

Minireview Article

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

Abstract

Hepatitis C virus is an epidemic in Egypt  which contains 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 antischistosomal injection 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 seroprevalence is 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 transmission are 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 as elevated liver function tests and negative HCV antibodies in serum, while HCV RNA is detectable in liver tissue and peripheral polymorphonuclear 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.

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%.

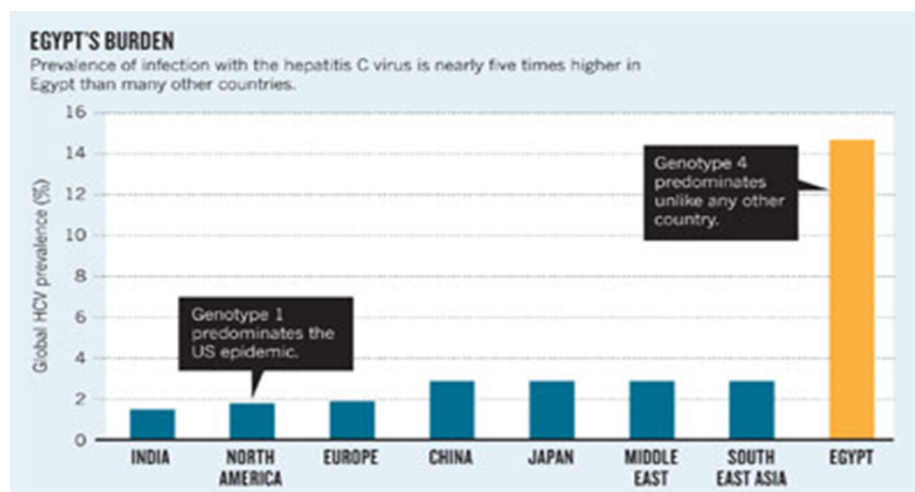


Fig. 2. Egypt — and the Middle East more generally — is a stronghold for genotype 4. By contrast, about 75% of HCV infections in Europe and the United States are of genotype 1 [8].

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.

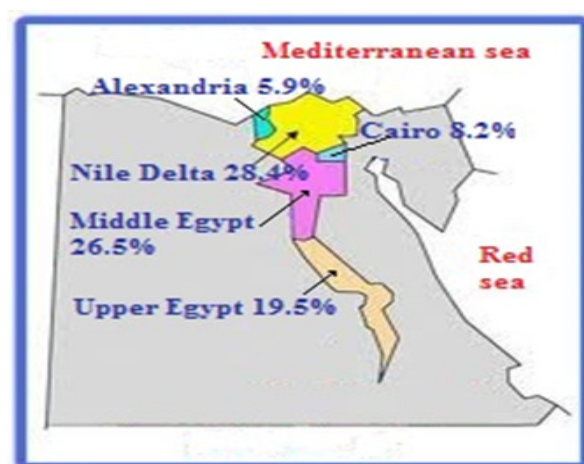


Fig. 3. HCV spread ratios across Egypt [9].

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

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.

