PERIPHERAL NEUROPATHY AND AUTONOMIC DYSFUNCTION IN HEPATITIS C VIRUS (HCV) RELATED CHRONIC LIVER DISEASE

thesis

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ABSTRACT

polyneuropathy occurs with a combination of multiple symptoms, signs, and abnormal electrodiagnostic studies so electrophysiological examination should always be done to avoid underestimating peripheral neuropathy.

Autonomic disturbance can be assessed by recording PASP even in subclinical conditions. Also it gives a quantitative data about the degree of damage of descending sympathetic fibers, so that it will be very helpful for early diagnosis of autonomic dysfunction

Key words:

HCV - Peripheral – Neuropathy - Autonomic– Neuropathy

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List Of Abbreviations

ALT	**Alanine aminotransferase**
AN	**Autonomic neuropathy**
ANA	**Antinuclear antibody**
Anti. HBs	**Anti hepatitis B surface antigen**
CNS	**Central nervous system**
C1	**Complement Component 1**
C3	**Complement Component 3**
C4	**Complement Component 4**
CHC	**Chronic hepatitis virusC**
Cox-2	**Cyclo oxygenase 2**
CTL	**Cytotoxic T lymphocyte**
DM	**Diabetes mellitus**
DNA	**Deoxy ribonuclease**
ECG	**Electro cardiogram**
EIA	**Enzyme immuno assay**
ELISA	**Enzyme linked immune sorbant assay**
EMC	**Essential mixed cryoglobulinaemia**
EVR	**Early virologic response**
GBS	**Guillain-Barre Syndrome**
GIT	**Gastro intestinal tract**
HBV	**Hepatitis B virus**
HCC	**Hepato cellular carcinoma**
HCV	**Hepatitis C virus**
HIV	**Human immune deficiency virus**
HSV	**Herpes simplex virus**
IFN	**Interferon**

IgG	**Immunoglobulin G**
IgM	**Immunoglobulin M**
IL	**Interleukin**
ITP	**Immune thrombocytopenic purupra**
LKM	**Liver Kidney microsomal antibody**
LP	**Lichen planus**
M. Nos	**Macrophage nitric oxide synthase**
MHC	**Major histocompatiblity**
MMP	**Matrix metallo proteinases**
NF	**Nuclear factor**
NHL	**Non-Hodgkin's lymphoma**
No	**Nitric oxide**
ORF	**Open reading fram**
PCR	**Polymerase chain reaction**
PEG IFN	**Pegylated interferon**
PN	**Peripheral neuropathy**
RA	**Rheumatoid arthritis**
RIBA	**Recombinant immunoblot assay**
RNA	**Ribonucleic acid**
RT-PCR	**Reverse-transcriptase polymerase chain reaction**
S.S	**Sjogren's syndrome**
SLE	**Systemic lupus erythramatous**
SMA	**Smooth muscle antibody**
SSR	**Sympathetic skin response**
SVR	**Sustained virologic response**
TNF	**Tumour necrosis factor**
Vs	**Versus**
γ. GT	**Gamma Glutamyle Transferase**

Introduction and Aim of the Work

INTRODUCTION

Hepatitis C virus (HCV) infection affects approximately 170 million persons world wide and is a pandemic 5 times larger than that of HIV. In united states and Brazil, approximately 2% of the population is seropositive for HCV. In Egypt, 28% of the population is seropositive for HCV ***(Frank et al., 2000).***

The most common mode of HCV transmission is percutanous exposure to contaminated blood, including situations associated with intravenous drug use and blood transfusions. HCV infection is a common cause of chronic liver disease, cirrhosis and hepatocellular carcinoma ***(Lauer et al., 2001).***

In addition to the liver manifestations, chronic HCV infection may be associated with a series of extra hepatic manifestations, such as mixed cryoglobulinaemia, membranoproliferative glomerulonephritis, auto immune thyroiditis and lymphoproliferative disorders.

