INTRODUCTION

The World Health Organization (WHO) estimates 170 million individuals worldwide are infected with hepatitis C virus (HCV). However, the prevalence of HCV infection varies throughout the world. ***Frank et al. (2000)*** reported that Egypt had the highest number of reported infections, largely attributed to the use of contaminated parenteral antischistosomal therapy. This led to a mean prevalence of HCV antibodies in persons in Egypt of 22 %.

Chronic infection with HCV is one of the most important causes of chronic liver disease which can progress to cirrhosis and hepatocellular carcinoma (HCC) ***(Forton et al., 2002)***.

In the majority of patients, extrahepatic manifestations of (HCV) infection can be observed. The most frequent are disabling chronic fatigue, cognitive decline, mood alterations, and musculoskeletal pain ***(Cacoub et al., 2002).*** Importantly, these manifestations are unrelated to the grade of liver disease ***(Wiese et al., 2005)***.

It is well established that advanced forms of the disease are accompanied by overt and global cognitive deficits (hepatic encephalopathy) ***(Mattarozzi et al., 2005)***. In addition, researchers and clinicians have become increasingly aware of a group of HCV patients with mild liver disease that present with a less-overt pattern

of neuropsychological impairment ***(Weissenborn et al., 2004)***. Although cognitive decline is subtle, it seems to interfere with the everyday living of hepatitis patients and negatively influences their quality of life (QOL) ***(Cordoba et al., 2003)***.

Executive function is a set of high-level abilities that control and regulate more basic abilities like attention, memory and motor skills. They are necessary for goal-directed behavior. They include the ability to initiate and stop actions, to monitor and change behavior as needed, and to plan future behavior when faced with novel tasks and situations. The ability to form concepts and to think abstractly are often considered components of executive function. They also allow people to manage the stresses of daily life ***(Wecker et al., 2000)***. People with poor executive functions often have problems interacting with other people. So; Executive functions are thus an important component of the ability to fit in socially ***(Bryan et al., 2000)***.

AIM OF THE WORK

The purpose of this study is to investigate the possible existence of alterations in the executive functions of HCV patients without liver cirrhosis.

HEPATITIS C VIRUS

HCV infection is a major public health problem worldwide and up until the introduction of anti-HCV screening tests for blood donors, introduced in 1990/1991 in Europe and the United States; it has represented the major cause of transfusion-associated hepatitis ***(Houghton, 1996)***.

Not only does viral hepatitis carry a high morbidity, but it also stresses medical resources and can have severe economic consequences. Chronic infection with HCV is one of the most important indications for liver transplantation in the United States ***(Verna et al., 2006)***.

Hepatitis C is an infectious disease primarily affecting the liver, caused by hepatitis C virus leading to sever inflammation of the liver. Most HCV infections persist, leading to chronic hepatitis, which can develop into chronic active hepatitis, liver cirrhosis and hepatocellular carcinoma ***(Weinbaum et al., 2003)***.

Hepatitis C virus (HCV) is a small (55-65 nm in size), enveloped, single-stranded RNA virus which belongs to the family Flaviviridae ***(Op De Beeck et al., 2003)***.

The structure of the virus particle consists of a core of genetic material (RNA), surrounded by a protective shell of

protein, and further encased in a lipid envelope of cellular origin. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope ***(Op De Beeck et al., 2003)***.

The virus replicates mainly in the hepatocytes of the liver. The virus may also replicate in peripheral blood mononuclear cells, potentially accounting for the high levels of immunological disorders found in chronically-infected HCV patients ***(Bartenschlager et al., 2000)***.

Genotypes:

Based on genetic differences between HCV isolates, the hepatitis C virus species is classified into six genotypes (1-6) with several subtypes within each genotype (represented by letters). Subtypes are further broken down into quasispecies based on their genetic diversity. The distribution of HCV genotypes varies globally, Genotype is clinically important in determining potential response to interferon-based therapy and the required duration of such therapy ***(Simmonds et al., 2005)***.