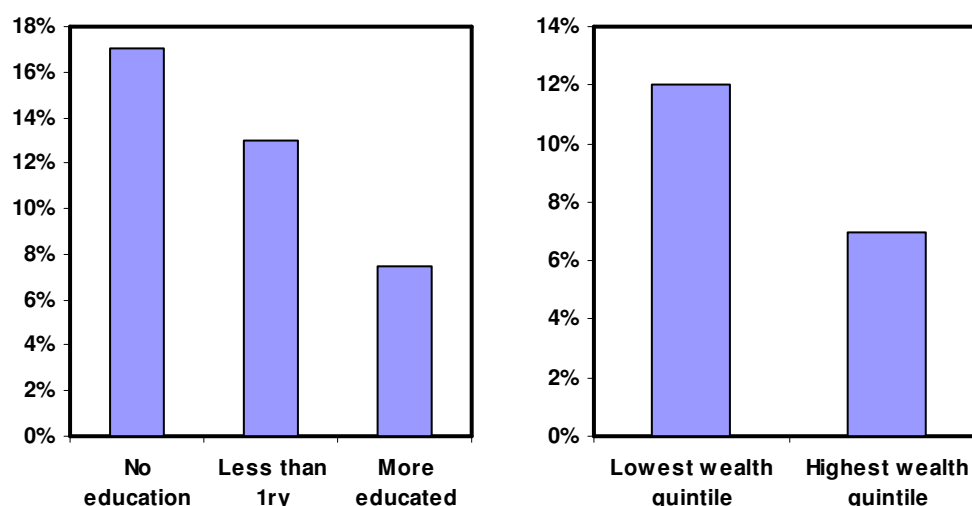


Fig. 4. The impact of level of education and the wealth quintile on HCV prevalence.

Explanations for this unique epidemic in Egypt have been an ongoing subject of controversy. The iatrogenic role of parenteral antischistosomal 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 Europe. Fig. 4, due to variations in population structure, immigration, and routes of transmission [13].

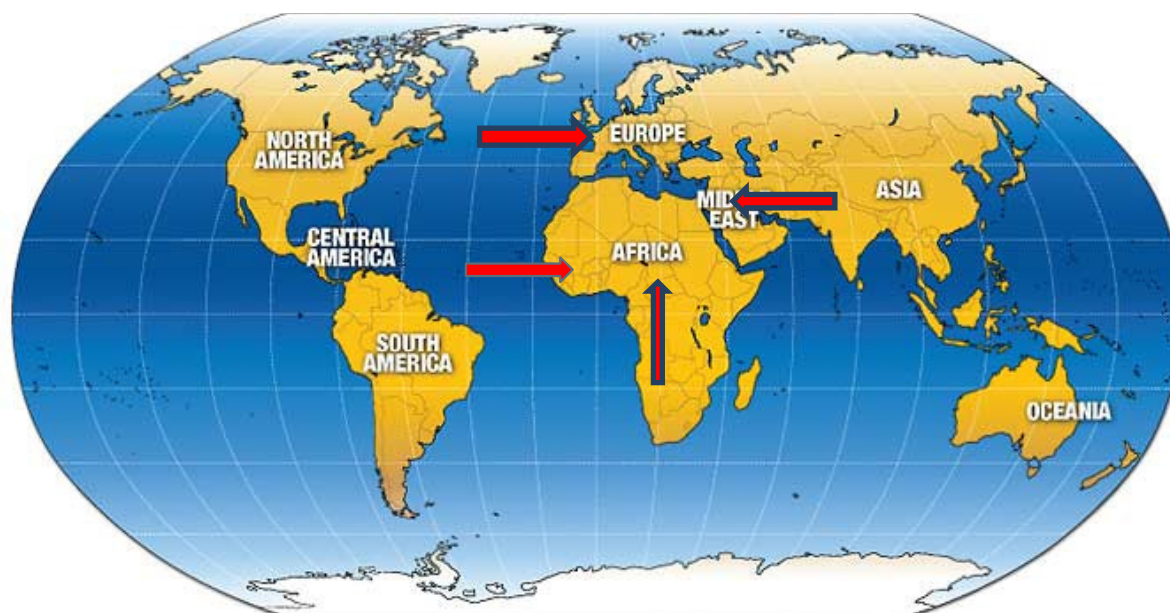


Fig. 5. Global origin and spread of HCV 4 infection [1].

The origin, evolution, and dynamics of HCV 4 are difficult to determine given the limited population-based epidemiological studies and phylogenetic analysis of this genotype 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 West Africa 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,

[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 HCV epidemic 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 and 1955 [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 the current 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 reported acute 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

between parenteral antischistosomal therapy campaign and 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 antischistosomiasis 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-based procedures

3.6.a. Blood transfusion

Prior to 1994, blood transfusion was 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]. Surgical procedures, 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,

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 HCV transmission 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 transmission play 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 complications. Part of the problem is that

