The role of ascitic fluid complement 3 level in development of spontaneous bacterial peritonitis

Thesis
Submitted for the partial fulfillment of Master Degree ***in Internal Medicine***

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2010

دور مستوى العامل المتمم (C3) لسائل الاستسقاء في حدوث الالتهاب البريتوني البكتيري التلقائي

رسالة
توطئة للحصول على درجة الماجستير في
الباطنة العامة

مقدمة من
الطبيب / إيهاب كمال يونس سالم
بكالوريوس الطب و الجراحة

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List of Abbreviations

μL ····· Micro Litter
AAE ····· Acquired Angioedema
AASLD····· American Association for the Study of Liver Diseases
Ab ····· Antibody
A.F ····· Ascitic Fluid
AFB ····· Acid-Fast Bacilli
Ag ····· Antigen
ALP ····· Alkaline Phosphatase
ALT ····· Alanine Aminotransferase
ANA ····· Antinuclear Antibody
AP ····· Alternative Pathway
APC ····· Antigen Presenting Cells
AST ····· Aspartate Aminotransferase
BT ····· Bacterial Translocation
BUN ····· Blood Urea Nitrogen
C3 ····· Complement 3
CIC ····· Circulating Immune Complexes
CNNA ····· Culture Negative Neutrocytic Ascites
CP ····· Classical Pathway
CR1 ····· Complement receptor 1
CT ····· Computed Tomography
CTP ····· Child-Turcotte-Pugh
DAF ····· Decay-accelerating factor
dl ····· Deciliter
DNA ····· Deoxyribonucliec Acid
DT ····· Dipstick Testing
EASL ····· European Association for the Study of the Liver
ELISA ····· Enzyme-Linked Immunosorbent Assay
FB ····· Factor B
FD ····· Factor D
g ····· Gram
GALT ····· Gut-Associated Lymphoid Tissue
GI ····· Gastro-Intestinal
HAE ····· Hereditary Angioedema

List of Abbreviations (Cont.)

HE····· Hepatic Encephalopathy
HRS····· Hepatorenal Syndrome
Hu ····· Human
Ig ····· Immunoglobulin
INR ····· International Normalized Ratio
IV ····· Intravenous
L····· Litter
LDH ····· Lactate Dehydrogenase
LP ····· Lectin Pathway
M cells····· Macrophage Cell
MAC····· Membrane Attack Complex
MASP ····· Mannan-Binding Lectin associated Serine Protease
MBL ····· Mannan-Binding Lectin
MCP ····· Membrane Cofactor Protein
MELD ····· The Model for End-stage Liver Disease score
mg····· Milligram
MLN····· Mesenteric Lymph Nodes
MNB····· Monomicrobial non Neutrocytic Bacterascites
NASH ····· Non Alcoholic Steatohepatitis
NO ····· Nitric Oxide
P····· Properdin
PAMP ····· Pathogen-Associated Molecular Pattern
PMN ····· Polymorphonuclear Leucocytes
PRR ····· Pattern Recognition Receptor
PT ····· Prothrombin Time
RCA ····· Regulators of Complement Activation proteins
SAAG ····· Serum Albumin -Ascitic fluid albumin Gradient
SBP ····· Spontaneous Bacterial Peritonitis
SIRS ····· Systemic Inflammatory Response Syndrome
SNP ····· Single Nucleotide Polymorphism
SRBC····· Sheep Red Blood Cell
TIPS ····· Transjugular Intrahepatic Portosystemic Shunt
TLR····· Toll like receptor
TP ····· Terminal Pathway
UNOS ····· United Network for Organ Sharing

Acknowledgement

First of all, thanks to ***Allah*** *the most merciful for giving me the strength to complete this work.*

I wish to express my deepest gratitude Dr. ***Amany Talaat,*** *Assistant Professor of Internal Medicine, Faculty of Medicine Ain Shams University, for her encouragement, support and kindness, which enabled me to go ahead and finish this work.*

I am also very grateful to ***Dr. Eman Nagib Osman,*** *Assistant Professor of Internal Medicine, Faculty of Medicine, Ain Shams University, for her kind, continuous support and her precious remarks.*

I also grateful to ***Dr. Rasha Youssef Shahin,*** *Lecturer of Internal Medicine, Faculty of Medicine, Ain Shams University, for her keen supervision, kind guidance, enormous support, brilliant teaching and precious advice.*

I also grateful to my colleagues, friends whose support was crucial to make me go on.

Ihab Kamal Younis

Introduction

Liver cirrhosis is a frequent phenomenon in chronic liver disease such as hepatitis B, hepatitis C, alcoholic-related liver damage, autoimmune hepatitis and hemochromatosis (***Van Erpecum, 2006).***

Ascites is the most common complication in patients with decompensated cirrhosis. Approximately 50% of patients with compensated cirrhosis will develop ascites over a 10-years period ***(Saadeh and Davis, 2004).***

Patients with cirrhosis and ascites show a higher susceptibility to bacterial infections mainly because of the inadequate defence mechanisms. The most frequent and the most severe one being Spontaneous Bacterial Peritonitis (SBP) ***(Garcia-Tsao, 2005).***

SBP is bacterial infection of the ascitic fluid without any intra-abdominal source of infection ***(Frances et al., 2004).***

The prevalence of SBP in cirrhotic patients with ascites has been estimated at 10 to 30% (***Evans et al., 2003).***

There are some mechanisms that are being proposed to explain bacterial translocation (BT) in cirrhosis: the intestinal bacterial overgrowth, the structural and functional alterations of the intestinal mucosal barrier and the deficiencies of the local immune response ***(Guarner and Soriano, 2005).***

