AIM OF THE WORK

The aim of this multicenter study is to retrospectively investigate the HCV seroconversion and prevalence of hepatitis C virus (HCV) infection among all hemodialysis patients in Aswan governorate and delineate events and factors associated with HCV seroconversion.

Chapter (1)

HCV OVERVIEW

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease **(*Williams, 2006*).**

Hepatitis C is a disease with a significant global impact, according to the World Health Organization there are 170 million people infected with the hepatitis C virus (HCV), corresponding to 3% of the world's total population, there are considerable regional differences. In some countries, eg, Egypt, the prevalence is as high as 20%. In Africa and the Western Pacific the prevalence is significantly higher than in North America and Europe ***(Anonymous, 2004).***

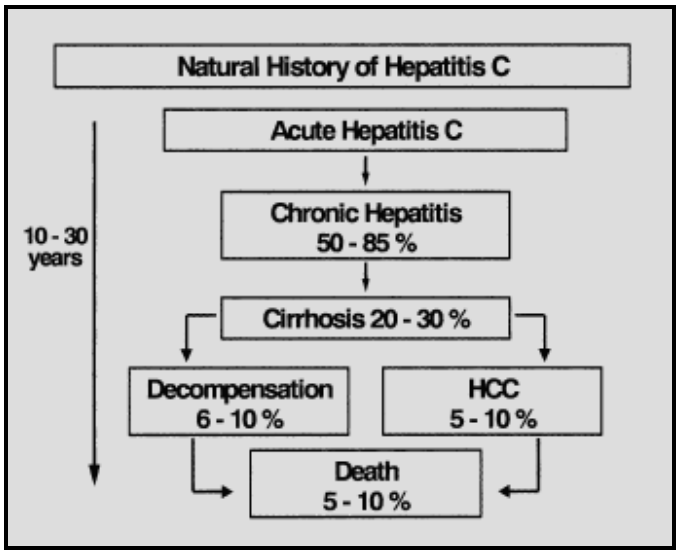

Fig. (1): General view on the natural history of HCV ***(Alberti and Benvegnu, 2003).***

Epidemiology:

It is difficult to determine the number of new HCV infections, as most acute cases will not be noticed clinically. Fewer than 25% of acute cases of hepatitis C are clinically apparent. In addition, the age of infection upon diagnosis is not possible to determine in most cases. Nevertheless, it has to be assumed that the number of new infections has considerably decreased over the past decades ***(Wasmuth, 2009).***

For the United States it is estimated that the number of new cases of acute HCV infection has fallen from approximately 230,000 per year in the 1980s to about 20,000 cases per year currently. This decrease is primarily associated with reduced infections in injection drug users, a probable consequence of changes in injection practices motivated by education about human immunodeficiency virus (HIV) transmission ***(Wasmuth, 2009).***

Hepatitis C in Egypt:

Genotype 4 represents over 90% of cases in Egypt. Chronic HCV is the main cause of liver cirrhosis and liver cancer in Egypt and, indeed, one of the top five leading causes of death. In Egypt, the major route of exposure appears to be due to injection therapy and inadequate infection control practices. In addition to blood transfusions prior to 1994, the major risk factor

associated with HCV infection is a history of antischistosomal injection treatment before 1986. Prior to 1986 the mainstay of treatment was intravenous tartar emetic. Widespread treatment campaigns were carried out in the countryside of Egypt in the 60's- 70's and early 80's. At the time of availability of only glass syringes, needles were routinely inadequately sterilized by boiling due to time restraints and limited resources ***(Mezban and Wakil, 2006).***

Overall, despite improvement in schistosomiasis-related morbidity between 1980- 1990, these treatment campaigns set the stage for the current large hepatitis disease burden in Egypt. Further, with such a high background prevalence rate, transmission of hepatitis C through other non medical routes has become more significant. For example, tattooing, circumcision or other medical procedures performed by non-medical personnel are more frequent routes of infection in Egypt than elsewhere. In addition, household transmission, vertical transmission and sexual transmission are routes that are also under investigation ***(Mezban and Wakil, 2006).***

In Egypt, the prevalence of HCV infection in HD patients was variable ranging from 52% to 82% from the year 1996 to 2004, It reached 52% at the year (2008) ***(Egyptian renal registry, 2008 report).***

