Epidemiology of hepatitis C virus in Europe

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Abstract: Epidemiology of Hepatitis C virus (HCV) infection in Europe is changing very rapidly since the main source of contamination was blood transfusion and the use of surrogate markers allowed to diminish dramatically the number of patients contaminated through HCV post transfusion hepatitis. The recent description of several genotypes with different distributions over Europe and different pathogenicity will allow to explain various evolutive aspects of the disease. At present, groups at risk are drug addicts (70%), hemophiliacs (contaminated with blood products before 1985), hemodialysis patients (20%) and patients with cirrhosis with or without hepatocellular carcinoma. The detection of HCV markers prior to blood transfusion allowed to detect asymptomatic carriers of HCV, some of them with latent chronic hepatitis which can be predicted by the detection of HCV RNA in the serum. Vertical and sexual transmission are rare but possible events observed with certainty in patients co-infected with HIV and controversial in other situations.

Key words: Hepatitis C; Epidemiology; Blood donors

Introduction

The description of the epidemiology in Europe was has recently become available and was mostly dependent on the availability of the tests. First-generation tests were used during the first year, with an inadequate sensibility due to the lack of structural protein in the tests. Second- and third-generation tests, containing more numerous proteins or peptides, from the different regions of HCV genome are now available, and allow more precise determinations of the presence or absence of the virus.

The recent description of the different genotypes of the virus is probably a main point from the epidemiological point of view, allowing classifications of the genotypes, and the study of the different repartitions of the genotypes over Europe.

One of the main sources of contamination with HCV in Western Europe was blood transfusion, and the detection of surrogate markers prior to blood transfusion and, when available, the detection of HCV antibodies in blood donors allowed a dramatic decrease of the incidence of post-transfusion hepatitis.

At present, the main epidemiological problems with HCV in Europe can be considered as a problem in high risk groups: hemophiliacs, hemodialysis patients and patients with hepatocellular carcinomas. However, the detection of HCV prior to blood donation allowed to describe a group of asymptomatic anti-HCV-positive blood donors, in which the histological lesions of the liver should be assessed in the near future.

Finally, several studies were conducted in Europe to determine the risk and prevalence of
vertical and sexual transmission, but the results of these studies are still controversial.

**Detection of HCV and prevalence in the general population**

The first-generation tests of detection of anti-HCV were available since 1989, and were widely used in several pathological groups as well as general population and blood donors. These tests contained only non-structural antigens, and the prevalence of anti-HCV in patients with non-A, non-B chronic hepatitis was approximately 75%. This rather low prevalence of anti-HCV was underestimated due to the lack of sensitivity of the tests.

Two years later, in 1991, second-generation tests containing structural and non-structural antigens were available, and the figures of the prevalence of anti-HCV obtained with these tests are certainly more precise. Third-generation tests, now available, will probably give similar results but reduce the number of undeterminate results. The presence of viremia could be detected with the PCR technique, but the fails and pitfalls of this technique are not yet solved, and quality control procedures are still needed to interprete the results from various laboratories. The quantification of RNA, with branched-chain DNA technology, is currently being evaluated and gives promising results.

The recent description of the genetic heterogeneity of HCV, and the identification of various genotypes is a main advance in the understanding of the pathogenicity of HCV. Several classifications are now published, and a standardization of the description of the various genotypes is urgently needed. However, the existence of a specific genotype, named II by Okamoto and IB by Simmonds, responsible for more severe disease, leading to cirrhosis, with high levels of viremia and bad response to treatment is now accepted by many authors [1]. The geographic distribution of the genotypes across Europe is under study but the figures obtained in Europe with various genotypes are clearly different from those observed in Japan, and more similar to those obtained in United States (Table 1).

The detection of anti-HCV was a main concern in blood transfusion to avoid non-A non-B posttransfusion hepatitis. Several steps were covered in this field. Before any tests in blood donors the occurrence of non-A non-B posttransfusion hepatitis was 6–14% in Europe and USA in multitransfused patients receiving more than 4 units of blood. The use of surrogate markers (anti-HBc and transaminases activity) considerably reduced the incidence of non-A non-B posttransfusion hepatitis which in France, was 3.4% before HCV testing. In 1990, the determination of anti-HCV was possible and mandatory for blood donors in many European countries. In France, the use of first-generation tests reduced the incidence of HCV posttransfusion hepatitis to 0.5%, and a recent prospective study of post-

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<td>Distribution of genotypes in Europe</td>
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Taken from Molecular diversity of HCV and its clinical significance. Satellite symposium, Tokyo 1993.
transfusion hepatitis cases over France demonstrated that the incidence of posttransfusion hepatitis was now reduced to 0.1% [2]. Therefore, the use of surrogate markers together with recent HCV tests was responsible for a dramatic decrease of non-A non-B or C posttransfusion hepatitis.

High risk populations

At present, the main concern is obviously with high risk populations, namely health care workers, hemophiliacs and hemodialysis patients. Another main point is to clarify the relation between HCV infection and hepatocellular carcinoma.

