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RESEARCH ARTICLE

The Natural History of Hepatit is C Viral Infection: Clinical Evaluation and Monitoring

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Abstract: Hepatitis C virus (HCV) infection is one of the most common causes of chronic liver disease in the world and represents a substantial burden on global health systems and individual patient wellbeing. Routine screening for HCV in certain high-risk populations is appropriate. HCV can cause both an acute and chronic hepatitis, and manifests as a variety of hepatic and extrahepatic symptoms, largely influenced by a combination of host and viral factors. It can be difficult to predict clinical outcomes in individual cases. In those who suffer a chronic infection, progression to cirrhosis carries the risk of decompensation and hepatocellular carcinoma. The natural history of HCV infection and our understanding of risk factors that are predictive of disease progression are discussed.

Keywords: Chronic hepatitis C, Cirrhosis, Hepatocellular carcinoma, Natural history.

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the most common causes of chronic liver disease, affecting as many as 185 million people worldwide [1]. Population-based representative studies administered by the National Health and Nutrition Examination Survey (NHANES) estimate that the prevalence of HCV-antibody positivity in the US between 2003 and 2010 was 1.3%, or, 3.6 million persons [2] although other studies estimate that the true prevalence may be as high as 5.1 million persons [3]. The sequelae of chronic HCV (CHC) infection include cirrhosis and hepatocellular carcinoma (HCC). In the US, HCV-related liver disease is a common diagnosis responsible for inpatient hospitalization, a leading cause of death and a frequent indication for liver transplantation [4]. Conservative estimates place the cost of the total burden of HCV-related liver disease on the medical system at more than $5 billion [5].

HCV BIOLOGY

The HCV genome is a positive-strand RNA molecule of 9,500 nucleotides which encodes a 3,000 amino acid polyprotein. This large protein undergoes post-translational processing by host and viral enzymes to form structural and nonstructural viral proteins. The polymerase enzyme of RNA viruses lack proofreading ability and are therefore unable to correct errors made during the process of replication. These nucleotide changes result in tremendous viral heterogeneity, with the exception of the 5' terminus of the viral RNA, which is highly conserved, and, therefore, a useful target for amplification in diagnostic assays. This heterogeneity plays an important role in the pathogenesis of disease, response to treatment, and to date, has made it difficult to develop an effective vaccine [6]. Six major genotypes and more than 50 subtypes of HCV have been identified [7], having risen out of unique infection patterns, population migration, immune selection, and replication efficiency [8].

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HCV TRANSMISSION AND SCREENING

Transmission is most efficiently achieved through parenteral exposure to HCV. Intravenous (IV) drug use is the most common means by which patients in the US acquire HCV, with studies suggesting that 60% of newly acquired infections occur in those who have injected illegal drugs and that up to 77% of IV drug uses are anti-HCV positive [9]. Therefore, it is broadly recommended that individuals who have ever used illicit IV drugs should be tested for HCV infection [10]. Prior to the initiation of donor screening for anti-HCV antibodies in the 1990s, blood transfusion was a major risk factor for HCV infection, with more than 10% of transfusion recipients acquiring infection [11]. Following the introduction of routine screening of blood donors, transfusion-related HCV infection has become exceedingly rare, with an estimated risk of 1 in a million per unit transfused [12]. Individuals who have received blood transfusions or organ transplant prior to 1992 should be tested for HCV [13].

Routine testing for HCV is also appropriate in patients with unexplained elevations in aminotransferase levels, hemophilia patients who received blood products before 1987 (when viral inactivation procedures were implemented), hemodialysis patients, children born to HCV-infected mothers, patients with human immunodeficiency virus (HIV) infection, healthcare workers following a needle stick injury or mucosal exposure to HCV-infected blood, or sexually intimate partners of HCV-infected patients [13]. Finally, the US Preventative Services Task Force and Center for Disease Control recommends one-time testing of all patients born between 1945 and 1965, regardless of other risk factors, citing the higher prevalence of HCV in patients of this age demographic [14].

ACUTE AND CHRONIC HEPATITIS

Infection with HCV can result in both acute and chronic hepatitis. Acute hepatitis following HCV exposure typically develops within 2-26 weeks, with a mean onset of 7-8 weeks [15]. More than two-thirds of patients with acute HCV are asymptomatic,16 however, in those who develop symptoms, the most commonly reported symptoms are jaundice (68%), dark urine or acholic stool (39%), nausea (34%), and abdominal pain (25%) [16]. In those who develop symptoms, the acute illness can last from 2-12 weeks. Laboratory testing during the acute phase demonstrates a highly variable degree of serum aminotransferase levels (up to 10-20 times the upper limit of normal) [17] and bilirubin concentration (often > 3-4). HCV causes approximately 20% of all cases of acute hepatitis in the US [18]. Fulminant liver failure caused by acute HCV is rare, but may be higher in those with co-infection with hepatitis B virus (HBV) [19].

Following an acute episode of HCV, the risk of chronic infection is high. Between 80-100% of patients remain HCV RNA positive and 60-80% have persistent elevation in liver enzymes [20]. Many host factors may be involved in the ability of the host to spontaneously clear the virus. These factors include the host's age, gender, and other comorbid conditions, such as body weight, hepatic steatosis, alcohol consumption, and co-infection with HBV and/or HIV.

There is a wide variability in serum aminotransferase concentrations among patients with CHC. Up to one-third of patients may have a normal ALT, and only slight enzyme elevations are typically found in remaining patients, with only 25% having a serum ALT concentration more than twice the upper limit of normal [21]. There is generally poor correlation between aminotransferase levels and liver histology [22].

