Natural history of hepatitis C virus infection

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Abstract. The natural history of hepatitis C virus infection is still unclear. This disease has a long clinical latency period and very frequently develops into chronic forms (in 70-80% of cases). Diagnosis of chronic HCV infection can only be based on liver biopsy. Histological scores permit rating disease severity and to compare successive biopsy specimens. Certain clinical peculiarities deserve to be underlined, such as the frequent asymptomatic forms with normal serum transaminase. Histologically, the liver can be either normal or the focus of chronic hepatitis. HCV RNA screening by PCR may or may not detect virus C replication. Histologically documented chronic hepatitis carry a 20% risk of developing into cirrhosis in 10 years. The risk of liver cell carcinoma is around 3% per year in cirrhotic patients. That risk justifies systematic surveillance, as is currently applied to cirrhotic patients in France. Immune disorders are frequent during HCV infection: presence of anti-tissue antibodies and especially anti-LKM1 antibody, cryoglobulinaemia, glomerulopathy, thyroid disease, Sjögren's disease, late skin porphyria, lichen planus, haemolytic anaemia, idiopathic thrombocytopenic purpura. The severity of chronic diseases induced by HCV is certainly increased by alcohol intake and all chronic HCV carriers should be advised not to drink any alcohol.

Introduction

The so-called 'non A-non B' hepatitis was clinically identified in the 1970s as one of the viruses responsible for post-transfusional hepatitis. It took 20 years of clinical monitoring of these patients and the detection of chronic liver disease, then called 'non A-non B Hepatitis', for the hepatitis C virus (HCV) and its characteristic markers to be identified [1,2]. In 5 years of epidemiological, clinical and molecular biology work on HCV-induced liver diseases, a large number of studies have provided a rather clearer picture of transmission, prevalence in the general population of several countries, high risk populations, and the therapeutic modalities of antiviral treatment when necessary.

Modes of transmission

HCV epidemiology is now well documented [3] and blood transmission comes well ahead (blood transfusion until 1988-91, intravenous drug addiction). Since the progressive introduction of indirect markers (anti-HBC antibody, transaminases) then of increasingly sensitive tests for HCV screening, HCV transmission by blood transfusion has been dramatically reduced, from 6% in the 1980s down to less than 0.5% today. It has indeed been accepted that third generation HCV tests have practically eliminated the risk of post-transfusional hepatitis. However, about one third of HCV infections are still unaccounted for and the existence of an unknown mode of blood contamination cannot be ruled out. The risk of sexual contamination appears to be low and the existence of other risk factors (drug addiction in particular) is frequent in sexual partners with HCV positive serology.

The possible influence of viraemia has been evoked as a risk factor of disease transmission, such as mother to child transmission, a rare occurrence except in case of dual HCV-HIV infection. Prevalence in the French general population is currently estimated as 1% of the overall population, which means that 600,000 individuals in France carry serological HCV markers. HCV seroprevalence in medical care personnel is, depending on studies, identical to or twice that of a control population. The risk of HCV transmission by incidental puncture has been evaluated at 3-10%.

Drug abuse is currently the second source of HCV infection in France, and according to studies, the prevalence of HCV markers is between 48% in Germany and 88% in the USA. A recent survey on France has revealed a 72% prevalence [4]. The HCV genotypes [5] in most studies appear to be different according to the contamination route, genotype 1b being more frequent after blood transfusion and genotype 3a in the drug-abusing population.

Prevalence of HCV infection

The seroprevalence of HCV infection in haemodialysed patients is about 20% in France [3]; it is related to both the transfusional risk (for patients transfused...
before erythropoietin was in use) and nosocomial transmission. It has to be added that in immunodepressed patients, there is a possibility of authentic HCV infection without detectable antibodies. In such cases, the proof for the presence of HCV will be provided by detection of its RNA by genomic amplification techniques [6].

The main peculiarity of HCV infection is the long clinical latency. When a subject has been contaminated by HCV, acute hepatitis occurs within 2–6 months, asymptomatic in more than two-thirds of cases. When the condition is symptomatic, in post-transfusional hepatitis in particular, it can manifest itself by asthenia, jaundice or marked liver enzyme increase. HCV antibody screening is preceded by an increase in transaminases and by detection of HCV RNA in serum. In most cases, acute infection step remains unnoticed because of the absence of symptoms and hepatitis C is inadvertently detected during follow-up surveillance of polytransfused subjects, or from unexplained asthenia, or when reporting to give blood, or during systematic examination. When HCV antibodies are present in serum and detected by ELISA, it is necessary to confirm their presence by an immunoblot test which will characterise the antigenic targets of serum antibodies: HCV non-structural or structural proteins [2].

Chronic HCV hepatitis

Development into chronic forms constitutes the major risk of HCV infection [7]. That chronic evolution has been observed in about 80% of cases. It represents the whole seriousness of HCV infection. At the outset of acute hepatitis, clinically detected or remained unnoticed, transaminases increase. This increase could take several forms, either a plateau increase at the outset of acute hepatitis, which is generally symptomatic, or fluctuating increase sometimes approaching near-normal figures, and which may increase secondarily, or lastly after a phase evocative of recovery from acute hepatitis, secondary transaminase increase. This evolution unfolds over several years. The chronic form of HCV infection may be signalled by asthenia and its discovery is often incidental. HCV markers are then present in serum. An ELISA test should be performed as a first intent and confirmed, as in acute phase, by immunoblotting. After making sure that increased transaminases have persisted for at least 6 months, the reasonable thing is to propose the patient a liver biopsy to assess the pathological lesions of the liver and to provide prognostic assessment.