Table (1): Annual reports of Egyptian renal registry from 1996 to 2008 ***(Afifi and Abdel-Mohsen, 2009).***

Year	HCV Ab prevalence in HD patient in Egypt
1996	52.3%
1997	60.2%
1998	55.5%
2000	62.0%
2003	64.3%
2004	82.3%
2008	52.1%

In a recent study, Egyptian children with infected parents are at high risk of infection with hepatitis C (HCV). Analysis of data collected during surveys of rural communities show children whose parents had antibodies to HCV (anti-HCV) were at higher risk for having anti-HCV than children whose parents did not. The association was greater with mothers than fathers and when the parent had HCV RNA ***(Mohamed et al., 2006).***

Transmission:

Risk factors associated with HCV infection include injection drug use (or intranasal if using a blood contaminated device), receipt of blood products, long term haemodialysis, organ transplantation, receipt of tattoo from an unsanitary facility, vertical transmission during pregnancy and sexual or

nosocomial exposure. Nosocomial transmission has been documented, such as from patient to patient by a colonoscope, during dialysis, and during surgery. Needle stick injuries in the health care setting continue to result in nosocomial transmission of the viru (***Sultan et al., 2009).***

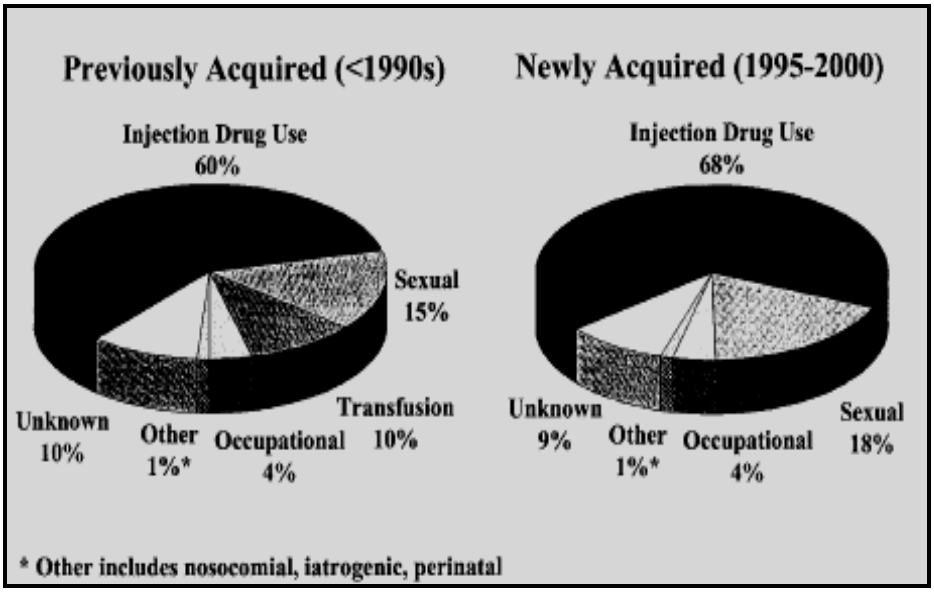

Fig. (2): Sources of infection for hepatitis C ***(Alter, 2002).***

Viral heterogeneity:

The polymerase enzyme of RNA viruses such as HCV, lacks proof-reading ability and is therefore unable to correct copying errors made during viral replication. Many of these nucleotide changes result in a nonfunctional genome or a replication incompetent virus (lethal mutants). However, others persist and account for the tremendous viral diversity that is characteristic of HCV ***(Chopra, 2009).***

This heterogeneity is extremely important in the diagnosis of infection, pathogenesis of disease, and the response to treatment; it prevents the development of conventional vaccines, allows the virus to escape eradication by the host's immune system, and affects the completeness of the response to antiviral therapies such as interferon. Viral heterogeneity takes several forms depending upon the degree of diversity. *QuasI-species* are families of different, but highly similar, strains that develop within an infected host over time. Nucleotide sequence homology is greater than 95 percent ***(Chopra, 2009).***

Genotypes:

Six major genotypes of HCV have been defined. More than 50 subtypes have also been described; the most common subtypes are 1a, 1b, 2a, and 2b. The evolution of genotypes has probably been influenced by several factors, including immune selection, infection patterns, replication efficiency, and population migration. so, there is a distinct geographic distribution of HCV genotypes:

- Genotype 1&2 is most common in the UnitedStates and Europe.
- Genotype 3 is most common in India, the Far East, and Australia.
- Genotype 4 is most common in Africa and the Middle East.
- Genotype 5 is most common in South Africa.