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 seroprevalence is 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 in Upper 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, Kalilet *et al.* from Assiut situated 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 Assiut University 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 who studied the frequency of HCV infection among children with T1DM in Upper Egypt [56]. In a cross sectional study involving 150

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	ELIS A	+veno(%)	PCR	+veno(%)	Others +veno(%)	Referen ce
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	3 rd gen	121(26%)	+	87 (72%)		(38)
2011	6-15	500	Alex	+	5.8%	+			(55)
2014	3-16	150 (T1DM)	Assuit	3 rd gen	18(12%)	+	12(75%)	Total bilirubin, diet 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 canoccur either directly or indirectly through shared needles or other possible fomites [5]. 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. 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 area and 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. A potential 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].

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 HCV RNA is detected by RT-PCR in the plasma and or in peripheral blood mononuclear cells (PBMCs) of donor blood and the recipients are

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.

References

- 1- Alter MJ. Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 2007; 13:2436–2441.
- 2- http://lloydbelcher.org/2011/07/28/hepatitis_c_hongkong_2011/. Accessed 15 September, 2014.
- 3- Egypt steps up efforts against hepatitis C, July 2014. <http://www.who.int/features/2014/egypt-campaign-hepatitisc/en/>. Accessed 23 September, 2014.
- 4- Kamel MA, Ghaffar YA, Wasef MA, Wright M, Clark LC, Miller FD. High HCV prevalence in Egyptian blood donors. *Lancet* 1992; 340:427.
- 5- Mohamed MK, Abdel-Hamid M, Mikhail NN, Abdel-Aziz F, Medhat A, Magder LS, *et al*. Intrafamilial transmission of hepatitis C in Egypt. *Hepatology* 2005; 42: 683–687.
- 6- Saleh DA, Shebl F, Abdel-Hamid M, Narooz S, Mikhail N, El-Batanony M, *et al*. Incidence and risk factors for hepatitis C infection in a cohort of women in rural Egypt. *Trans R Soc Trop Med Hyg* 2008; 102(9):921–928.
- 7- El-Zanaty F and Way A. Egypt Demographic and Health Survey 2008. (Egyptian: Ministry of Health and Associates and Macro International, Cairo) 2009; p 431.
- 8- <http://www.natureasia.com/en/nmiddleeast/article/10.1038/nmiddleeast.2011.83>. Accessed 2 October, 2014.
- 9- <http://www.hcv-egypt.net/encyclpdeia/transmission/index.htm>. Accessed 5 September, 2014.

- 10- Frank C, Mohamed MK, Strickland GT, Lavanchy D, Arthur RR, Magder LS, *et al.* The role of parenteral antischistosomal therapy in the spread of hepatitis C in Egypt. *Lancet* 2000; 355: 887–891.
- 11- Nakano T. An updated analysis of hepatitis C virus genotypes and subtypes based on the complete coding region. *Liver Int* 2011; 32 (2): 339–45.
- 12- http://www.hcvadvocate.org/hcsp%5Carticles/Egypt_06.html. Accessed 17 September, 2014.
- 13- Kamal SM and Nasser AI. Hepatitis C genotype 4: What we know and what we don't yet know. *Hepatology* 2008; 47(4): 1371–1383.
- 14- Xu L-Z, Larzul D, Delaporte E, Bréchet C, Kremsdorf D. Hepatitis C virus genotype 4 is highly prevalent in central Africa (Gabon). *J Gen Virol* 1994; 75: 2393–2398.
- 15- Angelico M, Renganathan E, Gandin C, Fathy M, Profili MC, Refai W, *et al.* Chronic liver disease in the Alexandria governorate, Egypt: contribution of schistosomiasis and hepatitis virus infections. *J Hepatol* 1997; 26: 236–243.
- 16- Smith DB, Pathirana S, Davidson F, Lawlor E, Power J, Yap PL, *et al.* The origin of hepatitis C virus genotypes. *J Gen Virol* 1997; 78: 321–328.
- 17- Ray SC, Arthur RR, Carella A, Bukh J, Thomas DL. Genetic epidemiology of hepatitis C virus throughout Egypt. *J Infect Dis* 2000; 182: 698–707.
- 18- Ndjomou J, Pybus OG, Matz B. Phylogenetic analysis of hepatitis C virus isolates indicates a unique pattern of endemic infection in Cameroon. *J Gen Virol* 2003; 84: 2333–2341.
- 19- Pybus O, Drummond A, Nakano T, Robertson BH, Rambaut A. The epidemiology and iatrogenic transmission of hepatitis C virus in Egypt: a Bayesian coalescent approach. *Mol Biol Evol* 2003; 20: 381–387.
- 20- Simmonds P. Genetic diversity and evolution of hepatitis C virus—15 years on. *J Gen Virol* 2004; 85: 3173–3188.
- 21- Tanaka Y, Agha S, Saady N, Kurbanov F, Orito E, Kato T, *et al.* Exponential spread of hepatitis C virus genotype 4a in Egypt. *J Mol Evol* 2004; 58: 191–195.
- 22- Genovese D, Dettori S, Argenti C, Villano U, Chionne P, Angelico M, *et al.* Molecular epidemiology of hepatitis C virus genotype 4 isolates in Egypt and analysis of the variability of envelope proteins E1 and E2 in patients with chronic hepatitis. *J Clin Microbiol* 2005; 43: 1902–1909.