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 ***(Laskus et al., 2001)***.

Epidemiology of Hepatitis C Virus infection:

Hepatitis C virus is a large health care burden to the world. Incidence rates across the world fluctuate and are difficult to calculate due to the asymptomatic, often latent nature of the disease prior to clinical presentation ***(Theodore et al., 2006)***.

Prevalence rates vary across the world, the WHO estimated a worldwide prevalence of about 3% with the virus affecting 170 million people worldwide ***(Frank et al., 2000)***. In the Third National Health and Nutrition Examination Survey (NHANESIII), an estimated HCV prevalence of 3.9 million people was found in the United States 2.7 million of these individuals suffer from chronic infection ***(Alter et al., 1999)***.

In Europe, general prevalence of HCV is about 1% but varies among the different countries ***(Touzet et al., 2000)***. In the United Kingdom, at least 200,000 adults carry HCV ***(Theodore et al., 2006)***. In France, the prevalence of HCV was estimated to be 1.3% ***(Pradat et al., 2001)***.

The prevalence also varies within the same country. In Italy prevalence of HCV Ab was 3.2% in Northen Italy ***(Bellentani et al., 2001)***. While Central and Southern Italy showed a higher rate of HCV (8.4%-22.4%), especially in the older population ***(Maio et al., 2000)***.

In Asia, a study performed in Japan showed that 0.49% anti-HCV Ab were detected among 3,485,648 blood donors ***(Tanaka et al., 2004)***. While in China prevalence rates were generally low with rates around 1% among donors ***(Wang et al., 1994)***. Low rates have been found in Malaysia (around 1.6%) and Singapore (0.54%) ***(Duraisamy et al., 1993)***. Higher rates of HCV have been found in Thailand (3.2-5.6%) ***(Apichartpiyakul et al., 1999)***.

In the middle east, a study came out of Pakistan showed that 751 out of 16,400 patients (4.57%) were found to have HCV Ab from 1998-2002 with the largest age group from 41-50 ***(Muhammad et al., 2005)***.

There have been fewer studies out of Africa, but lower rates have been reported (1.6%) among blood donors in Ethiopia and 0.9% in Kenya ***(Ilako et al., 1995)***.

In Australia the estimated prevalence has been recently reported as 2.3% with the virus affecting 210,000 people by 2001***(Amin et al., 2004)***.

Among Central and South America, a recent community based study in Peurto Rico, showed that estimated prevalence of HCV in 2001-2002 was 6.3% ***(Perez et al., 2005)***. In Mexico, the prevalence reported was about 1.2% ***(Uribe et al., 2002)***. Among blood donors in Chile and Brazil, prevalence of HCV Ab was low - 0.3%, 1.14% respectively ***(Munoz et al., 1998)***.

Prevalence of Hepatitis c virus in Egypt:

Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma. The recently published Egyptian Demographic Health Survey (EDHS) in 2009 was a national probability sample of the resident Egyptian population. This report estimated an overall anti-HCV antibody prevalence of 14.7% .The number of Egyptians estimated to be chronically infected was 9.8% ***(El-Zanaty et al., 2009)***.

Egypt has higher rates of HCV than neighboring countries as well as other countries in the world with comparable socioeconomic conditions and hygienic standards for invasive medical, dental, or paramedical procedures ***(Frank et al., 2000)***.

The strong homogeneity of HCV subtypes found in Egypt (mostly 4a) suggests an epidemic spread of HCV. Since a history of injection treatment has been implicated as a risk factor for HCV, a prime candidate to explain the high prevalence of HCV in Egypt is the past practice of parenteral therapy for schistosomiasis. The large reservoir of chronic HCV infection established in the course of these campaigns remains likely to be responsible for the high prevalence of HCV morbidity and may be largely responsible for the continued endemic transmission of HCV in Egypt today ***(Frank et al., 2000)***. More recent evidence suggests a continuation of iatrogenic

exposures that is contributing to ongoing HCV transmission ***(Talaat et al., 2006)***.

