Tissue Factor Pathway Inhibitor in Pediatric Patients with Nephrotic Syndrome

Thesis
submitted for the partial fulfillment of
Master Degree in Pediatrics

By
Rania Saleh Beltagi
M.B.B.Ch
Faculty of Medicine,Cairo University
Under Supervision of

Prof.Dr./ Farida Ahmed Farid
Professor of Pediatrics and Pediatric Nephrology
Faculty of Medicine,Ain Shams University

Dr./Ahmed Abdullah Mohammed
Assistant Professor of Pediatrics
Faculty of Medicine,Ain Shams University

Prof.Dr./ Hanaa Mohammed Afify
Professor of Clinical and Chemical Pathology
Faculty of Medicine,Ain Shams University

Faculty of Medicine
Ain Shams University
2010

مثبط مسار العامل النسيجي في الأطفال المصابين بالاوديما الكلوية

رسالة مقدمة للحصول على درجة الماجستير في طب الأطفال

من

الطبيبة/ رانيا صالح بلتاجى

بكالوريوس الطب و الجراحة

كلية الطب ،جامعة القاهرة

تحت إشراف

الأستاذة الدكتورة /فريدة احمد فريد

أستاذ طب الأطفال و أمراض كلى الأطفال

كلية الطب ،جامعة عين شمس

الدكتور/احمد عبد الله محمد

استاذ مساعد طب الاطفال

كلية الطب، جامعة عين شمس

الأستاذة الدكتورة/ هناء محمد عفيفي

أستاذ الباثولوجيا الإكلينيكية و الكيميائية

كلية الطب، جامعة عين شمس

كلية الطب

جامعة عين شمس

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ABSTRACT

Background: Tissue factor pathway inhibitor (TFPI) is the major down regulator of the procoagulant activity of the TF/ FVIIa complex. The mature TFPI protein, previously known as lipoprotein-associated coagulation inhibitor (LACI) or extrinsic pathway inhibitor (EPI), has a molecular weight of 34.000.

Aim: to monitor the level of TFPI in blood and urine in children with nephrotic syndrome . Correlation with activity of the disease, response to therapy and the degree of hypoproteinemia & proteinuria will be assessed .

Methods: Fifteen nephrotic patients in relapse (proteinuria>40mg/m^2/hour, hypoalbuminemia, and edema) before initiating steroid therapy (Group I), and another15 nephrotic patients in remission after withdrawal of steroid therapy (Group II) were compared to 15 age- and sex-matched healthy children. Besides clinical evaluation and routine laboratory investigations of nephrotic syndrome, tissue factor pathway inhibitor in plasma were measured by ELISA.

Results: Plasma TFPI level was higher in nephrotic patients [(102.53±14.23) and (82.93±3.83)ng/ml in both proteinuria & remission groups respectively] than control group (62.40 ± 7.53) ng/ml with highly significant statistical difference

($p< 0.0001$), and higher in proteinuria group than the remission group with highly significant statistical difference ($p< 0.0001$). There was a negative correlation between plasma TFPI level and total protein (strong association) ($p=0.0001$), serum albumin (strong association) ($p=0.0001$)and there was a positive correlation between plasma TFPI level and urine protein /creatinine ratio (moderate association) ($p=0.05$) with significant statistical difference ($p< 0.05$).

Conclusion: Nephrotic syndrome was associated with increased level of plasma tissue factor pathway inhibitor in comparison to control group and the increase was more apparent in patients with active disease. There was a negative correlation between plasma TFPI level and total serum protein, and serum albumin, while there was a positive correlation between plasma TFPI level and urine protein/creatinine ratio.

Acknowledgement

Thanks to Allah the greatest of all for helping me to complete this work.