- 23- Njouom R, Nerrienet E, Dubois M, Lachenal G, Rousset D, Vessière A, *et al.* The hepatitis C virus epidemic in Cameroon: genetic evidence for rapid transmission between 1920 and 1960. *Infect Genet Evol* 2007; 7: 361–367.
- 24- Simmonds P, Holmes EC, Cha TA, Chan SW, McOmish F, Irvine B, *et al.* Classification of hepatitis C virus into six major genotypes and a series of subtypes by phylogenetic analysis of the NS-5 region. *J Gen Virol* 1993; 74: 2391–2399.
- 25- Kamal SM, Madwar M, Bianchi L, Tawil AE, Fawzy R, Peters T, *et al.* Clinical, virological and histopathological features: long-term follow-up in patients with chronic hepatitis C co-infected with *S. mansoni*. *Liver* 2000; 20: 281–289.
- 26- Habib M, Mohamed MK, Abdel-Aziz F, Magder LS, Abdel-Hamid M, Gamil F, *et al.* Hepatitis C virus infection in a community in the Nile Delta: risk factors for seropositivity. *Hepatology* 2001; 33: 248–253.
- 27- Zakaria S, Fouad R, Shaker O, Zaki S, Hashem A, El-Kamary SS, *et al.* Changing patterns of acute viral hepatitis at a major urban referral center in Egypt. *Clin Infect Dis* 2007; 44: e30–e36.
- 28- Darwish NM, Abbas MO, Abdelfattah FM, Darwish MA. Hepatitis C virus infection in blood donors in Egypt. *J Egypt Public Health Assoc* 1992;13(3–4):223–236.
- 29- Selim O and El-Zayadi AR. Prevalence of hepatitis C virus among non-A, non-B- related chronic liver disease in Egypt. *J Hepatol.* 1992;13(2–3):416–417.
- 30- Abdel-Aziz F, Habib M, Mohamed MK, Abdel-Hamid M, Gamil F, Madkour S. Hepatitis C virus (HCV) infection in a community in the Nile Delta: Population description and HCV prevalence. *Hepatology* 2000; 32(1):111 - 115.
- 31- Arafa N, El Hoseiny M, Rekacewicz C, Bakr I, El-Kafrawy S, El Daly M, *et al.* Changing pattern of hepatitis C virus spread in rural areas of Egypt. *J Hepatol* 2005; 43(3):418-424.
- 32- DossW, Mohamed MK, Esmat G, El Sayed M, Fontanet A, Cooper S, El Sayed N. Egyptian national control strategy for viral hepatitis. 2008-2012.
- 33- Mohamed MK. Epidemiology of HCV in Egypt 2004. *The Afro-Arab Liver Journal* 2004;13(2):41–52.
- 34- Awadalla HI, Ragab MH, Nassar NA, Osman MA. Risk factors of hepatitis C infection among Egyptian blood donors. *Cent Eur J Public Health* 2011; 19 (4): 217–221
- 35- Abdelwahab S, Rewishac E, Hashem M, Sobhy M, Galal I, Allam WR, *et al.* Risk factors for hepatitis C virus infection among Egyptian healthcare workers in a National Liver Diseases Referral Centre. *Trans R Soc Trop Med Hyg* 2012; 106 (2): 98-103.

