Hepatitis C. A challenge to hepatologists and to the liver transplantation team

Hepatite C. Um desafio aos hepatologistas e à equipe de transplante de fígado

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ABSTRACT

Hepatitis C is the main cause of cirrhosis and hepatocellular carcinoma and the leading indication of liver transplantation. The aim of this article was to review specific epidemiological, clinical and therapeutic aspects of hepatitis C and their implication for the hepatologists belonging to liver transplantation services. These specific aspects were reviewed in the literature mainly using Medline. Data regarding the epidemiological, clinical and therapeutic aspects of hepatitis C are discussed, with emphasis on their consequences for the liver transplantation team. Hepatitis C is a challenge for hepatologists and for the liver transplantation team. The burden we observe today is the late consequence of infection that occurred in the past. Measures for early recognition of complications of liver disease are recommended. HCV treatment should always be performed before liver transplantation if possible, but if not, HCV recurrence should be recognized and treated early after transplantation.

Key words: Hepatitis C Complications. Liver Transplantation. Burden. Hepatitis C Reinfection.

INTRODUÇÃO

Hepatitis C virus (HCV) is a small-enveloped RNA virus belonging to the Flaviviridae family \(^1\). HCV was identified in 1989 \(^1\) and it is estimated to infect 170 million people worldwide (WHO). HCV infection frequently results in chronicity. After acute infection most cases develop chronic infection and may progress to a severe form of liver disease. It is estimated that 15-30% of HCV chronic hepatitis may progress to cirrhosis within years to decades after infection and 3-4% of them will develop hepatocellular carcinoma \(^3\). HCV shows remarkable sequence variation. More than 90 subtypes have been identified around the world \(^4\). Phylogenetic analysis of full-length or partial sequences of HCV has led to the identification of the 6 main genotypes numbered 1-6 and a large number of subtypes groups identified by lower case letters (a, b, c) \(^5\). HCV also exists as a pool of genetically distinct but closely related variants referred to as quasispecies \(^5\). The prevalence of different genotypes varies according to geographic region. The most prevalent HCV genotypes are 1a, 1b, 2a, 2b, 2c, 3a and 4a \(^6\). Genotype 1b was mainly transmitted by blood transfusion before blood screening for HCV became available whereas genotypes 1b and 3a were transmitted by intravenous drug use. However, in industrialized countries the proportion of genotypes 1a and 3a have been increasing in relation to genotype 1b since today intravenous drug is the main route of HCV transmission \(^6\). In Brazil, genotype 1 is the most...
frequent followed by genotype 3. The genetic variability of HCV has been shown to have important clinical consequences. Viral genotype is a strong and independent predictor of the sustained virologic response to treatment. The major viral factors associated with impaired response are genotype 1 and high viral load. The prevalence of HCV infection is variable in different geographic regions and may range from 0.6% to 22%. The highest prevalence is in Asia and Africa and the lowest in industrialized countries. In Brazil the prevalence varies among different regions. Population-based studies showed rates of HCV infection of 1.42% in São Paulo (Southeast of Brazil). At the Blood Center of Ribeirão Preto (Southwest of Brazil) 1.2% of 25,891 blood donors (1996-2001) were positive for serum HCV antibodies in initial screening tests. Hepatitis C infection is one of the 10 leading causes of death due to infectious disease worldwide. It is estimated to cause 476,000 deaths per year due to complications of end-stage liver disease. In the US about 4 million people were infected with HCV, 2.7 million of them have progressed to chronic liver disease. In the US about 4 million people were infected with HCV, 2.7 million of them have progressed to chronic liver disease. In the US the introduction of an arbitrary value for HCC in the MELD list resulted in an increased number of transplanted patients. In the first year the number of transplanted patients for HCC increased from 7% to 22% and the waiting time on the list decreased from 2.3 years to 0.69 years. Since MELD criteria were only recently introduced in Brazil, patients with HCC have received palliative treatment with ethanol injection or chemoembolization while on the waiting list. New perspectives are expected with the adoption of MELD criteria for listing patients.

