Psychiatric Morbidity in Patients with Hepatitis C

A review submitted for partial fulfillment of M.Sc. degree in neuropsychiatry .

By

Khaled Ragab Abdel- Hakim

M.B.,B.Ch (MISR University of Science and Technology)

Supervisors

Prof. Dr. Tarek Ahmed Okasha

Professor of Psychiatry
Faculty of Medicine
Ain Shams University

Prof. Dr. Ghada Abd El-Razek Mohamed

Professor of Psychiatry
Faculty of Medicine
Ain Shams University

Prof. Dr. Hanan Hussein Ahmed

Professor of Psychiatry
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
2013

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KHALED RAGAB

LIST OF ABBREVIATIONS

Abbreviations	Words
ALT	Alanine transaminase
AST	Asptartate transaminase
BDI	Beck depression inventory 1
CRH	Corticotrophin-releasing hormone
CRP	C- reactive protein
DALYs	Disability adjusted life years
DAT	Dopamine transporter
EHM	Extra hepatic manifestation
FDG	Fluoro-desoxy-glucose
HbsAg	Antigen of hepatitis B
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HPA	Hypothalamic pituitary adrenal
HRQL	Health related quality of life
IDUs	Injecting drug users
INF	Interferon
MRS	Mgnetic resonance spectroscopy
NAA	N- acetyl aspartate
NK	Natural killer
NI CE	National institute of clinical excellence
PET	Postiron emission tomography
PVN	Paraventicular nucleus
S.N.R.I	Serotonin and norepinephrine re-uptake inhibitors
S.S.R.I	Selective serotonin re-uptake inhibitors
SNS	Sympathetic nervous system
SPECT	Single- photon emission tomography
SVR	Sustained viral response
TNF	Tumor necrosis factor

ABSTRACT

The highest number of hepatits C virus all over the world is in Egypt. Depression, which occurs during the course of illness, can affect the treatment response, compliance to therapy and hence, disease outcome.

The presence of psychiatric, drug-, and alcohol-use disorders in hepatitis C virus (HCV)-infected patients may influence their management and prognosis. The frequency and the risk for these disorders among HCV-infected patients are unknown.

Hepatitis C virus infection is frequently associated with mental clouding, depression, neurocognitive impairment, and deterioration in the quality of life. In recent studies psychiatric symptoms have been linked to psychiatric comorbidity rather than to direct hepatitis C virus neurotoxicity. Infection of the central nervous system, however, is thought to play a role at least in hepatitis C virus associated neurocognitive deficits.

Application of the anti-hepatitis C virus agent interferon-alpha is regularly accompanied by psychiatric symptoms, most often depression. Antidepressant treatment may support interferon therapy, but its general indication and timing remain debatable.

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Hepatitis C virus (HCV) is a major cause of liver disease and death that affects 170 million people worldwide (**Shepard et al., 2005**). Recent epidemiological studies suggest more than 90% of transmission in developed countries occurs through the sharing of non sterilized needles and syringes in the intravenous drug-using population, 'unknown' sources, and 'other' sources such as dialysis, sexual transmission, and tattoos or piercing. Rates through blood transfusion are decreasing dramatically in the developed world due to improved screening for viruses in blood donations since the early 1990, although progress is somewhat slower in developing countries (**Poynard et al., 2003 and Alter 2007**).

At the same time, the diagnosis of HCV can have harmful effects on psychological well being. The emotional challenge becomes great, a person deals with a chronic disease without letting it take over his or her life (**Cornberg et al.,2002).**

Similarly like many chronic medical illnesses, hepatitis C is associated with an increased prevalence of psychiatric disorder particularly depression **(Yates and gleason 1998 and Bayliss et al.,1998),** 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 **(Dwight et al., 2000).** The association is also of particular importance in hepatitis C because patients often come from population groups at risk for psychiatric disorder, such as injecting

drug users (IDUs). In addition, treatment for hepatitis C involves interferon alfa, which has neuropsychiatric side effects. Psychiatric disorder is the main reason for delay or discontinuation of interferon alfa treatment **(Zdilar et al., 2000).** Successful medical treatment of hepatitis C therefore requires detection and management of depression both before and during treatment **(Dwight et al., 2000).** Presence of depression, which occurs in 30–50% of patients during IFN-α treatment, can alter response to therapy and compliance on treatment (**El-Zayadi ,2009**).

