Progranulin in patients with Immune Thrombocytopenic Purpura

Thesis

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In Internal Medicine

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List of Abbreviations

ADAMTS-7.....A disintegrin and metalloproteinase with thrombospondin motifs

ADCC.....Antibody- dependent cell- mediated cytotoxicity

ALPS.....Autoimmune lymphoproliferative syndrome

AMR .....Ashwell-Morrell receptor

ANA .....Antinuclear antibody

ANCA.....Anti-neutrophil cytoplasmic antibodies

APCs.....Antigen presenting cells

APS.....Antiphospholipid syndrome

ASH .....The American Society of Hematology

BMI.....Body mass index

Bregs .....B-regulatory cells

C2.....Complement 2

CBC .....Complete blood count

CD40 .....Cluster of differentiation

CI.....Confidence interval

CLL.....Chronic lymphocytic leukemia

COMP .....Cartilage oligomeric matrix protein

CpGODNs .....CpG-Oligodeoxynucleotides

CRD2.....Cysteine rich domain

CSA .....Cyclosporine A

CVID.....Common variable immune deficiency

DAT .....Direct antiglobulin test

DcR3 .....Decoy receptor 3

DCs.....Dendritic cells

DM.....Diabetes mellitus

List of Abbreviations

DR3 .....Death receptor 3
ELISA .....Enzyme-Linked ImmunoSorbent Assay
FcγRs .....Fc gamma receptors
FLi1.....Friend leukemia integration1
FOXP3.....Forkhead box protein p3
GEP .....Granulin–epithelin precursor
GPIIb-IIIa.....Glycoprotein IIb-IIIa
GRN.....Granulin
H pylori.....Helicobacter pylori
HCC.....Hepatocellular carcinoma
HCV.....Hepatitis C
HDMP .....High-dose methylprednisolone
HE4 .....Human Epididymus Protien 4
HIV.....Human immunedeficiency virus
HRQoL.....Health-related quality of life
IBD .....Inflammatory bowel disease
IgA.....Immuoglobulin A
IgM .....Immunoglobulin M
IQR.....Inter-Quartile Range
ITP.....Immune thrombocytopenic purpura
IVIG.....Intravenous immunoglobulins
IWG .....International Working Group
kDa.....Kilodaltons
LPS.....Lipopolysaccharide
mAb.....Monoclonal antibody
MAPK .....Mitogen activated protein kinase
MKs.....Megakaryocytes

List of Abbreviations

MMP .....Matrix metalloproteinase

MMR.....Measles, mumps, and rubella

mRNA.....Messenger Ribonucleic acid

NK .....Cells natural killer cells

PAQ .....Patient Assessment Questionnaire

PC.....Plasma cells

PCDGF.....PC-cell derived growth factor

PEPI .....Proepithelin

PKCb1 .....Protein kinase C beta1

PLT.....Platelet

PR3.....Protinase 3

PRGN.....Progranulin

PROs .....patient-reported outcomes

PsA .....Psoriatic arthritis

PsC .....Cutaneous psoriasis

pSS.....Progressive Systemic sclerosis

QoL.....Quality of life

RA .....Rheumatoid arthritis

RES .....Reticuloendothelial system

RR .....Relative risk

SCID .....Severe combined immunediffeciency

SD.....Standard deviation

SF-36.....The 36-item Short-Form Health Survey

SLE.....Systemic lupus erythematosus

SNP.....Single Nucleotide Polymorphism

SPSS.....Statistical package for social science

List of Abbreviations

SS .....Systemic sclerosis

TE.....thromboembolism

TG .....Triglycerides

Th1/Th2 .....T-helper cells

TL1A.....TNF-like ligand 1A

TLR9 .....Toll-like receptor 9

TNF-α .....Tumor necrosis factor alpha

TPO .....Thrombopoietin

TPO-RA.....Thrombopoietin receptor agonist

TRAs.....Thrombopoietin receptor agonist

Tregs .....T regulatory cells

Vs .....Versu

WT .....Wild type

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ABSTRACT:

Background: Immune thrombocytopenic purpura (ITP) is an idiopathic, autoimmune disorder characterized by low platelet count. The triggering event for ITP is unknown, but continued research is providing new insights into the underlying immunopathogenic processes as well as the cellular and molecular mechanisms involved in megakaryocytopoiesis and platelet turnover.
Progranulin (PGRN) is emerging as an important immune regulator involved in a variety of autoimmune disorders. However, its role in immune thrombocytopenia (ITP) remains unclear.
In our study Progranulin was significantly elevated in ITP patients.

