INTRODUCTION

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HCV is globally distributed and it is estimated that up to 3.0% of the world population is infected [1]. The prevalence of chronic hepatitis C virus infection in general pediatric population varies from 0.1% to 15% around the world, with the highest prevalence in the endemic areas of Africa[2].

Egypt has the highest HCV antibody prevalence in the world [3]. The start of epidemic is attributed to insufficiently sterilised intravenous injections during the mass anti-schistosomiasis treatment campaigns by antimony salts between 1960 and 1982 in rural areas [4]. There are an estimated 8 million infected habitants in 1999[4]. In rural areas, HCV prevalence ranges from 10% in children to 45% in adults [4]. The introduction of oral praziquantel for the treatment of schistosomiasis in 1982 halted this mode of transmission, and the current prevalence of Schistosoma mansoni infection in our Egyptian cohort is extremely low (2.4%) [5].

Hepatitis C virus (HCV) is an enveloped virus that, at present, chronically infects about 200 million people worldwide [3]. One hallmark of HCV is its high degree of sequence variability, which likely contributes to its ability to establish chronic infections. Different patient isolates are grouped into 6 genotypes and more than 100 subtypes within the genus Hepacivirinae of the family Flaviviridae [6]. The main (90%) HCV genotype is type 4[7]. Genotyping has proven to be a useful clinical tool because the response to therapy and prognosis is influenced by the viral genotype. Genotype 1 is less than half as likely as other genotypes to respond to therapy, and the combination therapy regimens vary depending on the different genotypes [8].

Finally, HCV variability within a patient gives rise to a number of phylogenetically related lineages referred to as quasispecies , also it can refer to individual variants themselves. Neonates infected with HCV by vertical transmission show changes in the composition of the infant's HCV quasispecies including new variants that were never found in the maternal quasispecies [9].

Persistent infection is associated with a variable degree of liver damage often progressing in severity over the course of decades [10].

INCIDENCE AND PREVALENCE

Infection with HCV occurs in children, as in adults, throughout the world. The proportion of the 28,000 new cases each year in the United States that are in children less than 18 years. HCV is the leading cause of liver transplantation in developed countries, and the most common chronic blood borne infection in the USA [11]. Although HCV is endemic in most parts of the world, there are significant geographic

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and temporal differences in the incidence and prevalence of HCV infection. Africa and Asia have the highest reported prevalence rates; while industrialized countries in North America, northern and western Europe and Australia have a lower prevalence. Nations with relatively low rates of HCV seroprevalence include Germany (0.6%), Canada (0.8%), France (1.1%), and Australia (1.1%). Low, but slightly higher seroprevalence rates have been reported in the USA (1.8%) and Japan (1.5–2.3%) [12].The few studies on prevalence of HCV infection in Italy suggest an average value of 7–8%, increasing with age and from north to south [13-15]. With regards to developing countries, there is less data available about the burden of disease. Considering the most populous countries, China has a reported seroprevalence of 3.2%; India, 0.9%; while Egypt has the highest reported prevalence rate of 22% [12].

