INTRODUCTION

Chronic hepatitis C virus (HCV) is a major cause of liver-related morbidity and mortality ***(Armstrong et al., 2000).*** Successful antiviral therapy with sustained viral clearance is associated with improved quality of life ***(Bonkovsky et al., 2007),*** and reduced risk of liver complications such as cirrhosis and hepatocellular carcinoma ***(Coverdale et al., 2004).***

Hepatitis C virus (HCV) infection is considered a systemic disease because of involvement of other organs and tissues concomitantly with liver disease. According to ***WHO (2018)*** the three most common extrahepatic manifestations are depression (24%), diabetes mellitus (15%) and chronic renal disease (10%). Among the extrahepatic manifestations, neuropsychiatric disorders have been reported in up to 50% of chronic HCV infected patients. Cognitive dysfunction, characterized by forgetfulness, attention and concentration difficulties, poor word recall, and delayed reaction times, has been documented in 13–50% of individuals with chronic HCV infection using comprehensive neuropsychological test panels ***(Fontana et al., 2007).***

Although cognitive abnormalities are more common in individuals with advanced fibrosis and medical comorbidities, they are present even in the absence of advanced fibrosis and significant psychiatric and medical comorbidities ***(Forton et al., 2002).***

The brain is a suitable site for HCV replication, where the virus may directly exert neurotoxicity; other mechanisms proposed to explain the pathogenesis of neuropsychiatric disorders in chronic HCV infection include derangement of metabolic pathways of infected cells, alterations in neurotransmitter circuits, autoimmune disorders, and cerebral or systemic inflammation. A pathogenic role for HCV is also suggested by improvement of neurological and psychiatric symptoms in patients achieving a sustained virological response (SVR) ***(Adinolfi et al., 2015).***

The most frequent psychiatric symptom reported in chronic HCV infection is fatigue mainly manifesting as physical and mental exhaustion, often in association with attention deficit and word-finding difficulty, depression, headache, osteoarticular pain, and sleep disturbances. Although insomnia has been reported in up to 60% of cases, it can also be dependent on other psychiatric comorbidities, such as depression, or on such medical conditions as anemia and hypothyroidism, frequently associated with chronic HCV infection ***(Goh et al., 1999).*** Old age, female gender, and single status have been found to be predictive of fatigue in HCV patients ***(Ashrafi et al., 2012).***

Impact of HCV treatment and Sustained virus response on neuropsychiatric disorders:

Although interferon-α treatment itself is known to possibly induce neuropsychiatric side effects, the drug ability to improve neurological and psychiatric symptoms in HCV patients achieving a sustained virological response (SVR) has been frequently reported in the literature ***(Sarkar et al., 2012).*** Moreover, SVR has also been associated with improvement in cognitive function ***(Thein et al., 2007).*** To date, studies addressing the issue of reversibility of cognitive deficits after HCV therapy are based on interferon treatment and to verify that improvement, more follow-up data need to be considered using a reliable change index approach to differentiate between practice effects and treatment related cognitive changes ***(Kleefeld et al., 2016).***

AIM OF THE STUDY

To evaluate the impact of HCV eradication using direct acting antiviral drugs (DAADs) on cognitive and sleep dysfunction among hepatitis c virus infected patients.

Chapter 1

HEPATITIS C VIRUS: CONCEPT OF SYSTEMIC DISEASE

INTRODUCTION AND EPIDEMIOLOGY:

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide ***(Lavanchy , 2009).*** The long-term hepatic impact of HCV infection is highly variable, the hepatic injury can range from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). There are approximately 71 million chronically infected individuals worldwide many of them are unaware of their infection, with important variations according to the geographical area ***(Blach et al., 2017; Razavi et al., 2017).***

Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, thanks to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention ***(Pawlotsky et al., 2018).***

Hepatitis C is found worldwide. The most affected regions are WHO Eastern Mediterranean and European Regions, with the prevalence of 2.3% and 1.5% respectively,

Prevalence of HCV infection in other WHO regions varies from 0.5 to 1 %.

Accurate HCV prevalence and incidence data are needed to analyze the magnitude of the pandemic in different regions and to design public health interventions. Thus, HCV screening is required to identify infected individuals and engage them in care and treatment ***(Pawlotsky et al., 2018).***

Prior to the 1990's, the principal routes of HCV infection were via blood transfusion, unsafe injection procedures, and `intravenous drug use. These modes of acquisition are estimated to account for approximately 70% of cases in industrialized countries. Screening of blood products for HCV by means of enzyme immunoassays and, in a number of European countries, nucleic acid testing, has virtually eradicated transfusion-transmitted hepatitis C. Currently, new HCV infections are primarily due to intravenous or nasal drug use, and to a lesser degree to unsafe medical or surgical procedures. Parenteral transmission via tattooing or acupuncture with unsafe materials is also implicated in occasional transmissions. The risk of perinatal and of heterosexual transmission is low, while recent data indicate that promiscuous male homosexual activity is related to HCV infection ***(van de Laar et al., 2010).***

