

Diagnosis and treatment of chronic hepatitis C with concomitant extrahepatic manifestations deserves a closer look

Xiao-Guang Dou, Han Bai

Department of Infectious Disease, Shengjing Hospital of China Medical University, Shenyang 110022, Liaoning Province, China

Chronic hepatitis C (CHC) is a systemic disease caused by the hepatitis C virus (HCV), with liver involvement as the main manifestation. In addition to the liver, HCV can also involve many other tissues and organs such as the lymph nodes, kidney, bone marrow, and thyroid. Diseases that have currently proved to be associated with HCV infection include membranous proliferative glomerulonephritis, mixed cryoglobulinemia, late-onset of cutaneous porphyria, Sjogren's syndrome, excess autoantibodies, and splenic lymphoma. Certain conditions may also be linked to HCV infection, such as lymph node hyperplasia, type 2 diabetes mellitus, systemic arterial vasculitis, and peripheral neutropenia. In addition, CHC is often accompanied clinically by a subset of disorders with yet undefined relationship with HCV infection, such as coronary artery fibrosis, ulcerative colitis, oral lichen planus, and thyroiditis.^[1-3] This paper discusses the correlation between CHC and the other clinically common comorbidities in CHC patients, including diabetes mellitus, kidney disease, autoimmune disease, and haematological system diseases, and especially focuses on the issues that should be noted when using drugs for antiviral therapy, such as Interferon. It aims to remind clinicians that CHC antiviral therapy should take into account both efficacy and safety of the drug and the treatment of other comorbidities.

RECOGNITION OF EXTRA-HEPATIC MANIFESTATIONS RELATED TO HCV INFECTION

Previous studies indicate that about 74% of patients with chronic HCV infection

will develop extrahepatic manifestations. The common clinical manifestations are mixed cryoglobulinemia, and thereby, the resultant systemic vasculitis, immune system disorders, autoimmune thyroiditis, hypothyroidism, type 2 diabetes mellitus, HCV immune complex associated nephritis, and non-Hodgkin's B cell lymphoma.^[1-3] In addition to these common extrahepatic diseases, many recent studies have found an association between HCV infection and the morbidity and mortality of cardiovascular disease (CVD). These findings indicate that HCV infection increases the CVD-related mortality, which is especially high in patients with concomitant diabetes mellitus and hypertension.^[4] The presence of these diseases complicates the clinical manifestations of CHC and also poses difficulties for antiviral treatment, particularly the Interferon containing regimens. On one hand, clinicians should endeavour to eliminate HCV and to relieve the concomitant extrahepatic diseases. On the other hand, antiviral drugs should be selected with caution to avoid aggravating extrahepatic diseases, especially autoimmune disease, and the potential occurrence of additional adverse reactions. Therefore, prior to antiviral therapy for CHC patients, the severity of liver disease and virus-related indicators, as well as the characteristics and severity of HCV infection-related extrahepatic diseases should be evaluated, so that proper antiretroviral treatment could be determined accordingly. For patients with CHC and severe extrahepatic diseases, carefully evaluated protocols for effective antiviral treatment not only eliminate the virus, but also significantly improve the symptoms of HCV-related extrahepatic diseases and reduce the risk of aggravating

Address for Correspondence:
Professor Xiang-Guang Dou, Department of Infectious Disease, Shengjing Hospital of China Medical University, Shenyang 110022, Liaoning Province, China.
Email: douxg@sj-hospital.org

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complications. In addition, antiviral treatment should be given to patients with chronic HCV infection and concomitant extrahepatic diseases, even if the liver disease is not serious and there is mild or no hepatic fibrosis.

