Prevalence of Extrapyramidal Signs in Patients with Chronic liver disease in a Tertiary Hepatology Center

Thesis

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By
Saeed Abdelhamid Hashem Hashem
MBBCh, Ain Shams University

Under Supervision of

Prof. Samia Ashour Mohamed Helal

Professor of Neurology
Faculty of Medicine - Ain Shams University

Prof. Ahmed Abdelmonem Gaber Mohamed

Professor of Neurology
Faculty of Medicine - Ain Shams University

Prof. Osama Aboulfotouh El-Sayed

Professor of Hepatology & Gastroenterology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ ورَسُولُهُ والْمُؤْمِنُونَ

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Saeed A. Hashem

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LIST OF ABBREVIATIONS

A1-AD	Alpha 1-antitrypsin deficiency
ADL	Activities of daily living
AHD	Acquired hepatocerebral degeneration
ALD	Alcoholic liver disease
ALT	Alanine transaminase
ANA	Anti-nuclear antibody
ANOVA	Analysis of Variance
AST	Aspartate transaminase
BAL	British anti-Lewisite
BFM	Fahn-Marsden scale
BG	Basal ganglia
CHE	Chronic hepatic encephalopathy
CLD	Chronic liver disease
COPD	Chronic obstructive pulmonary disease
CT	Computed Topography
DNA	Deoxyribo-nucleic acid
ERCP	Endoscopic retrograde cholangiopancreatography
EST	Elective sclerotherapy
EEG	Electroencephalogram
GABA	Gamma-amino butyric acid
GPe	Globus pallidus externa
GPi	Globus pallidus interna
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HE	Hepatic encephalopathy
INR	International normalized ratio
IVC	Inferior vena cava
MELD	Model for End-Stage Liver Disease score
MPTP	methyl-4-phenyl-l,2,3,6 tetrahydropyridine
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
NASH	Non-alcoholic steatohepatitis
PBC	Primary biliary cirrhosis
PD	Parkinson disease
PSC	Primary sclerosing cholangitis
PSE	Porto-systemic encephalopathy
RNA	Ribo-nucleic acid
SD	Standard deviation
SMA	Supplementary motor area
SNpr	Substantia nigra pars reticulate
SPSS	Statistical Package for Social Sciences
STN	Subthalamic nucleus
TGF-β_1	Tumor growth factor
UPDRS	Unified Parkinson Disease Rating Scale
VTA	Ventral tegmental area
WD	Wilson disease
TIPSS	Transjugular intrahepatic portosystemic stent shunting

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INTRODUCTION

The liver is the largest internal organ of the body, with blood supplied from both the hepatic artery and the portal vein. The liver performs many functions, including synthesis of most serum proteins, regulations of glucose and lipids, and production of bile. These essential functions are impaired when a liver develops cirrhosis. Cirrhosis is defined pathologically by the loss of normal microscopic lobular architecture with fibrosis and nodular regeneration. Chronic alcoholism and Chronic Hepatitis C are the leading causes of cirrhosis ***(Karnath, 2003)***.

Portal hypertension, a complication of chronic liver disease, results from the replacement of normal hepatic parenchyma with fibrotic tissue; leading to resistance to blood flow through the liver ***(Mohammad, 2012)***.

Portal hypertension can lead to other complications of chronic liver disease, including the development of varices and variceal bleeding, ascites and spontaneous bacterial peritonitis. In addition, the loss of hepatocytes and intrahepatic shunting of blood diminishes liver's metabolic and synthetic function; this may result in a reduction in ammonia metabolism, further leading to hepatic encephalopathy ***(Mohammad, 2012).***

Hepatic encephalopathy (HE), referred to as porto-systemic encephalopathy, is a syndrome of neuropsychiatric abnormalities caused by acute or chronic hepatic insufficiency. These neuropsychiatric disturbances of HE are often partly reversible ***(Mohammad, 2012).***

