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Minireview Article

Epidemiology of hepatitis C virus infection in Egypt; overt and occult

Abstract

Hepatitis C virus is an epidemic in Egypt whichcontains the highest prevalence in the world; 14.7%.Explanations for this unique epidemic may be dated back to iatrogenic role of parenteral antischistosomal therapy campaigns to control endemic schistosomiasis. Other routes of infection are contributing to the ongoing HCV transmission. The prevalent genotype in Egypt is type 4 (73%), the origin, evolution, and dynamics of which are difficult to determine. Risk factors for acquiring HCV infection include: history of antischistosomalinjection treatment before 1986, old age, male gender, and residence in rural areas. Other risk factors include; injection therapy, blood transfusion prior to 1994, exposure to various facility-based medical procedures, and occupational transmission among health care workers. In community settings, a set of risk factors, mostly related to prevailing social and cultural conditions, are responsible for maintaining the high rates of HCV transmission. Sexual transmission is a matter of controversy. 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. It kills an estimated 40,000 Egyptians a year.

When talking about children, current HCV seroprevalenceis high, approximately 5-8%. It is to be emphasized that HCV infection is not always benign in the childhood period in Egypt. It has been shown that blood transfusion, surgical procedures, dental treatment, male circumcision and age above 10 years are important risk factors associated with anti-HCV antibody prevalence. In addition, vertical transmissions, and household transmissionare routes that are under investigation. Finally, approximately 70% of acquired infections in children are due to unidentified risk factors.

Occult hepatitis C virus (HCV) infection is defined aselevated liver function tests and negative HCV antibodies in serum, while HCV RNA is detectable in liver tissue and peripheral polymorphnuclear cells (PBMCs). Interest in occult HCV has been emerged recently in Egypt. Studies at a national level are being carried out, but no results have yet been released. Many small scale studies have been performed among particular patient groups, which have highlighted the importance of this disease entity.

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Introduction

HCV currently infects nearly 2% of the world's population [1]. In Egypt the situation is very critical, Fig. 1. Hepatitis C virus is an epidemic in Egypt which contains the highest prevalence in the world. Nowhere else is there an HCV epidemic that effects a whole country. In all other countries, HCV is between 1% to 2%. There are a few exceptions where HCV is 3%. In Egypt however, HCV is 14.7%. Just about every family in Egypt is touched by hepatitis C, Fig. 1. The blood borne virus, which is highly infectious, infects at least 1 in 10 of the population aged 15 to 59 [3].

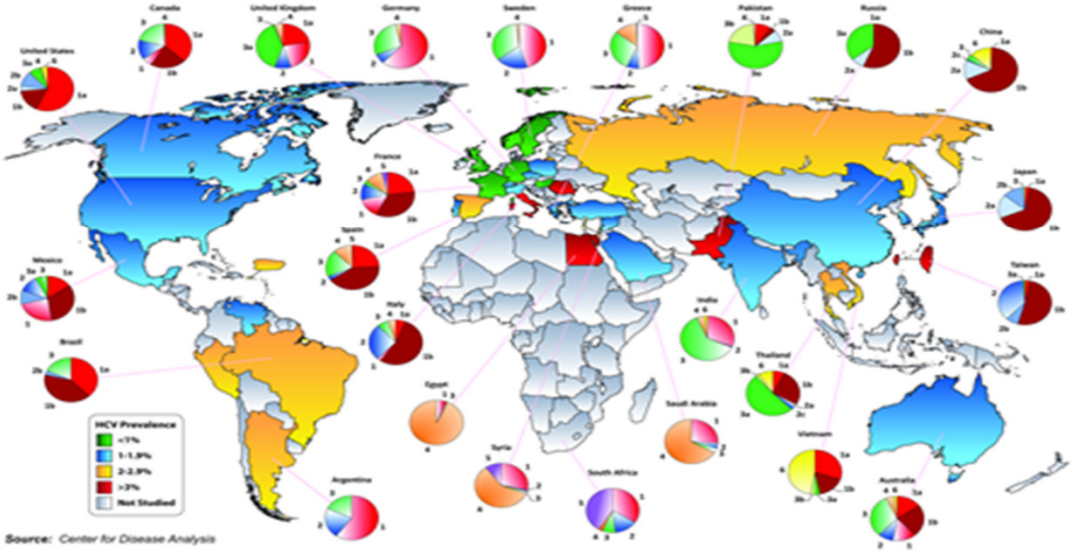

Fig. 1.HCV global prevalence among adults and genotype distribution [2].

