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Natural history of acute and chronic hepatitis C

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A B S T R A C T

Hepatitis C virus (HCV) infection remains a major global health burden. Hepatitis C causes significant liver-related morbidity and mortality due to hepatic decompensation and development of hepatocellular carcinoma. In addition, extra-hepatic manifestations of hepatitis C are frequent. There is a very large interindividual variability in the natural history of both acute and chronic hepatitis C which can be explained in part by a combination of various host, viral and environmental factors. Successful antiviral treatment can prevent short- and long-term complications of HCV infection in many patients. Still, the relative contribution of distinct risk factors for disease progression in different phases of HCV infection needs to be better defined. Personalized treatment approaches for HCV infection should consider individual risk profiles to avoid both under- and over-treatment – which will remain important also in upcoming era of interferon-free treatment of hepatitis C.

Introduction

Hepatitis C virus (HCV) infection is a global health burden affecting approximately 160–170 million people worldwide [1]. It is a major cause of liver cirrhosis and the increasing incidence of hepatocellular carcinoma (HCC) can be explained in part as a late complication of hepatitis C. Since the onset of nonA/nonB-hepatitis and the subsequent identification of HCV, numerous studies aimed to investigate the natural history of acute and chronic HCV infection. However, several limitations in study designs

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need to be considered and thus only very few unbiased prospective long-term cohort studies are available [2]. A major problem for all studies was that both acute and chronic HCV infection might be entirely asymptomatic. As a result many patients remain clinical unapparent and were not included in observational studies. Due common modes of transmission via blood contact or sexual intercourse, co-infections with the hepatitis B virus (HBV) or the human immune deficiency virus (HIV) are not infrequent in hepatitis C patients and thus it might be difficult to determine the relative role of HCV for the development of clinical endpoints. The same bias has to be considered regarding alcohol consumption which rarely has been defined in most studies. Moreover, it is not possible to determine the mode and exact time of infection in many patients and it was therefore difficult to investigate duration of infection as a variable. Other hurdles in studying the course of HCV infection include weaknesses in early virological diagnostics applied in the 1990s with less sensitive HCV RNA assays or difficulties to determine the HCV genotype and changes in clinical practice with lesser patients undergoing liver biopsy and more patients being treated by specialists in private practice.

Fortunately antiviral therapy for HCV infection has dramatically improved over the last 20 years. Well accepted, international treatment guidelines have been established [3] and the majority of HCV-infected patients in Western countries has access to antiviral treatment which may prevent progression of liver disease and development of clinical complications [2,4,5]. However, as a consequence it has been become ethically impossible to study the long-term natural history of the disease in the absence of treatment intervention.

Despite the methodological difficulties to investigate the natural history of acute and chronic HCV infection there have been several well-performed studies unravelling various aspects of HCV-associated liver disease. In this review we summarize the key findings on disease progression and HCV-related morbidity and mortality with a particular focus on factors potentially influencing the outcome of the disease.

Acute hepatitis C

Patients acquire HCV mainly via blood contact. Thus, the main risk groups are intravenous drug users, recipients of blood transfusions before 1992 and health care workers [6]. Sexual transmission accounts only for a minority of cases, however, acute hepatitis C has become a significant problem in HIV-infected MSM in recent years [7]. Within seven and 21 days after viral transmission HCV RNA becomes detectable in serum [8–10]. However, longer incubation periods can occur, especially in cases where only small amounts of viral loads have been transmitted [8]. These data suggest that the duration of the incubation period may vary between different transmission routes. HCV RNA levels rise rapidly after infection followed by a delayed increase of serum alanine aminotransferases (ALT) four–12 weeks after infection indicating hepatic injury [11]. ALT levels frequently reach values of more than ten times the upper limit of normal with concomitant rises of serum bilirubin [12,13]. Some patients also develop clinical symptoms two–12 weeks after viral transmission [9,14]. Still, the majority of patients remain asymptomatic during the acute phase and most of the infected individuals do not become aware of their disease. Therefore it is not easy to investigate the very early phase of HCV infection. Contrariwise, several studies have been published investigating patients recruited in the acute symptomatic phase of HCV infection with up to 81% of the patients presenting with diverse symptoms [13,15,16]. However, Even in symptomatic patients most of the clinical signs are unspecific. Commonly reported symptoms include fatigue, nausea, abdominal pain, loss of appetite, mild fever, itching or myalgia. 50–84% of the clinical overt patients with acute HCV infection develop jaundice as the most specific liver related symptom [13,15,17]. Fulminant courses of acute hepatitis C have been reported in only single cases which is in contrast to infections with other hepatotropic viruses [2].

Serological markers and diagnosis during acute HCV infection

Diagnosis of HCV infection is based on anti-HCV testing. Antibodies against HCV persist during all stages of the infection and also for some time after recovery. A decline of anti-HCV antibodies has been reported in some patients after more than ten years of follow-up after clearance of acute hepatitis [18]. In the introduction of tests to detect anti-HCV-antibodies has been a milestone in medicine since it lead