The question, of whether hepatic encephalopathy is completely reversible or not, is controversial; and some neurological deficits may persist ***(Romeiro et al., 2011).***

A minority of patients with chronic liver disease develop acquired hepatocerebral degeneration – a progressive neurologic disorder characterized by extrapyramidal signs, ataxia, and cognitive decline. Although the pathogenesis of acquired hepatocerebral degeneration is not known, diversion of portal blood into the systemic circulation appears to underlie the syndrome ***(Khokhar et al., 2005).***

Until now there is no consensus about whether or not does repeated hepatic encephalopathies constitute a key factor in a more chronic disease, acquired hepatocerebral degeneration ***(Romeiro et al., 2011).***

Acquired (Non-Wilsonian) hepatocerebral degeneration (AHD) is a rare irreversible complication of chronic liver disease (CLD) and was first described by Van Woerkom in 1914 and Victor and coworkers in 1965. They attributed it to prolonged exposure to metabolic toxins that cause encephalopathy. Dementia, dysarthria, cerebellar dysfunction, movement disorders, myoclonus, rigidity, dystonia, myelopathy, hyperreflexia, and extensor plantar responses have all been reported ***(Khokhar et al., 2005).***

Recent neuro-radiological imaging studies, mainly MRI; have shown hyper intense signals in the pallidum, putamen, mesencephalon, internal capsule, lentiform nucleus and cerebral peduncles on T1 weighted images ***(Khokhar et al., 2005).***

AHD is a chronic encephalopathy which occurs in ~1% of patients with liver cirrhosis and seems related to porto-systemic shunts. It is characterized by a combination of Parkinsonism and cerebellar signs. MRI pallidal and extrapallidal lesions are seen in most patients, probably reflecting intracerebral deposits of manganese ***(Fernández-Rodriguez et al., 2010).***

Excess dietary manganese is rapidly cleared by the liver before reaching the systemic circulation. In patients with cirrhosis and porto-systemic shunting, manganese bypasses the liver and accumulates in the internal pallidum, while serum manganese levels may be normal or increased ***(Meissner and Tison, 2011).***

Magnetic resonance imaging abnormalities mainly consist of a signal hyper intensity on T1-weighted images in the internal pallidum. It may also be seen in the putamen, the caudate nucleus, the internal capsule, the mesencephalon, and the cerebellum, and is believed to reflect local manganese accumulation. No specific treatment of AHD exists up till now ***(Meissner and Tison, 2011).***

AIM OF THE WORK

Aim of the Study:

This is a study to determine the prevalence of extrapyramidal signs in chronic liver disease patients for a possible further investigation of those patients in a later study.

Rationale:

To our knowledge, there is no available significant data about the prevalence of extrapyramidal signs in chronic liver disease patients in Egypt. This group of patients has limited chance of being properly studied to determine the pathophysiology and possible treatment options to improve their quality of life.

ANATOMY & PHYSIOLOGY OF BASAL GANGLIA AND LIVER

Basal Ganglia

Ensuring coordination of the nervous system functioning, communication between various structures, adjusting the functions to the changes in internal and external environment depends on processing of substantial amount of information ***(Groenewegen, 2007; Groenewegen and van Dongen, 2007).***

Before a motor signal descends from the motor cortex to the brain stem and spinal cord, several cortical and subcortical centers, including the basal ganglia and the cerebellum, pose their influence to 'shape' the final descending signal. The basal ganglia and the cerebellum exert their influence on the final motor output pathways largely via the thalamus on the descending, corticobulbar and corticospinal motor pathways that originate in the motor and premotor areas of the cerebral cortex ***(Groenewegen, 2003).***

The basal ganglia (BG) are a group of interconnected subcortical nuclei spanning the telencephalon, diencephalon, and midbrain; as shown in figure (1) adapted from Gorzelańczyk, 2011 ***(Gorzelańczyk, 2011).***