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TOPIC HIGHLIGHT

2015 Advances in Hepatitis C virus

What's new in hepatitis C virus infections in children?

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Abstract

The number of hepatitis C virus (HCV) infection cases is relatively low in children. This low number may be connected with the lack of screening tests and the asymptomatic course of infection. Currently, mother-to-infant transmission is the most common cause of HCV infection amongst children in developed countries. It is important to introduce routine screening tests for HCV in pregnant women. The risk of vertical transmission of HCV is estimated at approximately 5% (3%-10%). Currently, we do not have HCV transmission prevention methods. Some factors could potentially be eliminated by elective caesarean section. Currently, the method of prevention of perinatal HCV infection is the early identification and effective treatment of infections in young women in the preconception period. We describe genetic tests (IL-28B single nucleotide polymorphisms) to identify children with an increased chance of spontaneous clearance or sustained virologic response achievement and vitamin D level as a potential predictor of treatment response in children. It is also important to develop non-invasive tests that can predict liver fibrosis. The existence of differences in the mechanisms leading to liver injury between children and adults creates new perspectives of action to reduce liver disease progression in children in the early years of life.

Key words: Hepatitis C virus; Infection in children; Single nucleotide polymorphisms; Epidemiology; Biomarkers of liver injury; Vertical infection

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Core tip: Vertical transmission (VT) is the most common cause of hepatitis C virus (HCV) infection in children. It is important to introduce routine HCV screening tests in pregnant women. Some hopes for VTC prophylaxis are associated with directly acting antiviral agents. IL-28B single nucleotide polymorphisms may help to identify children with spontaneous clearance and with good

treatment prognosis. Developing non-invasive tests that can predict liver fibrosis in children is important. New biomarkers of liver injury (ITIH4, C4a, arginase 1) have been shown to reflect liver fibrosis and steatosis. The differences in liver injury between children and adults create new perspectives of action to reduce liver disease progression in children.

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INTRODUCTION AND EPIDEMIOLOGY

Hepatitis C virus (HCV) infection is a major health problem affecting approximately 150-180 million people worldwide, with its estimated 19 million persons infected in Europe[1]. Moreover, 3-4 million people worldwide are newly infected every year, and 350000 patients die every year due to HCV-related disorders[1,2]. According to a report from eighty-seven countries, the total global anti-HCV prevalence was estimated to be 1.6% (1.3%-2.1%)[3], whereas a recent study by the World Health Organization estimated that the prevalence of HCV varies between 2.4% in Western and Central Europe and 2.9% in Eastern Europe[1].

There are a few current global studies evaluating the prevalence of HCV infection in children, and accessible data are mainly estimated and local; there are no worldwide studies. The reason for this lack of data could be the lack of screening tests and the asymptomatic course of HCV infection. According to NASPGHAN recommendations, HCV screening should be performed in all children born to HCV-infected mothers (with assessment of anti-HCV antibodies in children after 18 mo of age and HCV RNA at a younger age), in children with chronically elevated transaminases and in children from regions with a high prevalence of HCV infection by assessing anti-HCV antibody levels. All positive anti-HCV antibody tests should be followed by a HCV RNA test to determine whether the infection is active[4].

The prevalence of HCV infection in children varies from 0.05%-0.36% in the United States and Europe and up to 1.8%-5.8% in some developing countries[5]. In studies conducted in Rio de Janeiro State in 1999-2012, Villar *et al*[6] collected data from approximately 1217 children aged 0 to 18 years. 20 individuals (1.7%) had anti-HCV antibodies in serum samples, but only 3 individuals (0.2% of all patients) were HCV RNA-positive. Recently, an epidemiological survey of HCV infection was conducted amongst children aged 10 to 19 years living in Brazil, and it reported an overall seroprevalence rate of 0.75%[7]. According to Abd-Elgawad *et al*[8], the global prevalence of HCV infection is relatively low in children, with an anti-HCV prevalence rate of 0.2%-0.4% in the Western world, with the exception of Egypt, which has the highest prevalence of adult HCV infection in the world, averaging 15%-25% in rural communities. In two Egyptian studies, anti-HCV antibodies were detectable in 3%-9% of children, depending on the region. Similar to global studies, the most common type of HCV infection in children is genotype 1. The following findings were confirmed in British research: 63% children were infected with genotype 1, 33% with genotype 3 and only 3% with genotype 2[9]. According to data from the National Institute of Public Health in Poland, the number of HCV infections in 2013 was 2641 (6.86 per 100000 people), and only 45 cases were registered in children from 0 to 18 years of age. There was also a significant decrease in cases amongst children and adolescents younger than 19 years of age[10].

