INTRODUCTION

Hepatitis C virus (HCV) infection is a worldwide problem. An estimated 170 million people are infected with hepatitis C worldwide leading to significant morbidity, mortality, and financial burden on healthcare. Out of 100 people who contract the infection, 75–85% will develop chronic infection, 60–70% will develop chronic liver disease, 5–20% will develop cirrhosis over the course of their chronic infection, and 1–5% will die of complications including hepatocellular carcinoma (HCC) ***(Lisa and William, 2013).***

The highest prevalence rate in the world is in Egypt; according to the most recent nation-wide survey of HCV in Egypt which was performed in 2008 on individuals aged 15-59, The prevalence of HCV antibodies (denoting past exposure) was 14.7%, while the prevalence of HCV Ribo - nucleic acid (RNA) (indicating current infection) was 9.8%, the prevalence is higher among men, in rural areas, and in older age groups ***(El-Zanaty et al., 2009).***

Chronic HCV infection has been estimated to be responsible for approximately 250.0000 to 350.000 deaths per year essentially related to decompensation of cirrhosis, end stage liver disease and HCC ***(Chevaliez and Pawlotsky, 2007).***

Much higher prevalence rates are reported in adult Egyptian with 12 % - 24 % anti – HCV seropositivity in the general population. The higher rate in adults is explained by the consistent increase of seropositivity with age ***(Zakeria et al., 2000).***

The peak of HCV prevalence in the 40-45 years age group corresponds to the aging of the cohort children infected through parenteral antischistomal therapy (PAT) in the 1960s - 70s. However, lower rates have been reported in children younger than 10 years (1.8% to 10%) ***(Abdelaziz et al., 2000 & Lehman and Wilson, 2008)*** reported that the prevalence of HCV in Egypt among adults is 15.7 % and in children is 4.0 %.

As regard HCV, unsafe therapeutic injections and blood transfusions are thought to be the major routes of transmission ***(Alter, 2006).*** However, recent studies in highly endemic areas have shown that a substantial proportion of HCV infections, particularly in children, cannot be accounted for by iatrogenic factors, strongly suggesting the involvement of other modes of transmission ***(Arafa et al., 2005).***

AIM OF THE WORK

The aim of this work was to study the risk factors of viral hepatitis (HCV) among Children attending the liver clinic, Alexandria University Children Hospital (AUCH).

Chapter (1)

HEPATITIS C VIRUS

Hepatitis C virus (HCV) infection is a worldwide problem. An estimated 170 million people are infected with hepatitis C worldwide leading to significant morbidity, mortality, and financial burden on healthcare. Out of 100 people who contract the infection, 75–85% will develop chronic infection, 60–70% will develop chronic liver disease, 5–20% will develop cirrhosis over the course of their chronic infection, and 1–5% will die of complications including hepatocellular carcinoma (HCC) ***(Lisa and William, 2013).***

Many countries worldwide face significant HCV infection rates. Despite aggressive programs toward education, care, and treatment over the last 10 years, Egypt faces the largest burden of HCV infection in the world with a 10% prevalence of chronic hepatitis C infection among persons aged 15–59 years, predominantly genotype 4 ***(Arafa, 2005).***

Egypt has the largest burden of HCV infection in the world, with a 10% prevalence of chronic HCV infection among persons aged 15–59 years ***(El-Zanaty et al., 2009).***

Chronic HCV infection has been estimated to be responsible for approximately 250, 000 to 350, 000 deaths per year, essentially related to decompensation of cirrhosis, end stage liver disease and hepatic cell carcinoma (HCC) ***(Chevaliez and Pawlotsky, 2007).***

Virology:

Hepatitis C virus and its genotypes:

The HCV is a small, single-stranded, enveloped RNA virus of the flaviviridae family ***(Thimme et al., 2001).***

Six HCV genotypes and a large number of subtypes (1a, 1b, 1c, etc.) Have been identified so far. The only natural host is man. All HCV genotypes have a common ancestor virus. However, HCV genotypes 1, 2, and 4 emerged and diversified in Central and Western Africa, genotype 5 in South Africa, and genotypes 3 and 6 in China, South-East Asia and the Indian subcontinent. In these areas, a large number of subtypes of these genotypes are found. The rest of the world, in particular industrialized areas, harbor a small number of HCV subtypes that could have been widely spread because they met an efficient route of transmission, such as blood transfusion or the intravenous use of drugs. They include genotypes 1a, 1b, 2a, 2b, 2c, 3a, 4a and 5a ***(Simmonds et al., 2005).*** Genotype 4 is found mainly in North Africa and especially Egypt, but has recently been spreading to Europe largely through intravenous drug users with a high incidence in Greece ***(Kamal and Nasser, 2008).***