The prevalence of HCV in children varies both by risk factors and geographic location. Children from all parts of the world who received multiple transfusions with either blood or acellular blood products before 1992 have infection rates from 50% to 95% [16]. Children with moderate transfusion exposure before 1992 have intermediate seroprevalence rates of 10% to 20% [16]. Studies in general pediatric populations, without identifiable risk factors, have reported seroprevalence rates ranging from as low as 0% in Japan [16] and Taiwan, [16] 0.4% in Italy,[16] and 0.9% in Saudi Arabia,[16] to as high as 14.5% in Cameroon[16]. In an urban adolescent population in Boston, the seroprevalence of antibody to HCV was 0.1[16]. Socioeconomic differences are likely to explain much of the geographic variability in the prevalence of antibody to HCV. Seroprevalence associations with demographic characteristics in Egyptian pediatric population in a recent study in Egypt revealed that the prevalence of anti-HCV in the 5–18 years old children was 8.2% in the Nile Delta community, and 2.5% in the Upper Egypt community. It did not differ by sex, but it increased by age in both communities: from 3.5% among those 5–9 years of age to 6.3% among those 15–18 years of age. After adjusting for age, circumcision by traditional health practitioners was significantly associated with anti-HCV for males ($P = 0.004$) but not for females ($P = 0.41$) [17] . In 1996, HCV antibody prevalence in urban areas was estimated around 9.1% during a national survey [18].In recent two-community based cross sectional studies done on pediatric Egyptian population [13,19], the first study from upper Egypt [13] revealed that; out of 2967 subjects 84 (3%) under 19 years of age screened for HCV antibody using ELISA technique were found to be positive. The overall prevalence in the 6033 screened subjects was 8.7%. In the study from Lower Egypt [19] out of the 2010 screened subjects under 19 years of age 178 (9%) were found to be positive. The overall prevalence in the 3999 screened subjects was 24.3% [19]. In a hospital based study done at Cairo University Pediatric Hospital, El-Raziky et al , reported that asymptomatic HCV infection is detectable in 2.02% of Egyptian children from 1-9 years[7]. In a previous study from Alexandria University Pediatric Hospital HCV antibody prevalence was present in 5.4% of cases with age range from 2-12 years old [20].

In rural area, having an anti-HCV-positive family member was the strongest predictor for incident HCV infection, after adjustment for iatrogenic and community exposures [21].

Pathophysiology

Hepatitis C virus is a member of the Flaviviridae family of RNA-containing viruses. Thus, it is not integrated into the host genome.

Although the liver is the primary target of infection, studies to better define the steps of hepatitis C virus infection are greatly hampered by the lack of a suitable animal model for such studies (the only animal known to be susceptible to hepatitis C virus is the chimpanzee). A tissue-culture system using recombinant DNA technology was recently developed and has advanced the scientific knowledge base considerably, including early forays into vaccine development.

The primary immune response to hepatitis C virus is mounted by cytotoxic T lymphocytes. Unfortunately, this process fails to eradicate infection in most people; in fact, it may contribute to liver inflammation and, ultimately, tissue necrosis [8].

The ability of hepatitis C virus to escape immune surveillance is the subject of much speculation. One likely means of viral persistence relies on the presence of closely related but heterogeneous populations of viral genomes. Further studies of these quasi-species enable classification of several genotypes and subtypes, which may have clinical implications [8].

MODES OF TRANSMISSION

HCV infection is a major public health problem worldwide [11, 22, 23]. In developing countries, blood transfusions and unsafe injections used during treatments are thought to be the major routes of transmission [11, 22-24] , accidental needle sticks, and other parental exposures, including nosocomial transmissions[25-28] are considerable risk factor. However, outbreaks in health-care settings have been consistently reported primarily attributed to contaminated medications or equipment and breaches in aseptic techniques in the United States, Europe, and Japan. Also occupational injury by needles or sharp instruments contaminated with blood, hemodialysis and tattooing are well documented modes of transmission [29-33]. 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 [34].

Historically, most hepatitis C virus infections result from blood transfusions. The risk of transfusion-borne hepatitis C virus began to decline in 1986, when surrogate-marker screening of blood donors started. Further declines were noted after the introduction of hepatitis C virus–directed antibody screening in 1990 (first generation) and 1992 (second generation). The current risk of transfusion-derived hepatitis C virus is estimated to be 1 case in every 100,000 units transfused [8].

Since the introduction of blood donor selection and screening for HCV antibodies and RNA , intravenous drug use and invasive medical procedures are the main current risk factors for HCV transmission worldwide[1,8].

Also gastrointestinal endoscopic examination and history of surgery was higher in subjects who were HCV RNA positive than those who were anti-HCV antibody negative, so the spread of HCV has relation with the previous risk factors. As surgical instruments have physical contact with injuries in human skin and mucous membrane during the operation and the dental treatment. Endoscopic inspection instruments could cause injury to the mucous membrane during the examination [28].

