Update in Hepatorenal Syndrome

Essay

By

Abdalla Mahmoud Tawfik Mohamed

M.B.B. Ch.

Submitted for partial fulfillment of Master Degree

In Internal Medicine

Under Supervision of:

Prof. Dr. Howaida Abdelhamid Al Shinawy

Professor of Internal Medicine and Nephrology

Faculty of Medicine-Ain Shams University

Dr. Heba Wahid El Said

Lecturer of Internal Medicine and Nephrology

Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2012

وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ
عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ

ACKNOWLEDGMENT

First and forever, thanks to ……..... *ALLAH*

I wish to express my deepest gratitude and sincere thanks to Prof. *Dr. Howaida Abdelhamid Al Shinawy* ***Professor of Internal Medicine and Nephrology, Faculty of Medicine-Ain, Shams University*** **for her great support and kind motivation, through her meticulous supervision, sincere guidance and valuable advices, this work was fulfilled.**

Wording is not enough to express my profound thanks and obligation to *Dr. Heba Wahid El Said* ***Lecturer of Internal Medicine and Nephrology, Faculty of Medicine – Ain Shams University,*** **who dedicated much of her effort, time and scientific experience in this work.**

CONTENTS

List of Figures

List of Tables

List of Abbreviations

ADH	Anti diuretic hormone
AFP	Alpha fetoprotein
All	Angiotensin II
ALF	Acute liver failure
ALT	Alanine transaminase
ANCA	Anti neutrophil cytoplasmic autoantibody
ANP	Atrial natriuretic peptide
ARF	Acute renal failure
ATN	Acute tubular necrosis
AVP	Arginin vasopressin
BLSS	Bioartificial liver support system
BM	Bone marrow
BUN	Blood urea nitrogen
CBC	Complete blood count
CCL4	Carbon tetrachloride
CD	Cluster of differentiation
CGRP	Calcitonin gene related peptide
CK	Cytokeratin
CKLT	Combined kidney- liver transplantation
CLD	Chronic liver disease
CO	Cardiac output
CRF	Chronic renal failure
CRRT	Continues renal replacement therapy
CVP	Central venous pressure

CVH	Continous venovenous haemofiltration
CVHD	Continous venovenous haemodialysis
ELAD	Extracorporeal liver assistant device
ELS	Extracorporeal liver support
ESRD	End stage renal disease
ET	Endothelin
FAH	Fumaryl acetoacetate hydrolase
GFR	Glomerular filtration rate
HCC	Hepatocellular carcinoma
HD	Hemodialysis
HLA	Human leucocyte antigen
HRS	Hepatorenal syndrome
HSCs	Haematopoietic stem cells
IAC	International ascites club
IGA	Immunoglobulin A
IL6	Interleukin 6
IMDs	Inherited metabolic disorders
LT	leukotriene
LTBI	Leukotriene biosynthesis inhibitor
LTRA	Leukotriene receptors antagonist
MARS	Molecular adsorbent recirculating system
MELD	Model of end stage liver disease
MELS	Modular extracorporeal liver system
MMPS	Matrix metaloproteinases
MSCS	Mesenchymal stem cells
NAC	N-acetylcysteine

NE	Nor epinephrine Nitric oxide
NSAID	Non steroidal anti- inflammatory drugs
OCs	Oval cells
OCT	Octreotide
OLT	Orthotopic liver transplantation
PAFs	Platelet activating factors
PF	Plasmafiltration
PGs	Prostaglandins
PRA	Plasma rennin activity
RAAS	Rennin angiotensin aldosterone system
RBF	Renal blood flow
RCT	Randomized controlled trial
RPF	Renal plasma flow
SBP	Spontaneous bacterial peritonitis
SCr	Serum creatinine
SHPCs	Small hepatocytes like progenitor cells
SNS	Sympathetic nervous system
SP cells	Side population cells
Thy-1	Thymocyte differentiation antigen
TIPSS	Transjugular intrahepatic portosystemic shunts
TNF-a	Tumour necrosis factor- alpha
TX	Thromboxane
UNOS	United network of organ sharing
VEGF	Vascular endothelial growth factors
VIP	Vasoactive intestinal peptide

Abstract

The hepatorenal syndrome is still a condition associated with poor prognosis. However, the knowledge of the pathophysiology behind this severe complication to cirrhosis has improved considerably. The future approach will probably be to attack different aspects in the pathophysiological process. A multi –target strategy should seek efficiently to counteract the arterial vasodilatation, central hypovolemia and arterial hypotension.

There are number of therapies that may be directed towards the management of renal failure in cirrhosis. Vasoconstrictor therapy with volume expansion remains the mainstay of treatment for the majority of patients with HRS.

Recently, the molecular adsorbent recirculating system (MARS) has been proposed as therapy for HRS-1

Liver transplantation remains the golden treatment for hepatorenal syndrome. However the lack of donors as well as the very high mortality rate before transplantation limits the advantages of this modality.

The poor prognosis of patients with HRS has led many clinicians to consider the use of standard renal replacement techniques, such as hemodialysis to be futile in this setting.

Bone marrow-derived medenchymal stem cells can effectively rescue experimental liver failure and contribute to liver regeneration and offer a ptentially alternative therapy to organ transplantation for treament of livers diseases and reversl of HRS.