HCV and hepatocellular carcinoma (HCC)

The incidence of HCC is increasing as a result of the spreading of HCV. The treatment of choice for patients with HCC and cirrhosis is still liver transplantation. The survival rate is 75% in 4 years when the criteria to indicate transplantation are 1 nodule smaller than 5 cm or up to 3 nodules all smaller than 3 cm each. Screening protocols for the early detection of HCC are recommended by using ultrasound and the serum alpha-fetoprotein test in high risk patients. The major concern about the diagnosis of HCC is the waiting list time for transplantation, which allow the progression of the disease and impair the prognosis. In US the introduction of an arbitrary value for HCC in the MELD resulted in an increased number of transplanted patients. In the first year the number of transplanted patients for HCC increased from 7% to 22% and the waiting time on the list decreased from 2.3 years to 0.69 years. Since MELD criteria were only recently introduced in Brazil, patients with HCC have received palliative treatment with ethanol injection or chemoembolization while on the waiting list. New perspectives are expected with the adoption of MELD criteria for listing patients.

HCV and liver transplantation

HCV infection is the main cause of cirrhosis and the leading diagnosis for end-stage liver disease in liver transplantation candidates in Europe and the US. HCV reinfection post liver transplantation evaluated by HCV RNA detection using the polymerase chain reaction occurs almost universally. The natural history of the infection is modified by the transplantation with rates of cirrhosis recurrence of 8-44% in 5-7 years. Studies have suggested intra-operative re-infection of the liver graft at time of reperfusion. There is a high probability that the source is the blood itself. The viral load can return to the pre transplant values within 4 days after transplantation and may be influenced by the intraoperative or perioperative use of corticosteroids. Despite the early re-infection, the graft injury occurs only after 3 weeks. Acute hepatitis occurs between 2-5 months post transplant and it is characterized by acute lobular hepatitis. A higher viral load and cellular immune response and a higher rate of cell proliferation and apoptosis are observed compared to chronic hepatitis.
A variant form of post transplant hepatitis C is a cholestatic hepatitis C that occurs in <10% of patients, frequently associated with high viral load and immunosuppression. Usually it occurs within 1-6 months post transplant and can progress to hepatic failure in 3-6 months. This form is characterized by very high viral load, cellular ballooning, low inflammation, and a Th2 intra-hepatic immunological response. These features suggest that the liver lesion is due to a direct cytopathic injury caused by HCV. Chronic hepatitis is established about 6-12 months post-transplantation. With the development of chronic hepatitis, a decrease of viral load is observed, with a pattern of immune-mediated injury. The specific response to HCV can be detected by the pattern of Th1 response and by fibrosis stimulation. The expression of genes induced by interferon is increased as also is the expression of genes associated with apoptosis and fibrosis. The best strategy for hepatitis C treatment is to perform it before the transplant. However, patients with advanced cirrhosis have a lower 5 and 10 year survival rates when compared to patients with HCV undergoing liver transplantation have increased morbidity and mortality and these patients have lower 5 and 10 year survival rates when compared to patients undergoing liver transplantation for other aetiologies of cirrhosis.

Final considerations

Hepatitis C is the main cause of cirrhosis and hepatocellular carcinoma and the main indication of liver transplantation. The burden we are seeing today is the late consequence of infection that occurred in the past before HCV was identified. The identification of HCV allowed better control of the infection but contamination still continues to occur. The treatment of chronic HCV hepatitis is far from ideal but should always be used when possible and before transplantation. Prophylactic measures against HCV infection such as vaccines being tested. Measures for early recognition of complications of liver disease are recommended. Screening for hepatocellular carcinoma is recommended in order to improve the prognosis. Post-transplantation hepatitis C must be recognized and treated and new therapeutic approaches are needed.

References


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