Furthermore, cross contamination continues to occur among injection drug users (IUDs) by the sharing of drug preparation equipment [35-37]. The seroprevalence of HCV among IUDs in the United States is high, ranging between 30% and 85%, with current estimates suggesting more than over 60% of newly acquired infections occur in individuals who have injected drugs [38, 39].

Hemodialysis is a possible cause of hepatitis C virus infection. Health care employees may be accidentally exposed [8].

Working in health care fields (medical, dental, or laboratory) that entail direct exposure to human blood carries an increased risk of HCV transmission [40].

Dental procedures were associated with an increased risk of HCV. This finding was previously reported by one study conducted in a rural areas of Egypt [34]. However, the findings reported by Arafa et al relied on a cross sectional study comparing individuals with and without anti HCV antibodies. Thus, dates of contamination were unknown, exposures assessment concerned long periods of time and exposures may have occurred after HCV infection. The results, based on incident cases reinforced the hypothesis of gum treatment as a risk factor for HCV transmission. Bleeding during dental procedures is frequent. A study reported the detection of HCV RNA on instruments after dental procedures in HCV infected patients [41]. Thus, the potential for contamination of the instruments is real in the context of a high HCV prevalence and inadequate sterilization procedures.

A strong risk factor for incident infection in the Egyptian children in our communities is that boys, who are often traditionally circumcised as small children in groups by non-medically trained persons during ceremonies in rural villages, were at

increased risk for HCV infection. However, girls, who are traditionally circumcised individually when older, showed no increased risk [42].

Tattooing, body piercing, and acupuncture with unsterile equipment are possible routes of infection [8, 56].

As HCV has been detected in several body fluids, including saliva, acute hepatitis C cases have occurred in subjects bitten by HCV-infected individuals [43]. Pooling studies in a systematic review, Ackerman and others reported that HCV RNA was found in the saliva of 79 (47%) of 168 patients with circulating HCV RNA and in 7 (7%) of 54 of patients with anti-HCV without circulating RNA [44-46].

While sexual transmission of HCV has been suggested [24, 47, 48], it is much less efficient for HCV than for other sexually transmitted viruses [24]. Data regarding the sexual transmission of HCV vary widely, with frequencies ranging from 0% to 27%. However, most studies report a percentage of 0% to 3% [11, 49]. The findings of studies involving specific populations, such as HIV-positive patients, patients with sexually transmitted disease (STDs), drug users, homosexuals and sex professionals, differ from those obtained from the general population, with the observation of a marked increase in the risk of HCV transmission[49,50] . Certainly, trauma to the mucosa during sexual intercourse increases the risk of viral transmission, as well as the high viremia levels and the presence of viral particles in the semen. Male-to-female transmission seems to be more common than female-to-male [51, 52]. Rooney and Gilson reported an estimated risk of HCV infection of 1.5 (CI: 1.05-2.2) per decade of marriage. In addition, women with HCV-positive partners presented a 3.7-fold higher chance of contracting the disease [53]. But there is some debate concerning the likelihood of heterosexual HCV transmission as there are a weak father-mother resemblance for HCV seropositivity (OR~2) ,as previously reported for stable couples from an Egyptian population from the Nile Delta study[54].

Mother-to-child transmission rarely occurs (<5%) in the absence of co-infection with the HIV [55]. The estimated risk of transmitting HCV infection from mother to child was 1.7% per pregnancy if the mother had detectable anti- HCV antibodies, 4.3% if the mother had detectable HCV RNA, and 7.1% if the mother tested positive for HCV RNA at least twice during pregnancy or around the time of delivery[55].

Density of viral infection with hepatitis C virus affects the likelihood of transmission from mother to child in utero. The authors hypothesized that the development of a cell mediated immune response during fetal life may contribute to the relatively low frequency of MCT [57].

