The Relationship Between Trace Elements And Hepatic Encephalopathy In Egyptian Patients With Liver Cirrhosis

Thesis submitted for partial fulfillment of master degree in internal medicine

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بسم الله الرحمن الرحيم
قالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ
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HE	Hepatic encephalopathy
RNA	Ribonucleic acid
MRI	Magnetic resonance imaging
mPT	Mitochondrial permeability transition
CNS	Central nervous system
GABA	Gamma amino butyric acid
HRQOL	Health-related quality of life
EEG	Electroencephalogram
MHE	Minimal hepatic encephalopathy
OHE	Overt hepatic encephalopathy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
WHO	World health organization
DALYs	Disability-adjusted life years
EPI	Expanded programme on immunization
DNA	Deoxy ribonucleic acid
HBeAg	Hepatitis B envelope antigen
PAT	Parenteral antischistosomal therapy
MOHP	Ministry of health and population
HBsAg	Hepatitis B surface antigen
EDHS	Egypt demographic and health survey
HIV	Human immunodeficiency virus
HAART	Highly active anti-retroviral therapy
ARE	Arab Republic of Egypt
CHB	Chronic hepatitis B
ALT	Alanine transaminase
TB	Tubercle bacillus
EMR	Eastern mediterranean region
Anti-HBc	Antibody to hepatitis B core antigen
US	United states
Anti-HCV	Antibody to hepatitis C virus
PAG	Phosphate-activated glutaminase
TIPS	Transjugular intrahepatic portosystemic shunts
pNH(3)	Partial pressure of ammonia
ALF	Acute liver failure
cGMP	cyclic guanosine monophosphate
PDE-5	Phosphodiesterase-5
EAAT-2	Excitatory amino acid transporter-2

NMDA	N-methyl-D-aspartate
mGluRs	Metabotropic glutamate receptors
GLT-1	Glutamate transporter-1
cAMP	cyclic adenosine monophosphate
ATP	Adenosine triphosphate
ROS	Reactive oxygen species
SNr	substantia nigra pars reticulata
VMT	Ventromedial thalamus
PCS	Portacaval shunt
GS	Glutamine synthetase
GLNase	Glutaminase
NS	Neurosteroids
THDOC	Tetrahydrodeoxycorticosterone
NSAID	Non-steroidal anti-inflammatory drugs
TNF	Tumour necrosis factor
IL-1	Interleukin-1
AChE	Acetylcholinesterase
ACh	Acetylcholine
ChAT	Choline-acetyltransferase
RNS	Reactive nitrogen species
NKCC1	Na-K-Cl-cotransporter-1
PBR	Peripheral benzodiazepine receptor
PTN	Protein tyrosine nitration
GAPDH	Glyceraldehydes-3-phosphate dehydrogenase
L-LTP	Late phase long-term potentiation
TACE	Transarterial chemoembolization
OTC	Ornithine transcarbamylase
CHESS	Clinical hepatic encephalopathy staging scale
ACG	American College of Gastroenterology
LOLA	L-Ornithine-L-Aspartate
MARS	Molecular adsorbent recirculating system
NRC	National research council
RDA	Recommended daily allowance
ESADDI	Estimated safe and adequate daily dietary intake
SMR	Standardized mortality ratio
MMT	methylcyclopentadienyl manganese tricarbonyl
CRIP	cysteine-rich intestinal protein
MT	Metallothionein
FDA	Food and Drug Administration
ATSDR	Agency for Toxic Substances and Disease Registry

EPA	Environmental Protection Agency
IOM	Institute of Medicine
NIOSH	National Institute for Occupational Safety and Health

Introduction

The liver and brain interact in numerous ways. The liver supplies nutrients to the brain and removes toxic substances that are harmful to the brain's nerve cells. Liver dysfunction can cause disturbance of brain function and even contribute to brain damage **(Butterworth RF, ٢٠٠٣a)**.

Hepatocerebral disorders are serious neuropsychiatric conditions that result from liver failure. These disorders are characterized neuropathologically by varying degrees of neuronal cell death in basal ganglia, cerebellum, and spinal cord, and include clinical entities such as Wilson's disease, post-shunt myelopathy, hepatic encephalopathy, and acquired non-Wilsonian hepatocerebral degeneration. Pathophysiologic mechanisms responsible for cerebral dysfunction and neuronal cell death in hepatocerebral disorders include ammonia toxicity and neurotoxic effects of metals such as copper, manganese, and iron **(Butterworth RF, ٢٠١٠)**.

Hepatic encephalopathy is a complex and potentially reversible neuropsychiatric syndrome complicating acute or chronic liver disease. Clinical manifestations are multiple and varied, ranging from minimal neurological changes to coma. Ammonia is the main toxic substance involved in the pathogenesis of hepatic encephalopathy, although other mechanisms, such as modifications of the blood-brain barrier, disruptions in neurotransmission and abnormalities in GABAergic and benzodiazepine pathways may also play a role. The identification and treatment of precipitating factors is crucial in the management of patients with hepatic encephalopathy **(Bismuth M et al., ٢٠١١)**.

Hepatic encephalopathy (HE) was classified as: Encephalopathy type A (associated with acute liver failure), type B (associated with porto-systemic bypass) and type C (associated with liver cirrhosis) **(Quero Guillen JC et al., ٢٠٠٣)**. Type C is further classified into ٣ categories: Episodic HE (precipitated, spontaneous or recurrent), persistent HE (mild, severe or treatment-dependant) and minimal HE (also called subclinical HE) **(Ferenci P et al., ٢٠٠٢)**.

Hepatic encephalopathy (HE) is a major complication encountered in nearly half of the patients with liver cirrhosis **(Romero-Gómez M, ٢٠١٠)**.

It is estimated to occur in ٣٠٪ to ٤٥٪ of patients with liver cirrhosis and in ١٠٪ to ٥٠٪ of patients with transjugular intrahepatic portosystemic shunts. It can be seen in cancer patients due to multiple factors. Early diagnosis and treatment are important but can be challenging, especially in mild forms with subtle findings **(Eroglu Y and Byrne WJ, ٢٠٠٩)**.

Ammonia plays a key role in the pathogenesis of hepatic encephalopathy. One consequence of ammonia action on the brain is astrocyte swelling, which triggers the generation of oxidative/nitrosative stress at the level of NADPH oxidase, nitric oxide synthases and the mitochondria. Consequences of the ammonia-induced oxidative/ nitrosative stress response are protein modifications through nitration of tyrosine residues and oxidation of astrocytic and neuronal RNA. Nitrosative stress also mobilizes zinc from intracellular stores with impact on gene expression. These alterations may at least in part mediate cerebral ammonia toxicity through disturbances of intracellular and intercellular signaling and of synaptic plasticity. RNA oxidation offers a novel explanation for multiple disturbances of neurotransmitter systems