

# **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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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا  
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم  
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## **List of abbreviations**

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

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

<b>EPA</b>	Environmental Protection Agency
<b>IOM</b>	Institute of Medicine
<b>NIOSH</b>	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, a**).

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, )**).

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., )**).

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.,** ). Type C is further classified into 3 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.,** ).

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

It is estimated to occur in 30% to 40% of patients with liver cirrhosis and in 10% to 20% 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,** ).

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