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Hepatitis C Virus in Thalassemia

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Abstract

Prevalence of hepatitis C virus (HCV) infection is relatively low in children. However, seroprevalence rates of 10–20% have been reported among children who received repeated transfusion. The development and the severity of liver fibrosis are strongly related to the extent of the liver iron overload and to the presence of chronic hepatitis C (CHC). In CHC, liver iron overload has been suggested as a negative prognostic factor exacerbating inflammation with subsequent progression of liver fibrosis and decrease in antiviral therapy effectiveness. CHC may be suspected based on medical history or accidentally discovered abnormal liver functions. Hepatitis C is diagnosed by positive serology for viral antibodies and confirmed by polymerase chain reaction (PCR) to detect virus RNA. The treatment of HCV infection in children was difficult due to the limitations of pegylated interferon- α and ribavirin. In 2017, FDA approved the first direct-acting antiviral agents (DAAs) for children including ledipasvir/sofosbuvir in the adult dose, 90/400 mg, to treat HCV in children and adolescents aged 12 years and older or weighing at least 35 kg. Similarly, giving half the adult fixed-dose of ledipasvir/sofosbuvir, 45/200 mg, to children aged 6–11 years is still under clinical trials with promising results.

Keywords: chronic hepatitis C, thalassemia, direct-acting antiviral agents

1. Introduction

The prevalence of hepatitis C virus (HCV) infection is relatively high in thalassemic children. The development and the severity of liver fibrosis in those children are strongly related to the extent of the liver iron overload and to the presence of chronic hepatitis C. Chronic

hepatitis C (CHC) in most infected patients lead to the development of liver fibrosis, cirrhosis, portal hypertension and hepatocellular carcinoma. Therefore, all persons with positive anti-HCV antibody tests must undergo additional testing for the presence of the HCV itself using polymerase chain reaction (PCR). Combined pegylated interferon- α and ribavirin with its limitations and serious complications remained the standard therapy for pediatric HCV infections until early 2017. Fortunately, the recent development of the direct-acting antiviral agents (DAAs) and the FDA approval of ledipasvir/sofosbuvir in the adult dose, to treat HCV in children and adolescents aged 12 years and older or weighing at least 35 kilograms has revolutionized the treatment of HCV infection.

2. Background

The prevalence of HCV is increasing and estimates of the future burden of CHC predict at least a threefold rise in chronic liver disease and cirrhosis by the year 2020 [1].

3. Epidemiology of hepatitis C

About 3% of the worldwide population is infected by HCV with a significant racial difference. Males are more commonly affected than females due to frequent exposure to intravenous drug and alcohol abuse. Females are frequently infected from blood product transfusions [2]. The most affected regions are Eastern Mediterranean and European Regions [3]. Egypt has possibly the highest HCV prevalence in the world where 10–20% of the general population is infected [3]. The prevalence of HCV in North Egypt and South Egypt is 15.8 and 6.7%, respectively [4].

The prevalence of HCV infection is relatively low in children. Asymptomatic HCV is detectable in 2.02% of Egyptian children [5]. However, seroprevalence rates of 10–20% have been reported among children who received blood products for conditions such as thalassemia or hemophilia or those with a variety of other potential exposures such as malignancy, hemodialysis, extracorporeal membrane oxygen, or surgery for different reasons [6, 7]. A study in Mid-Delta, Egypt, reports 40% of patients with thalassemia are infected with HCV [8].

4. Hepatitis C virus (HCV) and its genotypes

Hepatitis C virus is small, single-stranded, enveloped RNA virus of the flaviviridae family [9]. The only natural host is man. Currently, there are six HCV genotypes and many subtypes (1a, 1b, 1c, etc.). All HCV genotypes have a common ancestor virus. However, HCV genotypes 1, 2 and 4 are more prevalent in Central and Western Africa, genotype 5 in South Africa and genotypes 3 and 6 in China, South-East Asia and the Indian subcontinent [10]. Genotype 4 is widespread in East Africa and Egypt [11]. Approximately 90% of Egyptian HCV isolates belong to a single subtype, 4a, which responds less successfully to interferon therapy than other subtypes [12].

5. Modes of HCV transmission

The main mode of transmission in children has changed over time. Before 1990, when HCV had not been identified, transfusion of blood and blood products and organ transplantation were the usual mode of transmission. One of the major routes of transmission is the reuse or inadequate sterilization of medical equipment, especially syringes and needles in healthcare settings. Currently, perinatal transmission accounts for most of cases [13].