Most patients who develop CHC infection are asymptomatic or have mild, nonspecific symptoms, which may be difficult to solely ascribe to viral infection [23]. The most commonly reported symptom is fatigue, but other symptoms may also include nausea, anorexia, myalgia, arthralgia, weakness, and weight loss. Symptoms may not reliably reflect disease activity, but appear to be more common once cirrhosis develops [24].

In a subset of patients, an acute exacerbation of CHC can occur, with significant elevation of serum aminotransferase levels over the baseline in the absence of other identifiable triggers. The true incidence of this phenomenon is unknown, but may be affect approximately 10% of patients [25]. Such increases may be associated with more rapid progression of disease. In a study of 82 patients with CHC followed for a median of 36 months, a greater proportion of subjects with history of such acute exacerbations we found to have progression of fibrosis and inflammation [26].

CIRRHOSIS

The natural history of CHC is difficult to define because of the long course of the disease. A review of 111 studies demonstrated that the estimated prevalence of cirrhosis is approximately 16% (95% CI 14-90%) after 20 years of HCV infection [27]. In one case series of US patients with post-transfusion CHC who were followed for a mean of 22 years

after transfusion, 51% had developed cirrhosis, 23% had active chronic hepatitis, and 5% had HCC. The mean duration of infection among patients with cirrhosis was 20.6 years [28]. Asian and European studies have demonstrated similar results [29 - 31].

Just as not all patients with CHC will develop cirrhosis, not all patients with cirrhosis will develop complications. In a prospective cohort of 838 patients with CHC followed for, on average, 50 **months**, approximately 7% of the cohort developed liver-related morbidity and mortality, and the increased mortality was confined only to those who had cirrhosis at the time of presentation.[33] In a report of 200 patients with HCV cirrhosis, the most common forms of decompensation were ascites (48%), gastrointestinal bleeding (32.5%), severe bacterial infection (14.5%), and encephalopathy (5%) [32]. In a study of 384 HCV patients with compensated cirrhosis, the risk of developing decompensation was 3.9% per year [33]. The probability of survival after initial decompensation was 81.8% and 50.8% at 1 and 5 years, respectively.

HEPATOCELLULAR CARCINOMA

The mortality associated with CHC in the US is mostly associated with the consequences of decompensated end stage liver disease rather than hepatocellular carcinoma. In contrast to HBV, HCC in patients with HCV occurs almost exclusively in those with cirrhosis. Once cirrhosis secondary to CHC has developed, it is estimated that patients have a 0-3% per year risk of developing HCC [33, 34].

FACTORS PREDICTIVE OF DISEASE PROGRESSION

Both host and viral factors may be important contributors to the natural history of HCV. Faster progression of liver disease is seen in patients of male gender [35], those who acquire HCV at an older age [31], and those of higher body mass index [36]. Alcohol intake, even at very low amounts, can also promote disease progression [37, 38]. The daily use of marijuana is also a risk factor for progression of fibrosis in those with HCV, possibly through the stimulation of endogenous hepatic cannabinoid receptors [39].

The host cellular immune system to HCV may also play a role in severity of liver injury. A retrospective study of 355 patients with CHC demonstrated that African-Americans have a slower rate of progression of disease compared to non-African-Americans, possibly as a result of less immunological recognition of HCV-infected liver cells [40]. There is a correlation between severity of liver disease with human leukocyte antigen (HLA) genes; in particular, lower frequency of alleles TNFB*1, DRB1*1104, and DRB3*03 appears to be protective, while DRB1*1001 appears to be associated with worse disease severity [41]. The activity of TGF B1 and angiotensisn II have also been shown to have a significant relationship in the development of liver fibrosis [42].

IL28B genotype is a known predictor of spontaneous clearance of HCV infection and has implications for a patient's response to treatment with interferon and ribavirin, however, its effect on disease progression is unclear. Studies suggest that IL28B is not associated with fibrosis progression or risks of developing advanced liver disease; although this may be finding may be limited only with patients with non-genotype 1 infection [35 - 43].

The effect of viral factors on disease progression is unclear. Data on viral genotype and disease progression is contradictory. While some cross-sectional studies have shown genotype 1b HCV is overrepresented among patients with cirrhosis and HCC [44, 45], subsequent studies have failed to reproduce these results [46, 47]. Co-infection with more than one HCV genotype appears to lead to an accelerated disease course [46, 47]. Co-infection with HBV [48, 49] and/or HIV [50, 51] also predicts more rapid disease progression.

The best clinical predictor of disease progression is the amount of inflammation and fibrosis on liver biopsy. Yano *et al.* demonstrated those patients with mild inflammation (portal inflammation alone) and no fibrosis had only 1.2% per year risk of progression of fibrosis, while those with moderate chronic hepatitis (periportal inflammation greater than 30% of limiting plate) had a 4.6% per year risk of progression to cirrhosis [52]. 100% of patients with bridging fibrosis and severe inflammation developed cirrhosis.

CONCLUSION

An understanding of the natural history of HCV infection is an important part of the effort needed to reduce the impact of this worldwide health concern [53, 54]. There is a spectrum of clinical outcomes in those infected with HCV. Patients may develop asymptomatic self-resolving acute infection, or go on to suffer chronic infection, including the morbid consequences of cirrhosis and hepatocellular carcinoma. Certain host factors play a role in disease severity,

including male gender, advanced age, elevated BMI, coinfection with HBV or HIV, and drug or alcohol use. A tremendous heterogeneity in viral characteristics is clearly important to disease severity, however, the effect of viral factors on disease progression is less understood.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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