Chronic hepatitis B in pediatrics: to treat or not to treat, that is the question

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ABSTRACT

Chronic hepatitis B virus infection is one of the most prevalent diseases worldwide. It may progress to cirrhosis and hepatocellular carcinoma. An early detection, not using intravenous drugs, sex education, and immunization are critical for prevention. An infection in the neonatal period and in the first year of life becomes chronic in more than 90 % of children. Vertical transmission from a mother with hepatitis B virus to the newborn infant is currently the most common mode of transmission. Detection, immunoglobulin administration, and immunization help to reduce it. Antiviral therapy may accelerate the transition from the active to the inactive phase of infection by two or three years, without affecting the recovery process. A timely treatment of some selected cases may prevent hepatitis B progression.

Key words: hepatitis B, therapy, cirrhosis.

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INTRODUCTION

Hepatitis B is one of the most prevalent chronic infections. Worldwide, more than 350 million people are infected with this virus. Of them, 15-25 % will develop cirrhosis and, eventually, hepatocellular carcinoma.¹ Prevalence varies across the different world regions, with some areas still endemic. In our country, the prevalence is very low, but it is necessary to pay close attention to the virus brought in by immigrants from high-prevalence countries, which are increasing every year. An early detection, not using intravenous drugs, sex education, and immunization are relevant health measures to prevent this condition.

Virus characteristics

Hepatitis B virus (HBV) is a deoxyribonucleic acid (DNA) virus from the *Hepadnaviridae* family. It has a relatively small DNA genome, 3.2 kb, considering the proteins necessary to allow its replication inside the liver parenchyma. The same DNA section, using different transcription start sites, codes more than one messenger ribonucleic acid (mRNA) and, therefore, more than one protein.

A particular case is precore DNA sequence, with two transcription start sites; one of the mRNAs codes the e protein and the other, the core protein. The mutation in the sequence of the former may not affect the core protein reading, so the virus continues replicating, but the hepatitis B e antigen (HBeAg) disappears from circulation and anti-HBe antibodies emerge, in association with a viral load that is sort of relevant. Other mutations in the sequence that codes for the S protein have been observed in rare cases, which may lead to an escape to the immune response.

A specific characteristic of HBV is that it acts like a retrovirus. This means that it is capable of integrating into the host's genome and remaining in their body. Integration may occur rapidly after infection, but the duration of the replication period may favor this process.² Such specific property of HBV increases the possibility of developing carcinoma, depending on the integration site.³

Hepatitis B virus clinical characteristics and lab tests

The time of infection by HBV in children will determine the possibility of developing a chronic infection. If the infection occurs during the

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neonatal period and up to the first year of life, more than 90 % of children will become chronic. Such percentage decreases with age and reaches 5 % after 5 years old, similar to adults.

Vertical transmission, from a HBV positive mother to a newborn infant, is currently the most common mode of transmission, although screening for HBV during pregnancy controls, together with immunoglobulin administration and immunization in the first 12 hours of life, have considerably reduced this route of transmission. However, the rate of vertical transmission is still approximately 5 % among mothers with high viral replication, in spite of a strict compliance with prophylactic measures. Such small percentage of infection may be reversed by prescribing antiviral therapy to pregnant women in their third trimester.⁴

HBV may also be disseminated via horizontal, parenteral or sexual transmission. Therefore, intravenous drug prevention, hygiene measures, immunization, and sex education are key elements to fight these modes of transmission.

Chronic hepatitis B patients are asymptomatic, except if they develop cirrhosis, in which case clinical manifestations correspond to complications from certain extent of liver failure or portal hypertension. In general, a torpid progression with fibrosis and, finally, cirrhosis does not take place in the first years of life. Such clinical course has been seen in less than 4 % of pediatric patients; in these cases, it is worth paying special attention to the possibility of developing hepatocellular carcinoma, which

occurs in at least 1 out of 2 patients, although rare cases of hepatocellular carcinoma without cirrhosis have been reported. Such complications suggest a strict follow-up of these children with or without cirrhosis, at least once every year.^{5,6} A physical examination, liver enzymes and alpha-fetoprotein levels, and an abdominal ultrasound are indicated for control.

HBV co-infection with the hepatitis D virus may progress to cirrhosis in more than 25 % of children. Fortunately, such co-infection is very rare in pediatrics, especially in our country.

Natural history of hepatitis B virus

The natural history of HBV has four phases, depending on the anti-viral immune response. First of all, tolerance; secondly, active response; thirdly, inactivation; and finally, recovery (*Table 1*). The duration of each phase or stage varies over time. The transition from the tolerance to the active phase is marked by an increased transaminase level and a reduced viral load. In children infected via vertical transmission, the activation of the immune response generally occurs around puberty.⁶

During the pediatric age, i.e., until 18 years old, up to 85 % of children will reach the inactive phase, either spontaneously or after receiving treatment. Only 20 % in the same period will transition to the full recovery phase with the development of antibodies against hepatitis B surface antigen (anti-HBs). Such progression is not affected by treatment.^{5,7}

TABLE 1. Summary of the natural history of chronic hepatitis B virus infection in pediatrics

Natural history				
Phases	Tolerance	Active	Inactive	Recovery
GPT	Normal	Increased	Normal	Normal
HBeAg	+++	+	-	-
Anti-HBe	-	-	+	*
HBV-DNA	++++	++	Undetectable	Undetectable
HBsAg	+++	++	++	-
Anti-HBs	-	-	-	+
		Immune response	Minimum replication	

* Anti-HBe may be positive in precore mutation cases, in general, associated with an increased GPT level.

