Use of Fecal calprotectin as a screening parameter for hepatic encephalopathy, spontaneous bacterial peritonitis and hepatorenal syndrome in Egyptian cirrhotic patients

Thesis

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

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LIST OF ABBREVIATIONS

HE	Hepatic Encephalopathy
OHE	Overt Hepatic Encephalopathy
MHE	Minimal Hepatic Encephalopathy
ALF	Acute Liver Failure
GABA	Gama Amino Butyric Acid
PTBA	Peripheral Type benzodiazepine receptor
TIPS	Transijugular intra hepatic porto systemic shunt
ePTFE	Balloon-expandable pollytetra fluoro ethylene
SBP	Spontaneous bacterial peritonitis
PMN	Polymorphonuclear leucocytes
RES	Reticuloendothelial system
MELD	Model for end stage liver disease
TLR	Toll – like receptor
HLA	Human leucococytic antigen
SIBO	Small intestinal bacterial over grouth
BT	Bacterial translocation
NSBB	Non-selctive Beta Blockers
MRSA	Methicillin resistant staphylococcus aureus
ESBL	Extended spectural B-lactamase
NGAL	Neutrophil gelatinase associated lipocalia
ATN	Acute tubular necrosis
FC	Fecal calprotectin

Introduction

The gut flora and bacterial translocation play an important role in the pathogenesis of certain complications of cirrhosis(**Garcia-Tsao and Wiest,2013).**Cirrhotic patients are prone to develop bacterial infections, mainly spontaneous bacterial peritonitis (SBP), which is present in approximately 15% of patients with cirrhosis and ascites(**Moore and Aithal,2012).** In cirrhosis, numerous alterations in intestinal flora, mucosal barrier functions and immunological defense mechanisms have been described(**Wiest and Garcia-Tsao,2015).** For example, bacterial overgrowth is common ranging between 30 until 64% and seems to represent one of the main factors to trigger bacterial translocation(**Bauer et al.,2011).**

The gut flora and bacterial translocation also play a role in the pathogenesis of hepatic encephalopathy (HE). A recent study demonstrated that bacterial overgrowth is a responsible factor for minimal HE in cirrhotic patients(**McPhail et al.,2014).** Including all stages, the prevalence of HE in cirrhosis is presumably high and can be diagnosed in up to 80% of all cirrhotic patients(**Triger,2010).**

Endotoxin levels are usually elevated in patients with decompensated liver disease and more so in patients with Hepatorenal syndrome (HRS). This is believed to be due to increased bacterial translocation and portosystemic shunting(**Sheron et al.,2011).**Inflammatory response to infection as estimated by levels of cytokines in plasma or ascitic fluid is increased in cirrhotic patients leading to circulatory dysfunction, splanchnic vasodilatation and concomitant renal impairment and increased mortality(**Vermeire et al.,2014).**

Diagnosis of HRS, HE and SBP continues to be a major clinical problem. Patients may present with mild cognitive impairment or show no typical features of an acute peritoneal infection. It is important to recognize these complications and their early stages because adequate treatment of the condition reduces morbidity and mortality(**D' Inca et al.,2012).**

Calprotectin is a calcium and zinc-binding protein, representing more than 60% of the cytosolic proteins in neutrophils. The presence of calprotectin in feces quantitatively relates to neutrophil migration into the gastrointestinal (GI) tract(**D' Inca et al.,2012).**Therefore, it is considered as a valid marker of intestinal inflammation because it is released during cell activation and death As the GI tract of cirrhotic patients shows various alterations of its mucosal barrier including infiltrates of neutrophils, calprotectin might be a promising diagnostic parameter to diagnose the onset and course of HE, SBP and HRS(**Ferenci et al.,2012).**

Aim of the Work

To assess the value of fecal calprotectin as a screening test for diagnosis of certain complication of cirrhosis as hepatic encephalopathy, spontaneous bacterial peritonitis and hepatorenal syndrome in Egyptian cirrhotic patients.