<u>Epidemiology of Hepatitis c virus infection in Egypt.</u>

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 et al., 2009)..*** Accordingly, Egypt has the highest HCV prevalence in the world ***(Lavanchy, 2011).*** 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 ***(Shepard et al., 2005.).***

Today, HCV infection and its complications are among the leading public health challenges in Egypt ***(Strickland, 2006).***

Egypt has among the world’s highest prevalence rates of HCV (10-15% having HCV antibodies in rural areas) exposure ***(Evans et al., 2002).*** Numerous studies have confirmed that Egypt’s viral hepatitis epidemic, particularly with regards to HCV, originated in the 1960s and 1970s during a mass campaign of parenteral antischistomal therapy (PAT) using improperly sterilized glass syringes. Schistosomiasis, also known as bilharzias, is a parasitic infestation carried by snails living in the Nile that has plagued Egyptians for millennia. In 1918, it was discovered that “tartar emetic” (potassium antimony tartrate) could cure the infection, and between 1964 and 1982, over 2 million antimony injections were given per year to an average of 250, 000 patients. The treatment campaign peaked between 1966 and 1969, when over 3 million doses were given annually. The PAT campaign would have been particularly effective at transmitting blood-borne pathogens for several reasons. First, the tartar emetic was given in 10 to 12 intravenous doses spaced by one week, allowing for the onset of infectious viremia (2-4 weeks for HCV) in patients still undergoing treatment. Furthermore, the injections were administered to mixed age groups, matching higher-prevalence groups to lower-prevalence ones (particularly children). The absence of symptoms in the majority of acute HBV and HCV infections, and the masking side effects of PAT, meant that the burgeoning epidemic went unnoticed and, thus effective cycles of infection within the treatment units could have been established and sustained ***(Frank et al., 2000).***

Global epidemiology of virus C

Infection with hepatitis C virus (HCV) is a major global health care problem. The World Health Organization (WHO) estimates that up to 3% of the world's population has been infected with the virus ***(Thomson et al., 2005).***

In the Third National Health and Nutrition Examination Survey (NHANES III) from 1988 to 1994, an estimated HCV prevalence of 3.9 million people was found in the United States (US) with 2.7 million people found to have chronic infection with HCV (positive HCV RNA).Neither sex nor racial - ethnic group was found to be independently correlated with HCV infection.In Europe, general prevalence of HCV is about 1% but varies among the different countries. Prevalence of HCV antibody (Ab) is 0.87% (1993-1994) in Belgium. In the United Kingdom, at least 200, 000 adults carry HCV. In Northern Italy, prevalence of HCV Ab was 3.2%. Three studies in Central and Southern Italy showed a higher rate of HCV (8.4%-22.4%), especially in the older population ***(Theodor and Jamal, 2006).***

In 2005, the Global Burden of Hepatitis C Working Group, a consultant to the World Health Organization (WHO), estimated the global prevalence of HCV to be 2-3%, or 170 million individuals. The lowest HCV prevalence, between 0.01% and 0.1%, is in the United Kingdom and Scandinavia, while the highest prevalence, between 15% and 20%, is in Egypt (**Fig. 1)**.

Alter et al. (2007), hepatitis C is estimated to be the cause of 27% of cirrhosis and 25% of hepatocellular carcinoma (HCC) cases worldwide ***(Perz et al., 2006).***

