Study of Von Willebrand Factor and Factor VIII levels in children with newly diagnosed Acute Lymphoblastic Leukemia in relation to peripheral blast cells and Steroid Therapy

Thesis
Submitted for partial fulfillment of M.Sc degree
in Pediatrics

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كلية الطب – جامعة عين شمس

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الرؤيـــة

تصبو كلية الطب جامعة عين شمس إلى أن تكون الأولى بمنطقة الشرق الأوسط لتخريج أطباء ذوى قدرات تنافسية وأن تقود الإصلاح فى التعليم الطبى.

Vision

To be the first in the Middle East in providing graduates with a competitive edge and to lead reform of medical education.

الرسالـــة

تقوم كلية الطب جامعة عين شمس بإعداد خريج مدرب ذى مهارة تنافسية على المستوى المحلى والعالمى، وقادر على التعليم والتعلم والتدرب مدى الحياة وملتزم بمعايير الخدمة الطبية والأخلاق المهنية.

وتسعى الكلية إلى التطوير المستمر للبرامج والمقررات ودعم وتطوير البحث العلمى مع التوسع فى الأبحاث العلمية التطبيقية وبرامج الرعاية الصحية لخدمة احتياجات المجتمع وتنمية البيئة .

كما تهدف الكلية إلى توفير كوادر متميزة أكاديمياً وبحثياً من أعضاء هيئة التدريس ودعم الجهاز الإدارى والارتقاء بالنظم المؤسسية وتوفير الموارد الذاتية لتحقيق الغايات والأهداف.

Mission

Faculty of Medicine, Ain Shams University, prepares a competent graduate, who is able to compete on both national and international levels, capable of life long learning, training and tutoring, while adhering to the codes of practice of medical health services and ethics.

The college as well, seeks continuous development of programs and courses. It also enhances expansion of applied scientific research and health programs for community services and environmental development.

Moreover, through providing distinguished academic and research cadres of teaching staff, supporting the administrative system and sustainability of own resources, the college is able to achieve goals and objectives.

القيـــم

نحن نمارس عملنا بقصد **التميز** وليس لمجرد الأداء، ونمارس **الصدق** فى كل ما نفعل، ونسعى دائما لتحقيق **المساواة** فى الحقوق **والتوازن** بين الحق والواجب مع **الاحترام المتبادل**، ونحن **نعمل معاً** لمصلحة الفرد والمجموع .

Values

We carry out our job aiming at **excellence** and not just performance, we practice **honesty** in everything we do, we always strive to achieve **equality** and the **balance** between right and duty, with **mutual respect** and we **work together** for the benefit of one and all.

Acknowledgment

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I dedicate this work

To my lovely son

Peter Mina Botrous

May God keep you safe for me,
and May you grow up to be
always proud of your parents

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Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common childhood malignancy. With the advent of aggressive multimodality therapy, it has become curable disease for over 80% of patients, however, the treatment of ALL results in a significant morbidity and mortality***(Pui and Evans, 2006).***

Thrombosis is a well-known complication in children with ALL. The exact pathogenesis of thrombosis in association with ALL is unclear; it is thought to result from the interaction of the effects of leukemia and the antileukemic therapy***(Caruso et al., 2006).***

Its frequency reportedly ranges between 1.1% and 36.7%, a quite large variation related to several factors, such as different definitions of thrombosis (symptomatic vs asymptomatic), diagnostic methods for its detection, study design (prospective vs retrospective), and differences in treatment protocols. **(Athale and Chan, 2003).**

Many factors may be involved in the pathogenesis of thrombosis, including the prothrombotic properties of leukemic cells, genetic factors, the administration of drugs, such as L-Asparaginase (L-Asp) and steroids, the presence of indwelling central venous catheter (CVC), and septic complications***(Uszyn´ski et al., 2000).***

Asparaginase and steroids form the backbone of antileukemic therapy in children. Although Asparaginase is long known to be associated with thrombosis, only recently steroids are implicated in

the development of ALL-associated thrombosis ***(Nowak-Gottl etal., 2001).***

The available information of effects of steroid therapy on haemostatic system comes from various studies conducted in different populations of mainly adult subjects. In addition to the wide range of diseases (which may primarily affect some of the haemostatic functions) studied, there is no consistency of the type of steroid preparation and the dose or duration of the steroids used ***(Gaynon and Lustig, 1995).***

