PREVALENCE OF PSYCHIATRIC DISORDERS IN A SAMPLE OF PATIENTS WITH CHRONIC HEPATITIS C ON INTERFERON, RIBAVIRIN AND SOVALDI THERAPY

Thesis submitted for partial fulfillment for Masters Degree in neuropsychiatry

By

Hadeer Khairy Ali Hemida
(M.B., B.Ch)

Supervised By

Prof. Tarek Ahmed Okasha

Professor of Neuropsychiatry

Faculty of Medicine, Ain Shams University

Prof. Ghada Refaat Amin

Professor of Neuropsychiatry

Faculty of Medicine, Ain Shams University

Assist. Prof. Dalia Abd El-Moneim Mahmoud

Assistant Professor of Neuropsychiatry

Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2017

Abstract

Introduction: The World Health Organization considers chronic hepatitis C (CHC) as a major public health problem and estimates that 3% of the world's population (170 million people) is infected with hepatitis C virus (HCV) and is at risk of developing liver cirrhosis and liver cancer. The prevalence of hepatitis C virus (HCV) infection varies throughout the world with the highest number in Egypt, ranging from 6% to more than 40% with an average of 13.8%. In populations of blood transfusion recipients over the age of 30, HCV has been reported as high as 73% and in the general population aged 40–60 years it was estimated as high as 55%

Aims: a) To compare the rate of incidence of psychiatric disorders co morbid with chronic hepatitis C in patients groups of: a) those using combination of IFN, Ribavirin and Sovaldi, b) those using combination of Daklinza, Ribavirin and Sovaldi. b) To identify the risk factors that make the patients more vulnerable to have such psychiatric co morbidities.

Methodology: This study aimed at studying the prevalence of psychiatric disorders in a sample of 260 patients' males and females, aged (18-75), diagnosed with Hepatitis C by PCR and collected from the outpatient clinic of internal medicine and Interferon unit in Damanhur Medical National Institute.Then patients classified into two groups; the first group (G1) included patients receiving peg IFN-α, Ribavirin and Sovaldi, the second group (G2) included patients receiving Daklinza, Ribavirin and Sovaldi.

Results: Socio-demographic characteristics of the sample: The study sample was randomly selected from patients of the outpatient clinic of internal medicine and Interferon unit in Damanhur Medical National Institute. Males constituted 53.1% of the total sample size. The cause of having more men in the sample is probably due to the medical examination which is a perquisite for any locally or onboard job (any institution requires a negative HCV PCR examination). As a result more men are accidentally diagnosed with HCV.

Limitations: Relatively small sample size may not fully reflect factors among all hepatitis c patients in the population and some factors may be hidden. A larger sample selected by stratified randomization including all age groups, different socioeconomic profiles and occupations, and different marital conditions is recommended.

Recommendations: Application of the study or similar studies on larger sample size of patients with HCV. Comparingall available protocols of HCV treatment rather than only two protocols.

Keywords: Hepatitis C Virus, Chronic Hepatitis C, Ribavirin and Sovaldi therapy

Acknowledgment

*First of all, thanks to **Allah** whose magnificent help was the main factor in completing this work.*

I wish to express my deepest gratitude to all those who assisted me to complete this work.

*I'd like to express my sincere thanks and gratitude to **Professor Tarek Ahmed Okasha**, Professor of Neuropsychiatry Faculty of Medicine, Ain Shams University, **for** his support and valuable advice without which this work wouldn't have been completed.*

*I'd also like to warmly thank **Professor Ghada Refaat Amin**, Professor of Neuropsychiatry Faculty of Medicine, Ain Shams University, **for** her precious remarks, continuous support and guidance.*

*All my appreciation and regards to **Assist. Prof. Dalia Abd El-Moneim Mahmoud**, Assistant Professor of Neuropsychiatry Faculty of Medicine, Ain Shams University, **for** giving me much of her time, effort and valuable advice which lead to the progress and accomplishment of this work.*

*I'd also wish to express my thanks and regards to **my family** for their support all through this work.*

List of Abbreviations

3OH-KYN	3-hydroxy-kynurenine
5-HIES	5-Hydroxyindolylessigsäure
5-HT	5-hydroxytryptamine
ACTH	Adrenocorticotropic hormone
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANRS	Agence Nationale de Recherche sur le SIDA et les Hépatites Virales
AST	Aspartate aminotransferase
BDI	Beck Depression Inventory Scale
BMECs	Brain microvascular endothelial cells
CDC	Centers for Disease Control and Prevention
CES-D	Center for Epidemiologic Studies Depression
CHC	Chronic hepatitis C
Cho	Choline
CNS	Central nervous system
Cr	Creatine
CTP	Child-Turcotte-Pugh Score
DAA	Direct-acting antiviral
DAT	Striatal dopamine transporter
DCV	Daclatasvir
DDIs	Drug-drug interactions
DNA	Deoxyribonucleic acid
DNRIs	Norepinephrine dopamine reuptake inhibitors
DSM III	Diagnostic and statistical manual of

	mental disorders 3rd ed
DSM-IV	Diagnostic and statistical manual of mental disorders 4 th ed
EASL	European Association for the Study of the Liver
ECT	Electroconvulsive therapy
EDHS	Egyptian Demographic Health Survey
EHIS	Egypt Health Issues Survey
EIA	Enzyme immunoassay
EVR	Early virologic response
FDA	Food and Drug Administration
FDG	Fluoro-desoxy-glucose
GAD	Generalized Anxiety Disorder
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma-glutamyl transpeptidase
HAM-D	Hamilton Depression Rating Scale
Hb	Hemoglobin
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV-EHMs	Extra-hepatic manifestations
HIO	Health insurance organization
HIV	Human immune deficiency virus
HPA	Hypothalamic-pituitary adrenal –axis
HRQL	Health Related Quality of Life
IDO	Indoleamine-2,3-dioxygenase
IFN	Interferon
INR	International normalized ratio
Ins	Myo-Inositol

