levels were inversely related to platelets count. **Conclusions:** The predictors of progression to persistent ITP and chronicity among our pediatric patients with ITP were age of onset > 5 years old, high initial platelet count, low platelets count 4 weeks after diagnosis and high baseline thrombopietin levels. High baseline thrombopoietin levels were also associated with absence of initial response as well as loss of response (relapse) denoting a poor clinical outcome. Therefore, it is important to be incorporated in routine practice for ITP patients to predict therapeutic response and modify treatment regimen, accordingly. Further prospective studies with longer follow-up including larger number of newly diagnosed ITP patients to verify our results and investigate predictors of chronicity in childhood ITP.

INTRODUCTION

Childhood immune thrombocytopenic purpura (ITP) is an acquired autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count <100 x 10^9/L). ITP is one of the most common bleeding disorders in children, with an incidence of approximately four per 100.000 per year ***(Labarque and Van Geet, 2014; Roganović, 2015)***.

ITP most frequently presents with acute onset of purpura and bruising in an otherwise healthy child, often after a preceding mild viral infection. A benign and self-limited course is common, and major bleeding complications are exceptional ***(Bussel, 2013)***. The management including diagnostic investigations, treatment and follow-up is controversial ***(Kühne and Imbach, 2013)***.

International Working Group (IWG) of both pediatric and adult experts in ITP defined three different phases of ITP: "newly diagnosed ITP" (ITP within 3 months from diagnosis), "persistent ITP" (ongoing ITP between 3 and 12 months from diagnosis), and "chronic ITP" (ITP lasting more than 12 months). Severity of ITP is based on the presence of bleeding signs rather than the degree of thrombocytopenia. The term "severe ITP" should be used only in patients with clinically relevant bleeding, which is defined as bleeding at presentation sufficient to mandate treatment, or occurrence of new bleeding symptoms requiring additional therapeutic intervention or increase in drug dose ***(Rodeghiero et al., 2009)***.

ITP has a strikingly different clinical course in adults and children. Spontaneous remission in adults with ITP is less frequent and majority develops chronic ITP ***(Cines and Blanchette, 2002)***. Children, on the other hand, have a much more favorable prognosis. In more than 75%, the disease resolves within 6 months irrespective of treatment ***(George et al., 1996).***

In children, however, it is not possible to predict the course of the disease at the time of initial diagnosis. Thrombopoietin (TPO) is the major regulator of platelet production. Prior studies in animal models ***(Kuter and Rosenberg, 1994; Wendling et al., 1994)*** and in humans ***(Nichol et al., 1995)*** have demonstrated that TPO levels vary inversely with circulating platelet mass. Additional clinical studies have suggested that TPO levels also vary inversely with the rate of megakaryopoiesis ***(Chang et al., 1996; Yamazak et al., 2006)***. Thus, measurement of serum TPO levels may help distinguish between various causes of thrombocytopenia and predict treatment response to TPO receptor agonists ***(Makar et al., 2013)***.

One prospective study involved a cohort of adult patients presenting with a newly diagnosed episode of ITP described the clinical features of adult ITP and its evolution over a 12-month period and explored the baseline predictors of chronicity ***(Grimaldi-Bensouda et al., 2016)***. However, to our knowledge, no such prospective studies in children with ITP.

Aim of the Work

The aim of this study is to investigate the clinical features of immune thrombocytopenia in children and adolescents and to explore predictors of outcome including the diagnostic potential of thrombopoietin levels as well as its role in predicting response to therapy.