AIM OF THE WORK :

1- To review the available literature on the problem of psychiatric symptoms and disorders in hepatitis C.

2- To highlight recent updates of management of psychiatric disorder in hepatitis C patients.

3- To draw attention of psychiatrist to the high prevalence of psychiatric disorder with hepatitis c and raise their awareness about the important of detecting and managing them with respect to outcome of treatment of patients and their quality of life.

Hepatitis C is an infectious disease of the liver caused by a virus. Infection with Hepatitis C virus (HCV) can be either acute or chronic. An acute infection lasts less than six months and resolves spontaneously, in most cases remaining without symptoms, undiagnosed and without long-term liver damage **(Hepatitis Foundation International .,2012).**

A chronic infection persists longer than six months or even a lifetime and cannot be eliminated without treatment. Only 15 to 45% of patients clear the virus in the acute phase and the remaining 55 to 85% of patients will develop chronic HCV. Chronic HCV can cause severe inflammation of the liver with long term complications. Chronic HCV is a leading cause of chronic liver disease, liver failure and transplant **(World Health Organisation.,2012).**

The hepatitis C virus belongs to the genus Hepacivirus a member of the family Flaviviridae. Until recently it was considered to be the only member of this genus. However a member of this genus has been discovered in dogs - canine hepacivirus. There is also at least one virus in this genus that infects horses **(Burbelo et al.,2012).**

Hepatitis C virus has a positive sense single-stranded RNA genome. The genome consists of a single open reading frame that is 9600 nucleotide bases long. This single open reading frame is translated to produce a single protein product, which is then further

processed to produce smaller active proteins.At the 5' and 3' ends of the RNA are the UTR, that are not translated into proteins but are important to translation and replication of the viral RNA. The 5' UTR has a ribosome binding site (IRES - Internal ribosome entry site) that starts the translation of a very long protein containing about 3,000 amino acids (**Berry et al.,2011).**

Genotypes of hepatitis c virus:

Based on genetic differences between HCV isolates, the hepatitis C virus species is classified into seven genotypes (1-7) with several subtypes within each genotype (represented by lower-cased letters). Subtypes are further broken down into quasi-species based on their genetic diversity. Genotypes differ by 30-35% of the nucleotide sites over the complete genome. The difference in genomic composition of subtypes of a genotype is usually ~20-25%. Subtypes 1a and 1b are found worldwide and cause 60% of all cases **(Nakano and Tatsunori.,2011).**

Clinical importance of genotypes:

Genotype is clinically important in determining potential response to interferon-based therapy and the required duration of such therapy. Genotypes 1 and 4 are less responsive to interferon-based treatment than are the other genotypes (2, 3, 5 and 6).Duration of standard interferon-based therapy for genotypes 1 and 4 is 48 weeks, whereas treatment for genotypes 2 and 3 is completed in 24 weeks. Sustained virological responses occur in

70% of genotype 1 cases, ~90% of genotypes 2 and 3, ~65% of genotype 4 and ~80% of genotype 6 **(Yu and Chuang, 2009).**

Infection with one genotype does not confer immunity against others, and concurrent infection with two strains is possible. In most of these cases, one of the strains removes the other from the host in a short time. This finding opens the door to replace strains non-responsive to medication with others easier to treat **(Sarwar et al.,2011).**

Prevalence studies:

Hepatitis C is a disease with a significant global impact. According to the World Health Organization there are 130-170 million people infected with the hepatitis C virus (HCV), corresponding to 2-2.5% of the world's total population. There are considerable regional differences. In some countries, e.g., Egypt, the prevalence is as high as 22% **(Wiese., 2011)**. In Africa and the western Pacific the prevalence is significantly higher than in North America and Europe **(RKI 2004).**