1. Magnitude of the problem

In 1992, when HCV antibody testing became widely available, the prevalence of HCV in Egypt was reported to be 10.8% among first-time blood donors[4]. Since then, many prevalence estimates of HCV have been reported[5,6],including the Egyptian Demographic Health Survey (EDHS) [7]. The latter is a national probability sample of the resident Egyptian population, which concluded that, in general, anti-HCV antibody prevalence was 14.7%.

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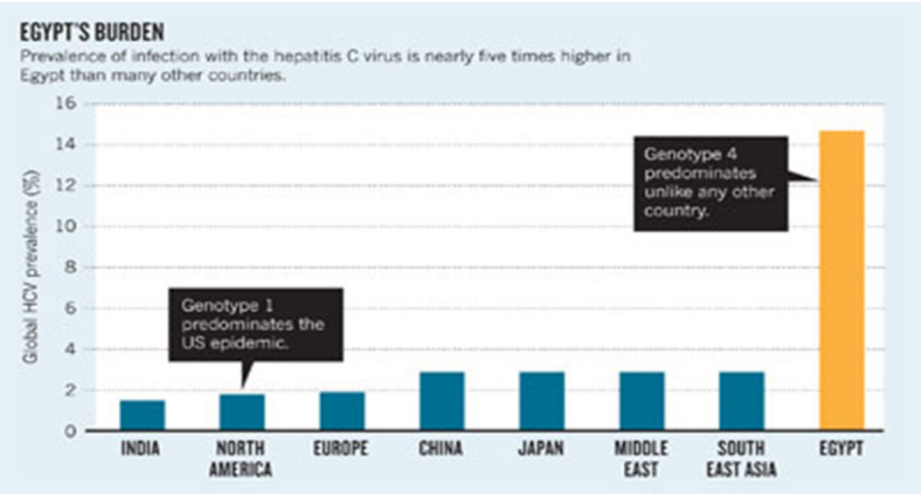

Fig. 2.Egypt — and the Middle East more generally — is a stronghold for genotype 4. By contrast, about 75% of HCV infections in Europe and the United States are of genotype 1[8].

Fifteen percent of the EDHS respondents aged 15-59 had antibodies to the HCV virus in their blood, indicating that they had been exposed to the virus at some point, and 10% were actively infected. Men were more likely to be infected than women; however,among both women and men, there was direct proportion between infection and age. Twelve percent of rural residents were infected versus, 7% of the urban ones. The prevalence was highest in rural Lower and rural Upper Egypt (19.5% and 28.4% respectively),while it was lowest in the Frontier Governorates and the Urban Governorates (5.9%, and 8.2% respectively) Fig. 3.

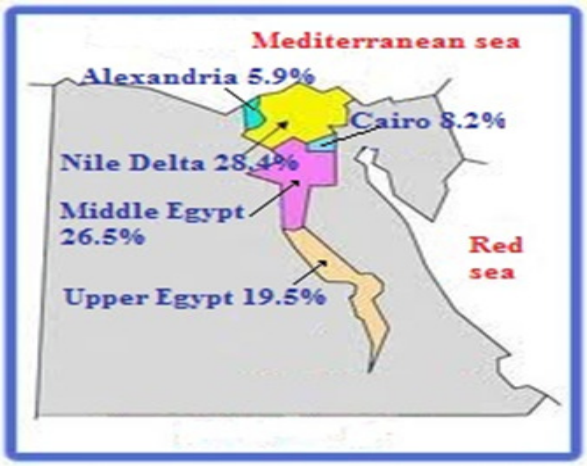

Fig. 3.HCV spread ratios across Egypt [9].

The level of education as well as the wealth quintile had an impact on HCV prevalence, Fig. 4. Individuals with no or less than primary education (17 and 13

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percent, respectively) were markedly more likely to be infected with the HCV virus than the more educated population (7-8 percent). Meanwhile, the likelihood of HCV infection also decreased with the wealth quintile from 12 percent among respondents in the lowest wealth quintile to 7 percent among respondents in the highest wealth quintile.