Neonatal hepatitis C infection is defined as detectable HCV RNA in an infant 's blood in the first 1 to 6 months of life. The results suggest that at least one third and up to a half of infected children acquired infection in utero. Neonatal HCV infection must be distinguished from perinatal transient viremia in which HCV RNA is detected in peripheral blood within 0 to 5 days of birth [58] . With respect to this transient viremia, detection of HCV rRNA in the cord blood is irrelevant. Maternal HIV coinfection has been associated with up to 2- to 3-fold increase in transmission of HCV [55], and women with HCV viraemia are more likely to transmit than non-viraemic women [61]. High maternal HCV viral load (> 600,000 IU/mL) appears to favor mother-to-infant HCV transmission [59, 60].

Fortunately HCV-infected mother is unlikely to transmit infection to more than one of her offspring, independently of HCV genotype and of the duration of infection. Indeed, the disparity of transmission among offspring of the same mother may have different explanations, such as fluctuations in the maternal viral load [62].
The role of breast feeding was evaluated as a risk factor for mother-to-infant transmission of HCV in 10 studies [63-65]. Only one of these studies defined the extent (duration and exclusivity) of breast feeding [65]. Overall rates of mother-to-infant transmission between breast-fed and non– breast-fed infants were similar. The weighted rate of mother-to-infant transmission was 3.7% and 3.9% for breast- fed and non-breast-fed infants, respectively (crude rate 6.0%,SD 1.1% and 6.3%, SD 0.8% for breast-fed and non- breast-fed infants, respectively). Although some investigators have detected HCV RNA in breast milk, no definite case of mother-to-infant transmission of HCV via breast milk has been reported [65] . Breastfeeding is not contraindicated for mothers with hepatitis C virus infection. The contraindication to breast feeding is HIV coinfection in high-income countries. Avoidance of breast feeding is not an effective intervention for preventing mother-to-infant transmission of HCV [61, 66]. It is prudent to avoid breast-feeding if the nipples are bleeding, if mastitis is present, or if the mother is experiencing a flare of hepatitis with jaundice postpartum [65, 67, 68].

However, the strong associations between fathers' and childrens' HCV status which observed even when the mother was anti-HCV negative, suggests the observed parent-child associations are not totally explained by neonatal transmission from the mother or from breast-feeding. In a previous Egyptian study, 1 in every 6–7.5 children in the Nile Delta village whose mothers or fathers had HCV RNA had been infected with HCV. Children whose parents had HCV RNA had increased odds of infection to 4.9 and 2.7 times respectively that of children whose mothers and fathers did not have anti-HCV [42].

A possible explanation for an observed association between a parent and child's HCV status is that particular community exposures are experienced in

common by a family. However, if this were the total explanation, we would not expect the association to vary depending on whether the parents were viremic. The fact that we observed highest seroprevalence among children whose parents had HCV RNA positive is more consistent with person-to-person transmission. Transmission might also occur during a common exposure from outside the household [13]. Such as a common parenteral exposure experienced by members of Egyptian communities through injections by formal or traditional health care providers [19]. And health care providers may reuse needles and multiple members of a family receive injections from the same needle; this could explain some of the concordances within the family. Intra-familial transmission by other means than blood is biologically plausible, since HCV RNA has been detected in semen [69], cervical smears [70] and saliva[44,46] of infected patients; nevertheless, it remains to be proved that this RNA represents infectious HCV[71].

A second possible explanation for the observed concordance is confounding by age. This could occur because seroprevalence increases by age and older parents are more likely to have older children. However, this observed association persists after controlling for age, which shows that it is not totally due to the confounding of age [69].

A third possible explanation is familial sharing of genes predisposing to HCV infection [69] .

Given that none of these possible explanations can totally account for the high risk of anti-HCV in children whose parents have antibodies to HCV and/or HCV RNA, these observations suggest a fourth possible explanation: concordance could be the result of person-to-person transmission within the household [42] by intra-familial transmission, possibly sexual or domestic (ie, unapparent parental transmission through sharing of nail trimmers or other grooming items such as razors or toothbrushes, nail clippers and manicure cutters might be an important factor for intrafamilial transmission[72], or through inconspicuous exposures to contaminated body fluids and blood[44-46]. In recent years, there have been several studies from Europe and USA which suggested that Intrafamilial transmission of HCV was a consequence of the sharing parenteral practices rather than of close household contacts or sexual transmission [72-74] .

