ASSESSMENT OF COAGULATION MECHANISM IN ACUTE GASTROENTERITIS

THESIS

SUBMITTED FOR PARTIAL FULFILMENT OF

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BY

ISMAIL SADEK ISMAIL

M .B .B .CH .,M .SC .PEDIATRICS

SUPERVISORS :

PROF. DR. OMAR HELMY ISMAIL

HEAD OF PEDIATRIC DEPARTMENT ,

FACULTY OF MEDICINE .

AIN SHAMS UNIVERSITY .

PROF. DR. KHALIL ABDEL HADY MOURAD

PEDIATRIC DEPARTMENT ,

FACULTY OF MEDICINE ,

AIN SHAMS UNIVERSITY .

PROF. DR. SALAH EL DIN ZAKY EID

BIOCHEMISTRY DEPARTMENT ,

FACULTY OF MEDICINE ,

AIN SHAMS UNIVERSITY .

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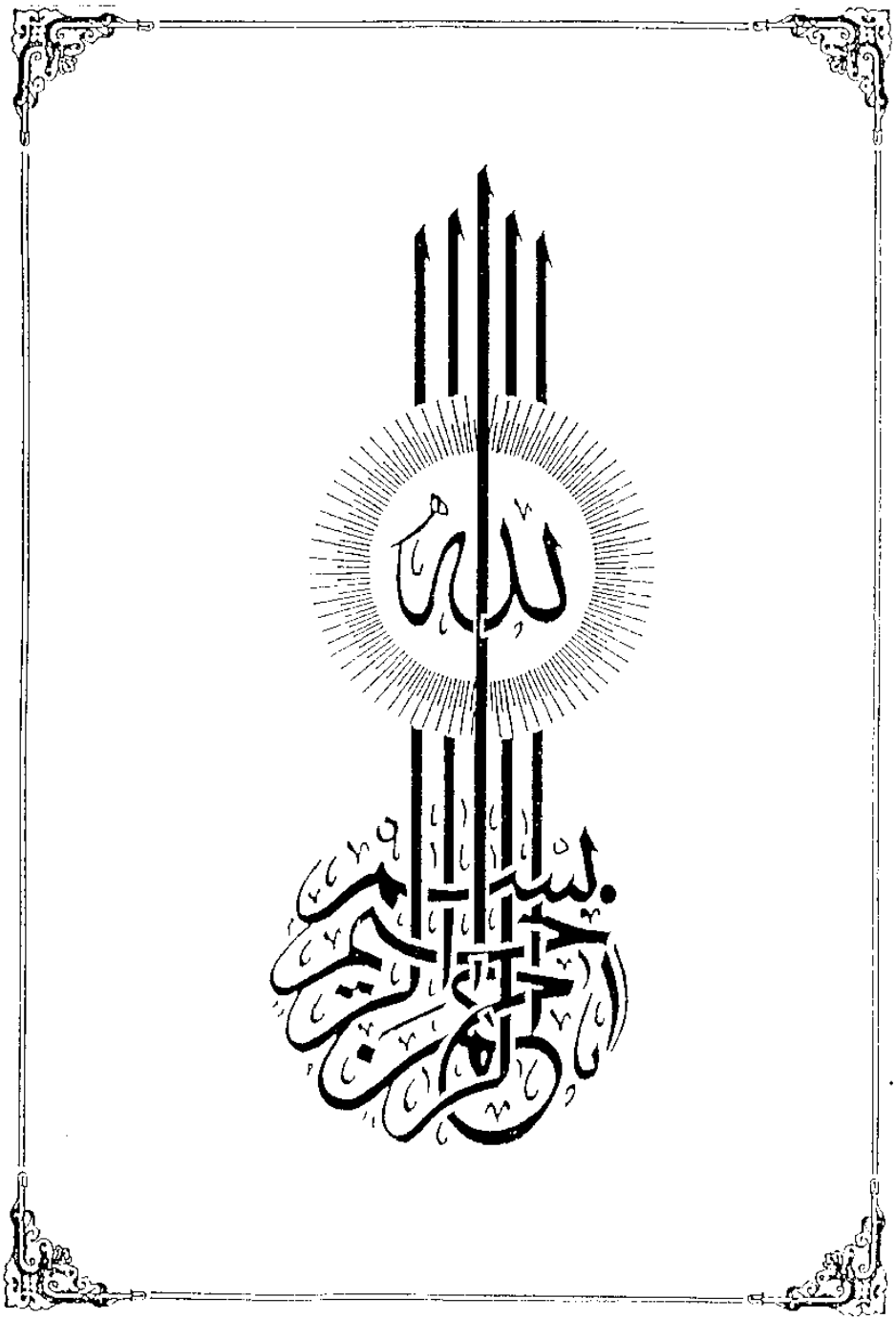
بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لاَعِلْمَ لَنَا إِلاَّ مَاعَلَّمْتَنَآ إِنَّكَ أَنتَ العَلِيمُ الحَكِيمُ