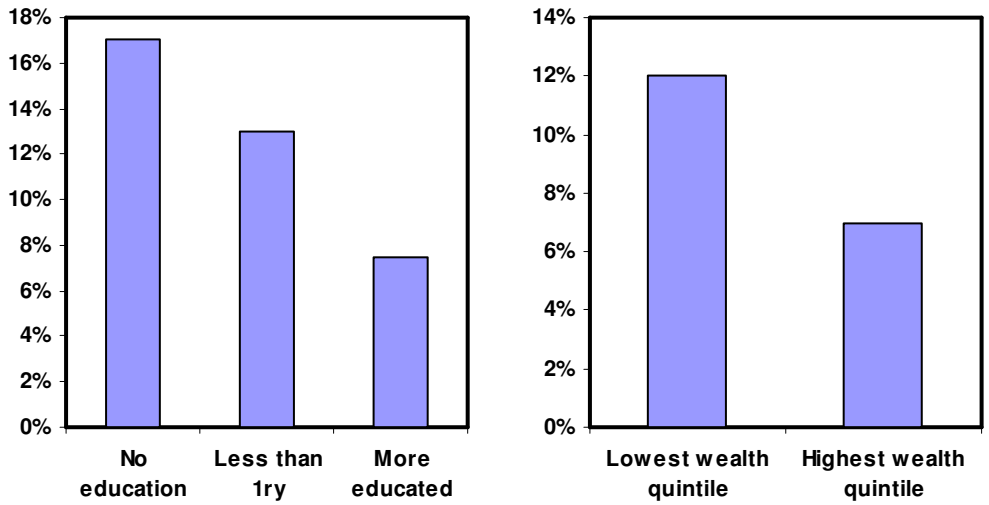

Fig. 4.The impact of level of education and the wealth quintile on HCV prevalence.

Explanations for this unique epidemic in Egypt have been anongoing subject of controversy. The iatrogenic role of parenteralantischistosomal therapy campaigns to control endemic schistosomiasis, which ceased some decades ago, is a widely held hypothesis [10]**.**

2. HCV genotypes

There are seven major genotypes of HCV, which are indicated numerically from one to seven, [11]**.**The prevalent genotype in Egypt is type 4 (73%) [12]followed by genotype 1 (26%), whereas mixed HCV genotypes infection was found in 15.7% in cases in Egypt[7].

Genotype 4 is also the most common genotype in Central and West Africa and the Middle East. Currently, HCV 4 infection is spreading beyond its strongholds in Africa and the Middle East. It has recently spread in several Western countries, particularly in EuropeFig. 4,due to variations in population structure, immigration, and routes of transmission [13]**.**

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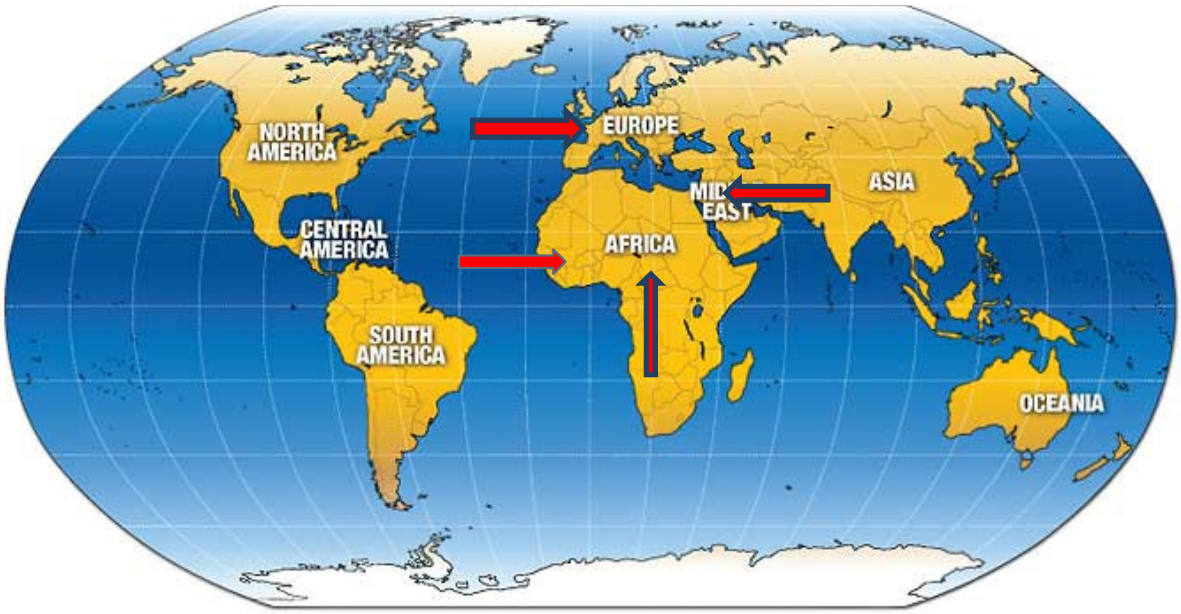