I would like to express my sincere and deep gratitude to ***Prof. Dr. Farida Ahmed Farid****, Professor of Pediatrics, and pediatric nephrology, Faculty of Medicine, Ain Shams University, for giving me the privilege of supervising this thesis and for her constructive encouragement, illuminating guidance as well as her support throughout this work.*

I am really very grateful and deeply indebted to ***Dr. Ahmed Abdullah Mohammad****, Assistant professor of Pediatrics, Faculty of Medicine, Ain Shams University, for his unfailing help, valuable suggestions and good support which helped me to put this work in its best form. It was a great honor and a chance of a lifetime to work with him.*

I really wish to express my deep gratitude to ***Prof. Dr. Hanaa Mohammad EL-Said Afify****, professor of clinical pathology, Faculty of Medicine, Ain Shams University, for her kind assistance, precious and effective effort.*

I wish to express my deep thanks to the children in nephrology and out patient clinics –children hospital, Ain Shams University.

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ACEIs	Angiotensin converting enzyme inhibitors
ACS	Acute coronary syndromes
AIIRAs	Angiotensin II receptor antagonists
APC	Activated protein C
ATIII	Anti thrombin III
aPTT	Activated partial thromboplastin time
ATE	Arterial thromboembolism
AUC	Area under curve
BMI	Body mass index
CGN	Crescentic glomerulonephritis
CPH	Cyclophosphamide
CsA	Cyclosporine A
CSVT	Cerebral sinovenous thrombosis
CAPD	Chronic ambulatory peritoneal dialysis
DIC	Disseminated intravascular coagulation
DVT	Deep venous thrombosis
ELISA	Enzyme linked immunosorbent assay

EGF	Epidermal growth factor
FN	False Negative
FRNS	Frequently relapsing nephrotic syndrome
FSGS	Focal segmental glomerulosclerosis
FVIIa	Activated factor FVII
FXa	Activated factor FX
HIB	Haemophilus influenza type B
HLE	Human leukocyte elastase
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
HSPGs	Heparin sulphate proteoglycans
IHD	Ischemic heart disease
HUVECs	Human umbilical vein endothelium contents
INS	Idiopathic nephrotic syndrome
IL-1	Interleukin-1
KD	Kilo Dalton
LMW	Low molecular weight
LMWH	low molecular weight heparin
LDL	Low density lipoproteins
LRP	LDLreceptor-related protein
MCNS	Minimal change nephrotic syndrome

MMF	Mycophenolate mofetil
MPGN	Membranoproliferative glomerulonephritis
NS	Nephrotic syndrome
NPV	Negative predictive value
PAD	Peripheral arterial disease
PC	Protein C
PCR	Polymerase chain reaction
PLT	Platelet count
Pr/Cr	Protein/creatinine ratio
PS	Protein S
PT	Prothrombin time
PPV	Positive Predictive value
PARs	Protease activated receptors
rTFPI	Recombinant tissue factor pathway inhibitor
ROC Curve	Receiver operating characteristic curve.
SDNS	Steroid dependent nephrotic syndrome
SLE	Systemic lupus erethromatosis
Sn	Sensitivity
SNS	Secondary nephrotic syndrome
SRINS	Steroid resistant idiopathic nephrotic syndrome

SRNS	Steroid resistant nephrotic syndrome
SP	Specificity
SSNS	Steroid-sensitive nephrotic syndrome
TE	Thromboembolism
TEC	Thromboembolic complication
TP	True positive
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TNF	Tumor necrosis factoractive factor VIII
TF/VIIa	Tissue factor-activated factor VII
TSP-1	Thrombospondin-1
VTE	Venous thromboembolism
WT	Weight

Introduction

Nephrotic syndrome is the most common cause of generalized edema in children above the age of 2 years. Diagnosis is confirmed by the presence of massive proteinuria, hypoproteinemia and hyperlipidemia ***(Orth and Ritz, 1998)***.

A hypercoagulable state with the risk of thromboembolism in both arterial and venous circulation is a relatively frequent and serious feature of nephrotic syndrome in children ***(Citak et al., 2000)***.

Tissue factor (TF) is a transmembrane procoagulant glycoprotein and a member of the cytokine receptor superfamily. TF functions as a protein cofactor for FVIIa. The TF/FVIIa complex then activates both factor IX and X leading to thrombin generation and fibrin formation ***(Lopes-Bezarra and Filler, 2003)***.

Tissue factor pathway inhibitor (TFPI) is a natural inhibitor that regulates the initiation of coagulation by inhibiting tissue factor-activated factor VII(TF-FVIIa) in