These manifestations result from lymphoproliferative and/or auto immune mechanisms, and occur in 40 to 75% of patients with chronic HCV infection ***(Gordon, 1996).***

The association of HCV infection with mixed cryoglobulinemia and peripheral neuropathy has been previously reported ***(Zaltron et al., 1998).***

However, its pathogenesis is not completely understood, nor do formal treatment guidelines exist. Peripheral neuropathy and detectable serum cryoglobulins appear in approximately one third of patients with HCV infection, but HCV-infected patients with peripheral neuropathy in the absence of serum cryoglobulins have also been described ***(Zaltron et al., 1998 and lidove et al., 2001).***

Cardiovascular autonomic and peripheral sensory neuropathy is a known complication of chronic liver disease ***(Szalay et al., 1998)***.

Cardiovascular autonomic neuropathy (AN) represents a serious complication as it carries a 5-fold risk of mortality in patients with chronic liver disease ***(Hendrickse et al., 1992)***.

Autonomic neuropathy may also be regarded as a potential etiologic factor of hyperdynamic circulation and portal hypertension ***(Kempler et al., 1996)***.

AIM OF THE WORK

Due to the importance and prevalence of HCV in Egypt, this study will be carried out to delineate the spectrum of HCV associated neuropathy and assess its relation to liver cirrhosis.

Review of literature

Review of Literature

Hepatitis C. Virus

HCV is a small RNA virus of about 9400 nucleotide bases ***(Choo et al., 1989).***

Details of the ultrastructure of hepatitis C virus virion remain unclear because it has proved extremely difficult to visualize virus particles from infected serum and tissues directly. Although much is known about the viral genome, first cloned in 1989, little is known about HCV morphogenesis, due to the lack of efficient in vitro culture system. Virus- like particles, obtained by expressing genes encoding the HCV structural proteins in mammalian cell, can be used as an alternative model for studying HCV morphogenesis. ***(Roingeard et al., 2004)***

Humans are the only host species found to be naturally infected by HCV.

The only animals that are consistently susceptible to experimental HCV infection are chimpanzees, which develop a persistent viraemia and signs of hepatitis. ***(Bassett et al., 1998)***

Also the cloning of viral genome was achieved from pooled chimpanzees plasma. ***(Choo, et al., 1989)***

Clinical and experimental data indicate the marked hepatotropism of HCV. Thus, in vivo, hepatocytes are currently believed to represent the major targets of virus replication. ***(Cho et al., 1996)***

Numerous attempts to grow HCV in vitro have been done, but to date, success has been modest. By using the reverse-transcriptase polymerase chain reaction (RT- PCR), evidence of low-grade viral replication has been obtained in primary human and chimpanzee liver cells. ***(Ito et al., 1996)***

In general, the virus titres produced have not only been low, but have also fluctuated markedly, with a tendency of the virus to disappear within days or weeks. ***(Shimizu et al., 1994).***

Further efforts are clearly needed to establish efficient means for reliable in vitro culture of HCV. ***(Morrica et al., 1999).***

The Genome and The Proteins Encoded:

HCV is a positive RNA virus with a genome which is a single stranded containing approximately 9500 nucleotides. It has an open reading frame (ORF) that encodes a large polyprotein of about 3000 aminoacids and is characterized by extensive genetic diversity ***(Lyra et al., 2004).***

The HCV- encoded polyprotein is cleaved post-translationally into multiple structural and non-structural peptides ***(Lauer et al., 2001).***

Classifications and nomenclature of HCV genotypes:

HCV has been classified into at least 6 major genotypes with many subtypes and circulate within an infected individual as a number of closely related but distinct variants known as quasispecies ***(Lyra et al., 2004).***

These genotypes differ by as much as 31 to 34 percent in their nucleotide sequences, whereas subtypes differ by 20 to 23 percent based on full-length genomic sequence comparisons ***(National Institute of Health, (NIH), 2002).***