PROGNOSTIC VALUE OF SERUM AUTOTAXIN IN LIVER CIRRHOSIS

Thesis

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BY:

Sarah Ahmed Hassan Ahmed

(M.B.B.Ch)

Faculty of Medicine, Cairo University

Supervised by:

Dr. Nagwa Ramadan Ahmed

Assistant professor of internal medicine, faculty of medicine, Cairo University

Dr. Ahmed Nabil El mazny

Assistant professor of internal medicine, faculty of medicine, Cairo University

Dr. Laila Ahmed Rashed

Professor of biochemistry, faculty of medicine, Cairo University

Faculty of Medicine
Cairo University

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Abstract

Background

Autotaxin (ATX) and its product lysophosphatidic acid (LPA) are considered to be involved in the development of liver cirrhosis and elevated levels of serum ATX have been found in patients with hepatitis C virus associated liver disease. However, the clinical role of systemic ATX in the stages of liver cirrhosis was unknown. So, in our study we investigated the relation between serum ATX levels and severity of cirrhosis as well as assessment of prognosis in cirrhotic patients.

Methods

Patients with liver cirrhosis were prospectively enrolled and followed for 6 months. Blood samples drawn at the day of inclusion in the study were assessed for ATX content by an enzyme-linked immunosorbent assay. ATX levels were correlated with the stage as well as complications of cirrhosis. The prognostic value of ATX was investigated by uni- and multivariate Cox regression analyses.

Results

90 patients were enrolled. Subjects with liver cirrhosis showed elevated serum levels of ATX as compared to healthy subjects (106$\pm$24 mg/l vs. 42.5$\pm$11mg/l, $P<0.000$). Patients with hepatic encephalopathy ($P=0.000$) and focal lesion ($P=0.02$) had higher ATX levels than patients without these complications. Low ATX

levels were a parameter independently associated with longer overall survival (sensitivity for focal lesion 91% and specificity 65% and sensitivity for encephalopathy 92% and specificity 64% with positive predictive value for focal lesion 70% and for encephalopathy 69%).

Conclusion

Serum autotaxin is a good prognostic factor for the development of hepatic focal lesion and hepatic encephalopathy and also a predictor of cirrhosis in patients with HCV.

Key words

Liver cirrhosis, autotaxin, ATX, LPS, hepatitis C virus

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Ab	Antibody
AIDS	Acquired immunodeficiency syndrome
ALKMA	Anti liver kidney microsomal antibody
ALP	Alkaline phosphatase
ANA	Antinuclear antibody
AST	Aspartate transaminase
ATX	Autotaxin
CBC	Complete blood count
CD	Catalytic domain
CPS	Child pugh score
DM	Diabetes mellitus
EIA	Enzyme immunoassay
ENPP-2	Ectonucleotide pyrophosphatase/phosphodiesterase 2
GGT	Gamma glutamyt transferase
GIT	Gastrointestinal tract
GPCRs	G protein coupled receptors
HALT-C	Hepatitis C antiviral long term treatment against cirrhosis
Hb	Hemoglobin
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HIV	Human immunodeficiency virus
HSCs	Hepatic stellate cells
HRS	Hepatorenal syndrome

HTN	Hypertension
HVPG	Hepatic vein pressure gradient
ICAM-1	Intercellular adhesion molecule 1
IFN	Interferon
INR	International normalized ratio
IVDA	Intravenous drug abuse
Kpa	Kilo pascal
LC	Liver cirrhosis
LDH	Lactate dehydrogenase
LPA	Lysophosphatidic acid
LPC	Lysophosphatidylcholine
MALT	Mucosa associated lymphoma tumors
MCP-1	Monocyte chemoattractant protein 1
MELD	Model for end stage liver disease
NFkB	Nuclear factor kappa beta
NPP	Nucleotide pyrophosphatase
OLT	Orthotopic liver transplantation
PC	Prothrombin concentration
PCR	Polymerase chain reaction
POCTs	Point of care screening tests
PT	Prothrombin time
QLSS	Quantitative liver spleen scan
RBV	Ribavirin
RCT	Randomized control trial
RDTs	Rapid diagnostic tests
RFLPs	Restriction fragment length polymorphism

RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SBLD	Somatomedin B like domain
SBP	Spontaneous bacterial peritonitis
SNP	Single nucleotide polymorphism
S1P	Sphingosine 1 phosphate
SPC	Sphingosylphosphorylcholine
SVR	Sofosbuvir
TIPS	Transjugular intrahepatic porto systemic shunt
TLC	Total leucocytic count
TMA	Transcription mediated amplification
TP	Total protein
UKELD	United kingdom model for end stage liver disease
VCAM-1	Vascular cell adhesion molecule 1

INTRODUCTION AND AIM OF WORK

Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma. Approximately 20% of Egyptian blood donors are HCV Ab positive. Egypt has higher rates of HCV than neighboring countries **(*Miller and Abu-Raddad, 2010*)**.

Liver cirrhosis is a result of chronic injury and fibrotic remodeling of the liver. The most common causes of liver cirrhosis are chronic infections with hepatotropic viruses, namely hepatitis C (HCV) and hepatitis B (HBV) viruses and non-alcoholic steatohepatitis. Patients suffering from liver cirrhosis are at risk of decompensation which is associated with impaired prognosis (***Wallace, et al., 2008*)**.

Autotaxin is widely expressed in tissues such as brain, placenta or high endothelial venules **(*Ikeda, et al 2003*)**.

Hepatic stellate cells (HSCs) are a major cell type involved in development of liver fibrosis. In continuously injured liver, hepatic stellate cells are activated and transdifferentiate into myofibroblasts, resulting in the production of abundant extracellular matrices (***Cárdenas and Ginès, 2011***). Lysophosphatidic acid (LPA), which is formed from lysophosphatidylcholine by autotaxin (ATX), a secreted glycoprotein possessing both phosphodiesterase and lysophospholipase

D activity, activates hepatic stellate cells, stimulates their contraction and inhibits their apoptosis

A connection between liver fibrosis and serum or plasma LPA and ATX emerged in patients with chronic HCV infection (***Van Meeteren, et al., 2006***).

However to our knowledge, relation between serum ATX in different stages of liver cirrhosis and its prognostic value has been investigated in few studies.

Aim of work: to correlate the serum autotaxin with the state of the liver disease and the development of complications.

LIVER CIRRHOSIS

Liver cirrhosis results from different mechanisms of liver injury that lead to necro-inflammation and fibro-genesis (***Schuppan and Afdhal, 2008***).

Histologically it is characterized 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 (***Dooley, et al., 2011*****).**

This distortion results in increased resistance to portal blood flow and hence in portal hypertension and in hepatic synthetic dysfunction.

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 P, et al., 2012***).

Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death, unless liver transplantation is done, and the only preventive strategies have been screening for oesophageal varices and hepatocellular carcinoma.

Lately, this perception has been challenged, because 1-year mortality in cirrhosis varies widely, from 1% to 57%, depending on the occurrence of clinical decompensating events ***(D'Amico, et al., 2006*****).**

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

The new concept in management of patients with cirrhosis is the use of non-specific therapies for prevention and early intervention to stabilize disease progression and to avoid or delay decompensation and the need for liver transplantation.

Epidemiology

Liver 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, ***(Lozano, et al., 2012)*** it results in 170 000 deaths per year in Europe, (***Blachier M, et al., 2013***) and 33 539 per year in the USA (***Hoyert and Xu, 2012***).

In 2010, Egypt, followed by Moldova, had the highest age-standardized cirrhosis mortality rates, 72.7 and 71.2 deaths per 100,000, respectively. In Egypt, almost one-fifth (18.1%) of all deaths in males 45- to 54-years old were due to liver cirrhosis (**Mokdad A.A., et al., 2010**).

Cirrhosis is the main indication for 5500 liver transplants each year in Europe **(*Blachier M, et al., 2013***).

The main causes in more developed countries are infection with hepatitis C virus, alcohol misuse, and, increasingly, non-alcoholic liver disease; infection with hepatitis B virus is the most common cause in sub-Saharan Africa and most parts of Asia.