40-45% of HCV infection occurs through persons with no clear risk factor that has been defined. HCV infection rates in populations not at overt risk for infection range from 0.06 to 14.5%. The rates of infection in household contacts or HCV-infected persons are higher than the infection rates in people who do not have household exposures. HCV prevalence is reported to be from 2 to 10 times higher in family members of HCV infected patients than in general population[75] . Several studies have reported that HCV infection may cluster in families or households, based on the higher prevalence of HCV infection among family members of infected

cases (mainly patients with chronic liver disease, haemophilia, or on haemodialysis) than in controls[21, 76, 77].

A recent epidemiological study in Egyptian cohort showed that the parenteral treatment of schistosomiasis may have been at the origin of the HCV epidemic in the Egyptian population, but this and other iatrogenic factors account for only half of all current infections in adults [34]. Moreover, no iatrogenic factor was identified for infected individuals under the age of 20 years, for whom seroprevalence in Egypt was 3%, so there are other mechanisms of HCV infection A recent study of intrafamilial transmission in Egypt showed that the incidence of offsprings to acquire HCV from anti-HCV-positive parents is slightly higher (incidence rate of 8.7/1000 per year) in the positive mother than in the anti-HCV-positive father (6.6/1000) [21]. A study in Egypt reported highest prevalence of anti-HCV in the world between 6 to 28% (mean 22%) in parenteral anti-schistosomal therapy receiving individual and their household contact[79] .A study of 300-household contacts of 60 index cases in Southern Iran (Khuzestan) estimated 1.33% HCV seroprevalence among the household contacts of HCV-seropsitive index cases[79]. Other studies such as Italian local health district study have reported a lower prevalence of 4.7% HCV infection in household contacts of index cases [79]. Seropositivity for HCV was found in 8.9% of the household contacts in a another study done in Italy recruited from Policlinico Gemelli in Rome as well as other hospitals in Central Italy between 1995-2000[80].

Some previous studies of household spread of HCV have arrived at differing conclusions regarding the possibility, and importance, of household spread. Most of these report small rates of household spread [81, 82]. Napoli and others found that among family contacts of patients chronically infected with HCV, excluding spouses, 5 of 76 were anti-HCV positive, in comparison with to 0 of 45 among members of control families[83]. They concluded intrafamilial transmission is an important route of HCV infection. In contrast, based upon finding that only 8 (3.3%) of 250 family contacts of anti-HCV–positive patients were positive, in comparison with 3 (1.8%) of 170 among control families, Kim and others concluded that familial transmission “if it occurs" is rare [81]. However, their reported two-fold increase in rate of anti-HCV in family members of anti-HCV–positive persons is compatible with household transmission. Ackerman et al, found that the severity of liver disease in the index patient, the number of family members infected with HCV and the duration of exposure with the index patient were connected to intrafamilial transmission [76].

This difference in the results of different studies may be a consequence of several factors such as the ELISA tests used to detect anti-HCV antibodies (first and second-generation ELISA used in previous studies have a relatively low sensitivity in relation to the newer third-generation assays), geographic area, viremia levels, sexual behaviors of the subjects studied, selection of the studied population, statistical methods used to assess within-household clusters of HCV infection and genotypes.

Clinical features of HCV infection in children

Acute HCV is rarely recognized in children, and fulminant cases have not been reported. Children with chronic infection are typically asymptomatic, with normal or mildly abnormal alanine aminotransferase levels [16]. The children with vertically transmitted HCV infection are usually completely asymptomatic in the first 4 years of life. spontaneous resolution is frequent at a median age of 15 months. About 4% of children are persistently infected at the age of three [84].