Vertical transmission is almost always confined to women with detectable HCV RNA. The rate of vertical transmission is approximately 5%. Mothers with higher titers of HCV RNA and those who are HIV positive are more liable to pass the infection to their babies with transmission rates varying from 2 to 12%, according to maternal infectivity. Hepatitis C antibody is passively transmitted, and so all infants will have HCV antibody for up to 13–18 months. Measurement of HCV RNA is necessary to detect active infection, but it is unreliable before 3 months of age. Breastfeeding is safe in mothers with low titers of HCV RNA [14]. In children with beta thalassemia, the blood transfusion is not the only way of transmission but community and environmental factors may play a role [8].

6. Iron overload and hepatitis C virus in patients with thalassemia

Multicenter cross-sectional studies have reported that the development and the severity of liver fibrosis are strongly related to the extent of the liver iron overload and to the presence of chronic HCV infection [15]. HCV infection is the main risk factor for liver fibrosis in transfusion-dependent thalassemia. Excess liver iron is now clearly recognized as a cofactor for the development of advanced fibrosis in patients with HCV infection [16]. Despite its clinical relevance, thalassemia-associated liver damage has been insufficiently characterized [17].

Most of HCV-RNA negative patients with low iron load did not develop liver fibrosis, while HCV-RNA positive patients infected with genotype 1 or 4 and iron overload more frequently developed advanced fibrosis. Adequate chelation therapy usually prevents the development of liver fibrosis in patients free of HCV infection and reduces the risk of developing severe fibrosis in thalasseemics with chronic hepatitis C (CHC) [15].

7. Relationship between chronic hepatitis C and liver iron concentration in thalassemia patients

Hepatitis C virus infection is responsible for 80–90% of post transfusion cases of hepatitis in patients who have received blood transfusions (more than 75% of HCV infection become chronic and up to 20–30% progress to cirrhosis) [18]. The main causes of liver fibrosis in transfusion-dependent thalassemia major are HCV infection and hepatic iron overload [16].

Chronic hepatitis in most infected patients lead to the development of liver fibrosis, cirrhosis and hepatocellular carcinoma. Patients with HCV have mildly to moderately increased hepatic iron concentration and occasionally have severe hepatic iron overload [13]. The increased iron stores may be due to release from damaged hepatocytes, to the virus itself or to genetic determinants so that the iron can influence the progression of chronic hepatitis C [19].

In patients with CHC, the degree of liver fibrosis and hepatic iron concentration were correlated. However, this correlation cannot be translated as a causal relation. It is not clear whether this correlation merely reflects the presence of more active disease or iron exacerbates chronic HCV-induced damage through activation of hepatic stellate cells (HSC) and regeneration of hepatocytes [20].

8. Pathogenesis and clinical consequences of iron overload in chronic hepatitis C

Iron overload induces oxidative stress leading to cell membrane damage, DNA instability and mutagenesis [21]. Due to these effects, iron can be considered a proinflammatory, profibrogenic factor and a potential carcinogen [22].

Increased hepatic iron potentiates progression toward liver fibrosis and contributes to poor response to interferon therapy [18]. There is evidence that excess iron is known to promote oxidative stress and cause direct liver damage and accelerate progression to both micronodular cirrhosis and hepatocellular carcinoma [23]. Based on the above-mentioned observations, iron overload has been suggested as a negative prognostic factor of chronic hepatitis C with influence on the increased aminotransferase activity, exacerbation of inflammation, progression of liver fibrosis and decrease in antiviral therapy effectiveness [24]. Iron accumulation in the liver induces oxidative stress which accelerates lipid peroxidation, resulting in destruction of organelle membrane and cell death via hepatocyte necrosis or/and apoptosis [25]. Also, oxidative stress products induce a focal inflammatory reaction which in turn stimulates hepatic macrophages and release of profibrogenic cytokines [26]. These mechanisms trigger the activation of hepatic stellate cells (HSC) which are major sources of collagen and other extracellular matrix elements that gradually accumulate in perisinusoidal spaces of liver parenchyma [27]. Longer hepatocyte exposure to excess iron is associated with greater risk of progressive fibrosis and development of liver cirrhosis with irreversible nodular reconstruction of the organ, replacement of the functional liver parenchyma with the connective tissue and loss of function [28]. Due to these effects, there is evidence that moderate to severe liver iron concentration and chronic HCV infection in thalassemia patients have a potentiating effect on hepatic fibrogenesis [29].

9. Symptoms and signs of hepatitis C

Acute HCV infection becomes chronic in 70% of patients, which represents a high rate of chronicity for a viral infection. Most patients with CHC and compensated hepatic synthetic

functions are usually asymptomatic. They may have nonspecific complaints like fatigue or malaise. However, patients with decompensated cirrhosis post HCV infection have the same symptoms observed in other patients with decompensated liver diseases.

Manifestations in patients with decompensated liver disease occur merely due to synthetic dysfunction and portal hypertension. These include mental status changes (hepatic encephalopathy), ankle edema and abdominal distention (ascites), and hematemesis or melena (variceal bleeding). Sometimes, extrahepatic manifestations of HCV are the first symptoms observed; most commonly, it involves the joints, muscle and skin [30].