There are a few most common routes of HCV transmission in children: blood transfusions, trans-plantations, unsafe injection procedures and vertical transmission. In studies conducted in Birmingham, Great Britain in 1991-2008, 133 children infected with HCV were analysed. The route of transmission was vertically acquired in 49%, transfusion acquired in 47% and transplantation acquired in 2%. Moreover, Abdel-Hady *et al*[9] showed that transfusion-associated hepatitis C was the main cause of HCV infection in children between the years 1991 and 1995. However, this route was superseded by vertically acquired HCV infection from 1995 onwards. These data correspond with other global studies. Prior to the 1990s, the principal routes of HCV infection were *via* blood transfusion and the unsafe use and reuse of injection equipment in hospitals. Unfortunately, in developing countries, these causes of HCV transmission are still reported amongst children[5].

Currently, mother-to-infant transmission of HCV is the most common cause of HCV infection amongst children in developed countries[1,5,9,11]. The incidence of HCV infection in pregnant women ranges from 1%-2% in the United States and Northern Europe and up to 8% in developing countries. Sood *et al*[12] estimated a HCV RNA prevalence rate of 1.43% in pregnant women in northern India, although this rate is comparable to those reported in other parts of the world (0.1%-2.4%)[9]. In a meta-analysis conducted by Benova *et al*[11], the risk of vertical HCV infection in children of HCV antibody-positive and RNA-positive women was 5.8% for children of human immunodeficiency virus (HIV)-negative women and 10.8% for children of HIV-positive women. These results correspond with data from Yeung *et al*[13], which showed that the risk was 1.7% amongst children born to all HCV antibody-positive women and 4.3% amongst children of HCV RNA-positive women. In Europe, the estimated rate of vertical HCV transmission also ranges

from 2% to 5%[1,9]. Therefore, routine screening tests for HCV infection need to be introduced in pregnant women.

PREVENTION OF VERTICAL HCV INFECTION

Mother-to-child transmission (MTCT) is currently responsible for 60%-90% cases of chronic hepatitis C in paediatric patients in developed countries[14]. For many years, many studies have been conducted to identify the risk factors of vertical transmission of HCV and potential ways to prevent this infection. Most of the published works come from developing countries.

High maternal serum viral load (HVL - $\geqslant 10^6$ copies/mL) during the perinatal period, the inflammatory activity in the maternal liver, coexisting HIV infection, and female sex of the baby are considered to be factors that potentially increase the risk of MTCT. Additionally, potential factors associated with higher risk of transmission are prolonged labour, premature rupture of the membranes, a long period from rupture of membranes to childbirth, newborn massive exposure to maternal blood and HCV-contaminated fluids, maternal intravenous drug abuse, HCV infection in the mother's sexual partner, maternal liver inflammation activity, the use of invasive foetal testing and assisted vaginal delivery (forceps and vacuum extractor)[1,9,11,12]. The length of labour and the time of rupture of membranes are associated with newborn exposure to the maternal blood and fluids, which are potential sources of infection. Maternal intravenous drug abuse is associated with a higher risk of the presence of HCV RNA in maternal peripheral blood mononuclear cells and thus with a higher risk of perinatal transmission[15]. Breastfeeding in the context of the risk of HCV transmission has also been the subject of many studies.

High maternal viral load in the perinatal period and coexisting HIV infection seem to be the most important factors that increase the risk of MTCT[16,17]. According to Murakami *et al*[17], the risk was higher in children of mothers with a high viral load in the perinatal period, prolonged exposure to the maternal blood and fluids in the genital tract and premature rupture of membranes. Cottrell *et al*[18] performed an extensive meta-analysis of published studies on the risk factors of vertical transmission of HCV, including invasive foetal testing and prolonged rupture of membranes. They found divergent data. Most of the available studies excluded the impact of breastfeeding on the risk of transmission.

