Hepatitis C. A challenge to hepatologists and to the liver transplantation team[1]

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 theirs 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.

RESUMO

O objetivo deste artigo foi revisar aspectos epidemiológicos, clínicos e terapêuticos da hepatite C e suas implicações para a equipe de transplante de fígado. Esses aspectos específicos foram revisados na literatura usando principalmente o Medline.Dados relativos a aspectos epidemiológicos, clínicos e terapêuticos da hepatite C foram discutidos com ênfase nas suas conseqüências para a equipe de transplante de fígado. A hepatite C é um desafio para hepatologistas e para a equipe de transplante de fígado. A epidemia que observamos atualmente é a conseqüência tardia da infecção que ocorreu no passado. São recomendadas medidas para o reconhecimento precoce das complicações da infecção. Recomenda-se que o tratamento da hepatite C deve ser feito sempre que possível e de preferência, antes do transplante, mas se isso não for possível, esforços devem ser feitos para o reconhecimento precoce da reinfecção e instituição do tratamento.

Descritores: Hepatite C. Transplante Hepático. Epidemia. Hepatite C Reinfecção.

Introdução

Hepatitis C virus (HCV) is a small-enveloped RNA virus belonging to the *Flaviviridae* family [1,2]. HCV was identified in 1989 [1,2] 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) [2]. 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 [7]. 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 [8]. The prevalence of HCV infection is variable in different geographic regions and may range from 0.6 % to 22% [9]. 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% [10] in São Paulo (Southeast of Brazil). At the Blood Center of Ribeirão Preto (Southeast of Brazil) 1.2% of 25,891 blood donors (1996-2001) were positive for serum HCV antibodies in initial screening tests [11]. Hepatitis C infection is one of the 10 leading causes of death due to infectious disease worldwide [9]. 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 infection. HCV causes 10,000 deaths per year in the US [12]. After World War II there was an increasing use of blood and blood products and of the intravenous route for drug injection. Post-transfusion non A non B hepatitis has been diagnosed since 1970 but only after identifying HCV in 1989 was it possible to recognize this virus as the most important cause of post-transfusion hepatitis. Thus, HCV has infected tens of millions of people worldwide by this route. After the introduction of the blood screening tests for HCV infection the number of post transfusion HCV infection decreased significantly. Currently the dominant form of HCV infection in industrialized countries is intravenous drug use. In developing countries unsterile medical procedures remain an important source. In Egypt several subjects were infected in a nationwide campaign for schistosomiasis treatment [13]. In Brazil we have seen several patients who were contaminated by intravenous injection of licit drugs with non discharged material. Although the incidence of HCV is decreasing, at least in some parts of world (Europe and US), it is still high. The WHO estimates that 3-4 million new infections are occurring per year worldwide with 30,000 cases/year in the US (CDC). The asymptomatic behaviour of HCV infection in most cases makes it more difficult to estimate and to control the disease. On the other hand the prevalence of HCV will not decrease until 2010 [12], due to the long time between infection and clinical manifestation of advanced liver disease. This time is usually estimated as several years; however, it can be reduced depending on genetic and environmental factors [14]. It is estimated that HCV will be responsible for increasing the cases of cirrhosis and hepatocellular carcinoma by two thirds compared to current data. The implications of these estimates are a source of concern and debate for liver transplantation services. The control of the infection with vaccines is still a challenge. Trials testing vaccines for HCV are in course [15]. There are many difficulties because HCV does not stimulate a strong immune response, its genomic variability is high and no small animal model is available. A significant progress regarding the treatment of HCV has been made in the last years, but treatment is still not ideal. The high costs associated with common side effects are limiting factors. The current therapy for HCV is based on two drugs, interferon and ribavirin. Pegylated interferon was recently developed, showing a longer half-life, better pharmacokinetics and enhanced biological activity compared to standard interferon. However, the rate of sustained virologic response with pegylated interferon and ribavirin is around 50% [16, 17], meaning that 50% of treated patients continue to have HCV infection after treatment. The treatment of HCV infection is an important tool for controlling the infection and it is the only way to avoid progression to more advanced liver disease. Due to the less than ideal rate of response with available drugs, new drugs or treatment schemes are needed for patients who do not respond to the usual regimen of interferon and ribavirin.

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 [18]. Screening protocols for the early detection of HCC are recommended by using ultrasound and the serum alpha-fetoprotein test in high risk patients [19]. 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 [20, 21]. 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 [22]. The natural history of the infection is modified by the transplantation with rates of cirrhosis recurrence of 8-44% in 5-7 years [23]. Studies have suggested intra-operative re-infection of the liver graft at time of reperfusion [24]. There is a high probability that the source is the blood itself [25]. The viral load can return to the pre transplant values within 4 days after transplantation and may be influenced by the intraoperative or peroperative use of corticosteroids. Despite the early re-infection, the graft injury occurs only after 3 weeks [26]. 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 [25].

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 pos transplant and can progress to hepatic failure in 3-6 months [27]. 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 [25]. Chronic hepatitis is established about 6-12 months post-transplantation [25]. 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 [25, 28]. The best strategy for hepatitis C treatment is to perform it before the transplant. However, patients with advanced cirrhosis have low tolerance to treatment. The ILTS suggests that patients with decompensate cirrhosis and MELD <18 should be considered for treatment [29]. The rate of sustained response in these groups was 20-24% [30]. In transplanted patients the rate of sustained virological response using pegylated interferon and ribavirin is 12-34% [31]. The survival rate of 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[32].

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. Pos-transplantation hepatitis C must be recognized and treated and new therapeutic approaches are needed.

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