Serum Calprotectin as a Marker for Diagnosis of Spontaneous Bacterial Peritonitis in Cirrhotic Patients with Ascites

Thesis

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Abdel Rahman

List of Contents

List of Abbreviations

AFP	Alpha fetoprotein
ADH	Antidiuretic Hormone
ALT	Alanine AminotransferaseAlpha-fetoprotein
ANP	Atrial natriuretic peptide
AST	Aspartate Aminotransferase
BT	Bacterial translocation
C3	Complement 3
CC	Cubic Centimeter
CNNA	Culture negativeneutrocytic ascites
CRP	C-Reactive Protein
CT	Computed Tomography
DIC	Disseminated intravascular coagulopathy
ELIZA	Enzyme linked immunosorbent assay
ESBL	Extended-spectrum beta-lactamases
g/d	Gram per day
GALT	Gut associated lymphoid tissue
gm	Gram
HBs Ag	Hepatitis B surface Antigen
HCC	Hepatocellular Carcinooma
HCV	Hepatitis C virus
HRS	Hepatorenal syndrome
HVPG	Hepatic venous pressure gradient

List of Abbreviations

i.e	Latin (id est) = that is
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL10	Interlukin 10
INR	International Normalized Ratio
IU	International Unit
IU/L	International unit per liter
LDH	Lactate dehydrogenase
LERS	Leukocyte Estrase Reagent Strips
LVP	Large volume paracentesis
MAC-1	Macrophage one
MPC-1	Monocyte chemotactic protein 1
MELD	Model of end stage liver disease
Mg	Milligram
mg/dl	Milligram per deciliter
ML	Milli liter
MLN	Mesentric lymph node
MMOL	Millli mol
MNB	Monomicrobial nonneutrocytic bacterascites
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-resistant Staphylococcus aureus
NAFLD	Non alcoholic fatty liver disease
NASH	Nonalcholic Steatohepatitis

ng/ml	Nanogram per milliliter
NO	Nitric Oxide
PG	Prostaglandin
PHT	Portal hypertension
PMNs	Polymorphonuclear leukocytes
PPI	Proton Pump Inhibitor
PV	Portal vein
RASS	Renin angiotensin aldosterone system
RCT	Randomized controlled trial
RNA	Ribonucleic acid
ROC curve	Receiving operating characteristic curve
SAAG	Serum Ascites Albumin Gradient
SBP	Spontaneous bacterial peritonitis
SIRS	Systemoc infilammatory response syndrome
TIPSS	Transjugular intrahepatic portosystemic shunt
TLC	Total leucocytic count
TNF	Tumour necrosis factor
WBC	White blood cells

List of Tables

List of Figures

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of the ascitic fluid and is diagnosed based on the following criteria: the presence of more than 250 neutrophils in ascitic fluid, which is not associated with surgery or an intra-abdominal origin of infection in liver cirrhosis patients ***(Lee, et al., 2009; Sammy et al., 2009).*** Its incidence in hospitalized patients with chronic liver disease and ascites varies from 10%-30% ***(Bonnel et al., 2011).***

It has been proven that delayed diagnosis of peritonitis was an important factor for its high mortality, Consequently, diagnosis of bacterial peritonitis continues to be a major clinical challenge, and an accurate biomarker for the early identification of peritonitis would be of great diagnostic value ***(Shi-kun et al., 2014).***

Unfortunately, the prolonged turn around time (1 to 2 days) of Ascitic fluid culture limits its utility for directing antibiotic selection in acute care settings. The culture has also been reported to be negative in approximately 20% of patients with clinical manifestations suggestive of SBP and an ascitic PMN count of >250, so-called culture-negative neutrocytic ascites. On the other hand, a low ascitic PMN count (<250) with positive culture can also occur in another SBP variant called bacterascites, or monomicrobial nonneutrocytic bacterascites ***(Justin et al., 2012).***

Calprotectin is an abundant, calcium- and zinc-binding protein found mainly in neutrophils ***(van Rheenen et al., 2010),*** and its presence in body fluids is proportional to the influx of neutrophils ***(Soyfoo et al., 2009).***

Measurement of Fecal Calprotectin concentrations serves as a screening tool for SBP ***(Gundling et al., 2011).*** However, the use of serum Calprotectin in diagnosis of SBP remains unexplored.