Introduction

Hepatorenal syndrome (HRS) is a reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure. It is a common problem in patients with advanced cirrhosis and ascites. The hallmark of HRS is intense renal vasoconstriction with predominant peripheral arterial vasodilatation. Tubular function is preserved with the absence of proteinuria or histologic changes in the kidney ***(Hani et al., 2006).***

There is no specific clinical finding in HRS. The majority of patients have features of advanced liver disease with hyperbilirubinemia, elevated prothrombin time, thrombocytopenia, hepatic encephalopathy, hypoalbuminemia, and a large amount of ascites. In addition, patients display low arterial blood pressure and reduced systemic vascular resistance as well as tachycardia and increased cardiac output ***(Ruiz et al., 2003)***.

Major elements for the development of HRS include the liver dysfunction and a systemic circulatory dysfunction with a preferential renal vasoconstriction ***(Angeli and Merkel, 2008).***

Two different clinical types of HRS have been described according to the intensity and form of onset of renal failure ***(Arroyo et al., 1996);*** *type I* and *type II HRS.*

Type I HRS is characterized by a rapid progressive impairment of renal function as defined by a doubling of the initial serum creatinine to a level higher than 2.5 mg/dl or a 50% reduction of the initial 24-h creatinine clearance to a level lower than 20 ml/min in less than 2 weeks. Type I HRS is associated with very low survival expectancy, the median survival time

being only 2 weeks ***(Gines et al., 1999).*** Type-1 HRS is the complication of cirrhosis associated with the worst prognosis and for many years, it has been considered as a terminal event of the disease. However, effective treatments of type-1 HRS have been introduced recently. These treatments improve survival and make it possible for a significant number of patients to arrive to liver transplantation ***(Arroyo et al., 2007).***

In contrast to type I, type II HRS is characterized by less severe and stable reduction of GFR that does not meet the criteria proposed for type I. Patients are usually in better clinical condition than those with type I HRS, and their survival expectancy is markedly longer ***(Arroyo et al., 2009).***

Many therapeutic methods have been used to improve renal function in patients with HRS ***(Bataller et al., 1997).***

However, most of these methods have no effect or only minor beneficial effects, except for liver transplantation, the administration of drugs with a vasoconstrictor effect in the splanchnic circulation, and the insertion of Transjugular Intrahepatic Portosystemic Shunts (TIPSS) ***(Arroyo et al., 1999).***

Liver transplantation remains the best treatment for suitable candidates with HRS because it offers a cure to both the diseased liver and the renal dysfunction. Indeed, subsequent to liver transplantation, renal sodium excretion and hemodynamic abnormalities normalize within 1 month, and renal indices return gradually to normal values during the first post transplantation year ***(Piscaglia et al., 1999).*** Survival of patients with type 2 HRS is sufficiently prolonged to enable them to receive a liver transplant; however, the clinical applicability of transplantation in patients

with type 1 HRS is limited by their shortened survival expectancy and long waiting times ***(Pham et al., 2005).***

Several studies have documented the potential for recovery of HRS following orthotopic liver transplantation (OLT) ***(Pham et al., 2000).*** Thus, liver transplantation only rather than combined kidney liver transplantation (CKLT) should be the initial consideration in patients with End Stage Liver Disease (ESLD) associated HRS ***(Pham et al., 2005).***

New modalities in treatment of HRS include Extracorporeal Liver Support (ELS) systems which are complex systems that have to substitute a much large spectrum of functions covered by the liver such as the detoxification of water insoluble and protein-bound solutes and toxins, synthesis and metabolism of a range of substances and metabolic regulation ***(Kazuhiki et al., 2006).***

These systems were divided into two groups: the biological artificial liver on one side, which aims at replacing the metabolic, detoxifying and synthetic functions of the hepatocytes and extracorporeal blood purification on the other side, which aims at eliminating toxins from the body ***(O'Grady, 2006).***

Bone marrow-derived mesenchymal stem cells can effectively rescue experimental liver failure and contribute to liver regeneration and offer a potentially alternative therapy to organ transplantation for treatment of liver diseases. There is increasing evidence suggesting bone marrow as a transplantable source of hepatic progenitors ***(Petersen et al., 1999).***

Aim of the Review

This essay aims to review the update in the etiology, presentation, diagnosis and treatment of HRS through collection and discussion of all available data.

Capter (1)

Hepatorenal Syndrome

Definition:

Hepatorenal syndrome (HRS) is a clinicopathologic condition that occurs in patients with chronic liver disease, advanced hepatic failure, and portal hypertension characterized by impaired renal functions without significant morphological changes in renal histology and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems ***(Gines et al., 2003).***

In the kidney, there is marked renal vasoconstriction that results in a low glomelular filtration rate (GFR), whereas in the extra renal circulation, there is predominance of arterial vasodilatation resulting in reduction of the total systemic vascular resistance and arterial hypotension ***(Arroyo et al., 1996).***

Transplantation of the kidney from a patient with HRS in a recipient without liver failure will function normally supporting the functional nature of the syndrome ***(Epstein, 1996).***

HRS is a serious complication of end-stage liver disease, occurring mainly in patients with advanced cirrhosis and ascites, who have marked circulatory dysfunction ***(Gines et al., 2003).***

HRS is defined as functional renal failure in cirrhotic patients in the absence of intrinsic renal disease ***(Friedman, 2000).***

HRS is a potentially reversible form of renal failure that occurs in patients with cirrhosis and ascites as well as in patients with acute liver failure. In cirrhotic patients with ascites, pre-renal failure (42%) and acute