Aim: To investigate the relationship between Progranulin plasma level and Immune Thromocytopenic Purpura.

Patients and Methods: The study included 30 patients aged 20-60 years old with Immune thrombocytopenic purpra. The patients were collected from The Hematology Outpatient Clinic – Ain-Shams University Hospitals.

Results: Our results showed that 20 patients out of the study group (66.67%) while only 8 patients (26.67%) of the control group had high serum level of progranulin, which is highly significant (p-value = 0.002)

CONCLUSIONS
Our study revealed that the progranulin is a promising regulator involved in the pathogenesis of ITP and provided a potetial strategy for updating the management of ITP.

Keywords: ITP, Progranulin, platelets, autoimmune

INTRODUCTION

Immune thrombocytopenic purpura (ITP) is defined as an idiopathic, autoimmune disease characterized by low platelet count (< 100×10^9/L) with a risk of mucocutaneous bleeding. ITP is a fairly common disorder in adults (5·8-6·6 in 100,000/year) and is thought to be caused by autoantibodies target the platelets leading to their premature sequestration ***(Cines and Blanchette, 2002; Cooper and Bussel, 2006).*** T cell mediated immunity could also be responsible for premature platelet destruction ***(Coopamah et al., 2003; Olsson et al., 2003).***

Immune thrombocytopaenic purpura is common in patients with immunodeficiency diseases, most commonly in B-cell disorders, including Common Variable Immunodeficency ***(Cunningham-Rundles and Bodian, 1999)***, secondary hypogammaglobulinaemia, selective IgA deficiency ***(Khalifa et al., 1976)***, autoimmune lymphoproliferative syndrome (ALPS) and CD40 ligand deficiency (hyper-IgM syndrome). Yet, the association between ITP and immunodeficiency is also likely to be related to T-cell dysregulation ***(Arkwright et al., 2002)***.

Progranulin (PRGN), found in human blood, urine, expressed widely in adipose tissue and to be one of the adipokines that involved in the development of insulin resistance ***(Matsubara et al., 2012 and Martens et al., 2012)***. It is known to play an important role in a variety of

physiologic and pathological processes, including wound healing, inflammation response, neurotrophic factor and host defense ***(Tang et al., 2011)***.

The association between PGRN levels and systemic inflammation and autoimmunity has been reported, for example, serum levels of PGRN were elevated in systemic lupus erythematosus and related with disease activity ***(Qiu et al., 2013; Yamamoto et al., 2014).*** Auto-antibodies against PGRN have also been reported in several autoimmune diseases, including rheumatoid arthritis, psoriatic arthritis, and inflammatory bowel disease, and such antibodies promoted a proinflammatory environment in a subdivision of patients ***(Thurner et al., 2013)***. Moreover, PGRN was found to protect Tregs from a negative regulation by TNF-a. However, the direct regulation of PGRN on Tregs has not been reported ***(Thurner et al., 2014; Wei et al., 2014).***

A recent study hilightened the potential role of progranulin in the pathogenesis of ITP and provided a potential strategy for management of ITP ***(Yu et al., 2018).***

Aim of the Work

This thesis is designed to evaluate the relationship between Progranulin plasma level and Immune Thromocytopenic Purpura.

Immune Thrombocytopenic Purpura

DEFINITION

Idiopathic or immune thrombocytopenic purpura (ITP) is an autoimmune-mediated acquired bleeding disorder of adults and children. It is characterized by destruction of platelets caused by anti-platelet antibodies. However, the mechanisms that trigger the development of platelet auto-antibodies remain poorly understood ***(Neunert, 2013)***.

The normal platelet count in healthy individuals is between ($150\text{-}450\times10^9$/L) while in ITP platelet count is characteristically ($<100\times10^9$/L). Traditionally ITP has been classified as: acute with sudden onset lasting less than 6 months, chronic persisting more than 6 months; or refractory where persistently low platelet counts remain despite appropriate treatment or splenectomy. In 2009, a new nomenclature for the phases of ITP based on time from diagnosis was proposed as follows; newly diagnosed ITP (within 3 months of diagnosis, persistent ITP (between 3 - 12 months of diagnosis), and chronic ITP (longer than 12 months of diagnosis) ***(Rodeghiero et al., 2009)***.

ITP is typically a diagnosis of exclusion, made by clinicians after ruling out other possible etiologies. It can be