Non organ-specific autoantibodies are commonly reported in European series but clinically apparent autoimmune manifestations are rare [16]. HCV-associated cryoglobulinemia, vasculitis, and porphyria cutanea tarda have not been reported in children. This lack of clinical signs or symptoms, and the fact that "routine" serum alanine aminotransferase determinations are not performed as part of pediatric medical care, indicating that chronic HCV infection in children is probably under recognized [16].

Most people (80%) with acute HCV infection have no symptoms. If symptoms occur, they may include loss of appetite, abdominal pain, fatigue, nausea, dark urine, and jaundice. In adults, HCV infection may lead to chronic hepatitis in about 80% of cases of which 5–15% may progress to liver cirrhosis over 20 years. Two to 5% of patients with liver cirrhosis will develop primary hepatocellular carcinoma [85].

The most common symptom of chronic infection is fatigue; severe liver disease develops in 10%–20% of infected people [86]. Of the chronically infected people, 15% to 30% will eventually develop cirrhosis, often 20 to 30 years after the initial infection. Eventually, symptoms develop. Symptoms of cirrhosis include the following:

- Fluid retention causing swelling of the belly (ascites), legs (edema), or whole body (anasarca)
- Persistent jaundice
- Fatigue
- Disturbances in sleeping
- Itchy skin
- Loss of appetite, weight loss, wasting
- Vomiting with blood in the vomit
- Mental disturbances such as confusion, lethargy, extreme sleepiness, or hallucinations (hepatic encephalopathy) [87].

To date, hepatocellular carcinoma appears extremelly uncommon in children with CHC. Only 2 cases have been reported in children [88]. Recent observations in adults with CHC indicate that hepatocellular carcinoma complicating CHC may develop in the absence of cirrhosis [89,90].

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Numerous extrahepatic disorders have been associated with CHC in adults. Glomerulonephritis, typically membranoproliferative, may occur in children with CHC. Unlike in the adult population, neither cryoglobulinemia nor lymphoma has yet been reported in children. HCV infection in the central nervous system has been identified as causing cognitive impairment in some adults with CHC [(91)].

Natural history of HCV infection in children

Although factors that influence the natural history of HCV infection in adults have been defined, they are less clear in children. The natural history of transfusion-associated HCV infection may differ according to the underlying disease for which the transfusion was given. 45 to 50%of children who received blood transfusions at the time of surgery for congenital heart disease developed chronic infection [(92)]. Among 29 children followed for a minimum of 4 years, half of those with persistent viremia had chronic hepatitis histologically, but none had cirrhosis [(92)]. Children treated for leukemia before 1990 are reported to have a high rate of HCV infection [(93)]. In one study, prolonged follow-up (13 to 27 years) of these children showed no evidence of serious liver disease [(93)]. The authors hypothesized that acquisition of HCV during a period of immunosuppression induced by chemotherapeutic agents may have prevented the development of an immune response that would cause the chronic injury in this disease. However, in a cohort of children treated for cancer at St. Jude 's Children 's Research Hospital, (Memphis, TN), 1 child died of liver failure 9 years after onset of HCV infection, and 2 others died of hepatocellular carcinoma after 25 and 27 years[(93)]. Among 58 surviving children with HCV infection who were followed longitudinally, 3 of 35 (8.5%) who underwent liver biopsy had cirrhosis [(93)]. Children with thalassemia requiring chronic transfusions have a very high prevalence of HCV infection [(94)]. Secondary hemochromatosis may contribute to the hepatic injury in this patient group, and response to therapy may be affected by the degree of hepatic iron overload [(94)]. Studies have also shown that HCV infection acquired from anti-hemophilic factor treatment of children with hemophilia can cause early mortality [(94)].

