

بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / هناء محمد علي

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

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		حامعتب		
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بركات وتكنولوجياراه





Factor VIII Level in The Potential Female Carrier mothers and its Impact on Joint Health

Thesis

Submitted for Partial Fulfillment of Master Degree in Pediatrics

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M.B.B.Ch - Menofia University - 2016

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سورة البقرة الآية: ٣٢

Acknowledgment

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

I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Azza Abd El Gawad Tantawy**, 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 **Prof. Dr. Iman Ahmed Ragab**, 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 am deeply thankful to Prof. Dr. Hossam Moussa El-Sayed Saqr Professor of Diagnostic Radiology, Faculty of Medicine - Ain Shams University, for his great help, active participation and guidance.

I am deeply thankful to Prof. Dr. Dalia Mohamed Ezz El Din El Mekkawy
Professor, Department of Physical Medicine, Rheumatology and
Rehabilitation - Faculty of Medicine - Ain Shams University
for his great help, active participation and guidance.

I am deeply thankful to **Dr. Salwa Mostafa Abd El Kader**, Lecturer of Pediatrics Faculty of Medicine - Ain Shams University, for her great help, active participation and guidance.

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 hemophilia patients and their mothers that participated in this study.

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List of Abbreviations

абб	Full name
aPCCs	activated PCCs
CDC	Centers for Disease Control and Prevention
CFC	clotting factor concentrate
CSA	chromogenic substrate assay
CVS	Chorionic villus sampling
EACA	epsilon amino caproic acid
FVIII	factor VIII
GRE	gradient echo
H2O2	hydrogen peroxide
HA	Hemophilia A
HB	hemophilia B
HTCs	Hemophilia Treatment Centers
IL	interleukin
IU	international unit
MMPs	matrix metalloproteinases
MRI	magnetic resonance imaging
NGS	next-generation sequencing
NHS	National Health Service
NO	nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	osteoarthritis

Tr.	
OPG	osteoprotegerin
OSA	one-stage assay
PCCs	prothrombin complex concentrates
PWH	people with hemophilia
RA	rheumatoid arthritis
RANK	receptor activator of nuclear factor κB
RANKL	receptor activator of nuclear factor κB ligand
RBC	red blood cell.
rFVIIa	recombinant activated factor VII
ROM	range of motion
S	Significant
SD	standard deviation
sEMG	surface electromyography
TNF	tumor necrosis factor
UDC	Universal Data Collection
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
WFH	world federation of hemophilia

INTRODUCTION

hemophilia A; is an X-linked bleeding disorder; owing to a mutation in the genes encoding for coagulation factor VIII (FVIII), which was first reported in the medical literature during the 18th century (Castaman and Matino, 2019). Estimations based on the world federation of hemophilia (WFH)'s annual global surveys indicate that the population with hemophilia in the world is approximately 400,000 (Stonebraker and Bolton, 2010).

While the characteristic phenotype in hemophilia is a lifelong prolonged post traumatic bleed, Studies suggests that the low to normal FVIII activity found in hemophilia A carriers compromises hemostasis sufficiently to cause joint bleeding (Gilbert et al., 2014).

Hemophilia A carriers also experience subclinical joint bleeding which could lead to structural joint damage which was demonstrated by soft tissue and osteo-chondral changes on joint MRI; in which ankle MRI Gilbert et al (2014).

Early signs of synovial hypertrophy and early cartilage damage can be demonstrated by magnetic resonance imaging (MRI) of the affected joint (Carotti et al., 2017).



Whether, hemophilia carriers develop subclinical joint arthropathies need to be studied.

Aim of Work

Primary objective:

To assess factor VIII level in mothers of known patients of hemophilia A.

Secondary objective:

- To assess the frequency of arthropathy in hemophilia A potential female carrier mothers.
- To correlate the level of factor VIII with the degree of arthropathy in both potential female carrier mother.

Chapter 1

Hemophilia

Epidemiology:

emophilia A & B are rare inherited bleeding (XLR) disorder caused by deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B) (World Federation of Hemophilia, 2018).

Currently; Hemophilia A has been recognized in all areas of the world and in all ethnic groups. Estimates of its incidence approximate 1 in 5000 male live-births, or 1 in 10000 livebirths (*Kadhim et al.*, 2019).

Hemophilia B is less common with an incidence of 1 in 30 000 male live-births. However, hemophilia C affects about 1 in every 100,000 populations. India ranked first in number of registered patients with hemophilia (A, B, and C) in 2016, with a total number of 18,383 patients with a prevalence of 1.4/100 000 populations, followed by the United States and China. (*Stonebraker et al.*, 2010)

According to the WFH, hemophilia has an estimated frequency of approximately one in 10,000 births. Hemophilia A is more common than hemophilia B, representing 80–85% of

the total hemophilia population. According to the WFH Global Survey, there were an estimated 5,050 people with hemophilia (PWH) in Egypt in 2013 (*World Federation of Hemophilia*, 2018).

Etiology and Pathophysiology:

Research has identified over 1000 mutations in the genes encoding factor VIII and IX, along arm of X-chromosome and around 30% are due to spontaneous mutation (*Bertamino et al.*, 2017).

Types of mutations:

Inversion mutations involving intron 22 (Inv22) and intron 1 (Inv1), account for about 45% and 2% - 5% of severe phenotype, respectively (*Gouw et al.*, 2012).

Point mutations are the most prevalent defect in 90% - 95% of patients who tested negative for inversion typing, followed by deletions in about 5% - 10%. Numerous types of previously reported HA gene mutations have been identified in exon 14. Being the largest exon in F8 gene, exon 14 provides a mutational hotspot and codes partially for two domains (A2 and A3) as well as the entire B-domain of F8 protein (*Bastida et al.*, 2017).



– Review of Iițerature —

Recently, targeted next-generation sequencing (NGS) is utilized to sequence the whole coding region of F8 (*Atik et al.*, 2020).

Factor VIII and IX in coagulation cascade:

Blood coagulation is part of an important host defense mechanism termed hemostasis. Upon vessel injury, platelets adhere to macromolecules (i.e. collagen) in the sub-endothelial tissues and aggregate to form a platelet plug (primary hemostasis) (*Periayah et al.*, 2017)

Activated platelets then stimulate the local activation of plasma coagulation factors that initiate a sequential amplifying cascade, resulting in the formation of a cross-linked fibrin clot that further strengthens the platelet plug (secondary hemostasis) (*Jain and Acharya*, 2018).