Review of Cases of TTP and Their Response to Different Modalities of Treatment

THESIS

Submitted in partial fulfillment of the requirement of
M.S.c.
Degree in internal medicine

By
Heba Mostafa Hassan Mostafa
M.B.BCh

Supervised by

Prof. Hadi Goubran
Professor of Internal Medicine
Faculty of Medicine-Cairo University

Dr. Hala Mahmoud
Assistant professor of Internal Medicine
Faculty of Medicine-Cairo University

Dr. Magdy El-Ekiaby
El-Shabrawishy hospital blood bank

2010

Abstract

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder causing extensive microscopic thromboses to form in small blood vessels throughout the body.

Most cases of TTP arise from inhibition of the enzyme ADAMTS13, a metalloprotease responsible for cleaving large multimers of von Willebrand factor (vWF) into smaller units. A rare form of TTP, called Upshaw-Schülman syndrome, is genetically inherited as a dysfunction of ADAMTS13.

The incidence of TTP is about 4-6 per million people per year.

Due to the high mortality of untreated TTP, a presumptive diagnosis of TTP is made even when only microangiopathic hemolytic anemia and thrombocytopenia is seen, and therapy is started.

Since the early 1990s, plasmapheresis has become the treatment of choice for TTP.

Most patients with refractory or relapsing TTP receive additional immunosuppressive therapy,

The mortality rate is approximately 95% for untreated cases, but the prognosis is reasonably favorable (80-90%) for patients with idiopathic TTP diagnosed and treated early with plasmapheresis.

Key Words:
Principles of hemostasis and thrombosis, **Platelets in hemostasis, Von Willebrand factor and hemostasis.**

Acknowledgement

First of all, thanks to great Allah for everything in my life.

I am immensely & deeply grateful to Dr.Hadi Alphons Goubran, professor of Internal Medicine, faculty of Medicine, Cairo University, for without his unitizing guidance& faithful efforts, this work would never have completed & thanks for his support & encouragement to be better.

I am greatly indebted & much grateful to Dr. Hala Mahmoud, assistant professor of Internal Medicine, faculty of Medicine, Cairo University, for huge assistance.

I would like to express my profound gratitude to Dr. Magdy El-Ekiaby, El-Shabrawishy hospital blood bank, for his great help in this work.

I wish to extend my deep thanks to Dr.Mona El-Quassas, Dr. Mirvat Mattar professors of Internal Medicine, Dr. Nehad Twfeek assistant professor of internal medicine, faculty of Medicine, Cairo University, for their great participation in data collection.

I wish also to extend my thanks to Dr. Noha El-Husseiny lecturer of internal medicine, Cairo University, for her helpful participation in data analysis.

To my family without their everlasting love, encouragement & sacrifices this work would never been completed

To my husband Dr. Sayed Seif , for standing by me in every step of this work, greatly pushing aside all obstacles and providing all the moral support I can ever need

Content

No **Page**

- **List of figures…….I**
- **List of tables……..II**
- **List of abbreviations……III**
- **Introduction & aim of work. ……1**
- **Review of literature……2**
  - **Principles of hemostasis and thrombosis (Chapter 1)……....2**
  - **Platelets in hemostasis (Chapter 2)……15**
  - **Von Willebrand factor and hemostasis (Chapter 3)…….....29**
  - **Thrombotic microangiopathy (Chapter 4)…….41**
  - **Thrombotic thrombocytopenic purpura (Chapter 5)…….60**

Content cont.

No **page**

- **Management of thrombotic thrombocytopenic purpura (chapter 6)…….73**

- **Patients & methods……...88**

- **Results…….91**

- **Discussion……..120**

- **Summary…… 133**

- **References……135**

- **Arabic summary……..179**

List of Figures

No **page**

Fig. I: Cascade model of coagulation.……...…….6

Fig. II: Cell-based model of coagulation…….8

Fig. III: Fibrinolysis…….10

Fig. IV: Natural anticoagulant system……...13

Fig. V: Ultra structure of mature platelet……..16

Fig. VI: von Willebrand factor……30

Fig. VII: von Willebrand factor (vWF) multimeric analysis ……...30

Fig. VIII: Proposed mechanism for proteolytic breakdown of von Willebrand factor (vWF)…….…….…… …. 33