صدق الله العظيم

(قرآن كريم . سورة البقرة . آية رقم ٣٢)



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C O N T E N T S

INTRODUCTION

AND

AIM OF THE WORK

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Acute gastroenteritis is a distinct clinico-pathological entity in infancy in which the most important problems are those of dehydration and electrolyte loss of a degree seldom encountered in older children and adult patients. The age of these patients render them more prone to severe diarrhea accompanied by vomiting, further enhancing the fluid and electrolyte loss. Although the mortality rate has been reduced in the developed countries, it is still considerable in the developing countries where poor hygienic conditions and malnutrition are both responsible for the higher morbidity and mortality rates (Boon, 1984).

In Egypt, acute gastroenteritis still constitutes a leading cause of death during infancy and early childhood (Abbassy, 1977). The disease is responsible for about 50% of the mortality rate of Egyptian infants (Ministry of Public Health, 1977).

Among the serious and fatal complications of acute gastroenteritis are those involving the alteration in hemostatic mechanisms. This can lead to the formation of localized thrombosis, or a disseminated form of thrombosis "Disseminated intravascular coagulopathy " in which thrombi and fibrin clots are deposited in various

body organs especially the lungs and kidneys and clinically presenting with a bleeding diathesis on top of the underlying condition .

The aim of this work is to assess the coagulation mechanism in acute gastroenteritis so as to detect any coagulopathy as well as to identify its exact nature .

REVIEW OF LITERATURE

PHYSIOLOGICAL ASPECTS OF THE CLOTTING MECHANISM

At the simplest level, the formation of a clot involves the gelation of a protein known as fibrin . This protein is not normally present as such in the circulation, but is produced in large quantities at the site of coagulation from a circulating precursor , fibrinogen . The production of fibrin from fibrinogen involves a sequence of reactions the effect of which is to amplify the tiny biochemical signal produced bya damaged blood vessel into a fibrin-generating reaction vigorous enough to from a clot capable of stopping the bleeding from the damaged vessel. Because this step of amplification occurs in a series of stages, the sequence of reactions by which the initial signal is transmitted into a fibrin clot is known as the clotting cascade (Fig 1).

The clotting cascade is a complex process. It consists of a pair of activation sequences that run in parallel namely the intrinsic pathway, so called because it is triggered by factors intrinsic to (i.e. present in) the plasma, and the extrinsic pathway which is trigerred by tissue factor which is extrinsic to plasma. Apart from the crossover reaction VIIa $\longrightarrow$ IXa , both pathways are

separate activating tracks that lead to the activation of factor X. From factor Xa onwards, there is only the single common pathway that ends in clot formation (Babior and Stossel, 1984).

