INTRODUCTION

Acquired haemophilia is a life-threatening haemorrhagic disorder characterized by antibodies directed against coagulation factor VIII ***(Franchini and Lippi, 2011).*** Autoantibodies against coagulation factor VIII occurring in Acquired haemophilia A patients have been characterized as polyclonal, mostly of the IgG4 isotype, similar to those arising in classical haemophilia ***(Shima, 2006).***

However, Acquired haemophilia A differs from classical hereditary haemophilia A in some aspects: patients with Acquired haemophilia A do not have past or family history of bleeding, and most of them do not present with haemarthroses. In fact, the clinical picture of patients with Acquired haemophilia A is characterized by haemorrhage into the muscles, soft tissues, skin and/or mucous membranes. Moreover, monoclonal autoantibodies (IgA or IgM class) have also been demonstrated in association with Acquired haemophilia A ***(Franchini et al., 2006)***. The detection of inhibitor autoantibodies against other coagulation factors such as FIX, FXI, FXIII, and vWF protein are extremely rare ***(Cohen and Kessler, 1996).***

About half of the patients with the acquired factor VIII inhibitor were considered as idiopathic ***(Sugishita et al.,1999***), but underlying conditions include: autoimmune disease, malignancy, pregnancy, infections and drugs (in particular antibiotics, psychiatric, immunomdulating drugs, etc) ***(Franchini and Lippi, 2011).***

The mechanism of the acquired factor VIII inhibitor production has not yet been clarified in non-hemophilic patients. Some underlying pathophysiological states, including collagen and autoimmune diseases, have been reported, and these conditions are known to induce immunological disorders and autoimmune antibodies ***(Sugishita et al., 1999).*** The development of these inhibitors in association with chronic hepatitis C is poorly understood ***(Franchini and Lippi, 2011).***

Chronic infection with the hepatitis C virus (HCV) causes various degrees of liver inflammation and fibrosis. In addition to liver disease, chronic HCV infection can have extrahepatic manifestations, especially autoimmune disorders ***(Cacoub et al., 2000).*** These are arthralgias, skin manifestations, xerostomia, xerophthalmia, and sensory neuropathy. The main biological abnormalities are mixed cryoglobulinemia and the presence of autoantibody. These antibodies include antinuclear antibody, rheumatoid factor, anti-cardiolipin, anti-thyroglobulin, and antismooth muscle cell antibody. Therefore, it is not unexpected that autoantibodies to factor VIII be foundin patients infected with the hepatitis C virus ***(Schreiber and Brau, 2005).***

So immunological dysregulation in hepatitis C and associated treatment effects may result in autoimmune phenomenon, but the mechanisms involved in the development of inhibitors against FVIII are not well understood. FVIII inhibitors are known to bind specifically to highly antigenic regions located on the FVIII molecule, mainly on its A2, A3, and C2 domains.

Moreover, the synthesis of these inhibitors was demonstrated to require CD4z (helper) T-cells specific for FVIII ***(Reding et al., 2006).*** Also these may occur in several ways: autoantibodies mayeither appear de novo during the treatment of hepatitis C, or existing antibodies may arise while patients are treated with interferon. hematological immune side effects of interferon- a treatment include autoimmune hemolytic anemia, immune thrombocytopenia, thrombotic thrombocytopenic purpura, increased incidence of cardiolipin antibodies, and acquired factor VIII inhibitors ***(Raanani and Ben-Bassat, 2002).***

However the studies about the association of acquired factor VIII activity defect and chronic hepatitis C viral infection are limited, they are in need to be clarified.

AIM OF THE STUDY

The aim of this study is to explore the presence of acquired factor VIII activity defect in patients with chronic hepatitis C viral infection.

Chapter One

HEPATITIS C VIRUS INFECTION

Hepatitis C is an infectious disease affecting primarily the liver. It is one of the main causes of chronic liver disease worldwide ***(Lavanchy, 2009).***

The long-term impact of HCV infection is highly variable, from minimal changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC) ***(Rockstroh et al., 2008).***

HCV infection is recognized as a major threat to global public health ***(Ayesh et al., 2009).*** Chronic infection with HCV is one of the most important indications for liver transplantation in the United States. So not only does viral hepatitis carry a high morbidity, but it also stresses medical resources and can have severe economic consequences ***(Verna et al., 2006).***

The hepatitis C virus (HCV) is a small, (55-65nm in size) enveloped, single-stranded, positive-sense RNA virus. 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. It is a member of the Hepacivirus genus in the family Flaviviridae ***(Rosen et al., 2011).***