GPT: glutamic-pyruvic transaminase.

HBeAg: hepatitis B e antigen.

Anti-HBe: antibody against hepatitis B e antigen.

HBV-DNA: hepatitis B virus DNA.

HBsAg: hepatitis B surface antigen.

Anti-HBs: antibody against hepatitis B surface antigen.

Treatment

Different treatments have been used in the past 20 years for the purpose of reducing or preventing complications from chronic HBV infection (Table 2). Initially, alpha interferon was used with similar results to those of current antivirals, but with more adverse events. Lamivudine was introduced later.^{8,9} However, this drug caused an important number of resistance mutations.

A subsequent study demonstrated the effectiveness of adefovir dipivoxil in children older than 12 years (23 %), but not in younger children; it caused a smaller percentage of mutations than lamivudine.¹⁰ Entecavir is well tolerated by children older than 12 years. Its effectiveness is similar to that of treatments described above, but it caused less than 1 % of resistance mutations after one year of treatment and 2.6 % after two consecutive years. Tenofovir disoproxil fumarate has been used in children older than 12 years with an effectiveness similar to that of the drugs described before, but it offers the advantage of not causing mutations, even after several years of consecutive use in adults.¹¹⁻¹³ However, long-term use may cause bone or kidney adverse events, which may be less severe if tenofovir-alafenamide is used, which is equally effective.¹⁴ This drug may also favor the immune response to HBV.¹⁵

Treatment is indicated for patients in the active phase. The following factors favor HBeAg seroconversion to antibody against hepatitis B e antigen (anti-HBe): 1) increased glutamic-pyruvic transaminase (GPT) level to more than twice the normal value; 2) reduced viral load before onset; and 3) the extent of inflammation observed in the liver biopsy.

TABLE 2. *Treatments available for children with chronic hepatitis B virus infection. Percentage of HBeAg+ seroconversion to anti-HBe+ in children and adults*

HBeAg seroconversion to anti-HBe		
Treatment	Children	Adults
Peg-interferon	26 %	27-32 %
Lamivudine	23 %	16-21 %
Adefovir	23 %	12 %
Entecavir	24.2 %	21 %

Peg-interferon: pegylated interferon.

HBeAg: hepatitis B e antigen.

Anti-HBe: antibody against hepatitis B e antigen.

The attempt to promote an immune response with interferon injections in the tolerance phase of infection, followed by an antiviral, emerged as an interesting idea but did not achieve the desired success.¹⁶ Considering the natural history of HBV infection, treatment would only be indicated in the first years of life in the case of an important GPT increase and in the presence of fibrosis so as to attain regression or prevent the progression to cirrhosis.¹⁷ Another option would be to treat children with precore mutations if associated with persistent increased transaminase levels.

Liver transplantation for chronic hepatitis B is rarely required in children; however, it is indicated in the case of hepatocellular carcinoma and cirrhosis with liver failure. The latter is more common in HBV co-infection with hepatitis D virus.

CONCLUSIONS

The treatment of chronic hepatitis B may, at best, accelerate the transition from the active to the inactive phase of infection by two or three years. Transition from the inactive to the recovery phase is not affected by treatment. A modest objective, such as achieving HBeAg seroconversion to anti-HBe status, which indicates the transition to the inactive phase (with normalized transaminase levels), is probably enough in most cases, with the disappearance of hepatitis, to prevent the progression to cirrhosis and, subsequently, to hepatocellular carcinoma. As pointed out, treatment advances the moment of inactivation, which would occur somewhat later without treatment.

A potential assumption may propose that the acceleration of viral replication control would reduce the possibility of HBV becoming integrated into the hepatocyte genome. In opposition to this hypothesis, the virus has been found inside the hepatocyte genome even in liver biopsies from patients with acute massive liver necrosis caused by HBV, who rapidly enter the recovery phase within days.

Unfortunately, in children with cirrhosis, the development of hepatocellular carcinoma may be detected years after the inactivation of viral replication. Based on this, it may be suspected that the process of cell differentiation loss probably occurred a long time ago or that virus integration into pro-oncogenic regions expressed late.

Considering the low effectiveness of existing treatments, approximately 20 % of treated children transition from the active to the inactive

phase at the end of the first year. This percentage is approximately 10 % among placebo groups. A major argument in favor of antiviral therapy is that a lower viral replication reduces the extent of liver inflammation during treatment.

Ideally, treatment should cause only a few viral resistance mutations or none at all. At present, the most effective drug is tenofovir, but long-term administration leads to kidney and bone adverse events. This treatment may be justified for adults at risk, but hardly in pediatrics.

It would be desirable to “activate” the immune response to facilitate the subsequent control of viral replication. This strategy would be rapidly adopted to minimize the complications of HBV infection in the long term.

The detection of HBV infection in pregnant women and an adequate management, as well as the implementation of preventive measures in the newborn infant, may reduce the rate of vertical transmission, the most common mode in pediatrics. Monitoring chronic hepatitis B patients is critical to prevent and diagnose associated complications. A timely treatment of selected cases may prevent hepatitis B progression. ■

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