- 36- Mahamoud YA, Mumtaz GR, Riome S, Miller DW, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. *BMC Infect Dis* 2013; 13: 288.
- 37- Mostafa A, Taylor SM, El-Daly M, El Hoseiny M, Bakr I, Arafa N, *et al*: Is the hepatitis C virus epidemic over in Egypt? Incidence and risk factors of new hepatitis C virus infections.*Liver Int* 2010; 30(4):560–566.
- 38- Kalil KA, Farghally HS, Hassanein KM, Abd-Elsayed AA, Hassanein FE. Hepatitis C virus infection among paediatric patients attending University of Assiut Hospital, Egypt. *Eastern Mediterranean health journal* 2010; 16(4):356-361.
- 39- Talaat M, Kandeel A, El-Shoubary W, Bodenschatz C, Khairy I, Oun S, *et al*. Occupational exposure to needlestick injuries and hepatitis B vaccination coverage among health care workers in Egypt. *Am J Infect Control* 2003; 31: 469–474.
- 40- El Katsha S, Labeeb S, Watts S, Younis A. Informal health providers and the transmission of hepatitis C virus: pilot study in two Egyptian villages. *East Mediterr Health J* 2006; 12: 758–767.
- 41- Kamal SM, Amin A, Madwar M, Graham CS, He Q, Al Tawil A, *et al*. Cellular immune responses in seronegative sexual contacts of acute hepatitis C patients. *J Virol* 2004; 78: 12252–12258.
- 42- Stoszek SK, Abdel-Hamid M, Narooz S, El Daly M, Saleh DA, Mikhail N, *et al*. Prevalence of and risk factors for hepatitis C in rural pregnant Egyptian women. *Trans R Soc Trop Med Hyg* 2006; 100: 102–107.
- 43- Magder LS, Fix AD, Mikhail NN, Mohamed MK, Abdel-Hamid M, Abdel-Aziz F, *et al*. Estimation of the risk of transmission of hepatitis C between spouses in Egypt based on seroprevalence data. *Int J Epidemiol* 2005; 34: 160–165.
- 44- Aceijas C and Rhodes T. Global estimates of prevalence of HCV infection among injecting drug users. *Int J Drug Policy* 2007; 18(5):352-8.
- 45- Aceijas C, Friedman SR, Cooper HL, Wiessing L, Stimson GV, Hickman M. Estimates of injecting drug users at the national and local level in developing and transitional countries, and gender and age distribution. *Sex Transm Infect* 2006; 82 S(3):10-17.
- 46- El-Ghazzawi E, Drew L, Hamdy L, El-Sherbini E, SadekSel-D, Saleh E. Intravenous drug addicts: a high risk group for infection with human immunodeficiency virus, hepatitis viruses, cytomegalo virus and bacterial infections in Alexandria Egypt. *J Egypt Public Health Assoc* 1995; 70(1-2):127-50.
- 47- Elkareh S. HCV screening of donors in Governmental Blood Transfusion Centers at Menoufia Governorate (from Jan. 2008 to Oct. 2008). *Vox Sang* 2009; 13:89–90.