Chapter 1

Hepatic Encephalopathy

Introduction

Hepatic encephalopathy reflects a spectrum of neuro-psychiatric abnormalities seen in patients with liver dysfunction, after exclusion of other known brain disease and hepatic encephalopathy is divided into two primary components: overt HE (OHE) and minimal HE (MHE) **(Ferenci et al.,2012).** Overt hepatic encephaloparhy can be diagnosed clinically through a constellation of signs and symptoms, whereas MHE requires specialized testing. It has been estimated that OHE is present in 30–45% of patients, with an annual risk of development in 20% of patient with cirrhosis. MHE is manifested by impairment in specialized testing and is considered by most of the clinicians to be a preclinical stage of OHE **(Poordad,2011).** Approximately 60–80% of patients with cirrhosis tested have evidence of cognitive dysfunction or MHE **(Ortiz et al., 2011).** This condition is associated with increased progression to OHE, poor quality of life and a high risk of traffic violations and accidents **(Bajaj et al.,2012).**

The burden of OHE and MHE is immense considering their wide-ranging effects on the patients, family and society. A recent report showed that although there is a reduction in hospital stay for patients with OHE, the costs are likely to increase over the coming years. Considering that these syndromes affect the overall survival, quality of life, ability to work and drive and are associated with traffic accidents, the study and diagnosis of these conditions are of utmost concern to practicing gastroenterologists and hepatologists. A review of diagnosis and

treatment of HE from 2000 to 2012, including book chapters, reviews and abstracts, was conducted with the terms ‘hepatic encephalopathy’, ‘minimal hepatic encephalopathy’ and ‘subclinical hepatic encephalopathy’, and key references outside this date range were also included**(Poordad,2011).**

Pathogenesis of hepatic encephalopathy:

A number of theories have been proposed to explain the development of hepatic encephalopathy in patients with cirrhosis. Some investigators contend that hepatic encephalopathy is a disorder of astrocyte function. Astrocytes account for about one third of cortical volume. They play a key role in the regulation of the blood-brain barrier. They are involved in maintaining electrolyte homeostasis and in providing nutrients and neurotransmitter precursors to neurons. They also play a role in the detoxification of a number of chemicals, including ammonia **(Brusilow, 2011).**

It is theorized that neurotoxic substances, including ammonia and manganese, may gain entry into the brain in the setting of liver failure. These neurotoxic substances may then contribute to morphologic changes in astrocytes. In cirrhosis, astrocytes may undergo Alzheimer type II astrocytosis. Here, astrocytes become swollen. They may develop a large pale nucleus, a prominent nucleolus, and margination of chromatin. In acute liver failure, astrocytes may also become swollen. The changes of Alzheimer type II astrocytosis are not seen in acute liver failure. But, in contrast to cirrhosis, astrocyte swelling in ALF may be so marked as to produce brain edema. This may lead to increased intracranial pressure and, potentially, brain herniation **(Brusilow,2011).**

In the late 1990s, authors from the University of Nebraska, using epidural catheters to measure intracranial pressure (ICP), reported

elevated ICP in 12 patients with advanced cirrhosis and grade 4 hepatic coma over a 6-year period. Cerebral edema was reported on CT scan of the brain in 9 of the 12 patients. Several patients transiently responded to treatments that are typically associated with the management of cerebral edema in patients with ALF. Interventions included elevation of the head of the bed, hyperventilation, intravenous mannitol, and phenobarbital-induced coma **(Donovan et al.,2012).**

In the author's opinion, patients with worsening encephalopathy should undergo head CT scan to rule out the possibility of an intracranial lesion, including hemorrhage. Certainly, cerebral edema, if discovered, should be aggressively managed. The true incidence of elevated ICP in patients with cirrhosis and severe hepatic encephalopathy remains to be determined **(Donovan et al.,2012).**

Work focused on changes in gene expression in the brain has been conducted. The genes coding for a wide array of transport proteins may be up regulated or down regulated in cirrhosis and acute liver failure. As an example, the gene coding for the peripheral-type benzodiazepine receptor is upregulated in both cirrhosis and ALF. Such alterations in gene expression may ultimately result in impaired neurotransmission. **(Butterworth,2013).**

Hepatic encephalopathy may also be thought of as a disorder that is the end result of accumulated neurotoxic substances in the brain. Putative neurotoxins include short-chain fatty acids; mercaptans; false neurotransmitters, such as tyramine, octopamine, and beta-phenylethanolamines; manganese; ammonia; and gamma-aminobutyric acid (GABA) **(Brusilow,2011).**