10. Diagnosis of hepatitis C

As most patients of hepatitis C experience no or non-specific symptoms during acute phase, they usually do not seek medical advice and diagnosis is rarely made at this phase of the disease. The clinical diagnosis of hepatitis C in chronic phase is also challenging as the patient may spend decades with compensated liver functions lacking any specific symptoms until advanced liver disease develops [31].

Chronic hepatitis C may be suspected clinically on the basis of the medical history. A history of unsafe injections as IV drug abuse or inhaled substance usage, such as cocaine, piercings or tattoos, sharing toothbrushes or personal sharp objects (e.g. nail scissors or cutters) with HCV patient raise the suspicion of HCV infection. Unexplained easy fatigability, with abnormal liver enzymes or liver function tests found during routine blood testing may be the clue. Also, hepatitis C may be diagnosed as a result of targeted screening; such as screening of blood donors or HCV contact tracing [32].

Diagnosis of HCV can never be made on clinical bases only. Serological blood test is the first step in diagnosis. The test is used to detect antibodies to HCV. Anti-HCV antibodies can be detected in 80% of patients within 15 weeks after exposure, in >90% within 5 months, and in >97% by 6 months after exposure and may persist for life even in treated patients. This makes the test more valuable to diagnose infection but not to test cure of HCV chronic infection. HCV antibody tests have a strong positive predictive value for exposure to HCV but may miss patients in early phase who have not yet developed antibodies, or those who have an insufficient level of antibodies to detect [31, 32].

Immunocompromised individuals infected with HCV may never develop antibodies to the virus. So, using HCV antibody test is of no value in screening immunocompromised patients for HCV, and they should be screened using a test to detect the virus itself if HCV infection is suspected [33].

Anti-HCV antibodies indicate exposure to the virus but cannot determine the presence of ongoing infection. So, all persons with positive serology must undergo additional testing to confirm the presence of current infection. Molecular nucleic acid testing methods, such as polymerase chain reaction (PCR) are used to test the presence of virus RNA in the blood [34]. HCV RNA PCR is a quantitative test that has the capacity to detect not only the presence but also the amount of virus copies present in the blood which is also known as "viral load". HCV

viral load neither indicate disease severity nor prognosis. It was a predictor of response to interferon-based therapy but not important now with the current therapy [33].

Genotype testing was generally recommended before therapy as it was used to determine the required length and potential response to interferon-based therapy. This concept was changed with the introduction of direct-acting antiviral drugs [35].

11. Treatment of hepatitis C

11.1. Standard PEG interferon/ribavirin (PEG-IFN/RBV) combination therapy

The treatment of HCV infection in children was difficult as few options were available. The standard therapy for children aged 3 years and older was combined pegylated interferon (PEG-IFN) α -2a or 2b and ribavirin, and the duration of therapy was dependent on HCV genotype. This treatment regimen was developed first in adults [36, 37]. Combined pegylated interferon- α and ribavirin with its limitations and serious complications remained the standard therapy for pediatric HCV infections till 2017 [38].

11.2. New direct-acting antiviral agents

In recent years, many direct-acting antiviral agents (DAAs) are under development for treatment of CHC. DAAs reduce the amount of HCV in the body by blocking viral replication inhibiting directly one of the several steps of the HCV lifecycle preventing the virus from multiplying, and in most cases, they cure HCV. DAAs are classified into several categories based on their molecular target [39, 40]. The recent development of DAAs has shown promising results in clinical trials for use in children and adults and has dramatically increased the rates of sustained virological response (SVR) while improving side effect profiles as compared to interferon-based treatments [41]. Prior to 2017, new DAAs available for adults have still not been approved for treatment in children [37, 38, 41, 42].

Recently (on April 7, 2017), the US Food and Drug Administration (FDA) approved the first DAAs for children that included sofosbuvir (Sovaldi) and sofosbuvir/ledipasvir (Harvoni) to treat HCV in children and adolescents aged 12 years and older or weighing at least 35 kg. These DAAs (Harvoni and Sovaldi) were previously approved to treat HCV in adults. These approvals will help change the landscape for HCV treatment by addressing an unmet need in children and adolescents [43]. The adult fixed-dose of ledipasvir/sofosbuvir, 90/400 mg, resulted in similar plasma exposure of ledipasvir, sofosbuvir and GS-331007 (the inactive metabolite of sofosbuvir) in adolescents as in adults, thus the adult dose was used for this age group [44]. Similarly, giving half the adult fixed-dose of ledipasvir/sofosbuvir, 45/200 mg, to children ages 6–11 years resulted in comparable plasma exposure of ledipasvir, sofosbuvir and GS-331007 as in adults, without any severe adverse events or laboratory abnormalities [45].

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