CLINICALLY COMMON COMORBIDITIES OF CHRONIC HCV INFECTION

Persistent HCV infection can cause lymphatic proliferation and metabolic disorders. Studies have shown that 38-76% of patients with chronic HCV infection will develop at least one condition associated with autoimmune or metabolic disorders caused by hyperplasia of the lymphatic system. Clinically, common diseases include rheumatoid arthritis, lichen planus, mixed cryoglobulinemia, Sjogren's syndrome, autoimmune thyroid disease, type 2 diabetes mellitus, glomerulonephritis, B cell lymphoma and late-onset cutaneous porphyria.^[5,6] Among these diseases, type 2 diabetes mellitus is the most frequent comorbidity which, if present, may increase the mortality of HCV infection.

HCV infection and diabetes mellitus

Compared with patients with other infectious liver diseases including chronic hepatitis B (CHB), CHC patients are more likely to develop diabetes mellitus. Studies have shown that the prevalence of diabetes mellitus is higher in patients with HCV infection than in the general population. In CHC patients with cirrhosis, the prevalence of diabetes mellitus can be as high as 25-30%.^[7,8] HCV infection is a risk factor for diabetes mellitus, and in turn, the presence of diabetes mellitus is associated with the severity of liver damage.^[7,8] In addition, the curative effect of antiviral treatment in CHC patients with diabetes mellitus seems relatively poor. Research shows that HCV infection can lead to metabolic and autoimmune disorders, and diabetes drugs can lead to hypoglycaemia and lactic acidosis in these patients. Therefore, the relationship between hepatogenic diabetes, diabetes mellitus and HCV infection as well as the prognosis of CHC with diabetes mellitus has always been a hot issue in clinical research.^[9] In addition, it is noteworthy that after the type 2 diabetes mellitus patients are infected with HCV, the disease can progress more rapidly, and is more likely to deteriorate into liver fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC), with a poor prognosis. Therefore, blood glucose should be monitored in CHC patients, especially in patients receiving Interferon therapy. Also, patients with diabetes mellitus should be on regular monitoring for HCV infection.^[10]

HCV infection and kidney diseases

HCV infection can cause kidney-related diseases including membranous proliferative glomerulonephritis and mixed cryoglobulinemia, leading to chronic kidney disease

(CKD). About 36% of patients developed CKD after HCV infection, and 35% of CKD patients experienced rapid disease progression. The risk factors for CKD in CHC patients include age, female, concomitant diabetes mellitus, hypertension, liver cirrhosis, and intravenous drug addicts.^[11] More and more clinical evidence is emerging to support the correlation between HCV infection and glomerular disease, and membranous proliferative glomerulonephritis, with type II cryoglobulinemia being the most predominant form of kidney damage in patients with HCV infection. Glomerulonephritis and membranous nephropathy not accompanied by cryoglobulinemia are rarely associated with HCV infection.^[12] Since Interferon therapy may aggravate kidney diseases, a renal biopsy is usually required before starting anti-HCV treatment and determining the role of HCV in inducing membranous proliferative glomerulonephritis. Patients with significant renal histological damage require treatments combining immunosuppressants. Despite the currently widespread use of oral direct-acting antiviral agents (DAAs) in clinical practice, few studies have been conducted on the efficacy of DAAs in HCV-infected patients with CKD, resulting in mixed conclusions on the treatment of these patients.^[13]

HCV infection and other diseases

In addition to diabetes and kidney diseases, the concomitant extrahepatic manifestations of HCV infection also include thyroid disease and haematological diseases. In recent years, more and more attention has been drawn to the increased risk of morbidity and mortality of cardiovascular diseases, secondary to atherosclerosis caused by HCV infection. However, the mechanism by which HCV infection causes extrahepatic diseases remains unclear, and maybe multifaceted, involving the replication of HCV in extrahepatic cells or increased systemic immune response. Anti-HCV treatments, especially the use of oral DAAs without Interferon, can benefit patients with extrahepatic manifestations by ameliorating certain concomitant conditions (such as cryoglobulinemia), reducing insulin resistance and occurrence of diabetes or stroke, and improving fatigue and cognitive dysfunction.^[14]

Conflict of Interest

None declared.

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