The situation in Egypt:

Hepatitis C virus (HCV) infection is a major public health burden in Egypt, where it bears the highest prevalence rate in the world. Estimates for prevalence are based upon data reported from the 2008 and 2015 Egypt Demographic Health Surveys ***(Gomaa et al., 2017).***

The recently released Egyptian Health issues Survey [EHIS] 2015 tested a representative sample of the entire country for HCV antibody. The sample included both urban and rural populations and included all 27 governorates of Egypt. A total of 27, 549 adults and children were eligible for hepatitis testing. Around 5 percent refused to provide a blood sample for the testing or were not at home when the EHIS team visited their households with overall prevalence positive for antibody to HCV was 10% ***(El-Zanaty , 2015).***

Compared to DHS 2008 where Over 11, 000 individuals were tested at that time, the overall prevalence (percentage of people) positive for antibody to HCV was 14.7% ***(El-Zanaty and Way, 2009).***

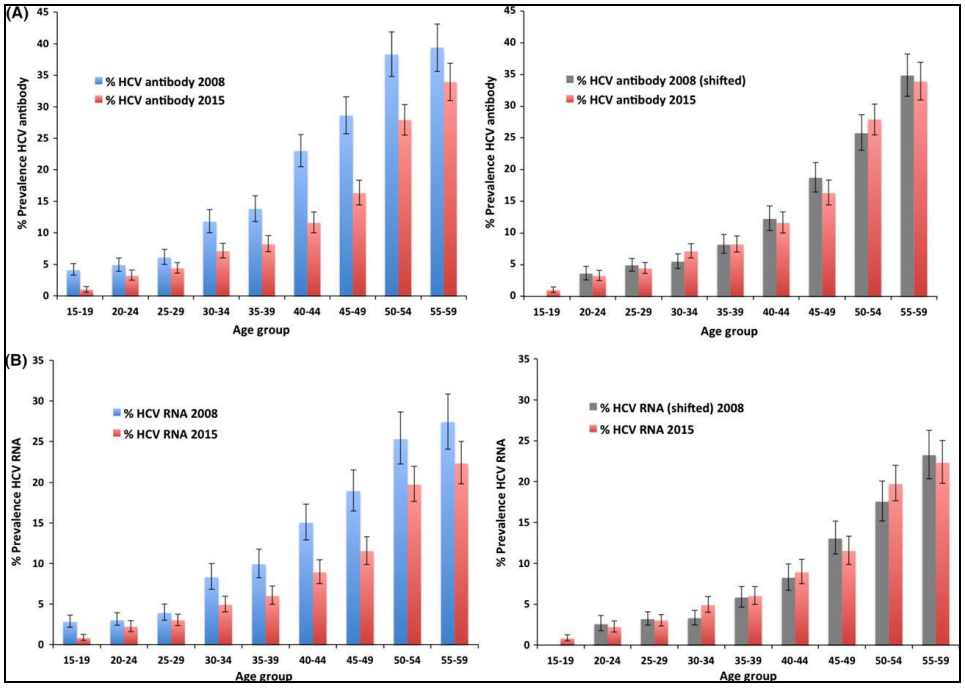

Figure (1): (A) Age-specific prevalence of hepatitis C virus (HCV) antibody-positive persons in 2008 and 2015 (left), then shifted (by 7 years) 2008 and 2015 (right). (B) Age-specific prevalence of HCV RNA-positive persons in 2008 and 2015 (left), then shifted (by 7 years) 2008 and 2015 (right).

THE DHS 2015 estimates that the overall HCV prevalence is estimated to be declining. However, the clinical impact of chronic HCV infection is expected to grow considerably. A mathematical model shows that by increasing the rate of treatment, the expected number of patients will decline significantly in 2030 ***(Gomaa et al., 2017).***