Incidence rates are difficult to calculate due to the asymptomatic nature of the acute infection. A national study performed in 2009 provided an opportunity to apply established epidemiologic models to estimate incidence. Validated mathematical models for estimating incidence from age-specific prevalence were used. All previous prevalence studies of HCV in Egypt were reviewed and used to estimate incidence provided that there was sufficient age-specific data required by the models. The study estimates that there are more than 500,000 new HCV infections per year ***(DeWolfe et al., 2010)***.

Prevalence of Hepatitis c virus in Elderly:

The prevalence of HCV infection in the elderly varies among different studies.According to the study of the National Health and Nutrition Examination Survey III that included 21,241 participants aged 60 years and above, the prevalence of positive HCV antibody was found to be 0.9% and 1.0% in subjects who were in the age groups of 60 to 69 years, and 70 years and older, respectively ***(Alter et al., 1999)***.

In another study that was performed in Italy among 496 elderly with a mean age of 79.31 years, the prevalence of positive HCV antibody was found to be around 11%. HCV-antibody positivity was associated significantly with being between the ages of 70 and 79 ***(Baldo et al., 2000)***.

While in a more recent Italian study that was conducted among 1646 subjects, the prevalence of positive HCV antibody was reported around 5% in patients ages 58 to 67 years and around 2% in patients ages 68 and 77 years ***(Mazzeo et al., 2003)***.

In another study performed in Italy comparing prevalence of HCV infection among people under 30 years and elderly the rate among persons younger than 30 years of age was only 1.3% compared with 33.1% in those above 60. The use of glass syringes for medical treatment, a common practice before 1970 in Italy contribute to the high prevalence in elderly population ***(Lemonet al., 1995)***.

In Japan the prevalence of HCV infection is low among children and young adults, but it increases at the age of 40 years and continues to increase during aging. In a community-based study in Japan, the prevalence of anti-HCV seropositivity was 3% (1 of 38 persons) in the 20–29-year-old group and increased to 41% (13 of 32) among persons aged 80–89 years ***(Okayama et al., 2002)***.

Risk Factors:

1. Intravenous drug use:

Transmission of Hepatitis C virus has been strongly associated with intravenous and percutaneous drug and needle use. Reported cases of hepatitis C from intravenous drug use is on the rise in the US. In a study of injection drug users in Maryland from 1988 to 1996, 30.3% of participants developed anti-HCV antibodies with most in the first 2 years of the study ***(Villano et al., 1997)***.

The Hepatitis C European Network for C-operative Research (HENCORE) group reported a prevalence of hepatitis C of 80% among intravenous drug users (IVDU) ***(Touzet et al., 2000)***. A recent study in England took 428 IVDU below the age of 30 and found that 44% had antibodies to hepatitis C ***(Judd et al., 2005)***.

In a Lithuanian study to determine the association between route of infection and age of the study subjects. It was found that the most common hepatitis C transmission route in younger patients were intravenous drug use and tattoos which is not a common route in elderly patients ***(Liakina et al., 2009)***.

2. Blood exposure:

Transfusion of blood and blood products has been a leading cause of transmission of HCV; however, due to

improved screening, transmission through transfusions has decreased in most developed countries. In the US, incidence of post-transfusion hepatitis C dropped from 3.84% to 0.57% per patient (0.03% per unit blood) after HCV screening was introduced in 1990 ***(Donahue et al., 1992)***. In England, the frequency HCV infected donations dropped from 1 in 520,000 (1993-98) to 1 in 30 million (1999-2001) when donations were tested for HCV RNA ***(Soldan et al., 2003)***.

However, incidence of transfusion related hepatitis C is still higher in other areas of the world. In A study performed in the largest blood bank in Santa Catarina, Brazil from 1991-2001 it showed a significant drop in risk of acquiring HCV, but the lowest risk of 1:13721 was still almost 10 times higher than that of developed countries ***(Kupek, 2004)***.