During HCV chronic infection, liver biopsy reveals the signs of portal and lobular damage: there is a lymphocyte infiltrate in portal spaces, sometimes rather typically pseudo-lymphoid and nodular. The second peculiarity is the lobular damage with lymphocyte infiltrates randomly distributed in the liver lobule. Some authors have found a relation between the importance of the lobular infiltrate and the importance of transaminase increase. Knodell's score is currently the most widely used to quantify pathological lesions. A new score has recently been described by French pathologists; this is the METAVIR score, better adapted to describe HCV-related lesions, and to distinguish between the degree of histological activity and the extent of fibrosis, whereas Knodell's total score is the sum of all the elementary lesion scores [8].

HCV chronic hepatitis outcome

The evolution of HCV chronic hepatitis is hard to predict. There are in fact several possibilities whose respective incidence poses the entire problem of the current HCV epidemic.

There is now an asymptomatic form of HCV infection. During that form of infection, there is no histological damage to the liver or it is minimal; transaminases are normal at several tests and the disease remains in latency. Nevertheless, detection of HCV RNA by PCR (polymerase chain reaction) is positive. This is observed in about 20% of cases. This asymptomatic HCV carrier status with viral multiplication (authenticated by positive viral RNA detection by PCR) is to be distinguished from other forms where the presence of HCV markers is not associated with viral multiplication (negative PCR) that may reflect a situation of recovery from HCV infection. In contrast, several studies involving groups of patients with anti-HCV antibodies and HCV RNA have shown that it was not possible, in such a situation, to predict the histological condition of the liver, and that active chronic hepatitis lesions, or even cirrhosis, may be revealed by liver histological examination in asymptomatic subjects [9]. The diagnostic value of transaminases is therefore limited in such a situation.

In about 80% of cases, conversely, chronic infection is expressed by histologically detectable hepatic lesions of variable extent and according to the severity of these lesions it is possible to appreciate the activity of the so-called chronic active hepatitis (CAH). In the case of minimal or mild activity, the histological lesions are really minor. Fibrosis is restricted and symptomatology is very poor. The final outcome of these hepatitis remains to be assessed and the risk of evolution to cirrhosis has not been clearly established. During more active hepatitis, either moderate or severe, symptoms sometimes exist, such as asthenia, but clinical signs of liver damage are exceptional. It is common practice to monitor disease evolution by performing iterative liver biopsies; they reveal gradual aggravation of fibrotic lesions and cirrhosis may occur after several years. That risk is estimated at about 20% of cases. When cirrhosis is histologically confirmed, there are additional risks of three potential complications: portal hypertension, hepato-cellular failure and liver carcinoma. It is then necessary to investigate portal hypertension, both by upper GI endoscopic exploration and by liver ultrasonography. The onset of hepato-cellular failure is more uncommon in HCV-linked cirrhosis.

The direct carcinogenic role of HCV has long been
discussed. A similar role is now well documented for HBV. It is still debated but probably real for HCV [10]. Nevertheless, in the great majority of cases, the liver carcinomas observed during HCV infection are associated to cirrhosis. Conversely, the risk to develop liver carcinoma in patients with hepatitis C at the cirrhotic stage justifies systematic monitoring of patients every six months at least, and more often for some teams, by ultrasonographic examination and measurement of serum alpha foetoprotein.

**Dysimmune lesions during HCV infection [11]**

Clinically, HCV chronic disease is often asymptomatic. However, dysimmune disorders may complicate the outcome. These symptoms were for a long time attributed to an autoimmune disease and the presence of HCV has now been demonstrated in a number of such diseases. Conversely, anti-tissue antibodies may be detected during certain forms of hepatitis C, anti-LKM1 antibodies in particular.

Immune disorders linked to HCV are mainly type II, IgG and IgM mixed cryoglobulinemia. During these cryoglobulinemia, the hepatitis C virus was found in serum and in the cryoprecipitate. These cryoglobulinemia are often complicated by glomerulonephritis and renal failure and vasculitis-type skin lesions. Interferon treatment, usually indicated during chronic hepatitis C, has also been proposed to treat systemic cryoglobulinemia and its effectiveness has been questioned. In parallel, low concentration cryoglobulin, often asymptomatic, is frequent (50% of cases) during HCV-related chronic hepatitis. HCV-linked glomerulopathies are membranoproliferative glomerulonephrites (type I).

Other immune disorders have been described: thyroid disorders, often revealed or aggravated by interferon treatment, Sjögren disease, late skin porphyria, lichen plan, haemolytic anemia, idiopathic thrombocytopenic purpura [12].

The role of alcohol in HCV infection

Alcohol intake is not recommended during any liver disease, but there is probably a synergistic effect of alcohol intake and HCV infection, viral replication being enhanced by alcohol [13,14]. Using HCV markers during severe alcoholic cirrhosis revealed that in fact a large number of cirrhoses were linked to viral infection. The risk of aggravation of pathological lesions and of liver carcinoma occurrence is increased by alcohol intake during an HCV-related condition. In addition, anti-viral treatments using interferon are ineffective in patients using large quantities of alcohol.

It is therefore crucial, in terms of public health, to achieve drastic cuts in the amount of alcohol daily intake in HCV-infected patients.

**Conclusion**

HCV infection is frequent, affecting about 1% of the whole French population. It takes very disparate clinical and evolutive forms which are not easily predictable. The incidence of cirrhosis and its subsequent risk of liver carcinoma is around 20% of patients with histologically proven chronic active hepatitis. A policy of systematic serological screening should now be implemented. The aggravating role of alcohol is now clear and this crucial message must be widely publicised.

**References**