LDV	Ledipasvir
MDD	Major Depressive Disorder
MMSE	Mini Mental State Examination
MOHP	Ministry of Health and Population
MRI	Magnetic resonance image
MRS	Magnetic resonance spectroscopy
NAA	N-acetylaspartate
NCCVH	National Committee for the Control of Viral Hepatitis
NIH	National Institutes of Health
NTCs	National viral hepatitis treatment centers
NTP	National Treatment Program
PAT	Parenteral-antischistosomal-therapy
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
Peg-IFNα	Peginterferon alpha
PET	Positron emission tomography
P-gp	P glycoprotein
QUIN	Quinolinic acid
RBV	Ribavirin
RIBA	Recombinant immunoblot assay
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
RVR	Rapid virologic response
SCID CV	The Structured Clinical Interview for DSM-4 Disorders—Clinician Version
SERT	Mesencephalic/hypothalamic serotonin
SGA	Second generation antipsychotics
SIM	Simiprevir

SNRIs	Serotonin and norepinephrine reuptake inhibitors
SOF	Sofosbuvir
SPECT	Single-photon emission tomography
SSRI	Selective serotonin reuptake inhibitors
SUDs	Substance use disorders
SVR	Sustained virological response
TAG	Technical Advisory Group
TCAs	Tricyclic antidepressants
TNF-alpha	Tumor necrosis factor alpha
TSH	Thyroid-stimulating hormone
WHA	World Health Assembly Resolution
WHO	World Health Organization

List of Tables

List of Figures

INTRODUCTION

Introduction

The World Health Organization considers chronic hepatitis C (CHC) as a major public health problem and estimates that 3% of the world's population (170 million people) is infected with hepatitis C virus (HCV) and is at risk of developing liver cirrhosis and liver cancer **(Poynard et al., 2003; Shepard et al., 2005; Lavanchy, 2009; Dan et al., 2012; S. Pol et al., 2012)**.

The prevalence of hepatitis C virus (HCV) infection varies throughout the world with the highest number in Egypt, ranging from 6% to more than 40% with an average of 13.8%. In populations of blood transfusion recipients over the age of 30, HCV has been reported as high as 73% and in the general population aged 40–60 years it was estimated as high as 55% **(Frank et al., 2000; Kamal, 2007; El Sharkawi, 2008; El-Zayadi, 2009)**.

The Egyptian Demographic Health Survey (EDHS), a cross sectional survey including hepatitis C virus (HCV) biomarkers, was conducted in 2008 on a large nationally representative sample. It estimated HCV prevalence among the 15–59 years age group to be 14.7% **(El-Zanaty and Way, 2009)**.

The diagnosis of HCV itself has harmful effects on psychological well being and the emotional challenge becomes great. Hepatitis C infection may negatively impact the patient's quality of life and normal activities of daily living (e.g., driving) **(Corm berg et al., 2002; Wein et al., 2004)**.

Hepatitis C is now the leading cause of end-stage liver failure and the leading indication for liver transplant in the developed world. It is the leading risk factor for hepatocellularcarcinoma (HCC) in Egypt **(Jeannette et al., 2005; Strickland, 2006; Zakaria et al., 2007; Dan et al., 2011; Brown et al., 2012)**.

The major route of exposure to HCV appears to have been widespread parental antischistosomal treatment, with more than 35 million injections administered over a 20-year period (1960–1980). However, transmission continues despite termination of this program and the implementation of measures to reduce infection **(Frank et al., 2000; Strickland, 2006; Lehman and Wilson, 2009)**.

Like many chronic medical illnesses, hepatitis C is associated with an increased prevalence of psychiatric disorder particularly depression. The presence of depressive symptoms in hepatitis C, as in other chronic medical illnesses, is important because they have an

adverse effect on the course of illness, with amplification of physical symptoms, functional impairment, reduced treatment compliance and reduced quality of life. It may lead to mild cognitive changes to overt hepatic encephalopathy, which represents a significant complication of liver disease **(Dwight et al., 2000; Evon et al., 2009; Afsar et al., 2009)**.

Today, HCV infection and its complications are among the leading public health challenges in Egypt **(Miller and Abu-Raddad, 2010)**.

The combination of pegylated interferon (peginterferon) and ribavirin is now considered the optimal therapy for chronic hepatitis C. A 48- week course of this combination results in sustained eradication of HCV RNA from serum in approximately 50% of patients **(Manns et al., 2001; Hadziyannis et al., 2004; Roulot et al., 2007; Lehman and Wilson, 2009; Sarrazin et al., 2010)**.

Treatments with interferon-alpha (IFN-α) have the potential to alter the course of chronic hepatitis, prevent complications, and improve outcome. Peginterferon and ribavirin (RBV) may also be successful in selected non responders or relapsers to standard interferon with or without ribavirin. SOVALDI is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for