Alpha one Antitrypsin Deficiency in ICU

Essay

Submitted for the partial fulfillment of *Master Degree in Intensive Care*

By

Mahmoud Ahmed Mahmoud Shousha

M.B.B.Ch,

Under supervision of:

Prof.Dr.Mohammed Ibrahim Mohammed Shehata

Professor of Anesthesiology and Intensive Care

Faculty of Medicine, Ain Shams University

Dr.Noha Mohammed Elsharnouby

Assistant Professor of Anesthesiology and Intensive Care

Faculty of medicine, Ain Shams University

Dr.Nevein Gerges Fahmy

Lecturer of Anesthesiology and Intensive Care

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

(2015)

Acknowledgement

First, thanks are all to **ALLAH** for blessing this work until it has reached its end.

My profound thanks and deep appreciation to **Prof.Dr.Mohammed Ibrahim Mohammed Shehata**, Professor of Anesthesiology and Intensive Care Faculty of Medicine, Ain Shams University for his great support and advice, his valuable remarks that gave me the confidence and encouragement to fulfill this work.

I am deeply grateful to **Dr.Noha Mohamed Elsharnouby,** Assistant Professor of Anesthesiology and Intensive Care Faculty of medicine, Ain Shams University for adding a lot to this work by her experience and for her keen supervision.

Dr.Nevein Gerges Fahmy, Lecturer of Anesthesiology and Intensive Care Faculty of Medicine, Ain Shams University by her patience and support, she helped me accomplish this work.

I am extremely sincere to my family who stood beside me, support me throughout this work.

Contents

Contents I

Abbreviations II

Aim of the work..... IV

Introduction. 1

1. Chapter one: Etiology and pathophysiology of alpha-1 antitrypsin deficiency 4

2. Chapter two: Symptoms and signs of alpha-1 antitrypsin deficiency. 19

3. Chapter three: Management of alpha-1 antitrypsin deficiency. 44

4. References 80

5. Arabic summary. ..... -

Abbrevations

1-A1AT **:** alpha one antitrypsin.

2- AACT **:** alpha-1 antichymotrypsin.

3- ANCA **:** anti-neutrophil-cytoplasmic-antibodies.

4- ATS **:** American thoracic society.

5-BAL **:** broncho-alveolar lavage.

6-BMD **:** bone mineral distribution.

7-BMI **:** body mass index.

8- CAD **:** coronary artery diseases.

9- CBG **:** corticosteroid binding globulin

10- COPD **:** chronic obstructive pulmonary disease.

11- DBS **:** dried blood spot.

12- DVT **:** deep venous thrombosis.

13- EELV **:** end expiratory lung volume.

14- ERS **:** European respiratory society.

15- FEV1 **:** forced expiratory volume in first second.

16- FVC **:** forced vital capacity.

17-HCC **:** hepatocellular carcinoma.

18-HNF : hepatocyte nuclear factor.

19- HRQoL : health related quality of life.

20- IEF : isoelectric focusing.

21- IL : interleukine.

22- LVRS : lung volume reduction surgery.

23- NE :neutrophil elastase.

24- NHLBI : national heart, lung and blood institute.

25-NPPV :non invasive positive pressure ventilation.

26- PAS :periodic acid Schiff.

27- PBA : phenyl butyric acid.

28- PCI :protein C inhibitor.

29- PCR : polymerase chain reaction.

30- PE : pulmonary embolism.

31-PEEP : positive end expiratory pressure.

32- RFLP : restriction fragment length polymorphism.

33- SLPI :secretory leukoprotease inhibitor.

34- VTE : venous thrombo- embolism.

35- WHO : World Health Organization.

Aim of the work

The aim of this essay is to study the pathophysiology, symptoms, signs, and management of alpha-1 antitrypsin deficiency in ICU.

Introduction

AAT is an antiprotease which inhibits neutrophilderived proteases and protects the fragile tissues of the lung. Absence of this key antiprotease renders the lung susceptible to proteolytic degradation. Alpha-1 antitrypsin deficiency (AATD) is a hereditary disorder characterised by low circulating levels of alpha-1 antitrypsin (AAT). The lung disease associated with the condition is characterized by neutrophil-dominated airway inflammation and elevated intra-pulmonary protease levels **(Greene et al, 2008).**

In addition, the abnormal accumulation of the glycoprotein in hepatocytes results in programmed cell death, hepatic inflammation, fibrosis, and cirrhosis. Histopathologic examination of liver specimens from patients with alpha 1-antitrypsin deficiency demonstrates the classic intracellular globules that stain positive with periodic acid-Schiff (PAS) after treatment with diastase.

These globules represent polymerized mutant protein retained in the rough endoplasmic reticulum **(Stoller and Aboussouan, 2005)**.

