Alpha 1. antitrypsin in neonatal sepsis

Thesis

Submitted for Partial Fulfilment of the
M.Sc., Degree in Pediatrics

By

Souzy Magdy Farag

M.B.B. CH.

Supervisors

Prof . Dr. Yehia El Gamal

Prof . of Pediatrics, Ain Shams University

Dr, Mona El Samahi

Lecturer of Pediatrics, Ain Shams University

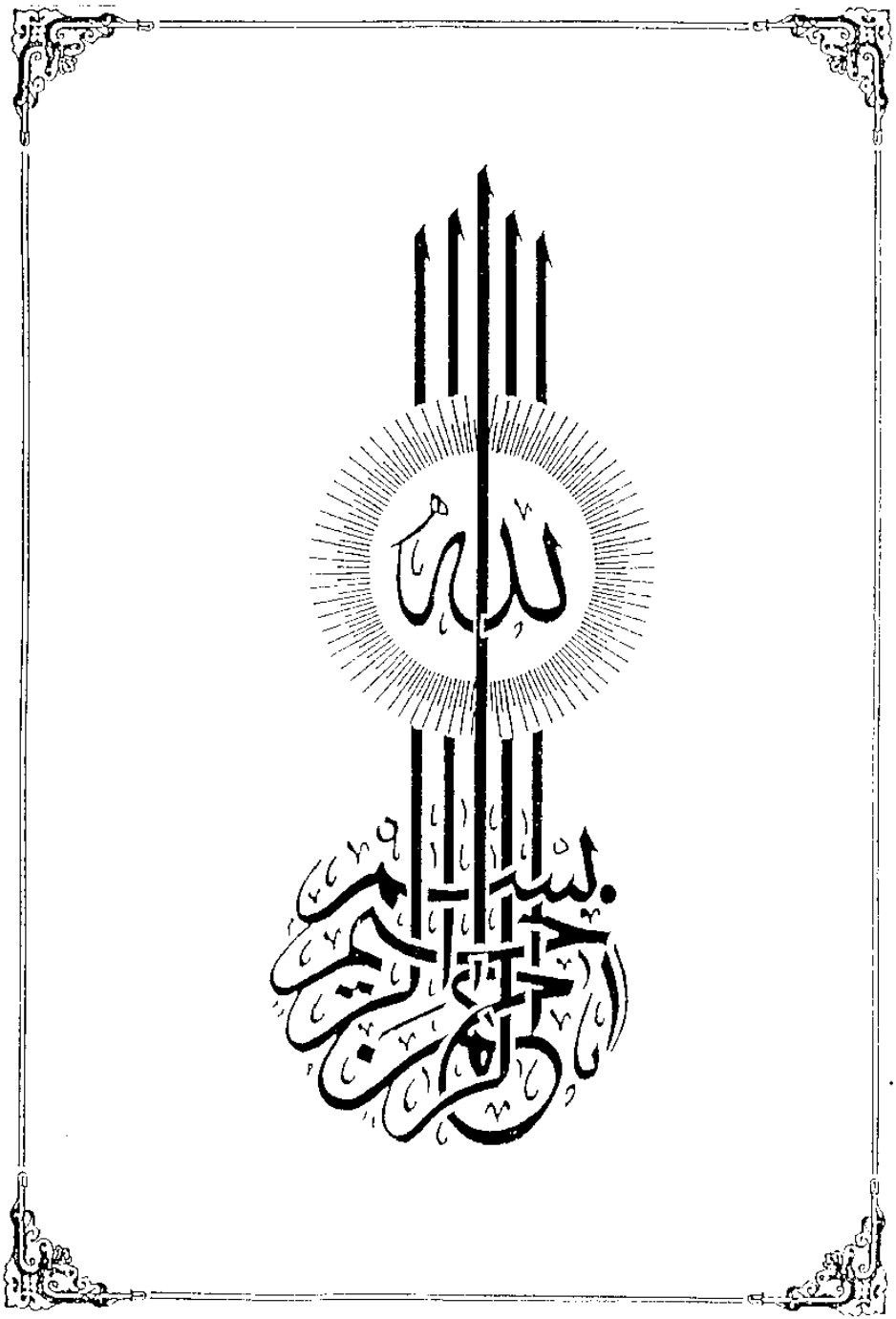
Dr. Maha El Tahawi

Lecturer of Clinical Pathology, Ain Shams University

Faculty of Medicine, Ain Shams University

1987

TO MY PARENTS, MY HUSBAND, MY SONS
AND MY MOTHER IN LAW .