Various investigators have consistently shown that steroid therapy leads to elevation of Factor VIII, VonWillebrand factor antigen, prothrombin, antithrombin, and reduction in fibrinolytic potential ***(Ozturk etal., 2004).***

Despite these observations the contribution of steroids in the development of prothrombotic state in children with ALL is not completely understood; partly because of multi-agent combination therapy used for ALL. So far only few studies have evaluated the haemostatic effects of isolated steroid therapy in children with ALL and none of these studies have correlated the steroid effects with the disease activity***(Payne and Vora, 2007).***

Aim of Work

The aim of this study is to assess children with newly diagnosed ALL for procoagulant factors namely, VonWillebrand factor antigen and Factor VIII relevant to peripheral blast cells and effect of steroids therapy on their levels.

Subjects and Methods

This study will include thirty newly diagnosed ALL children, who will be recruited from the hematology/ oncology clinic, children's hospital, Ain Shams university.

All patients will be subjected to:

1. Full history taking with special emphasis on:

- Onset of the disease

- Age and sex of the patient.

2. Thorough clinical examination.

3. Laboratory investigations, including:

1. Complete blood picture initially and day 8 of steroid therapy to assess:

   -total leucocytic count.

-platelets count.

-the percentage of peripheral blast.

2. VonWillebrand factor antigen at day 1 and day 8 after steroid therapy.
3. Factor VIII assay at day 1 and day 8 after steroid therapy.

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LIST OF ABBREVIATIONS

6-MP	6-Mercaptopurine
ACCP	American College of Chest Physicians
ADAMTS13	Acronyon of a disintegration like and mettallprotease with thrombospondin type 1 motif no. 13
ALL	Acute Lymphoblastic Leukemia
ALs	Acute Leukemias
APC	Activated Protein C
aPTT	activated Partial Thromboplastin Time
Ara-C	Cytosine Arabinoside
AT	Antithrombin
CALLA	Common Acute Lymphoblastic Leukemia antigen
CBC	Complete Blood Count
CCG	Childhood Cancer Group
CD	Cluster of Differentiation
CDMP	Conventional Dose Methylprednisolone
cIg	cytoplasmic Immunoglobulin
CNS	Central Nervous System
CNSTs	Central Nervous System Thrombosis
CP	Cancer Procoagulants
CR	Complete Remission
CRY	Cryoprecipitate
CVC	Central Venous Catheter
DTI	Direct Thrombin Inhibitor

DVT	Deep Venous Thrombosis
EDTA	Ethylene Diamine Tetra Acetic acid
ELISA	Enzyme-Linked Immunosorbent Assay
EMFs	Electromagnetic Fields
FAB	French-American-British
FDP	Fibrinogen Degradation Product
FFP	Fresh Frozen Plasma
FITC	Fluorescein Isothiocyanate
FVIII	Factor VIII
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
H_2O_2	Hydrogen Peroxidase
HB	Hemoglobin
HDMP	High Dose Methylprednisolone
HK	High molecular weight Kininogen
HRP	Horse Radish Peroxidase
IL-6	Interleukin-6
ITP	ImmunothrombocytopenicPurpura
L-ASP	L-Asparaginase
LDH	Lactate Dehydrogenase

LL	Lower Limb
LMH	Low Molecular weight Heparin
mAB	monoclonal Antibodis
MLL	Mixed Lineage Leukemia
MPO	Myeloperoxidase
MRD	Minimal Residual Disease
NCI	National Cancer Institute
OD	Optical Density
PAI 1	Plasminogen Activator Inhibitor 1
PARKAA	Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia treated with Asparaginase
PCR	Polymerase Chain Reaction
PE	Pulmonary Embolism
PEG	Poly Ethylene Glycol
PK	Prekallerein
PLT	Platelet
POG	Pediatric Oncology Group
PT	Prothrombin Time
SCT	Stem Cell Transplantation
SD	Standard Deviation
TAT	Thrombin Antithrombin complex
THA 2	Thromboxane A2
TCR	T-Cell Receptor
TF	Tissue Factor