Fig. IX: Domain structure of the plasma VWF-cleaving metalloprotease, ADAMTS13…….. 34

Fig. X: Cleavage of Unusually Large Multimers of von Willebrand Factor on Endothelial Cells by the von Willebrand Factor–Cleaving Metalloprotease, ADAMTS 13……..35

Figure XI: Proposed Mechanisms of Platelet–Fibrin Formation in the Hemolytic–Uremic Syndrome……....46

Figure XII: Proposed Relation among the Absence of ADAMTS 13 Activity in Vivo, Excessive Adhesion and Aggregation of Platelets, and Thrombotic Thrombocytopenic Purpura……66

Figure XIII: Typical histological findings of acute thrombotic thrombocytopenic purpura (TTP) (cardiac muscle)…… 72

List of Figures cont.

No **page**

Figure XIV: Schistocytes in peripheral blood smear…….74

Figure 1: Sex distribution of TTP cases……..101

Figure 2: Age distribution of TTP cases……..102

Figure 3: Time elapsed from onset of symptoms to diagnosis ……..103

Figure 4: clinical characteristics of TTP patients……...104

Figure 5: Different therapeutic modalities used for treatment of TTP cases……105

Figure 6: Outcome of TTP cases……..106

Figure 7: classification of patients according to outcome……..107

Figure 8: Sex distribution and outcome of TTP……108

Figure 9: Comparison between sex distribution of study groups…….109

Figure 10: Age distribution and outcome of TTP……..110

Figure 11: Comparison between median ages of study groups…….111

Figure 12: Relation between time elapsed from onset of symptoms and diagnosis (in days) and outcome of TTP…….112

Figure 13: Comparison between the time elapsed from onset of symptoms and diagnosis (in days) in study groups……113

Figure 14: Comparison between clinical characteristics of study groups…….114

Figure 15: Comparison between laboratory data of study groups…...115

Figure 16: Comparison between initial platelet counts in study groups…….116

Figure 17: Comparison between LDH levels in study groups……...117

List of Figures cont.

No **page**

Figure 18: Comparison between numbers of sessions of plasmapheresis in study groups……118

Figure 19: Comparison between Azathioprine as a part of initial treatment in study groups……...119

List of Tables

No **page**

Table. I: Relation between Defects in Plasma von Willebrand Factor–Cleaving Metalloprotease, ADAMTS 13, and Thrombotic Thrombocytopenic Purpura (TTP)……67

Table 1: Demographic data of TTP patients……. 91

Table 2: Clinical data of TTP patients ……..92

Table 3: Laboratory data of TTP patients…….93

Table 4: Comparison between demographic, clinical, and laboratory data of study groups…….97

Table 5: comparison between number of sessions of plasmapharesis received by study groups…….99

Table 6: Comparison between azathioprine as apart of initial therapy of study groups……100

List of Abbreviations

ADAMTS : **A d**isintegrin-like **a**nd **m**etalloprotease (reprolysin type) with **t**hrombo**s**pondin type 1 motif.

ADP : Adenosine diphasphate.

aPTT : activated partial thromboplastin time.

ATP : Adenosine triphasphate

BFU-M : Burst forming-unit megakaryocyte.

βHCG : β-human chorionic gonadotropin

BUN : Blood urea nitrogen.

C3 : Complement 3.

CBC : Complete blood count

CD : Cluster of differentiation.

CFU-M : Colony forming-unit megakaryocyte.

CLL : Chronic lymphatic leukemia.

CPP : Cryo poor plasma.

DIC : Disseminated intravascular coagulation.

FDPs : Fibrin degradation products.

FFP : Fresh frozen plasma.

- GP Ib : Glycoprotin Ib.
- GP IIb/IIIa : Glycoprotein IIb/IIIa.
- Hb : Hemoglobin.
- HK : high molecular weight kininogen.
- HUS : Hemolytic–Uremic Syndrome.
- INR : International normalized ratio.
- ITP : Idiopathic(Immune) thrombocytopenic purpura.
- LDH : Lactate dehydrogenase.
- MAHAs : Microangiopathic hemolytic anemias.
- N:C ratio : Nuclear-cytoplasmic ratio.
- NSAIDs : Non steroidal anti inflammatory drugs.
- PAF : Platelet activating factor.
- PAIs : Plasminogen activator inhibitors.
- PAR : Protease activated receptor.
- PDGF : Platelet-derived growth factor.
- PF3 : Platelet factor 3.
- PG E : Prostaglandin E
- PROZ : Protein Z.
- PT : prothrombin time.
- RBC's : Red blood cells.