Acknowledgement

Without the aid of God, this work would have never been accomplished .

I wish to express my sincere gratitude and appreciation to Professor Dr.Yehia El Gamal, Professor of Pediatrics, Ain Shams University, who was kind enough to offer me much of his time, valuable advice and experience .

I am also grateful to Dr. Mona El Samahi, Lecturer of Pediatrics, Ain Shams University for her kindness, supervisions and continuous encourgement throughout the whole work .

My deep gratitude to Dr. Maha EL Tahawi, Lecturer of Clinical Pathology, Ain Shams University , for her cooperation and for directing the practical work.

To everyone who participated in some way or other in this work, I owe my utmost gratitude.

Abbreviation

Alpha 1-	A_1
Antigen	Ag
Cerebrospinal fluid	CSF
Escherichia coli	E.coli
Erythrocyte sedimentation rate	ESR.
Full term	F.T.
Gastro intestinal tract	G.I.T.
Immunoglobulins	Ig
Haemophilus influenzae	H. influenzae
Litre	L.
Low birth weight	L.B.W.
Microgram	Ug
More than	>
Part Per Million	P.P.M.
Total leucocytic count	TLC.

Contents

INTRODUCTION AND AIM OF WORK

Alpha 1. antitrypsin in neonatal sepsis

Introduction and aim of the work :

Neonatal septicaemia is an acute systemic disease of the newborn associated with invasion of blood stream and various tissues by micro-organisms and their toxic products.

Despite the rarity of proven bacterial sepsis, dessiminated bacterial infections during the first month of life remains a significant cause of neonatal morbidity and mortality (Harris and Polin, 1983).

Alpha I antitrypsin is a glycoprotein of low molecular weight. It is an acute phase reactant protein. Its concentration increases considerably under various physiologic and pathologic conditions . Its level increases in inflammations and tissue reactions (Pelet,1980); but being the major serum protease inhibitor it was found to be low in case of acute bacterial pneumonia and in newborn with respiratory distress syndrome.(Albow et al 1976).

The aim of the work is to study the level of the alpha -1- antitrypsin in neonatal sepsis and in the high risk neonates so as to be used as predictive test for diagnosis of neonatal infections.

REVIEW OF LITERATURE

Review

Alpha -1- antitrypsin

Historical review :

Shultz and colleagues in (1955) were the first to discover this protein and named it 3.5 S A_1 glycoprotein in plasma later on it was found that it is the major trypsin inhibitor in plasma; so named it A_1 antitrypsin (Shultz et al, 1962).

Researches after that time proved the broad spectrum activities of this A_1 antitrypsin against a large number of serum proteinases as leucocyte elastase, plasmin, Cathepsin G, chymotrypsin and trypsin . So it was renamed as alpha 1- proteinase inhibitor-(Pannel et al, 1974).

In 1963 this plasma protease inhibitor alpha 1-antitrypsin became of clinical interest, when its deficiency was found to be associated with early onset of emphysema and several years later an association was also observed with childhood liver cirrhosis (Cox and mansfield, 1985).