Occupational exposure to infection through accidental exposure to blood through needle sticks or blood spatters to the eyes or open wounds. Also personal care items such as razors, toothbrushes, cuticle scissors, and other manicuring or pedicuring equipment can easily be contaminated with blood. Sharing such items can potentially lead to exposure to HCV ***(Lock et al., 2006)***.

Another way that increases the risk for HCV transmission is tattooing dyes and piercing implements. They can transmit HCV-infected blood from one person to another if proper sterilization techniques are not followed ***(Vescio et al., 2008)***.

3. Hemodialysis:

Patients on hemodialysis have a higher rate of aquireing HCV infection. The possible risk factors include failure to disinfect devices between patients, sharing of single-use vials for infusions, poor sterile technique, and poor cleaning of dialysis machines ***(Zampieron et al., 2004)***.

A report from Saudi Arabia showed a prevalence rate of HCV among hemodialysis patients to be 9.24% compared to 0.30% among blood donors ***(Qadi et al., 2004)***, and in a tertiary-care hospital in Mexico City, Mexico, the rate of anti-HCV was 6.7% compared to the roughly 1.2% prevalence in the population of Mexico ***(Mendez-Sanchez et al., 2004)***.

In another study performed in Saudi Arabia included 198 patients with end-stage renal disease enrolled for long-term hemodialysis therapy to determine the relationship between advancing age and the risk of acquiring (HCV) infection in different age groups of patients on long-term hemodialysis, it was found that there is Significantly higher annual seroconversion rates in those aged 55 to 64 and 65 to 74 during a shorter dialysis period (35.6 and 32.7 vs 58.0 months), suggest the greater susceptibility of the middle-aged and elderly patients to acquisition of HCV infection than the younger (15-24 years) group ***(Saxena et al., 2004)***.

This could be attributed to the combined effect of immunosuppression associated with advancing age, uremia, and undernutrition ***(Saxena et al., 2004)***.

4. Sexual activity:

Sex as a mode of HCV transmission remains a subject of debate. Heterosexual couples in long-term relationships with single partner (i.e. monogamous relationship) represent the most common form of sexual partnership. While the available data indicate that the risk of HCV transmission in persons with single partner lowers than those with multiple partners ***(Terrault, 2002)***.

In a prospective study done in Italy included 895 monogamous heterosexual partners of HCV chronically infected individuals for evaluation of the risk of sexual transmission of HCV the participants were followed up for seroconversion for 10 years the incidence rate was 0.37 per 1,000 person-years indicating that the risk of sexual transmission of HCV within heterosexual monogamous couples is extremely low or even null ***(Vandelliet al., 2004)***.

In another study by Veysel et al. in this issue, none of the 216 HCV-negative spouses seroconverted over the 3-yr mean follow-up period ***(Veysel et al., 2005)***.

In a study among spouses in Egypt, it was estimated that wife to husband transmission was 34% and Husband to wife

transmission was estimated at 3%. Overall, 6% were estimated to have contracted HCV from their spouse ***(Magder et al., 2005)***.

In a Japanese study it was found that sexual transmission do not appear to be the main routes of HCV infection in elderly ***(Hayashi et al., 1997)***.

5. Iatrogenic medical or dental exposure:

People can be exposed to HCV via inadequately or improperly sterilized medical or dental equipment. Equipment that may harbor contaminated blood if improperly sterilized includes needles or syringes and oral hygieneinstruments. The WHO estimates that approximately 16 billion injections are administered worldwide each year and that in developing countries 6.7billion unsafe injections are administered (39.3% of allinjections). This contributes to more than 2 million HCV infections per year ***(Kane et al., 1999)***.

In elderly medical interventions were found to play an important role in the spread of HCV infection, because elderly patients became infected via contaminated blood transfusions or when contaminated syringes and needles were used ***(Hayashi et al., 1997)***.

The ongoing iatrogenic transmission of HCV infection occurs mainly in poor regions of the world and has 2 main