- Serpin : Serine protease inhibitor.
- SLE : Systemic lupus erytheromatosus.
- TCT : Thrombin time.
- TF : Tissue factor.
- TFPI : Tissue Factor Pathway Inhibitor.
- TGFβ : Transforming growth factor-β.
- TLC : Total leucocytic count.
- tPA : tissue plasminogen activator.
- TTP : Thrombotic thrombocytopenic purpura.
- TXA_2 : Thromboxane A_2.
- vWD : von Willebrand Disease.
- vWF : von Willebrand Factor.
- ULvWF : Unusually Large vWF.
- ZPI : protein Z-related protease inhibitor.

Research completion form

A) Title: Review of Cases of TTP and Their Response to Different Modalities of Treatment.

B) Summary:

- **Background**: Thrombotic thrombocytopenic purpura (TTP)is a rare disorder of the blood-coagulation system, causing extensive microscopic thromboses to form in small blood vessels throughout the body (thrombotic microangiopathy).
- **Objectives**: This study is a retrospective study describes the demographic, clinical and laboratory data of TTP patients and different modalities of treatment they were subjected to, and to investigate the relation between these data and the outcome of treatment in a trial to identify pretreatment prognostic factors that could be useful in predicting the response to treatment.
- **Methods**: 30 TTP patients 13 males and 17 females, They are subjected to 1.Full history taking 2. Thorough clinical examination. 3.Laboratory assessment for(CBC,Reticulocytic count, Direct and indirect Coomb's test, Liver & Kidney function tests, Serum LDH level, coagulation profile).
- **Results**: There is significant relation between the initial platelet count in non relapsed patients and relapsed patients
- **Conclusion:** the initial platelet count is lower in relapsed patients .

- **Keywords:** TTP: thrombotic thrombocytopenic purpura.

C) Date of completion:

D) Papers resulting from this research:

E) Personal data of principal investigator:

Heba Mostafa Hassan Mostafa
Resident of internal medicine, Faculty of medicine-Cairo University
Address: 6 Khaled Ebn EL-Waleed ST., Cairo. Mob. 0183692916

F) Personal data of supervisors:

Prof. Dr. Hadi Goubran
Professor of internal medicine
Faculty of medicine-Cairo University.
Dr. Hala Mahmoud
Associate Professor of internal medicine
Faculty of medicine-Cairo University
Dr. Magdy El-Ekiaby
El-Shabrawishy hospital blood bank

Introduction and aim of work

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder causing extensive microscopic thromboses to form in small blood vessels throughout the body (thrombotic microangiopathy) **(Moake, 2002).**

Most cases of TTP arise from inhibition of the enzyme ADAMTS13, a metalloprotease responsible for cleaving large multimers of von Willebrand factor (vWF) into smaller units. A rare form of TTP, called Upshaw-Schülman syndrome, is genetically inherited as a dysfunction of ADAMTS13 **(Turner et al., 2009).**

The incidence of TTP is about 4-6 per million people per year (**Zheng et al., 2004).**

Due to the high mortality of untreated TTP, a presumptive diagnosis of TTP is made even when only microangiopathic hemolytic anemia and thrombocytopenia is seen, and therapy is started. **(Crowther &George, 2008).**

Since the early 1990s, plasmapheresis has become the treatment of choice for TTP **(Fontana et al., 2004).**

Most patients with refractory or relapsing TTP receive additional immunosuppressive therapy **(Dierickx et al., 2007).**

The mortality rate is approximately 95% for untreated cases, but the prognosis is reasonably favorable (80-90%) for patients with idiopathic TTP diagnosed and treated early with plasmapheresis (**Tsai & Han-Mou, 2006).**

Approximately one-third of patients experiencing a TTP episode have a relapse within 10 years following their first attack **(Hovinga et al., 2010).**

This study is a retrospective study describes the demographic, clinical and laboratory data of 30 TTP patients presented to our stuff since 1999, and different modalities of treatment they were subjected to, and to investigate the relation between these data and the outcome of treatment in a trial to identify pretreatment prognostic factors that could be useful in predicting the response to treatment.