- Genotype 6 is most common in Hong Kong, Vietnam and Australia.

(Chopra, 2009).

The clinical significance of viral genotypes is not entirely clear, but they have a significant effect upon the response to interferon-based therapy. The sustained virologic response to pegylated interferon plus ribavirin ranges from about 40 to 50 percent with genotype 1 (including 1a and 1b) to as high as 70 to 80 percent with genotypes 2 and 3 ***(Chopra, 2009).***

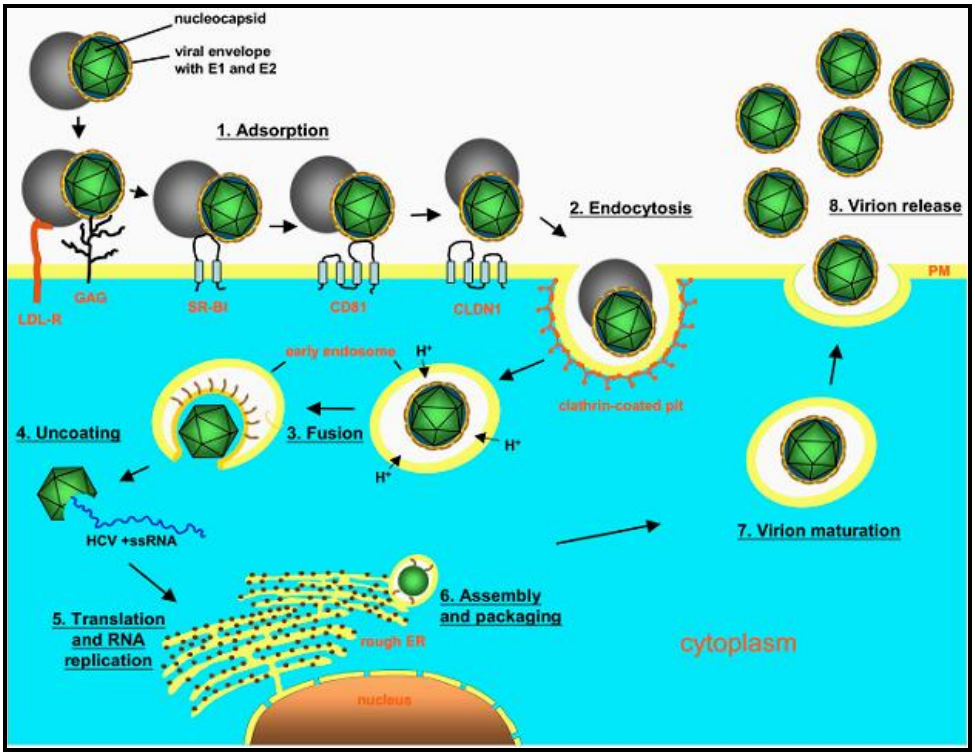

Fig. (3): Current model of the HCV lifecycle ***(Kupfer, 2009).***

Factors exist that affect the course of hepatitis C:

1. *Host related factors:*

Modeling of the natural history of hepatitis C indicates that fibrosis progression is not linear over time, being slower in the younger ages of life and accelerating significantly after the age of 45-50 years, independently of other cofactors and variables. Male gender and race have also been shown to affect disease progression in hepatitis C. Some studies have suggested that genetic factors might also play a role based on HLA class II antigen expression but this is quite controversial and has not been confirmed in all reports ***(Alberti and Benvegnu, 2003).***

2. *Metabolic abnormalities and disease progression:*

Recently, there have been a number of reports indicating that several metabolic abnormalities and comorbidities may cause significant worsening of the clinical course of chronic hepatitis C contributing to higher rates of cirrhosis development. These conditions include increased hepatic iron stores, liver steatosis, increased body mass index and type II diabetes ***(Alberti and Benvegnu, 2003).***