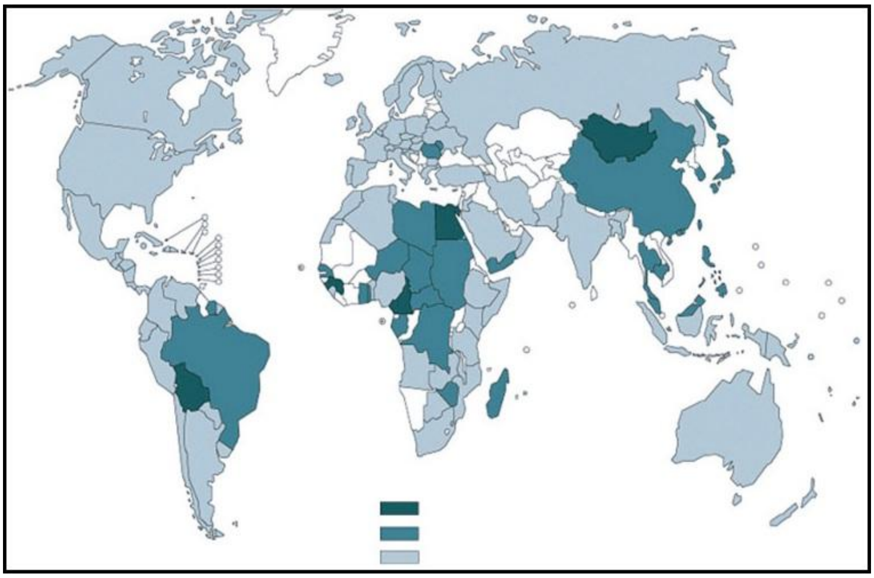

Fig. (1): Geographic distribution of hepatitis C infection worldwide, 2007**.**

(Data from International Travel and Health [Internet]. Geneva: World Health Organization; 2007

<u>Prevalence of hepatitis C virus</u>.

There are geographical differences in the prevalence, which range from 0.6-22%. Egypt has the highest prevalence of hepatitis C virus (HCV) in the world, ranging from 6% to 28% with an average of approximately 15% in the general population ***(El-Zanaty et al., 2009).***

The infection rate ranges from as low as 0.1% in Canada to the extremely high rate of 18.1% in Egypt ***(Global, 2002).*** Indeed, HCV infection is now the leading reason for liver transplantation worldwide. Few studies have evaluated the epidemiology and risk factors of HCV infection in children in Egypt. In community-based studies the prevalence of HCV antibodies in Egyptian children was 3% and 9% in the Upper and Lower Egypt areas respectively ***(Medhat et al., 2002).***

Iatrogenic transmission occurred in Egypt where large sectors of the older population between 7-15 million people have become HCV infected during parenteral anti-schistosomiasis treatment (PAT) campaigns in the past when the capacity to sterilize needles and syringes was insufficient ***(Frank et al., 2000).***

PAT (potassium antimony tartarate) was extensively practiced in Egypt from the 1920s to the 1980s and was gradually replaced by oral treatment from the 1970s onward. In 2008 the Egypt Demographic and Health Survey (EDHS) was conducted in a nationally representative sample of 19, 500 individuals aged 15-59 years in all governorates of Egypt and the prevalence of HCV Ab (denoting past infection) was 14.7%, while the prevalence of HCV RNA (indicating current infection) was 9.8%, the prevalence is higher among men, in rural areas, and in older age groups ***(El-Zanaty et al., 2009).***

Geographical distribution in Egypt:

Individuals living in Lower Egypt experienced a greater burden of schistosomiasis and therefore a greater level of exposure to PAT ***(El-Zayadi et al., 2005).***

Age distribution:

Much higher prevalence rates are reported in adult Egyptians with 12%-24% anti-HCV seropositivity in the general population. The higher rate in adults is explained by the consistent increase of seropositivity with age ***(Zakaria et al., 2000).***

The peak of HCV prevalence in the 40-54 year age group corresponds to the aging of the cohort of children infected through PAT in the 1960s- 70s. However, lower rates have been reported in children younger than 10 years (1.8% to 10%) ***(Nafeh et al., 2000 and Abdel Aziz et al., 2000).***

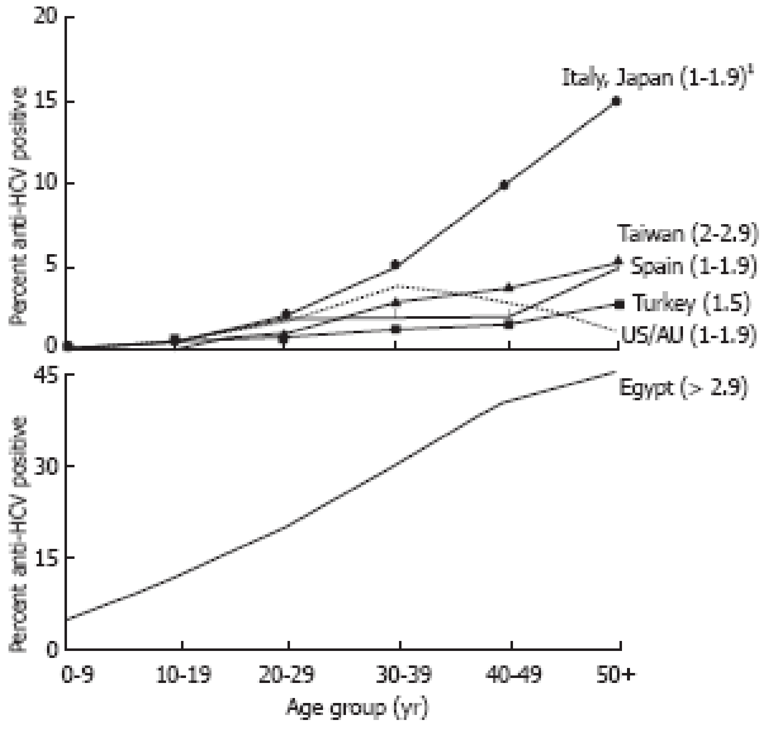

Fig. (2): Age-Specific prevalence of antibody to hepatitis C virus by selected countries.