Fig. 5.Global origin and spread of HCV 4 infection [1].

The origin, evolution, and dynamics of HCV 4 are difficult to determine given the limited population-based epidemiological studies and phylogenetic analysis of thisgenotype in the geographic regions in which it is endemic. The information available from small-scale field surveys from Central African countries (Zaire, Gabon, Central African Republic, and Tanzania) and Cameroon in addition to sequence analysis studies indicate that HCV 4 strains circulating in Central Africa and Cameroon are extremely heterogeneous, and suggesting that it probably has been endemic for a long time[14- 23]. An exponential spread of genotype between 1920 and 1960 was detected in Cameroon, which coincided with the mass campaign against trypanosomiasis and mass vaccinations[18, 23]**.** The great genetic diversity in sub-Saharan Africa might lead to the hypothesis that HCV 4 originated and propagated in Central and WestAfrica before spreading to other regions[16, 20]**.**However, it is not clear how HCV infection was maintained for long periods among these populations prior to the known parenteral routes of transmission such as blood transfusion and injection. It is likely that other routes of transmission such as scarification, circumcision practices, or sexual transmission might have contributed to persistence and propagation of HCV transmission in tropical and subtropical settings [13]**.**

In Egypt several combined population genetic and epidemiological analyses were conducted to determine the origin and the historical changes in Egyptian HCV prevalence [10, 15, 19, 20, 24, 25]**.**Despite the high prevalence of HCV in Egypt, studies have suggested that the epidemic pattern of type 4a infection in Egypt was more recent and quite different from the endemic pattern in sub-Saharan Africa,

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[15, 21].HCV's lack of genetic diversity in Egypt compared with the sub-Saharan African strains and the predominance of HCV 4a suggest a relatively common source for the epidemic rather than long endemicity and propagation. Molecular evolutionary analysis on Egyptian genotype 4a isolates indicates that the Egyptian HCVepidemic was initiated and propagated by extensive antischistosomiasis mass treatment campaigns [10, 15, 19, 21, 24, 25].The spread of HCV 4a increased exponentially in rural areas during the 1930s through the early 1980s, coinciding with the mass campaigns, with the most rapid exponential growth between 1930 and1955 [19, 21].Although the anti-schistosomal campaigns were terminated in the early 1980s, the prevalence and incidence of HCV remains high in Egypt. Thus, it seems that thecurrent status of HCV in Egypt is not only a consequence of the mass anti-schistosomal therapy but also due to new infections acquired beyond that era, given that HCV currently represents more than 30% of the annually reportedacute hepatitis cases [27].

3. Risk factors and transmission

3.1. History of antischistosomal injection treatment before 1986.

Schistosomiasis was a common parasitic disease in Egypt acquired through swimming or wading in contaminated irrigation channels or standing water. Schistosomiasis can lead to urinary tract or liver damage over many years. 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. Egypt's hepatitis C epidemic dates back decades when glass syringes used during a mass vaccination campaign were not properly sterilized between uses. This reservoir of infection was sustained for years because there was no awareness and no efforts to control the spread. Overall, despite improvement in schistosomiasis-related morbidity between 1980-1990[28, 29],it appears to have caused widespread infection with HCV, which by the 1990s, had replaced schistosomiasis as the primary cause of liver disease in Egypt[28].Active infection rates are particularly high among individuals who reported receipt of at least one injection to treat schistosomiasis compared to those who had not received such an injection[7].

3.2. Age

Different studies have shown a dramatic increase in HCV prevalence with age; a cohort effect that may be explained, at least in part, by the early association

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between parenteral antischistosomal therapy campaignand HCV transmission[30-32].