Currently, we do not have HCV transmission prevention methods that could be used in newborns, in contrast to HIV and HBV. A vaccine against HCV or a specific immunoglobulin has not yet been developed, and recommended chemoprophylaxis is not available. The identification of risk factors for MTCT is therefore the basis for developing recommendations of procedures to prevent or at least reduce the likelihood of transmission. The most important risk factor seems to be a high viral load in the mother during the perinatal period. Its reduction can only be achieved by the use of antiviral treatment. There is currently no recommended chemoprophylaxis of perinatal HCV infection.

The use of pegylated interferon (PegIFN), especially during the first trimester of pregnancy, may be associated with an increased risk of miscarriage and low birth weight, and ribavirin (RBV) is classified by the FDA as category X because of its teratogenic effects. Accordingly, prevention using standard therapy cannot be applied during pregnancy, and women who have begun treatment before pregnancy should discontinue the therapy immediately after the confirmation of pregnancy. Some hopes are associated with direct acting antiviral agents, which appear to have a greater safety profile in pregnancy and show no teratogenic effects; they are applicable and effective without PegIFN and RBV[19]. Another proven risk factor for MTCT is concomitant HIV infection. The risk of transmission of HCV infection in children of HCV- and HIV-positive mothers without antiretroviral treatment is estimated to be 15%, which is 3 times higher than in children of HIV-negative mothers. To some extent, we have the opportunity to reduce this risk through the use of highly active antiretroviral therapy. The effectiveness of such a procedure in reducing HIV viral load is indicated by the significant reduction in the risk of HCV transmission, probably by reducing the HCV viral load[20].

Another group of potential risk factors for MTCT is related to the duration of labour or rupture of membranes time (more than 6 h), as well as the use of invasive foetal testing and assisted vaginal delivery. These factors could potentially be eliminated by performing an elective caesarean section. The effectiveness of this approach is the subject of a number of prospective and retrospective studies, the results of which are divergent; currently, there is no evidence to recommend elective caesarean section to reduce the risk of perinatal transmission of HCV. The results of the analysed studies were inconsistent; some showed a reduction in the risk of infection by using elective caesarean section compared with vaginal delivery or emergency caesarean section, but the differences in most studies were not statistically significant, and subsequent studies have not confirmed these observations. The conclusion was that it is not currently possible to indicate any particular intervention that would involve a reduction in the risk of infection[18].

A meta-analysis conducted by Ghamar Chehreh *et al*[20] showed that caesarean section does not reduce the risk of perinatal transmission of hepatitis C virus from HCV-RNA (+)/HIV (-) mothers to their infants. However, Murakami *et al*[17] conducted a prospective study, which, inter alia, assessed the risks associated with various modes of delivery in patients with high viral load in the perinatal period. According to the obtained data, elective caesarean section in patients

with HVL was associated with a significant reduction in the risk of transmission of infection; MTCT was found in 41% of infants born vaginally and none of those born by elective caesarean section. The authors therefore suggested that elective caesarean section could be an effective method to prevent MTCT in women with HVL. Furthermore, in a retrospective study, it was found that the effectiveness of elective caesarean section reduced the risk of transmission of HCV infection in patients co-infected with HIV[21].

Currently, there are no recommendations regarding chemoprophylaxis of perinatal HCV infection. There is also no obvious evidence that the mode of delivery affects the risk. Therefore, despite the significant progress that has been made in recent years in the treatment of chronic HCV infection, the only unequivocally recommended method of prevention of perinatal HCV infection is the early identification and effective treatment of infections in young women in the preconception period, but the treatment should be completed at least 6 mo before a planned pregnancy due to the potential teratogenicity of currently used drugs.

NEW TESTING DIRECTIONS

The rest of the work describes only the latest aspects and directions of the research recently conducted in paediatric patients with chronic hepatitis C (CHC), which may have a potential impact on the development of diagnostic tests for monitoring patients, on the prediction of adverse consequences in the course of the disease and on treatment results.