- 48- Abu-Raddad L, Akala FA, Semini I, Riedner G, Wilson D, Tawil O.** Characterizing the HIV/AIDS epidemic in the Middle East and North Africa: time for Strategic Action. Middle East and North Africa HIV/AIDS Epidemiology Synthesis Project. World Bank/UNAIDS/WHO Publication. Washington DC: The World Bank Press; 2010 a.
- 49- Abu-Raddad LJ, Hilmi N, Mumtaz G, Benkirane M, Akala FA, Riedner G, et al.** Epidemiology of HIV infection in the Middle East and North Africa. *AIDS* 2010b; 24(12):S5-23.
- 50- Miller DW and Abu-Raddad LJ.** Evidence of intense ongoing endemic transmission of hepatitis C virus in Egypt. *PNAS* 2010; 107 (33): 14757–14762
- 51- Williams R.** Global challenges in liver disease. *Hepatology* 2006; 44(521):26.
- 52- Rao MR, Naficy AB, Darwish MA, Darwish NM, Schisterman E, Clemens JD, et al.** Further evidence for association of hepatitis C infection with parenteral schistosomiasis treatment in Egypt. *BMC Infect Dis* 2002; 2: 29.
- 53- Medhat A, Shehata M, Magder LS, Mikhail N, Abdel-Baki L, Nafeh M, et al.** Hepatitis C in a community in upper Egypt: risk factors for infection. *Am. J. Trop. Med. Hyg* 2002; 66(5): 633–638
- 54- El-Raziky MS, El-Hawary M, Esmat G, Abouzied AM, El-Koofy N, Mohsen N, et al.** Prevalence and risk factors of asymptomatic hepatitis C virus infection in Egyptian children. *World J Gastroenterol* 2007; 28; 13(12): 1828-1832
- 55- Barakat SH and El-Bashir N.** Hepatitis C virus infection among healthy Egyptian children: prevalence and risk factors. *J Viral Hepat* 2011; 18(11):779-84.
- 56- Farghaly HS, Metwalley KA, Abd El-Hafeez HA.** Hepatitis C virus infection in Egyptian children with type 1 diabetes mellitus: A single center study. *Indian Journal of Endocrinology and Metabolism* 2014; 18(2): 197-201.
- 57- El-Raziky MS, El-Hawary M, El-Koofy N, Okasha S, Kotb M, Salama K, et al.** Hepatitis C virus infection in Egyptian children: single center experience. *J Viral Hepat* 2004;11(5):471-6.
- 58- Irshad M and Peter S.** Spectrum of viral hepatitis in thalassemic children receiving multiple blood transfusions. *Indian JGastroenterol* 2002; 21: 183-184
- 59- Bortolotti F, Resti M, Giacchino R, Crivellaro C, Zancan L, Azzari C, et al.** Changing epidemiologic pattern of chronic hepatitis C virus infection in Italian children. *J Pediatr* 1998; 133: 378-381.
- 60- Agha S, Sherif LS, Allam MA, Fawzy M.** Transplacental transmission of hepatitis C virus in HIV-negative mothers. *Res Virol* 1998; 149(4):229-234.