For SBP diagnosis, the number of polymorphonuclear leucocytes (PMN) from the ascitic fluid obtained by paracentesis must exceed 250 cells/mm3 and from bacteriological cultures only one germ must be isolated ***(Mandell et al., 2005).***

Early start with antibiotic treatment, the short term prognosis of cirrhotic patients with SBP has improved significantly. Unfortunately, the long term prognosis remains extremely poor due to the severity of subjacent liver disease ***(Caruntu and Benea, 2006).***

In cirrhosis, because of the local and systemic immune deficiencies, the BT process is followed by bacteremia and ascitic fluid inoculation. If the ascitic fluid complement level is low, this will determine a low bactericidal activity and thus a higher risk of SBP ***(Thalheimer et al., 2005).***

Aim of the Work

This prospective case-control study is to compare the level of ascitic fluid C3 concentration in cirrhotic patients with and without spontaneous bacterial peritonitis monthly over a period of 3 months, to determine its possible protective role against acquiring infection.

Chapter One:
Hepatic Cirrhosis

The word "cirrhosis" is derived from the Greek word kirrhos, meaning orange or tawny, and osis, meaning condition ***(Cheney et al., 2004)***.

Definition:

Cirrhosis is a slowly progressive disease, causing irreversible scarring and nodularity of the liver in response to chronic injury from a variety of causes ***(Rimola et al., 2000).*** This process distorts the normal liver architecture, interferes with blood flow through the liver and disrupts the biochemical functions of the liver ***(Mathews et al., 2006).***

Classification of Cirrhosis:

I- Morphological classification:

Cirrhosis was historically classified morphologically as micronodular, macronodular, or mixed ***(Anthony et al., 1978).*** Micronodular cirrhosis, characterized by nodules less than 3 mm in diameter, was believed to be caused by alcohol, hemochromatosis, cholestatic causes of cirrhosis, and hepatic venous outflow obstruction. Macronodular cirrhosis, characterized by various sized nodules larger than 3 mm, was believed to be secondary to chronic viral hepatitis ***(SherLock and Dooley 2002).***

Although important from a historical prospective, the morphological classification system has a number of limitations and has thus largely been abandoned. **First**, it is relatively nonspecific with regard to etiology. **Second**, the morphologic appearance of the liver may change as the liver disease progresses; micronodular cirrhosis usually progresses to macrondular cirrhosis. **Third**, serological markers available today are more specific than morphological appearance of the liver for determining the etiology of cirrhosis ***(Shibili et al., 2006)***.

II- Etiological classification of cirrhosis:

1- Hepatitis and other viruses: (Post hepatitic)

Worldwide, hepatitis B is the most common causes of cirrhosis, but in Egypt and in the United States hepatitis C is a more common cause ***(Gebo et al., 2002a)***.

2- Drugs, Toxins, and infections:

This is rare. Long-term infections with various bacteria or parasites can damage the liver and cause cirrhosis ***(Scott and Thomas, 2004)***.

3- Bile duct obstruction (Biliary cirrhosis):

In adults, the most common cause is primary biliary cirrhosis, a disease in which the ducts become inflamed, blocked, and scarred ***(Jones, 2003)***.

Secondary biliary cirrhosis can happen after gallbladder surgery if the ducts are inadvertently tied off or injured, gall stones or sclerosing cholangitis ***(Giorgini et al., 2005)***.

4- Autoimmune cirrhosis:

In autoimmune hepatitis, the body's immune system attacks the liver, causing cell damage that leads to cirrhosis ***(Al Varez et al., 2002)***.

5- Inherited disease: (metabolic)

They include Wilson disease, cystic fibrosis, alpha-1 antitrypsin deficiency, hemochromatosis, galactosemia, and glycogen storage disease ***(NDDIC, 2003)***.

6- Chronic alcoholism: (Alcoholic)

The most common form of cirrhosis in the United States. The amount of alcohol needed to injure the liver varies widely from individual to individual ***(Sheth et al., 2002).***

7- Nonalcoholic Steatohepatitis (NASH)

This is a condition in which fat built up in the liver, eventually causing scar tissue ***(Petrides et al., 1994).***This kind of cirrhosis is linked to diabetes, obesity, coronary artery disease, protein malnutrition and treatment with corticosteroids ***(Mathews et al., 2006).***

Pathogenesis:

Liver fibrosis results from the perpetuation of the normal wound-healing response, resulting in an abnormal continuation of fibrogenesis (connective tissue production and deposition). Fibrosis progresses at variable rates depending on the cause of liver disease, environmental factors, and host factors ***(Sherlock and Dooley, 2002).***

Cirrhosis is an advanced stage of liver fibrosis that is accompanied by distortion of the hepatic vasculature. The resultant vascular distortion leads to shunting of the portal and arterial blood supply directly into the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma ***(Schiff et al., 2003).***

The hepatic sinusoids are lined by fenestrated endothelia that rest on a sheet of permeable connective tissue in the space of Disse, which also contains hepatic stellate cells and some mononuclear cells. The other side of the space of Disse is lined by hepatocytes that execute most of the known liver functions. In cirrhosis, the space of Disse is filled with scar tissue and endothelial fenestrations are lost, a process known as sinusoidal capillarisation ***(Sherlock and Dooley, 2002).***

Histologically, cirrhosis is characterised by vascularised fibrotic septa that link portal tracts with each other and with central veins, resulting in hepatocyte islands surrounded by fibrotic septa and that are devoid of a central vein. The major clinical consequences of cirrhosis are impaired hepatocyte (liver) function, an increased intrahepatic resistance (portal