3.3. Gender

Higher HCV prevalence rates are observed in males compared to females. These differences may also be in part attributed to the parenteral antischistosomasis campaigns (PAT), as males were more affected by the schistosomiasis disease burden and hence were main targets of these campaigns[33- 36].

3.4. Geographical differences

Higher prevalence was observed in rural dwellers compared to individuals living in urban areas. These differences may also be in part attributed to the PAT campaigns, as rural areas were more affected by the schistosomiasis disease, consequently, were more involved by these campaigns [33, 36, 37].

3.5. Injection therapy: for any other indication, like for hemorrhoids, or urinary incontinence [36].

3.6. Hospital-basedprocedures

3.6.a. Blood transfusion

Prior to 1994,blood transfusionwas a common route for HCV transmission in Egypt [26]**.** After that date, blood and blood products were screened for HCV which eliminated the possibility of HCV transmission via this route [10, 27].

3.6.b. Other procedures.

Experiencing various facility-based medical procedures however minor they are, contributes to susceptibility to HCV [7]**.** Surgicalprocedures, perinatal care, and dental treatment have been incriminated in HCV transmission in many studies [6, 31, 38]**.**

3.6.c. Occupational hazards

Transmission among health care workers through needle sticks and sharp injuries is common in Egypt and contributes to the high rates of HCV infection,

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given that needleless systems are not adopted in all Egyptian hospitals and health care units [39, 40].

3.7. Community-based risk factors

3.7.a. Social and cultural factors.

A set of risk factors, mostly related to prevailing social and cultural conditions, are responsible for maintaining the high rates of HCVtransmission in Egypt. In several large community-based studies, dentistry, excision, and wound treatment performed by informal health care providers in rural health units were identified as important risk factors [39- 42]. In rural Egypt, about 50% of deliveries are attended by traditional birth assistants who do not perform appropriate cleaning or disinfection of the equipment used [40, 42].Traditional scarification and tattooing practices may play some role in transmission of HCV in rural Egypt [40].

3.7.b. Intrafamilial and sexual transmissionplay a role in the high prevalence of HCV in Egypt [41, 43].

3.8. IDUs:

Despite being a major driver of HCV incidence and prevalence in many countries [44], the relative contribution of IDUs to HCV incidence and prevalence in Egypt is much smaller. This is because of the specific context of the Egyptians. Illicit drug use is not common in Egypt and does not represent a major risk of HCV transmission [10, 27].Still, there is a contribution from injecting drug use to HCV transmission that is, in terms of absolute scale, comparable to other countries. The prevalence of injecting drug use in Egypt is estimated to be 0.21% [45] and according to the only study found, HCV prevalence among IDUs is 63% [46]. Considering that HCV prevalence in the population is 14.7%, injecting drug use may explain at most only about 1% of the national HCV prevalence in Egypt [47]. Injecting drug use is unlikely to contribute much to HCV prevalence among women, again given the context of Egyptian. Moreover, injecting drug use among women in the Middle East and North Africa region is believed to be marginal with only about 10% or less of IDUs being females [48, 49].

4. Complications

HCV infection most often leads to an asymptomatic chronic state, which can later progress to active liver disease, and grave compilations.Part of the problem is that

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hepatitis symptoms can take a long time to show. Most people do not know they are infected, as they often do not have symptoms until they develop serious liver disease, which can be years later [50].
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 [12]**.**HCV kills an estimated 40,000 Egyptians a year [3]**.**