- 61- Kassem AS, El-Nawawy AA, Massoud MN, Abou El-Nazar SY, Sobhi EM. Prevalence of hepatitis C virus (HCV) infection and its vertical transmission in Egyptian pregnant women and their newborns. *J Trop Pediatr* 2000; 46(4):231-233.
- 62- Abdul Qawi K, Youssef A, Metwally MA, Ragih I, AbdulHamid M, Shaheen A. Prospective study of prevalence and risk factors for hepatitis C in pregnant Egyptian women and its transmission to their infants. *Croat Med J* 2010; 51(3):219-228.
- 63- Zahran KM, Badary MS, Agban MN, Abdel Aziz NH. Pattern of hepatitis virus infection among pregnant women and their newborns at the Women's Health Center of Assiut University, Upper Egypt. *Int J Gynaecol Obstet* 2010; 111(2):171-174.
- 64- Abo Elmagd EK, Abdel-Wahab KS, Alrasheedy ZE, Khalifa AS. An Egyptian study of mother to child transmission of hepatitis C virus. *Int J Virology* 2011; 7(3):100-108.
- 65- Madwar MA, El-Gindy I, Fahmy HM, Shoeb NM, Massoud BA. Hepatitis C virus transmission in family members of Egyptian patients with HCV related chronic liver disease. *J Egypt Public Health Assoc* 1999; 74(3-4):313-332.
- 66- Shebl FM, El-Kamary SS, Saleh DA, Abdel-Hamid M, Mikhail N, Allam A, *et al.* Prospective cohort study of mother-to-infant infection and clearance of hepatitis C in rural Egyptian villages. *J Med Virol* 2009; 81(6):1024-1031.
- 67- El-Nanawy AA, El Azzouni OF, Soliman AT, Amer AE, Demian RS, el-Sayed HM. Prevalence of hepatitis-C antibody seropositivity in healthy Egyptian children and four high risk groups. *J Trop Pediatr* 1995; 41(6):341-343.
- 68- Kandil ME, Rasheed MA, Saad NE. Hepatitis C and B viruses among some high risk groups of Egyptian children. *J Med Sci* 2007; 7(8):1259-1267.
- 69- Hammad AM, Zaghloul MH. Hepatitis G virus infection in Egyptian children with chronic renal failure (single centre study). *Ann Clin Microbiol Antimicrob* 2009; 8:36.
- 70- El-Karakasy H, Anwar GH, El-Raziky MS, El-Hawary M, Hashem M, El-Sayed R, *et al.* Anti-HCV prevalence among diabetic and non-diabetic Egyptian children. *Curr Diabetes Rev* 2010; 6(6):388-392.
- 71- El Gohary A, Hassan A, Nooman Z, Lavanchy D, Mayerat C, El Ayat A, *et al.* High prevalence of hepatitis C virus among urban and rural population groups in Egypt. *Acta Trop* 1995; 59(2):155-161.
- 72- Abdalla NM, Galal A, Fatouh AA, Eid K, Salama EEE, Gomma HE. Transfusion transmitted virus (TTV) infection in polytransfused Egyptian thalassemic children. *J Med Sci* 2006; 6(5):833-837.
- 73- Breban R, Doss W, Esmat G, Elsayed M, Hellard M, Ayscue P, *et al.* Towards realistic estimates of HCV incidence in Egypt. *J Viral Hepat* 2013; 20(4):294-6.

- 676 **74- Castillo I, Pardo M, Bartolome J, Ortiz-Movilla N, Rodriguez-Inigo E, de Lucas S, et al.**
677 Occult hepatitis C virus infection in patients in whom the etiology of persistently abnormal
678 results of liver-function tests is unknown. *Journal of Infectious Diseases* 2004; 189, 7-14.
679
- 680 **75- Carreño V, Bartolomé J, Castillo I, Quiroga JA.** New perspectives in occult hepatitis C
681 virus infection. *World J Gastroenterol.* 2012; 21; 18(23): 2887-2894.
682
- 683 **76- Saad Y, Zakaria S, Ramzy I, El Raziky M, Shaker O, Elakel W, et al.** Prevalence of
684 occult hepatitis C in Egyptian patients with non-alcoholic fatty liver disease. *Open Journal of*
685 *Internal Medicine* 2011; 1 (2): 33-37.
686
- 687 **77- Youssef SS, Nasr AS, El Zanaty T, El Rawi RS, Mattar MM.** Prevalence of occult
688 hepatitis C virus in Egyptian patients with chronic lymphoproliferative disorders. *Hepatitis*
689 *Research and Treatment* 2012; Volume 2012, Article ID 429784, 6 pages.
690
- 691 **78- Gad YZ, Mouas N, Abdel-Aziz A, Abousmra N, Elhadidy M.** Distinct immunoregulatory
692 cytokine pattern in Egyptian patients with occult Hepatitis C infection and unexplained
693 persistently elevated liver transaminases. *Asian Journal of Transfusion Science* 2012; 6 (1): 24-
694 28.
695
- 696 **79- Amin RS, AbdElaziz MM, El lawindi M.** Evaluation of an Isolation Program of Hepatitis
697 C Virus Infected Hemodialysis Patients in Some Hemodialysis Centers in Egypt. *ISRN*
698 *Nephrology* 2013; (2013), Article ID 395467, 5 pages.