Cirrhosis has been reported in 1% to 2% of children with CHC, and liver transplantation has been performed for end-stage liver disease in advanced disease. The natural history of CHC in children and teenagers may be affected by certain biological factors. Genotype 3 may be more likely to clear spontaneously [(95)]. While Persistent viral replication lead to end-stage liver disease which is related to perinatal exposure, maternal drug use, and infection with HCV genotype 1a Children with such features should be considered for early treatment [(96)].Also medical conditions associated with increased risk of more severe disease include obesity (obesity is associated with progression of chronic hepatitis C virus (HCV) infection and poor response to interferon therapy among HCV-infected adults [(97,98)], survivors of childhood cancer, congenital anemia requiring chronic transfusions[(94)], children co-

infected with HIV[99], or hepatitis B virus (HBV), iron overload[100] and chemotherapy [101].

The natural history of perinatally acquired HCV infection is of particular importance. In general, HCV infection acquired vertically is often associated with biochemical evidence of hepatic injury early in life, which persists for many years in the majority of, but not all, instaces, causes only mild liver disease in the first 1 or 2 decades. However, a small proportion of perinatally infecred children develop advanced liver disease during childhood. According to the studies of Pediatric Liver Transplantation (SSPLIT) Registry that collects data from 37 North American pediatric liver transplant centers, chronic hepatitis C was the reason for transplantation in 9 of 941 children who underwent liver transplantation between 1995 and 2001[16].

In summary, the natural history of HCV infection in childhood is relatively benign because hepatitis C is rarely associated with severe or decompensated liver disease during the childhood years. However, HCV infection acquired during childhood persists for many years, causes chronic hepatic damage, and may, at least in some instances, be responsible for significant morbidity and mortality later in life.

Host Contribution to Disease

Little information is available about how host responses characteristic of infants and children actually contribute to the pathobiology of HCV infection. Factors relating to enhanced disease severity identified in adults may be relevant to children and adolescents with CHC. For example, a genome-wide scan strategy was used to identify 2 genes, DDX5 and CPT1A, which may be associated with increased susceptibility to liver fibrosis in adult patients with CHC [102]. Other preliminary data suggest numerous candidate genes related to HCV clearance or persistence [103]. Infants may have certain defense mechanisms, possibly age- related, which explain the relative inefficiency of mother-to-infant HCV transmission. In one study, infants with human leukocyte antigen (HLA) DR13 appeared significantly less likely to develop CHC after mother-to-infant transmission [104]. Subsequent reports have suggested that additional HLA loci may influence disease transmission[105,106]. Another study showed that infants exposed to HCV develop CD4 b lymphocytes with specific reactivity to HCV even in the absence of detectable anti-HCV; however, infants who had vertical infection showed either no response or response to only 1 viral peptide [107]. Infants with the Rs12979860 CC genotype for the IL28B polymorphism may be more likely to spontaneously clear the virus.

Spontaneous clearance of HCV

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Resolution of CHC may be spontaneous or treatment induced. Spontaneous clearance of HCV was defined as _ two positive anti-HCV antibody tests with negative HCV-RNA at least 6 months apart without any treatment [108].

Anti-HCV antibodies may persist in patients with resolved infection or may disappear at some time after a self limiting hepatitis. It may be difficult to define the extent of liver disease as there is no correlation between HCV seropositivity and the development of chronic liver disease, although the likelihood of coexisting liver disease is increased if hepatic transaminase values are raised [109].

Infants infected by vertical transmission have a high rate of spontaneous resolution approaching 25% to 40%. Most have spontaneous resolution by 24 months of age, but some may have spontaneous resolution as late as 7 years after vertical infection [80, 95, 108-110].

The overall rate of spontaneous viral clearance was 17.5% with higher clearance (27%) in the transfusion group compared to the vertically acquired group (9%) in another study [111, 112].

Approximately 6% to 12% of older children experience spontaneous resolution [80, 113] with a few reports of strikingly higher proportions [108].