It is estimated that there are 2-5 million HCV-positive persons in Europe. The prevalence of HCV antibodies in otherwise healthy blood donors is approximately 1.6% in the United States, 1.15% in Italy, 0.4% in Germany, and 0.23% in Scandinavia **(RKI 2004 and Hatzakis et al., 2011).**

Prevalence in Egypt :

On average, over half a million people in Egypt get infected by the Hepatitis C virus (HCV) each year, far more than any other country in the world, according to a new study published in the *Proceedings of the National Academy of Sciences*. The epidemic has raged in the country for several decades now and shows no signs of abating. Nearly seven out of every 1,000 of Egypt's 77 million people get infected each year. Around 10% of Egyptians are chronically infected and infectious, creating a large reservoir that supplies the spread of the disease, mainly through hospitals and clinics **(Miller, F.D. and Abu-Raddad.,2010).**

Egypt has the highest prevalence of Hepatitis C in the world. Overall, estimates of the HCV rate in the general population have range between 10 and 20 percent. **(Deuffic-Burban et al.,2005)** Geographically, the Hepatitis C prevalence has been shown to be higher in Lower Egypt (Nile Delta) than in Upper Egypt and lower in urban compared to rural areas **(Mohamed.,2004).**

According to 2008 Egypt Demographic and Health Survey (EDHS), **(El-Zanaty and Way,2009)** use of contaminated needles/syringes during mass schistosomiasis treatment campaigns during the 1960s- 1980s has been identified as a key mode of transmission for HCV infection. Suggesting the continuing role for parenteral exposure, Mohamed found that medical interventions including surgery, blood transfusion, dental treatment, and use of shared needles to be associated with increased risks of HCV infection among Egyptian workers. Sexual contact and prenatal exposure are associated with HCV infection

but HCV transmission by these routes is relatively inefficient **(Mohamed.,2004).**

Prevalence among high risk groups and psychiatric patients:

Previous studies have reported a higher infection rate with HBV and HCV in specific groups, such as parenteral drug users, male homosexuals, immunosuppressed patients, those with hemophilia, and patients undergoing dialysis. A higher incidence of hepatitis has also been identified in healthcare workers, ambulance personnel and staff in institutions such as retirement homes and institutions for the intellectual disability and those suffering serious mental illness **(Sherman et al.,2007).**

Associated with their psychiatric impairment, persons with severe mental illness are at an increased risk for several co-morbid conditions, including substance use disorder. They are also likely to be overrepresented in high risk categories for infections such as HBV and HCV. However, few studies have focused on HBV and HCV infection rates among institutionalized patients with severe mental illness, especially in a country with a high prevalence of HBV **(Ichai andSamuel.,2011).**

Routes of infection

HCV is transmitted parenterally. Routes of infection include blood transfusions, any source of blood or blood products, contaminated needles, razors and tattooing instruments, and under certain conditions sexual contact with an infected person **(Hepatitis Foundation International.,2012).**

The most common causes of HCV infection worldwide are unscreened blood transfusions and re-use of needles and syringes that have not been adequately sterilized **(World Health Organisation., 2012).**

The sharing of needles, syringes and paraphernalia by injecting drug users is another significant contribution, especially in the 53 countries of the WHO European region. In Europe, on average 60% of injecting drug users are estimated to have HCV **(Reid ., 2012).**

Yeung et al reported that uncommon routes of transmission of HCV, which affect less than 5% of the individuals at risk, include high-risk sexual activity and maternal-fetal transmission. Co-infection with human immunodeficiency virus (HIV) type 1 appears to increase the risk of both sexual and maternal-fetal transmission of HCV. Casual household contact and contact with the saliva of those infected are inefficient modes of transmission. No risk factors are identified in approximately 10% of cases **(Yeung et al.,2001).**