5. HCV infection in children

5.1. Magnitude of the problem

In the Western world the prevalence of HCV infection is relatively low in children, with an anti-HCV prevalence rate of 0.2%-0.4% [51]. In Egypt, although mass campaigns to control schistosomiasis that took place decades earlier may have been responsible for much of seropositivity in the old-age people,current seroprevalenceis also high in children too young to have been involved in those campaigns [10, 25]. The prevalence in those under age 20 is approximately 5-8%, demonstrating the continued presence of significant hepatitis C transmission in modern-day Egypt [33].
The magnitude of HCV infection in children has been studied by many authors. Two community-based cross sectional studies to determine the prevalence of HCV among Egyptian children were carried out.The first was inUpper Egypt [53]and the second was in Lower Egypt [26]. In the first;84 (3%) out of 2967 subjects under 19 years of age screened for HCV antibody using ELISA technique, were found to be positive. In the second; 178 (9%) out of the 2010 screened subjects in the same age group were found to be positive. In **2007,El-Raziky*et al***. [54] concluded that asymptomatic HCV infection was present in 2.02% of 1042 children at the age of 1-9 years who were tested for HCV by ELISA and PCR and tested for alanine aminotransferase (ALT) levels. In **2010,Kalil*et al*.**from Assiutsituated in Upper Egypt [38], measured the rates of anti-HCV positivity by 3rd-generation ELISA test and of HCV-RNA positivity by PCR among children at the age of 1-9 years attending AssuitUniversity Hospital. ELISA-positive cases were 121. The rate of HCV-RNA positivity among ELISA-positive cases was 72.2%**.**On the next year [55], researchers from Alexandria, located on the Mediterranean Coast estimated the prevalence of HCV infection among healthy children. A representative random sample of 500 children, age between 6 and 15 years, was selected from 10 schools in Alexandria. HCV seroprevalence of 5.8% was found, with HCV viraemia in 75% of the studied children**.**The most recent work published was that of**Farghaly*et al*. in 2014** whostudied the frequency of HCV infection among children with T1DM in Upper Egypt [56]**.**In a cross sectional study involving 150

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children the frequency of anti-HCV positivity by ELISA was significantly high(12%), while the frequency of HCV-RNA positivity by PCR among the cases testing positive by ELISA was 75%.Summary of the most recent studies performed is shown in Table.

It is worth mentioning that HCV infection is not always benign in the childhood period in Egypt[57]. It was reported that ALT levels were elevated in up to half of the HCV RNA-positive children. Symptoms such as diarrhea, abdominal pain, history of fatigue and school absence because of illness were also common [54]**.**Whereas the first group of authors reported histological abnormalities in three quarters of the HCV RNA-positive children they studied, the second investigators found thatnone of the HCV positive children was diagnosed as having signs of advanced liver disease upon clinical or ultrasonographic examination.As regards children with T1DM, HCV infection was not associated with significant changes in hepatic biochemical parameters [56] and there were no significant impact on serum levels of liver biochemical profile.

Year	**Age**	**Study sample**	**location**	**ELISA**	**+veno(%)**	**PCR**	**+veno(%)**	**Others +veno(%)**	**Reference**
2000	<19	2010	Lower egypt		178 (9%)	-			**(26)**
2002	<19	2967	Upper Egypt	+	84 (3%)	-			**(53)**
2007	1-9	1042	Hospital-based	+	15 (1.4%)	+	5	ALT(6)	**(54)**
2010	2m-15y	465	Assuit University	3rd gen	121(26%)	+	87 (72%)		**(38)**
2011	6-15	500	Alex	+	5.8%	+			**(55)**
2014	3-16	150 (T1DM)	Assuit	3rd gen	18(12%)	+	12(75%)	Total bilirubin, diect bilirubin, protein, ALT, AST	**(56)**

Table. Summary of the most recent studies performed in Egypt, as regards the prevalence of HCV among children.

5.b. Risk factors

In the Western World, blood transfusion is the principal route of transmission of HCV in children [58]**.**Earlier evidence suggested that new cases are due to perinatal (vertical) transmission [59]**.**

Studies in Egypt suggest that children are exposed to HCV vertically through mother-to-child transmission [60- 64].High RNA prevalence was documented among infants of HCV positive mothers, ranging between 3.8% and 11.1% [65, 66]**.** Moreover, Egyptian children are at high risk of being horizontally infected with HCV by their parents,or household exposure [66]. The latter canoccureither directly or indirectly through shared needles or other possible fomites [5]**.** Analysis

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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. Sequencing isolates from 13 families with parent(s) and children having HCV RNA showed 10 of 18 had genetically similar viruses.