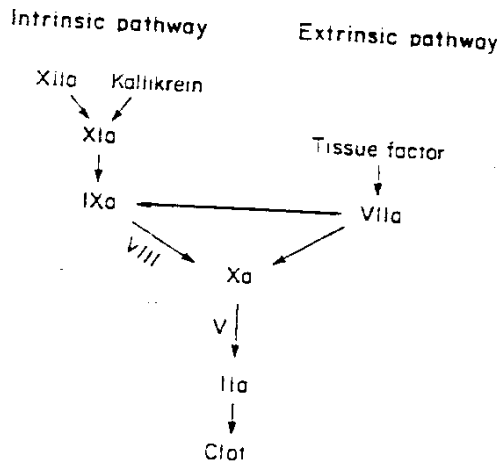

Fig.1:Clotting cascade.The clotting consists of two separete activating pathways- the intrinsic pathway and the extrinsic pathway which converge to a common pathway at factor X. Except for factors V and VIII, all the clotting factors named in this diagram are proteases (Babior and Stossel, 1984).

THE CLOTTING FACTORS

The protiens involved in the formation of a clot are all present in the plasma, but they circulate as precursors with little or no activity. When blood vessels and surrounding tissues are damaged , two of these clotting factors, factor VII and factor XII (contact or Hageman factor), are converted from an inactive to an active form .In their active form, these two clotting factors activate the next factors. These in turn activate the succeeding factors, the final outcome being the production of a fibrin clot . In every case , the inactive clotting factor is converted to the active form by the cleavage of one or two particular peptide bonds, a process known as activation by limited proteolysis (Davie and Fujikawa, 1975).

The clotting factors are :

* Vitamin K - dependent clotting factors

Factor II (Prothrombin)
Factor VII (Proconvertin)
Factor IX (Christmas factor)
Factor X (Stuart - Prower factor)
Protein C

* Thrombin - sensitive clotting factors

Factor I (Fibrinogen)

Factor V (Proaccelerin)

Factor VIII (Antihaemophilic factor)

Factor XIII (Fibrin stabilising factor)

* The contact factors

Factor XII (Hageman factor)

Factor XI (Plasma thromboplastin antecedent)

High molecular weight kininogen (Fitzgerald factor)

Prekallikrein (Fletcher factor).

(Hougie and Baugh, 1980)

Biosynthesis of clotting factors

The liver is the site of biosynthesis of most clotting factors . Fibrinogen, prothrombin , as well as factors V, VII , IX , X and XIII are synthesized in the liver. Factor VIII is synthesized in parts, one portion (von Willebrand factor) is secreted by megakaryocytes and endothelial cells, and the rest being produced at unkown site (Tuddenham et al, 1981). It is not known where the remaining clotting factors are made (Williams, 1983).

Vitamin K is required for the production of factors II (prothrombin), VII, IX and X. The N-terminal (activation peptide) protions of these four clotting factors contain a series of γ-carboxyglutamyl residues that appear to funtion in calcium binding , and are essential for full expression of the proteolytic activity of the active forms of these factors .The residues are not incorporated into the proteins during translation, but rather are produced by the post-translational addition of CO_2 to selected glutamate residues in the protein chain. It is this carboxylation reaction that requires vitamin K. Thus in the absence of vitamin K , these clotting factors are still synthesized , but with glutamic rather than carboxyglutamic acid residues, a form in which they are inactive (Fig. 1a).

Vitamin K is also required for the production of the anticoagulant protein known as protein C (Hougie and Baugh, 1980).

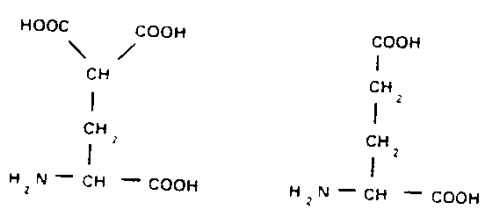

Fig. 1.a γ-carboxyglutamic acid and glutamic acid.

(Hougie and Baugh, 1980)

STAGES OF THE CLOTTING CASCADE

The clotting cascade can be divided into three stages : the initial stage , the intermediate stage, and the stage of clot formation (Table 1).

Table 1. Stages and the clotting factors activated during each stage (Babior and Stossel, 1984).

Stage	Factors Activated
Initial	XII, prekallikrein, XI, VII
Intermediate	IX, X, prothrombin
Clot formation	Fibrinogen, XIII

Initial Stage

The initial stage consists of two distinct events: the so-called " contact phase " of coagulation and the activation of factor VII.