Several studies were conducted to determine the prevalence of anti-HCV in health care workers. In France and in Spain, the prevalence of anti-HCV is clearly higher in health care workers as compared to the figures from general population. Several points were outlined by these studies: the prevalence is similar in nurses and in unexposed workers, demonstrating that hygienic measures should be recommended to any category of personnel; the prevalence of anti-HCV increased with the number of years at risk, reaching more than 5% in the personnel present in the hospital for more than 20 years [3,4].

Hemophiliacs were a group of patients with a high prevalence of HCV infection prior to the 1985 period, when blood products were heated and HCV was inactivated. A recent study conducted in France on the RIBA profiles of anti-HCV-positive hemophiliacs [5] demonstrated the presence of structural antigens (C-22c) in all of them, but the possible lack of non-structural antigens, mainly the C-100 protein. Since 1985, the number of cases of contamination of hemophiliacs by blood products decreased dramatically.

Hemodialysis patients are clearly a group of patients with a very high prevalence of anti-HCV. Several studies conducted in different centers in Europe gave comparable results in terms of incidence of the disease, with a prevalence of anti-HCV varying from 21 to 51% in Italy. The presence of HCV viremia detected by PCR is particularly high in these immunocompromised patients (50–95%). Several points were outlined by the various studies conducted in hemodialysis centers: (i) there is a clear relation between the presence of HCV infection and the blood transfusions given to these patients. The use of erythropoietin allowed a dramatic reduction of the number of blood transfusions in hemodialysis patients, and very rare cases of HCV infection were observed in non-transfused patients. However, the possibility of nosocomial infection cannot be excluded in hemodialysis centers. Several studies were conducted to determine the clinical, histological and virological status of HCV-infected hemodialysis patients [6,7]: these studies pointed to the possibility of obvious histologically demonstrated chronic hepatitis in the absence of biological features, namely the increase of transaminase activity. Therefore, a liver biopsy (by the safe transvenous transjugular route) is frequently needed to precise the histological status of the liver in such patients. Furthermore, virological studies with simultaneous determination of HCV serological markers (ELISA and confirmatory tests) and PCR studies for the detection of HCV replication demonstrated the possibility of HCV replication (positivity of the PCR assay) in the absence of positive serological tests [8].

The relationship between the presence of HCV markers and the occurrence of hepatocellular carcinoma was underlined very soon. In Italy, large series of patients with cirrhosis and hepatocellular carcinoma were extensively studied, and the high prevalence of HCV markers was noted in patients with cirrhosis (approximately 50%). Moreover, HCV was proven to be an additive risk factor for the development of hepatocellular carcinoma by several authors. However, the development of hepatocellular carcinoma in patients with normal liver, a rare event in hepatitis B chronic carriers was never observed with HCV [9–11].

Asymptomatic carriers

The determination of HCV markers prior to any blood donation allowed the recent description of a group of so-called asymptomatic HCV carriers, namely patients with normal liver tests
at several successive determinations and presence of anti-HCV confirmed by RIBA. A recent study in Italy [12] in these subjects demonstrated the predictive value of the determination of HCV replication by PCR, in terms of chronic liver damage. In fact chronic liver disease was histologically demonstrated in patients with normal transaminases at several determinations, but with HCV replication detected by PCR. In contrast, no liver damage could be detected when HCV replication was not detected by PCR. Therefore several studies are needed, based on the predictive value of PCR to detect histological lesions, in this group of subjects.

**Vertical and sexual transmission**

The transmission of HCV by other routes than blood transfusion or drug addiction, namely vertical and sexual transmission, are still controversial. Vertical transmission was studied in several countries in Europe, and is still unclear. Several points can be assessed: vertical transmission is possible from HIV-HCV-infected mothers, even without breast feeding; it was observed in 20% of the HIV-HCV-infected mothers, and acute hepatitis can develop in infected babies. However, HCV infection was observed in only 3% of the HCV mothers without HIV infection [13]. The prevalence of obvious transmission from mother to child can be assessed by the determination of HCV replication by PCR and several studies confirmed the low risk of transmission which, however, is observed in some series. Furthermore, the passive transmission of anti-HCV was documented from mothers to babies, and the disappearance of antibodies with age was proven [14–16]. Sexual transmission was also widely studied in Europe, and different results were obtained in northern Europe, where sexual transmission was not demonstrated [17], and in southern Europe, where the prevalence of anti-HCV was higher in sexual contacts to HCV carriers and in the household, compared to the general population [18]. Therefore, the risk of sexual transmission can considered to be low but present. Different geno-

types of HCV could explain discrepancies between these various studies.

**Conclusion**

In conclusion, the epidemiology of HCV is now widely studied in Europe with adequate tools, and several problems are cleared, mainly those concerning transmission by blood transfusion. However, the high prevalence of HCV infection in high risk groups is a matter of concern, as well as the investigation of the group of so-called asymptomatic HCV carriers. The possibility of vertical and sexual transmission is demonstrated in many studies but the real incidence of this risk is still controversial in different countries.

**References**

8. Bouchardieu, F., Chauveau, P., Zins, B., et al. (1993) Detection of HCV RNA by polymerase chain reaction in hemodialysis patients during a 18 month follow-up. Inter-