In Egypt also, medical exposures to HCV at a very young age have been incriminated [67- 70]. High HCV levels were reported among thalassemic children [67, 71, 72]**,** children on hemodialysis [68, 69] and diabetic children [67, 68, 70]**.**Residence in rural areaand low socioeconomic class are also significant risk factors [56].It was also shown that history of previous blood transfusion (odds ratio[OR] = 34.8, 95% CI=4.39-272.95), intravenous injections (OR=4.68, 1.89-11.59), surgical intervention (OR=5.64, 2.55-12.52), dental treatment (OR = 6.81, 2.64-17.39), [54]injection (OR=2.29, 1.08-4.89) and circumcision for boys by informal health care providers (OR=2.6, 1.0-6.73), age above 10 years (OR=6.83, 2.44-19.07), are the most significant risk factors for HCV infection [38, 55]**.**

6. Has HCV incidence rates declined or not?

Some studies have concluded a decline in HCV incidence, while others did not. Barban et al. [73]have recently suggested through their incidence has estimated that it seems plausible that HCV incidence rate has declined drastically in the last two decades since the discovery of the epidemic in 1991–1992. That is because some of the potential drivers of this epidemic, such as the PAT campaigns and contaminated blood, are no longer present. Moreover, results of the time trend analysis of **Mahmoud *et al*. (2013)**, suggest that, contrary to expectations, there appears to be a small decline, though statistically not significant, in HCV prevalence over time in the general population and high risk population in Egypt [36].

On the other hand, other authors reported the lack of substantial decline in HCV incidence. Apotential explanation is the very high baseline HCV prevalence in the country. For a given mode of transmission, such as reuse of unclean needles or syringes, the transmission risk is dependent on the probability that the needle/syringe was used previously on an HCV infected person, which is HCV RNA prevalence. Even if the prevalence of the modes of transmissions in Egypt today is similar to other neighboring countries, the high background prevalence can drive much more incidence. In neighboring Libya for example, with an HCV RNA prevalence of less than 1% [48]a reuse of an unclean needle is more than ten-fold less likely to lead to an HCV transmission than in Egypt[7]**.**

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7. Occult HCV

7.1. Background

In January 2004, the role of occult hepatitis C virus (HCV) infection in chronic liver disease was first described by Castillo et al. Patients with elevated liver function tests and negative HCV antibodies and serum RNA may have detectable HCV RNA in their liver tissue and PBMCs [74].
Occult hepatitis C has been also been found in chronic hepatitis of unknown origin, in several groups at risk for HCV infection such as hemodialysis patients or family members of patients with occult HCV RNA,also in healthy populations without evidence of liver disease. Occult HCV infection seems to be less aggressive than chronic hepatitis C although patients affected by occult HCV may develop liver cirrhosis and even hepatocellular carcinoma [75].

7.2. Occult HCV in Egypt

Interest in occult HCV has emerged recently in Egypt. Studies at a national level are being carried out, but no results have yet been released. Many small scale studies have been performed among particular patient groups.
In 2011, occult HCV was found to be highly prevalent among Egyptian nonalcoholic fatty liver disease patients (NAFLD) (40.7%). It seemed to induce a mild liver disease. The study recommended that NAFLD patients with elevated ALT and negative HCV RNA in sera are to be investigated for tissue (liver) HCV RNA, and followed up for the occult HCV to monitor progression to overt disease [76]**.**
In 2012, two studies were published addressing OCI. **Youssef *et al*. (2012)** detected OCI in 20% of patients group with lymphoproliferative disorders, compared to only 4% OCI in controls group [77]**.** There was a male predominance in both HCV and OCI. All HCV positive patients were genotype 4. **Gad *et al*. (2012)** reported a high prevalence of occult HCV infection (25%) in patients with - unexplained persistently abnormal liver function test results [78]**.** Those patients exhibited a distinct immunoregulatory cytokine pattern, favoring viral persistence and leading to less aggressive course of this disease entity than chronic HCV infection [77, 78].
In **2013, Amin *et al*.**investigated the risk of post-transfusion transmission of HCV in the circumstances of occult HCV when anti-HCV is undetectable by ELISA and HCVRNA is detected by RT-PCR in the plasma and or in peripheral blood mononuclear cells (PBMCs) ofdonor blood and the recipients are

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immunocompromised.The risk of acquiring post-transfusion HCV infection from an occult HCV blood unit is 5% [79].

8. Conclusions and closing remarks

HCV infection is a major health problem in Egypt. The beginning was iatrogenic, however, other routes of transmission led to continuation of the problem up till now. Both adults and children are affected by this disease. Routes of transmission and risk factors for this infection are well established.

Occult HCV infection is an entity which has been recently described. Studies at national level are being conducted. However studies for special groups of patients have highlighted its importance.

All efforts should be exerted to bring HCV disease to an end.

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