3. *Environmental and external factors:*

Co-infection with HBV or HIV has been shown to accelerate the course of chronic hepatitis C and facilitate

progression to cirrhosis and hepatocellular carcinoma **(*Alberti and Benvegnu, 2003).***

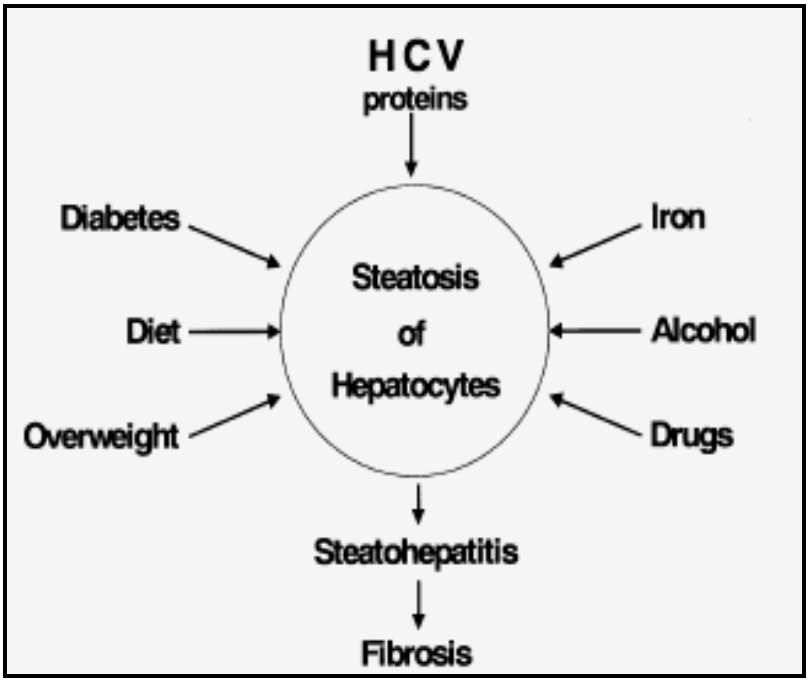

Fig. (4): Multifactorial mechanisms leading to hepatitis steatosis in HCV **(*Alberti and Benvegnu, 2003).***

Clinical manifestations of HCV infection:

1-Acute Hepatitis C Virus Infection:

Acute hepatitis C is typically asymptomatic and unrecognized. When identified, cases present with an elevation of the levels of serum aminotransferases anywhere from 2 to 26 weeks after exposure. The mean incubation period is intermediate between that for Hepatitis A and Hepatitis B, with a peak onset of 7 to 8 weeks after infection. Serum ALT levels are usually high, with

about three fourts of patients having elevations more than 15 times the upper limit of normal**.** HCV RNA is present in the blood within days of exposure and usually remains detectable throughout the infection ***(Eugene et al., 2008).***

The most common symptoms are flu like and include anorexia, weight loss, abdominal pain, myalgia, arthralgia, and fatigue. Less common symptoms include fever and rash. Jaundice occurs in less than one third of all patients and is most common in symptomatic patients. The symptoms associated with acute hepatitis usually resolve within 1 to 3 months **(*Eugene et al., 2008).***

2-Chronic Hepatitis C:

About 85% of those infected with HCV will not clear the virus and will develop chronic hepatitis of varying severity **(*Marcellin, 1999).***

Many patients with chronic hepatitis C have no symptoms of liver disease, if symptoms are present they are usually mild non specific and intermittent. Symptoms may include fatigue, mild right upper quadrant abdominal discomfort or tenderness, nausea, poor appetite, muscle and joint pains. Similarly, the physical examination is likely to be normal or show only mild enlargement or tenderness of the liver. Some patients have a vascular spiders or palmer erythema ***(Abdeen et al., 2004).***

3-Liver Cirrhosis:

Cirrhosis is the final irreversible stage of chronic hepatitis and/or cell injury. It is a diffuse process of fibrosis and nodule formation following hepatocellular necrosis ***(Sherlock and Dooley, 2002).***

Once a patient develops cirrhosis, symptoms and signs are more prominent. In addition to fatigue, the patient may complain of muscle weakness, poor appetite, nausea, weight loss, itching, dark urine, fluid retention and abdominal swelling. Physical examination of cirrhosis may include enlarged liver, splenomegaly, jaundice, muscle wasting, ascites and lower limb edema **(*Abdeen et al., 2004).***