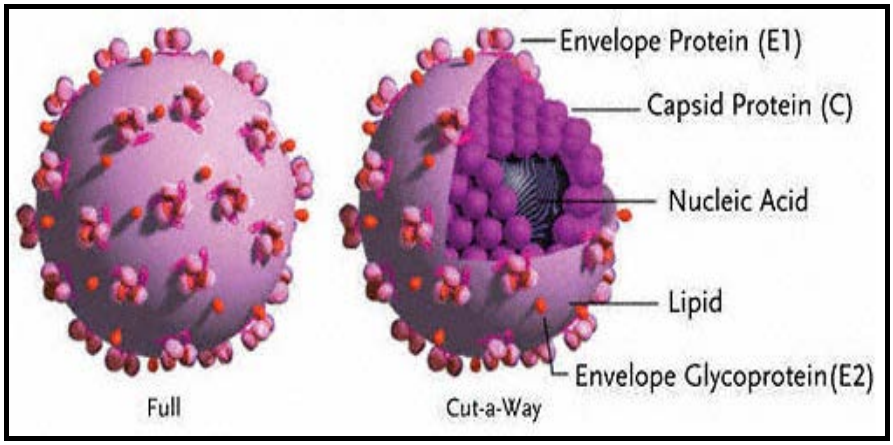

Figure (1): Showing structure of HCV.

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 patient ***(Lavanchy, 2009)***.

Epidemiology of HCV:

Hepatitis C virus (HCV) infection is a major public health problem with an estimated 3-4 million people infected each year worldwide and about 170–200 million carriers. These latter are at risk of developing liver cirrhosis and/or liver cancer. More than 350,000 people die from HCV-related liver diseases each year. Moreover, these estimates do not take into account the extrahepatic aspects of HCV infection ***(Zignego et al., 2012).***

The number of chronically infected persons worldwide is estimated to be about 160 million, but most of them are unaware of their infection ***(Kamili et al., 2012),*** and worldwide hepatitis C is the cause of 27% of cirrhosis cases and 25% of hepatocellular carcinoma***,*** and it is estimated that, in the United States alone, 12,000 people die annually of HCV-related complications including liver failure or cancer ***(Alter, 2007).***

There are large disparities in the prevalence of HCV infection among different countries ***(Ismail et al., 2009)***. Current estimates are that between 7.3 and 8.8 million persons are infected with HCV in the European Union, i.e. twice as many as an estimate made in 1997 ***(Lavanchy, 2011).***

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 ***(Awadalla et al., 2011)***. The strong homogeneity of HCV subtypes found in Egypt (mostly 4a HCV subtype) 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 ***(Metwally et al., 2013)***.

Evidence suggests iatrogenic exposures are contributing to ongoing HCV transmission ***(Talaat et al., 2006)***.