NEW TESTING DIRECTIONS FOR THE PREDICTION OF PERSISTENT INFECTION

The estimated rates of spontaneous clearance of the HCV RNA in vertically infected children vary considerably, and in the European population, the rates do not exceed 30%[22-24]. Spontaneous clearance of HCV in vertically infected children has been associated with HCV genotype 3 infection and with transaminase flare in the first year of life. Recently, Garazzino *et al*[22] confirmed the results of previous studies by showing that the resolution of infection is higher in patients infected with HCV genotype 3 and in patients with higher ALT levels in the first two years of life. Currently, we are additionally able to identify a group of children with an increased chance of spontaneous clearance by performing a genetic test determining the single nucleotide polymorphisms (SNPs) in the *IL-28B* gene. In 2011, a preliminary study showed the independent association of the rs12979860 polymorphism with the spontaneous clearance of HCV genotype 1 in infants infected by perinatal transmission[25]. This connection was confirmed by multicentre collaborative studies[26,27]. One of these studies enrolled 177 Italian children, of which 30 (16.9%) had spontaneous clearance and 147 had a persistent HCV infection[27]. This study demonstrated that the favourable CC *IL-28B* genotype increases the chances of spontaneous elimination of the HCV more than twice compared to the CT and TT genotypes combined (OR = 2.7; 90%CI: 1.3-5.8). Additionally, an ethnically matched control group with unknown hepatitis C status obtained from the 1000 Genome Project data was used for the analysis. It was demonstrated that in children with spontaneous viral clearance, the prevalence rate of the favourable genotype CC is significantly higher compared to that of ethnically matched individuals (56.7% and 34.7%, respectively, $P = 0.03$). However, the predictive potential of IL-28B variation is diversified, which is associated with variations in geographical distributions of HCV genotypes and differences in frequency of *IL-28B* SNPs by race. The adult study showed that the global pattern of *IL-28B* SNPs distribution may partly explain the observed discrepancy in the frequency of viral clearance across various ethnic groups[28]. In a recent study conducted in 130 Chinese paediatric patients with spontaneous clearance, rs12979860 and rs8099917 SNPs independently predicted spontaneous clearance[29]. The odds ratio was 7.39 (95%CI: 1.07-50.41) and 14.27 (95%CI: 3.07-108.50) for rs12979860 and rs8099917, respectively. In this study group, the frequency of spontaneous clearance was 47%, which is related to a high frequency (> 85% for both) of favourable genotype CC of rs12979860 and genotype TT rs8099917.

NEW TESTING DIRECTIONS FOR THE PREDICTION OF TREATMENT RESPONSE

Currently, in the case of a confirmed HCV infection, to comprehensively qualify a patient for treatment, the HCV RNA levels, HCV genotype and SNPs of the *IL-28B* gene should be determined. These are well-known predictors of response to interferon-based therapy in adults. The connection between high baseline HCV viral load and the unfavourable HCV genotypes 1 and 4 with a higher likelihood of failed interferon and RBV combination therapy was also confirmed in children[30-32]. The importance of the favourable genotypes CC rs12979860 and TT rs8099917 in the *IL-28B* gene associated with higher sustained virologic response (SVR) rates in PegIFN-based treatment for HCV infection in children has been demonstrated in several studies[33-36]. Thus, the determination of the *IL-28B* SNPs may be useful in clinical practice in enhancing the correct prediction of SVR achievement in children. In contrast, no associations were found between the rs8099917 marker and the final treatment outcome in Japanese children who were treated with response-guided PegIFN or a PegIFN plus RBV combination[37]. The results of these studies suggests that, similar to adults, the SNPs of IL-28B appear to have limited

potential for predicting treatment response, and *IL-28B* genotype testing cannot be used alone to predict the final outcome. Despite limited prognostic potential, *IL-28B* SNPs - as one of the strongest pretreatment predictors of SVR - are greatly needed for standard PegIFN-based therapy in CHC children. Although new specifically targeted antiviral agents are being introduced in adults, currently, these types of drugs are not allowed to be used in children because the safety of this therapy in children has still not been determined. Therefore, further paediatric studies are needed to evaluate the potential role of *IL-28B* genotype testing together with other known prognostic factors in new treatment strategies targeting children who poorly tolerate IFN-based regimens.