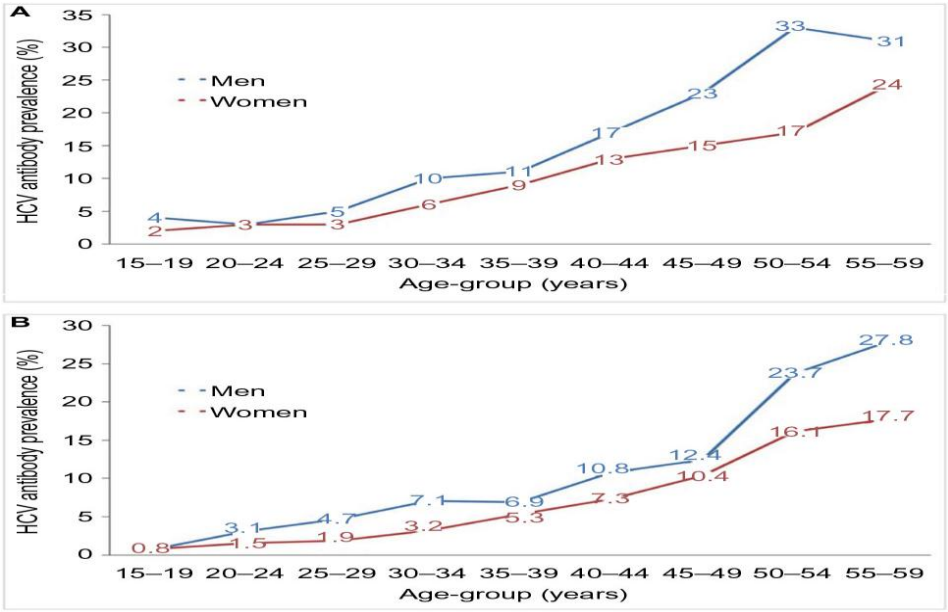

Figure (2): Percent of men and women with hepatitis C antibody by age in Egypt in (**A**) 200812 and (**B**) 2015.

During the roughly seven-year period between the 2008 EDHS and 2015 EHIS, the percentage of adults positive on the test (i.e., who had an active hepatitis C infection) decreased by 30 percent. That decline reflects the aging out of the population tested of individuals who were age 53-59 at the time of the 2008 EDHS. Individuals in that age group accounted for around 25 percent of the active hepatitis infections at the time of the 2008 EDHS ***(El-Zanaty, 2015).***

Figure (3): Trends in percentage of the population age 15-59 testing positive on the hepatitis C RNA test, Egypt 2008-2015.

The national treatment strategy for control of HCV infection in Egypt was set by the National Committee for Control of Viral Hepatitis (NCCVH) which was established by the ministry of health (MoH) in 2006, in response to the magnitude of the HCV problem and burden of disease in Egypt. To date, more than one million patients were evaluated and more than 850 000 received treatment under the umbrella of the programme since 2006. It established a nationwide network of digitally connected viral hepatitis-specialized treatment centers covering the country map to enhance treatment access. Practice guidelines suiting local circumstances were issued and regularly updated and are applied in all affiliated centers ***(El-Akel et al., 2017).***

HCV infection burden on health related quality of life:

Chronic infection with HCV is a major cause of liver-related morbidity and mortality**.** HCV infection is postulated to result in an 8-12-year reduction in overall life expectancy in infected individuals, as well as in reduced health-related quality of life ***(Ryder, 2007).*** The incubation period for hepatitis C is 2 weeks to 6 months. Following initial infection, Incident infection is associated with early symptoms in about 20% of persons. Spontaneous clearance occurs within six months of infection in 15–45% of infected individuals in the absence of treatment. More than 55-85% of infected individuals develop chronic infection. Acute hepatitis is icteric (symptomatic) in only 20% of patients and is rarely severe. The majority of patients who develop chronic HCV infection are asymptomatic; but 60-80% develop chronic hepatitis as indicated by elevated alanine aminotransferase (ALT), around 30% maintain persistently normal ALT levels despite having detectable HCV-RNA in serum. One-third (15% to 30%) of chronically infected patients develop progressive liver injury, fibrosis and cirrhosis over a period of 20-30 years. The relationship between virus load, HCV genotype, quasi-species variability and progression of liver disease is controversial. Acquired infection after age 40, male sex, excessive alcohol-consumption, hepatitis B virus (HBV) or HIV co-infection, steatosis, and immunosuppressed state have been identified as co-factors associated with

progression of fibrosis and development of cirrhosis. In patients with cirrhosis, the incidence of hepatocellular carcinoma is 2-5% per year. At present, HCV-related end-stage cirrhosis is the first cause of liver transplantation ***(Leone and Rizzetto, 2005).***

According to ***WHO (2015)*** Approximately 399, 000 people die each year from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma.

There is currently no vaccine for hepatitis C; however research in this area is ongoing.

Extra hepatic manifestation syndrome:

HCV infection is also associated with several extra-hepatic manifestations, which add to the morbidity and mortality burden of HCV. Patients infected with HCV may develop, among many other disorders, mixed cryoglobulinemia, insulin resistance, several cardiovascular diseases, fatigue, depression, and cognitive impairment, translating into a significant public health impact in terms of both direct and indirect costs. The prevalence of these extrahepatic manifestations is usually independent of the degree of liver fibrosis ***(Negro et al., 2015; Younossi et al., 2016).***

HCV has also notable effects on the health-related quality of life and other outcome impacting both physical and psychological well-beings.