Histological features of the liver in HCV infection in children

The spectrum of histological findings in HCV-infected children has been the topic of 3 published studies. In all 3 series, the characteristic histological lesions of HCV infection, including portal lymphoid aggregates or follicles, sinusoidal lymphocytes, and steatosis, were seen with approximatelythe same frequency as in adults [16]. Kage et al, from Japan, described findings in 109 children, most of them were infected by blood transfusion. Necro-inflammatory activity was on average mild (average score, 3.8 in the Scheuer system). No child had cirrhosis, and only 3.6% had bridging fibrosis with architectural distortion (stage 3 fibrosis). Viral genotypes were not reported, and the average duration of infection was only 2.6 years. In contrast, in a series from the United States, the overall histological activity (using the Scheuer and METAVIR scoring systems) was generally mild, but portal fibrosis was much more frequent, described in 78% of 40% children. The degree of fibrosis was rated as mild in 26%, moderate in 22%, severe in 22%, and as cirrhosis in 8% of children. Two children with cirrhosis were young adolescents who had acquired HCV infection perinatally. In this series, 60% of children had HCV genotype 1a and 32% had genotype 1b. Mean duration of infection in children for whom it could be determined was 6.8±5.3 years. A third histological series consisted of 80 children from Italy and Spain, most of them were infected with HCV genotype 1, with a mean duration of infection of 3.5±4.3 years [16]. Overall, necroinflammatory scores were low (grade 1 or 2). The frequency and severity of the bile duct damage and lymphoid follicles increased with patient age. Fibrosis was present in 72.5% of cases, and increased in frequency with duration of disease and patient age, just as in American series. Only 1 child (1.3%) had cirrhosis [16].

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Thus, histological features of chronic hepatitis C in childhood are similar to those reported in adults. Although, necrosis and inflammation are usually mild, fibrosis is common and appears to progress with increasing age and duration of infection. This progressive fibrosis suggests that the natural history of HCV infection acquired in childhood may lead to significant morbidity as the children enter young adulthood [16].

Treatment

Children with hepatitis C who demonstrate persistently elevated serum aminotransferases or those with progressive disease (ie fibrosis on liver histology) should be considered for treatment. Although in adults the presence of bridging fibrosis on liver biopsy is an important predictor of future progression to cirrhosis [114], this observation has not been confirmed in children [115, 116]. One can also argue that children with CHC and only mild disease (low/normal aminotransferases, minimal inflammation, or fibrosis on biopsy) could be considered for treatment given the real possibility of viral eradication and the lack of predictors of progression.

The best available treatment, a combination of polyethylene glycol (PEG)-conjugated interferon alpha (IFN-α) and ribavirin , is not effective in every patient and can be associated with severe adverse effects. Based on multiple smaller open-labeled, uncontrolled single-center and large blinded, multicenter pediatric studies combination treatment with PEG-IFN- a has demonstrated superiority in achieving sustained virological response (SVR) over IFN- a alone. PEG-IFN-a also requires only once weekly dosing rather than 3 times per week dosing as is necessary for standard IFN- a. Factors predictive of a higher virological response to treatment include HCV genotypes 2 and 3 (typically> 80% SVR) and a lower viral load in those with genotype I (< 600,000 IU/mL or< 2 6 copies/ mL) [117-119]. IFN- is a cytokine that has important functions in the innate antiviral immune response [120]. Circulating IFN- a attaches to cell-surface receptors .For chronically infected patients, treatment with recombinant polyethyleneglycol (PEG)-interferon α-2b and daily ribavirin has now been approved as standard treatment for children 2-17 years of age. In five large prospective studies, a total of 318 children and adolescents aged 3-17 years were treated either with subcutaneous PEG-interferon α-2b at a dose of 1-1.5 μg/kg or 60 μg/m² once a week in combination with oral ribavirin (15 mg/kg per day) or PEG-interferon α-2a with ribavirin. Subjects with genotype 1 and 4 received the medication for 48 wk and individuals with genotype 2 and 3 mainly for 24 wk.

Overall sustained viral response (SVR) was achieved in 193/318 (60.7%) of treated patients. Stratified for genotype; 120/234 (51%) with genotype 1, 68/73 (93%) with genotype 2/3, and 6/11 (55%) with genotype 4 showed SVR. Relapse rate was between 7.7% and 17% [121].

A prophylactic or therapeutic vaccine is so far is not available.

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