Numbers in parentheses indicate average regional prevalence in which country resides; look fig. 2 ***(Alter, 2007).***

Lehman and Wilson (2008) reported that the prevalence of HCV in Egypt among adults is 15.7% and children are 4.0%.

Gender distribution:

In the Nile delta, prevalence rates in the above 20 years age group were higher in males (45.8%) as compared to females (37.6%) ***(Abdel Aziz et al., 2000).***

Similarly in Upper Egypt, males over 30 years of age had higher (28.4%) rates of infection as compared to females (13.6%) ***(Arafa et al., 2005).***

Chapter (2)

RISK FACTORS OF HEPATITIS C VIRUS INFECTION IN CHILDREN

Egypt has the highest prevalence of hepatitis C virus (HCV) infection of any country in the world. It is estimated to be 8% in urban and 25% in rural areas, with 8 million to 10 million inhabitants having HCV antibodies (anti-HCV) and 5 million to 7 million having active infections (i.e. HCV-RNA positive) ***(Plancoulaine et al., 2008).***

This high HCV prevalence has been linked to the intravenous tartar emetic injections given with reusable glass syringes during mass treatment campaigns to control schistosomiasis from the 1960s until 1982 ***(Frank et al., 2000).***

The prevalence of HCV infection in children younger than 10 years in rural villages ranged from 2 to 7% ***(Medhat et al., 2002),*** while incidence was 5.9/1000 person-years (PY). ***(Mohamed et al, 2005).*** Children living with HCV-infected mothers and other family members were at highest risk of infection ***(Mohamed et al. 2006).*** also recently reported prevalence and incidence of HCV infection in a large cohort of women living in three villages in the Nile Delta, as well as perinatal HCV infection rates of infants born to these women. Herein, the incidence of, and risk factors for, community-acquired HCV antibodies and RNA in children born to this cohort of women ***(Shebl et al., 2009).***

A 2 percent seroprevalence rate was found in an incarcerated juvenile population in Washington, DC As a general rule, the risk of HCV infection in children who were exposed to blood products before routine screening is related to the number of units of blood or blood products received. Most of these at-risk children are now young adults, as routine testing of the blood supply has virtually eliminated transmission via this route in developed countries ***(Murray, 2003).***

Transfusion-associated HCV infection was a worldwide risk before HCV testing became available. It has been virtually eliminated in those countries that implemented routine HCV testing of donors ***(Busch et al. 2005)*** but in others, receipt of blood transfusions remains an important source for infection. Some countries continue to use commercial donors to supplement their blood supplies, have not considered blood safety a priority, and lack the resources to implement donor screening ***(Hladik et al., 2006).***

Risk factors associated with acquiring infection as determined from cohort (prospective) and case control (retrospective) studies of persons with acute disease (or infection) have included transfusion of blood and blood products and transplantation of solid organs from infected donors, injecting drug use, unsafe therapeutic injections, occupational exposure to blood (primarily contaminated needle sticks), birth to an infected mother ***(Alter, 2002).*** Among these, transfusion from unscreened donors, injecting drug use, and unsafe therapeutic injections have been the most important, however, there are temporal and geographical differences in the extent to which these risk factors have contributed to HCV transmission (Table 1) ***(Alter, 2007).***

Table (1): Importance of different exposures to HCV transmission patterns in low, moderate and high prevalence areas worldwide:

The extent exposure contributes to HCV transmission by level of HCV prevalence.			
Exposure	**Low**	**Moderate**	**High**
Injecting drug use	+ + + +	+ +	+
Transfusions (unscreened)	+ + +	+ + +	+ + +
Unsafe therapeutic njections	+	+ + + +	+ + + +
Occupational	+	+	+
Perinatal	+	+	+
High-risk sex	++	+	+/-

(Alter, 2007).

A – <u>Nosocomial transmission of HCV infection:</u>

1- <u>Blood transfusion:</u>

Regular blood transfusions improve the overall survival of multitransfused children but despite the progress made in preventing transfusion-transmitted infections (TTIs) over the last few years, TTIs continue to be a problem in many parts of the world ***(Lopez et al., 2005).*** Blood transfusion is the main risk factor