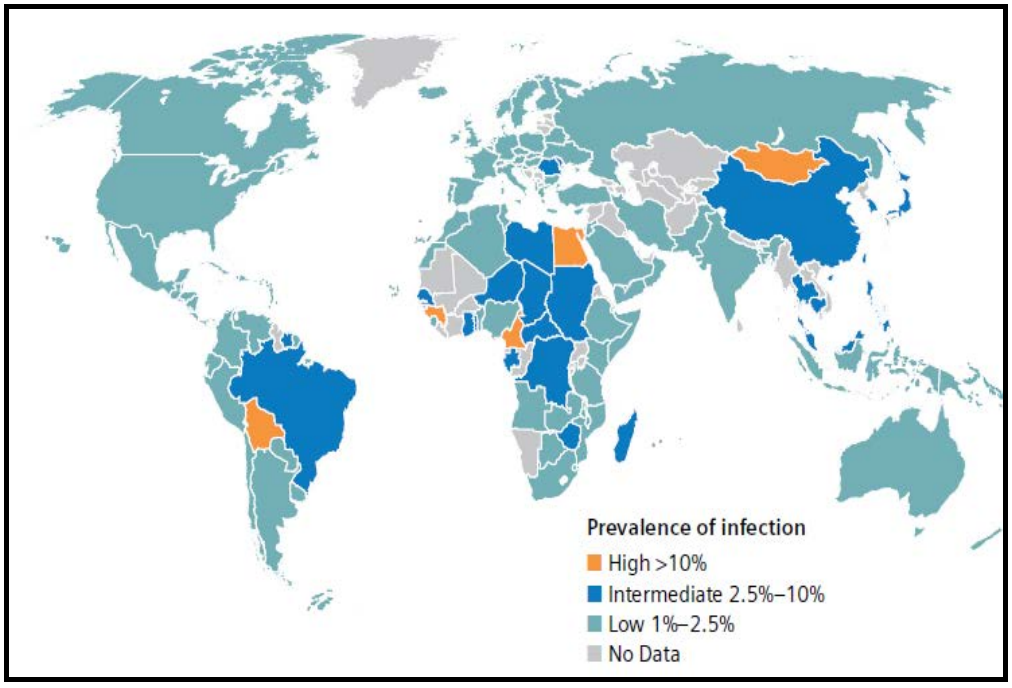

Figure (2): Showing HCV prevalence worldwide 2013.

As shown by these figure, some articles documented that Egypt has the highest HCV prevalence in the world with a 10–13% prevalence rate of HCV antibody positivity amongst the general population ***(Abdul Qawi et al., 2004)***. Moreover the published Egyptian Demographic Health Survey (EDHS), across sectional survey including hepatitis C virus (HCV) biomarkers, was conducted in 2009 on a large nationally representative sample. The number of Egyptians estimated to be chronically infected was 9.8% ***(El-Zanaty et al., 2009)***.

HCV antibody prevalence nationwide was 14.7% in the 15-59 years age group. HCV antibody prevalence gradually increased with age, reaching, in the 50-59 years age group, 46.3% and 30.8% in males and females, respectively. It was higher in males compared to females (17.4% versus 12.2%, respectively), and in rural compared to urban areas (18.3% versus 10.3%, respectively). In multivariate analysis, age, male sex, poverty, past history of intravenous anti-schistosomiasis treatment, blood transfusion, and living outside of the Frontier Governorates were all significantly associated with an increased risk of HCV infection. In addition, in rural areas, lack of education and being circumcised for females were associated with an increased risk of HCV infection ***(Guerra, 2012).***

HCV prevalence was very high across all special clinical population groups. The average HCV prevalence among non-Hodgkin's lymphoma (NHL) patients was roughly 41%, while among orthopedic patients it was about 39%. HCV prevalence among hepatocellular carcinoma (HCC) cases ranged between 61.0% and 90.3%, with a higher prevalence observed among rural versus urban populations ***(Ezzat et al., 2005).***

Moreover, HCV prevalence among pregnant women ranged between 5-15%, among blood donors between 5-25%, and among other general population groups between 0-40%. HCV prevalence among multi-transfused patients ranged between 10-55%, among dialysis patients between 50-90%, and among other high risk populations between 10% and 85% ***(Mohamoud et al., 2013)***

This unparalleled level of exposure to this infection appears to reflect a national level epidemic. It has been postulated that the epidemic has been caused by extensive iatrogenic transmission during the era of parenteral-antischistosomal-therapy (PAT) mass-treatment campaigns from 1960 to 1987 ***(Strickland, 2006).***

Today, HCV infection and its complications are among the leading public health challenges in Egypt ***(Mohamoud et al., 2013).*** 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. It is estimated that there are more than 500,000 new HCV infections per year ***(Milleret al., 2010)***.

Genotypes of HCV:

The identification of HCV genotypes and subtypes is not only of epidemiological interest, but it determines the type and duration of antiviral therapy, including the risk of selecting resistance associated variants during therapy ***(Nakan et al., 2011).***

There are seven major genotypes of HCV, the genotypes are divided into several subtypes with the number of subtypes depending on the genotype. In the United States, about 70% of cases are caused by genotype 1, 20% by genotype 2 and about 1% by each of the other genotypes. Genotype 1 is also the most common in South America and Europe ***(Rosen et al., 2011).***

Genotype 1 is the most prevalent genotype worldwide, with a higher proportion of subtype 1b in Europe and 1a in the USA. Genotype 3a is highly prevalent in the European population of people who inject drugs. This group is currently experiencing an increasing incidence and prevalence of infections with HCV genotype 4. Genotype 2 is found in clusters in the Mediterranean region, while 5 and 6 are rare in Europe ***(Smith et al., 2013).*** The novel genotype 7 was identified in patients from Canada and Belgium, possibly infected in Central Africa ***(Antaki et al., 2010).***

Risk Factors of HCV:

Up to the 1990's, the principal routes of HCV infection were blood transfusion, unsafe injection procedures, and intravenous drug use. Taken together, these routes are estimated to be responsible for approximately 70% of chronic cases in developed countries ***(Kamili et al., 2012).***