It may be discovered by liver biopsy in the asymptomatic patient or present as variceal hemorrhage or jaundice. Evidence of portal hypertension is rare; splenomegaly is present in only one half of the patients at presentation. Bleeding from oesophageal varices is unusual until later on. Thrombocytopenia develops as the spleen size increases and this is a good indication that cirrhosis has developed ***(Sherlock and Dooley, 2002).***

4-Hepatocellular Carcinoma (HCC):

This is generally associated with cirrhosis. It can be found in the compensated case and can be clinically silent for long periods. Screening for HCC is done by 6-monthly serum

α-fetoprotein levels and ultrasound of the liver. These should be performed in all cirrhotic patients, particularly if male and more than 40 years old ***(Sherlock and Dooley, 2002).***

The risk factors for developing HCC in patients with chronic hepatitis C include male gender, older age, hepatic fibrosis and cirrhosis, and hepatitis disease activity as indicated by elevations in serum aminotranseferase levels and inflammation and necrosis on liver biopsy. Other potentially modifiable risk factors include co-infection with hepatitis B virus (HBV), chronic alcohol use, smoking, iron overload, diabetes and/or obesity ***(Fattovich et al., 2004).***

Extrahepatic manifestations of HCV:

Hepatitis C virus (HCV) is at the same time a hepatotropic and a lymphotropic virus and may cause hepatic and extrahepatic diseases. Extrahepatic manifestations linked to HCV range from epidemiologic data and biological plausibility, to anecdotal observations without clear proof of causality. B cell lympho-proliferative disorders (ie, mixed cryoglobulinemia and non-Hodgkin's lymphoma) are the extrahepatic conditions most closely linked to HCV, having been investigated extensively, and represent a model for both pathogenetic and clinico–therapeutic deductions. An association between HCV infection and other morbid conditions, including dermatologic, nephrological, neurologic,

endocrinologic, cardiocirculatory, and lung disorders also has been suggested ***(Zignego and Craxı, 2008).***

Overlap syndromes characterized by the presence in one patient of manifestations belonging to various pathologic conditions typically of autoimmune/lymphoproliferative natured would suggest that chronic HCV infection is a distinct systemic disease with a varying spectrum of clinical manifestations ***(Zignego and Craxı, 2008)***.

A tentative classification of EHMs-HCV Is suggested:

Group A includes EHMs-HCV characterized by a strong association proven by both epidemiologic and pathogenetic evidence. This category includes B-cell lymphoproliferative disorders (LPDs). **Group B** includes disorders for which a significant association with HCV infection is supported by substantial epidemiologic data and **groups C and D** associations still require confirmation and/or a more detailed characterization as opposed to observations that are of similar pathologic nature but of different etiology, or idiopathic in nature ***(Zignego and Craxı, 2008)***.

Table (2): HCV-related extrahepatic manifestations

ORGAN /SYSTEM	*MANIFESTATION*
Endocrine disorder	Autoimmune thyroidopathies (in particular, Hashimoto thyreoiditis)
	Insulin resistance/diabetes mellitus*
	GH-insufficiency
Rheumatic disorders	Mixed cryoglobilinaemia*
	Cryoglobulinaemic vasculitis*
	Peripheral neuropathy*
	Membrano-proliferative glomerulonephritis(GN)*
	Membranous GN*
	Rheumatoid arthralgias/oligo-polyarthritis
	Rheumatoid factor positivity*
	Sicca syndrome
Haematologic disorders	Lymphoproliferative disorders/Non-Hodgkin Lymphomas*
	Immune thrombocytopaenic purpura (ITP)
	Monoclonal gammopathies*
	Autoimmune haemolytic anaemia
Dermatologic disorders	Palpable purpura
	Porphyria cutanea tarda (PCT)
	Lichen planus
	Pruritus
Miscellaneous	Chronic fatigue*, subclinical cognitive impairment psychomotoric deceleration, symptoms of depression*,
	Myopathy
	Cardiomyopathy/Myocarditis
	Idiopatic pulmonal fibrosis

**** Associations that rest upon strong epidemiological prevalence and/or clear pathogenetic mechanisms (Cacoub et al., 2000)***