Thus, overall, the public health burden of extrahepatic manifestations associated with HCV is a major one, as underlined by the total estimated annual direct costs of 1506 million USD for the US alone, a figure where indirect costs – such as those linked to decreased productivity at work – are not even considered. A sizable proportion of the costs linked to HCV can be offset by viral eradication. A prospective cohort study reported that patients with chronic HCV infection have an increased risk of death from both liver- and non-liver-related diseases, including cardiovascular and renal diseases, compared to uninfected persons and those with anti-HCV but undetectable HCV RNA ***(Lee et al., 2012).***

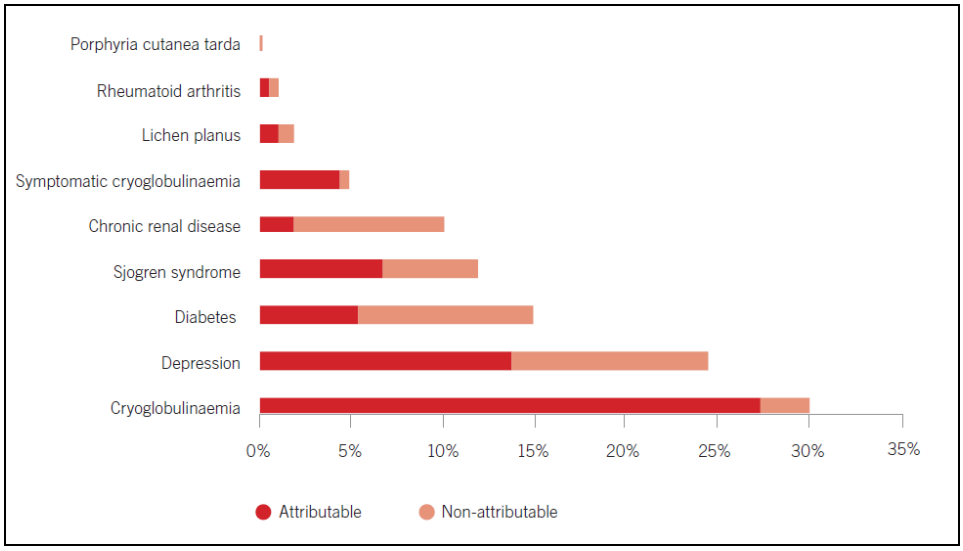

Figure (4): Prevalence of comorbidities among persons with HCV infection, including the fraction that is attributable to HCV infection (calculated on the basis of Younossi et al. 2016, using attributable fractions among those exposed)

Studies focusing on single extrahepatic manifestation have provided convincing evidence in favor of the benefits of viral clearance. Thus, SVR is associated with reduced levels of insulin resistance and risk of type 2 diabetes, and resolution of most MC (mixed cryoglobulinemia) -related complication, Including the remission of some forms of HCV-associated B cell lymphoma, reduced incidence of stroke and other cardiovascular outcomes (especially in the presence of diabetes), and improved patients' reported outcomes such fatigue and health-related quality of life ***(Negro and Esmat, 2017)***

The advent of well-tolerated interferon-free treatment regimens has increased the number of patients eligible for therapy, extending the access to treatment to those in whom interferon was contraindicated, e.g. because of uncontrolled depression, severe fatigue, autoimmune disorders and cardiovascular diseases. Systematic reviews of the effectiveness of DAADs for the treatment of chronic HCV infection indicate that SVR rates generally exceed 90%, except for those with the most advanced stages of cirrhosis ***(Falade et al., 2017)***

Physicians other than hepatologists should be aware about the role of HCV infection and its extrahepatic effect helping the diagnosis of unexplained manifestations as arthralgia and unexplained fatigue ***(Chen et al., 2010).***

Importantly, a multicenter study has shown that curing HCV with antivirals reduces both liver-and non liver related mortalities **(van der Meer et al., 2012).**

The pathogenesis of the extra-hepatic features of HCV is not always clear and may involve endocrine effects, direct toxic effects due to HCV replication n in extra-hepatic tissues, or disproportionate immune reactions with systemic effects. According to a recent meta-analysis, the most frequent extrahepatic manifestation occurring in HCV infected persons is depression, with a pooled prevalence of 24.5% vs. 17.2% in uninfected controls ***(Younossi et al., 2016).***

Another major manifestation is represented by type2 diabetes, The pooled prevalence of diabetes in hepatitis C patients has been estimated at 15%, compared with 10% in the uninfected population, with a pooled odds ratio for diabetes of 1.58 vs. controls ***(Younossi et al., 2016).***

HCV infection as a risk factor of physical and mental fatigue:

Fatigue is one of the most commonly reported symptoms of infection with hepatitis C, and can be persistent and debilitating ***(Poynard et al., 2002; Dwight et al., 2000; Hilsabeck et al., 2003).***