The following table adapted from recommendations published by the Centers for Disease Control, Atlanta, Georgia, outlines the list of persons who should be routinely tested for

HCV infection. For some of these categories (*e.g.*, injection drug users, persons with hemophilia), the HCV prevalence is high (90%); for others (*e.g.*, recipients of blood transfusions), the prevalence is moderate (10%). For still others (*e.g.*, persons exposed by needle stick, sexual partners of HCV-infected persons), it is quite low (2%-5%) ***(Doris et al., 2004).***

Table (1): Persons for Whom HCV Testing Is Recommended

- Persons who have injected illicit drugs in the recent and remote past, including those who injected only once and do not consider themselves to be drug users
- Persons with conditions associated with a high prevalence of HCV infection, including:
  - Persons with HIV infection
  - Persons with hemophilia who received clotting factor concentrates before 1987
  - Persons who were ever on hemodialysis
  - Persons with unexplained abnormal aminotransferase levels
- Prior recipients of transfusions or organ transplants, including:
  - Persons who were notified that they had received blood from a donor who later tested positive for HCV infection
  - Persons who received a transfusion of blood or blood products before July 1992
  - Persons who received an organ transplant before July 1992
- Children born to HCV-infected mothers
- Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood
- Current sexual partners of HCV-infected persons*

Currently, however, screening of blood products for HCV by means of enzyme immunoassays (EIA) and nucleic acid testing has virtually eradicated transfusion-associated hepatitis C. Similarly, in the developed world, new HCV infections are infrequently related to unsafe medical or surgical procedures. Spread among the community – facilitated by sharing paraphernalia, unstable housing, frequent cocaine use, and history of imprisonment – now accounts for the vast majority of incident cases in developed countries. High coverage of combined harm reduction programs (e.g. opiate substitution treatment and needle exchange programs) may reduce HCV incidence in the community, and some modeling studies suggest that implementation of HCV treatment may even reduce transmission within this population ***(Murphy et al., 2007).***

Other invasive behaviors, such as tattooing or acupuncture with unsafe materials, are also implicated in occasional HCV transmissions ***(Martin et al., 2011).*** They can transmit HCV-infected blood from one person to another if proper sterilization techniques are not followed ***(Vescio et al., 2008)***.

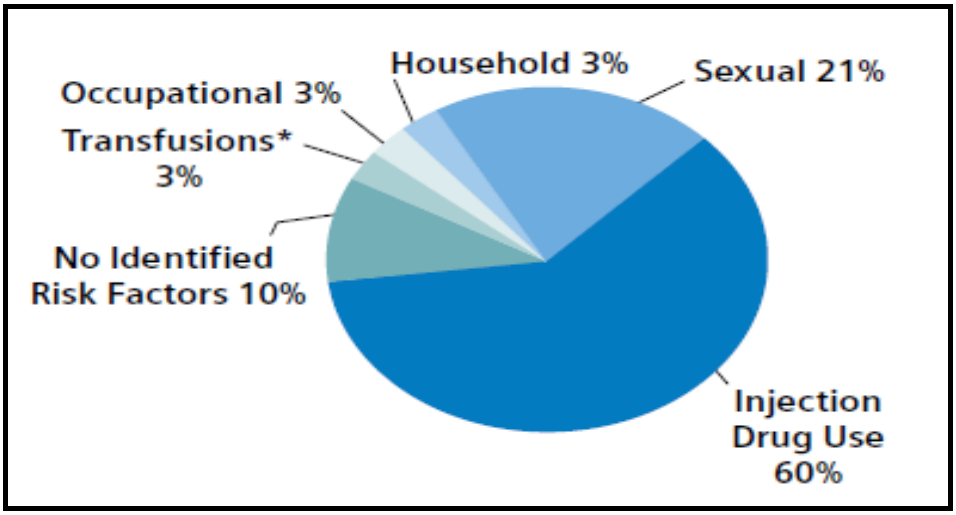

Figure (3): Risk factor of HCV transmission.

On the other hand, the situation is quite different in resource-poor countries, where lack of public awareness and continuous use of unsafe medical tools still account for a considerable proportion of new HCV infections ***(Kamili et al., 2012).***

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)***.

Patients on hemodialysis have a higher rate of acquiring 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)***.

The risk of perinatal and of heterosexual transmission of HCV is low, while male homosexual activity has become an important transmission route in Western countries ***(Martin et al., 2011).*** In a prospective study done in Italy included 895 monogamous heterosexual partners of HCV chronically