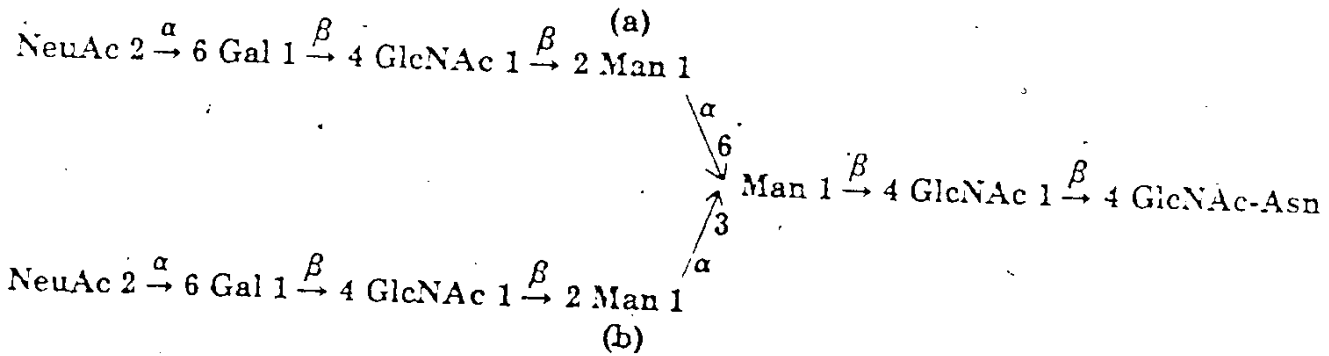


Diagram (1) showing chemical structure of alpha 1- antitrypsin molecule .

Mera et al , (1980)

Chemical Structure :

It is an alpha 1- globulin of glycoprotein nature (Bundy and Mehl, 1959).

Mega et al, (1980) reported that the polypeptide chain is formed of 394 amino acids (a. a.) having three oligosaccharides side chains attached to asparagine at location 46,83 and 247. It has a molecular weight of 51.000 dalton .

The carbohydrate portion constitutes about 12% of the total molecular weight and is formed of 7. Galactose, 9-mannose, 10. N-acetyl glucosamine 8 N-acetyl muramic acid, acetyl hexosamine and sialic acid. (Carrel et al, 1982). Alpha 1- antitrypsin has a single reactive site centered on methionine at position 358. The molecule has only one cysteine residue located at the position 232 and available for SH - SS interchange reaction both in vitro and vivo .

Chemical properties :

Oxidation of the critical methionine residue of alpha 1- proteinase inhibitor reduces the association

with leucocyte elastase by a factor of more than 2000, and also lowers the association with the other enzymes tested with the exception of chymotrypsin . So oxidising agents in the lungs could indirectly augment elastolysis in this tissue, resulting in the development of pulmonary emphysema. (Beatty et al, 1980).

Cigarette smoke by its oxidants causes a major reduction of alpha 1- antitrypsin activity. This can be prevented by adminstration of reducing agents (Janoff et al, 1979).

Ozone inactivates alpha 1- antitrypsin by forming methionine sulfoxide and oxidized tyrosine and tryptophan. Inhalation of ozone could inactivate alpha 1- antitrypsin; thus creating a localized alpha 1- antitrypsin deficiency which might contribute to the development of emphysema .

The Environemental Protection Affairs Agency adapted an air quality standard for ozone of 0.12 P.P.M in order to avoid the hazardous concentration of ozone (Jhonson, 1980).

It's also indicated that cysteine active site prote-

inases as papin and cathepsin G, have been found to inactivate this alpha 1- antitrypsin by proteolytic cleavage of scissilie peptide bond. (Johnson and Travis, 1977).

Alpha 1- antitrypsin is unstable to heating and to pH values below 5.5 (Bundy and Mehl 1959).

Genetics of A_1 antitrypsin

Inheritance of alpha 1- antitrypsin gene complex and studies have suggested a genetic model with multiple codominant alleles at a single autosomal locus named Pi for protease inhibitor(Fagerhol, 1976). This single locus is on the long arm of chromosome number 14 .(Cox et al, 1982).

Over fifty allelic variants have been described .The alleles have been labelled on the basis of their electorphoretic mobility; with the Z allele representing a very slow variant. In the homozygotes (zz) it leads to severe alpha 1- antitrypsin deficiency(Kidd et al, 1983).

The PiM is the most common allele of alpha 1- antitrypsin (80-95 % of subjects) and is associated with a normal level of it in the serum (160 - 350 mg%)(Laurell and