The most frequent clinical complications of AAT deficiency are pulmonary emphysema of the panacinar type, which may present as early as the third or fourth decade, and liver disease, which typically presents early in infancy as neonatal hepatitis with a diverse degree of liver involvement and outcome **(ATS&ERS, 2003).**

There are several forms and degrees of deficiencies, principally depending on whether the sufferer has one or two copies of the affected gene, because it is a co-dominant trait. Severe A1AT deficiency causes panacinar emphysema or COPD in adult life in many people with the condition, (especially if they are exposed to cigarette smoke),as well as various liver disease in a minority of children and adults, and occasionally more unusual problems **(Needham & Stockley, 2004).**

The natural history of COPD consist of progressive deterioration in pulmonary function, and progressive increase in the frequency of respiratory symptoms, negatively affecting the quality of life of patients and limiting their autonomy. The gradual deterioration tyical of the disease can be interspersed with periods of acute worsening of the clinical and functional status of patients, known as periods of acute COPD exacerbations, which can manifest as increased respiratory effort, and respiratory failure, requiring ICU admission and ventilator support **(Anzueto et al, 2007).**

Chapter one:

Etiology and pathophysiology of

Alpha -1 Antitrypsin deficiency

Alpha-1 antitrypsin deficiency is a genetic disorder that manifests clinically as chronic bronchitis, pulmonary emphysema, liver disease, and, much less frequently, skin disease (**Kohnlein et al, 1999**).

Alpha-1antitrypsin (synonym:alpha-1 proteinase inhibitor; al-PI) is a 52 kDa molecule produced primarily in hepatocytes and released into the blood stream. The normal daily rate of synthesis is approximately 34 mg per kg, leading to a serum concentration ranging from 1.5to 3 g/l. Alpha-1 antitrypsin can be detected in all body tissues but appears to have its primary physiologic significance in the lungs, where it protects the healthy but fragile alveolar tissue from the proteolytic effect of neutrophil elastase(NE) and other damaging proteases (**Brantly et al,1991**).

Function:

The most important physiologic function of alpha-1 antitrypsin is its antiprotease function: alpha-1 antitrypsin

quickly reacts with proteases, thereby inactivating them. As the archetype of a large group of protease inhibitors, the so called serpins, alpha-1 antitrypsin is able to inhibit a whole range of serine proteases, for example, trypsin, chymotrypsin, neutrophil elastase (NE), cathepsin G, and proteinase-3. Initial research focused on alpha-1 antitrypsin as a trypsin inhibitor thereby prompting the naming of the protein, and the customary name still reflects the historical condition. A more modern nomenclature is alpha-1 proteinase inhibitor, which takes into account the broader inhibitory spectrum **(Gadek and Pacht , 1990).**

Inhibition of proteases by alpha-1 antitrypsin is irreversible. It occurs through formation of a covalent complex of the protease with the active site of alpha-1 antitrypsin in a molecular ratio of 1:1. At the active site, located on the surface of the molecule, the amino acid methionine renders the active site vulnerable to oxidation. Beyond oxidative inactivation , alpha-1 antitrypsin can get

inactivated by proteolytic degradation (eg, by bacterial metalloproteinases), or by complex formation with a protease **(Gadek and Pacht , 1990).**

An excess of uninhibited NE in the lungs can lead to destruction of extracellular structural proteins, in particular elastin, which constitutes about 10% to 30% of the fibrous lung structure. In addition, an excess of free NE and, to a lesser extent, the serine proteases cathepsin G and proteinase-3, can produce a series of further pathophysiologic effects: these include impairment of local host defense mechanisms and induction of airway hypersecretion **(Travis and Fritz ,1991).**

Prevalence/Incidence:

Severe alpha 1-antitrypsin deficiency (PiZZ) is found in approximately 1:3500 live births, and has been described in all races **(de Serres , 2002).**

It is, however, most commonly a disease of whites, as the most prevalent deficiency alleles, Z and S, are overwhelmingly derived from Northern European ancestry (Z and S alleles), and some Southern European ancestry (S allele). Although it has been described in all races, the frequency of PiZ varies greatly, being extremely rare in Asian and Mexican Americans, uncommon in Black Americans (2.6 per 1,000), and more common in Hispanic (9.1 per 1,000) and White Americans (14.0 per 1,000) **(de Serres et al, 2003).**

The frequency of alpha-1 antitrypsin deficiency in European and North American populations is approximately 1 in 2000 to 1 in 7000.This is similar to the rates of occurrence of cystic fibrosis and type 1 diabetes mellitus. Alpha-1 antitrypsin deficiency variants are most often found in Caucasian populations,including inhabitants of the Middle East **(Steenbergen ,1993).**

A smaller than predicted number of alpha-1antitrypsin

deficient patients,only 600 to 800, have been identified in Germany. There are several possible explanations for this finding. Patients with homozygous alpha-1 antitrypsin deficiency may not develop the commonly seen symptoms. Some patients may only be classified as usual COPD patients without identification of alpha-1 antitrypsin deficiency. Various external factors are sometimes blamed for the development of pulmonary symptoms, such as smoking, air pollution, and lower respiratory tract infection**(Kohnlein et al,1999).**

Nomenclature and Discovery:

In the 1950s, techniques of serum electrophoresis were improved and became part of routine hospital practice. As much as 90% of the alpha-1 globulin band was found to consist of a protein that inhibits the protease trypsin; hence, the name''alpha-1 antitrypsin'' was established **(Kohnlein and Welte , 2007).**