AIM OF THE WORK

The aim of this work is to study the role of serum Calprotectin as a non-invasive marker for diagnosis of spontaneous bacterial peritonitis in patients with liver cirrhosis compared to C-reactive protein.

CIRRHOTIC ASCITES

Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterised by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture ***(Schuppan et al., 2008).***

Histopathologists have proposed that the histological term cirrhosis should be substituted by advanced liver disease, to underline the dynamic processes and variable prognosis of the disorder ***(Hytiroglou et al., 2012).***

Moreover, fibrosis, even in the cirrhotic range, regresses with specific therapy if available, such as antiviral treatment for chronic hepatitis B ***(Marcellin et al., 2013)*** or C ***(Morgan et al., 2010).***

the current understanding of cirrhosis is reviewed as a dynamic process and outline current therapeutic options for prevention and treatment of complications of cirrhosis, on the basis of the subclassification in clinical prognostic stages ***(Garcia-Tsao et al., 2010).***

Epidemiology

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries. It is the 14th most common cause of

death in adults worldwide but the fourth in central Europe; it results in 1·03 million deaths per year worldwide ***(Lozano et al., 2012)***.

Pathophysiology

Following multiple injurious insults and/or exposure to inflammatory cytokines such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and interleukin (IL)-1, Hepatic stellate cells HSCs undergo the transition from a quiescent to activated state. HSC activation is a pivotal event in initiation and progression of hepatic fibrosis and a major contributor to collagen deposition ***(Lakner et al., 2012)***. Activation of HSCs is characterized by cell proliferation and migration, contraction after transforming into myofibroblasts, generation of a large amount of collagen and other extracellular matrix (ECM), ultimately leading to liver fibrosis ***(HE et al., 2012)***.

This process leads to pronounced hepatic microvascular changes, characterised by sinusoidal remodelling (extracellular matrix deposition from proliferating activated stellate cells resulting in capillarisation of hepatic sinusoids), formation of intrahepatic shunts (due to angiogenesis and loss of parenchymal cells), and hepatic endothelial dysfunction ***(Fernández et al., 2009).***

The endothelial dysfunction is characterised by insufficient release of vasodilators, of which the most important is nitric

oxide. Release of nitric oxide is inhibited by low activity of endothelial nitric oxide synthetase (as a result of insufficient protein-kinase-B-dependent phosphorylation, lack of cofactors, increased scavenging resulting from oxidative stress, and high concentrations of endogenous inhibitors of nitric oxide), with concomitant increased production of vasoconstrictors (mainly adrenergic stimulation and thromboxane A2, but also activation of the renin-angiotensin system, antidiuretic hormone, and endothelins) contributing to portal hypertension ***(García-Pagán et al., 2012).***

Etiology

The etiology of cirrhosis varies geographically, with alcoholism, chronic hepatitis C virus infection, and nonalcoholic fatty lives disease (NAFLD) being the most common causes in western countries ***(Innes et al., 2013)*** whereas chronic hepatitis B is the primary cause of liver cirrhosis in the Asia-Pacific region ***(Lv et al., 2013)***. Liver cirrhosis has many other causes, include inherited diseases such as hemochromatosis and Wilson's disease ***(Olynyk et al., 2008; Deutsch et al., 2013),*** primary biliary cirrhosis, primary sclerosing cholangitis ***(Wu et al., 2011)*** and autoimmune hepatitis ***(Deutsch et al., 2013)***. Some cases are idiopathic or cryptogenic. In recent decades, NAFLD has become a leading cause of chronic liver disease in Western countries such as the United States, with a prevalence of as high as 30% in the general population ***(Lazo et al., 2011)*** Thus, NAFLD has attracted