Recently, vitamin D levels have also been identified as potential predictors of response to HCV therapy in children. A study of Egyptian HCV children showed a high frequency of vitamin D deficiency and significant decreases in bone density compared with healthy children control groups matched by age and sex[38]. It was demonstrated that children treated with vitamin D showed higher early and sustained virological responses. Therefore, the authors suggest that the assessment of vitamin D levels before the start of PegIFN/RBV therapy and correction of any detected deficiency during the course of therapy may be needed to improve viral response.

NEW DIRECTIONS FOR BIOMARKERS OF LIVER INJURY

Whereas chronic hepatitis C is usually asymptomatic during childhood, long-term infection can lead to severe and decompensating liver disease in later childhood or adulthood[22,39]. The results of several paediatric studies reveal that the degree of liver injury generally correlates with age and duration of infection[8,40-42], although progression seems to be slower than observed in those infected later in life. In contrast to previous studies[43,44] that suggest that co-infection with HBV and HCV is associated with more severe liver disease and frequent progression to cirrhosis, in a recent study conducted in Polish children, HBV/HCV co-infection did not enhance fibrosis compared with HCV or HBV mono-infection groups[45]. However, in this study group, HBV/HCV co-infection was associated with moderate to severe necro-inflammation, irrespective of age of biopsy or duration of infection, and led to significantly higher necro-inflammatory activity than HCV mono-infection.

Liver biopsy still represents the gold standard for evaluating the current status of liver injury, including inflammatory and fibrosis scores in CHC. However, in children, this may result in a higher risk of complications; therefore, it is less accepted in paediatric patients than in adults[46]. Thus, developing non-invasive tests that can predict liver fibrosis, especially in paediatric populations, is attractive. Several years ago, Fibrotest and ActiTest were found to be potential non-invasive assays for the assessment of hepatic fibrosis and necro-inflammatory activity in CHC paediatric patients in comparison with liver biopsy[47-49]. In fact, they have limited prognostic potential. In the Hermeziu *et al*[48] study, it was shown that the global concordance between FibroTest-ActiTest and METAVIR scores was found in 48% of paediatric cases. A recent study that used proteomic analysis of serum from adult patients with CHC revealed that Complement C4a and inter-alpha-trypsin inhibitor heavy chain 4 (ITIH4) were potential factors to predict liver fibrosis[50]. A study including 30 Egyptian CHC children showed that C4a was not associated with histological scores, but it could predict significant fibrosis (presence of bridging fibrosis) with acceptable clinical performance[51]. The paediatric experience with serum level of ITIH4 showed notable correlation of this marker with later stages of fibrosis[52]. ITIH4 serum levels were substantially higher in patients with significant fibrosis than in those at lower fibrosis stages. Based on the available data, non-invasive tests designed to predict the degree of liver injury currently have too many limitations to constitute an alternative to liver biopsy; however, they may be useful to detect significant fibrosis. Non-invasive detection of significant fibrosis is very important for treatment decisions. Patients with significant fibrosis progression are commonly prone to cirrhosis, so antiviral treatment should be strongly considered in this group. In another preliminary study conducted in children, the aberrant expression of arginase 1 in liver tissue correlated with liver steatosis in HCV infection[53]. Immunochemistry and western blot analysis showed that there was higher expression of arginase 1 in HCV patients with steatosis than in those without it. These findings open new horizons for diagnostic markers for steatosis, but the tools need to be confirmed by larger studies.

There is relatively little information on the histopathology of chronic hepatitis C in children. It is currently accepted that both immune system-mediated reactions and viral cytopathic effects are involved in CHC pathogenesis; however, the effects of each component on the final result in children and adults have not been previously studied. In a recent preliminary study, Valva *et al*[54] evaluated an intrahepatic viral infection by comparing apoptosis and portal and periportal infiltrates in paediatric and adult patients. The results of this comparative study provided the first suggestions that liver injury in paediatric CHC may be substantially associated with viral cytopathic effects mediated by apoptosis, whereas in adults, it could be mainly associated with an exacerbated immune response. Knowing the existence of differences in the mechanisms leading to liver injury between children and adults creates new perspectives of action to reduce liver disease progression in children in the early years of life.

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