Registry of liver biopsies from hepatitis C infected patients in the Alpes-Maritimes (France)

Results from the first 2 years (1997-1998)

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Objective — To perform a descriptive analysis of patients with chronic hepatitis C based on a local registry of liver biopsies.

Patients and method — Collection of clinical, biological and histological data from all HCV-infected patients who underwent liver biopsy between January 1997 and December 1998 in the Alpes-Maritimes (France).

Results — One thousand and fifty six patients including 924 who lived in the Alpes-Maritimes (515 male, 409 female, mean age: 44.9 years old) were included. Intravenous drug use (30.1%) was the major suspected source of infection before blood transfusion (28.2%). Among intravenous drug users, 36% of patients were infected with genotype 1a and 37.4% with genotype 3. The METAVIR fibrosis severity score was distributed as follows: F0: 10.8%, F1: 53.7%, F2: 15.9%, F3: 14.7%, and F4: 4.9%. In a multivariate analysis adjusted for the duration of infection, independent risk factors associated with the severity of fibrosis were age at contamination ≥ 30 years, genotype other than 1a and alcohol intake ≥ 50 g/day.

Determination of HCV antibody and liver biopsy were performed an average of 12.5 and 14 years after presumed date of contamination, risk factors associated with the severity of fibrosis were age at contamination ≥ 30 years, genotype other than 1a and alcohol intake ≥ 50 g/day.

Conclusions — These data provide a clearer view of the impact of this condition in this area and could help to define a comprehensive policy for patient management.

SUMMARY


Hepatitis C virus (HCV) infection is a major cause of chronic hepatitis, cirrhosis and liver cancer [1]. Seroprevalence studies have demonstrated that 10,000 to 20,000 patients are contaminated in the Alpes-Maritimes region in France [1, 2]. Apart from local surveys conducted by the hospital direction at reference sites [1, 2], and the Côte-d’Or registry [1], there is, to our knowledge, little data concerning the characteristic features of the HCV infected population managed in our area.

In metropolitan France, the prevalence of human immunodeficiency virus (HIV) positive persons is the second highest in the Provence-Alpes-Côte d’Azur (PACA) region after the Parisian region [1]. The same is true for drug abusers [2]. These facts would suggest that the Alpes-Maritimes region would have one of the highest rates of HCV infection in France.

It was thus felt that an epidemiology watch program for HCV infection should be implemented in our area in order to define coherent prevention program to control this endemic disease and to evaluate the impact of measures adopted. Liver needle biopsy is a key element for management HCV-infected patients and must be performed before initiating antiviral treatment. In addition, hospitalization for liver biopsy is an appropriate time for collecting clinical, biological and histological data.

The purpose of this work was to provide a descriptive analysis of the patient population with HCV-positive serology who underwent a needle biopsy between January 1st 1997 and December 31st 1998 in the Alpes-Maritime area and to search for severity factors of liver fibrosis. In addition, management schemes used for hepatitis C patients in the different healthcare facilities were recorded.

Patients and methods

Study population

All patients with positive HCV serology and liver biopsy between January 1st 1997 and December 31st 1998 were included in this study. The physician who performed the liver biopsy filled out a data sheet indicating the city and the type of medical practice (public hospital/private practice) as well as the social and demographic features of the patient, mode and date of presumed contamination, alcohol consumption, viral genotype, and the result of the liver biopsy (METAVIR score) [1]. All data were centralized at the Nice University Hospital where an anonymous database was constructed. Data from prior liver biopsies was recorded retrospectively. The first liver biopsy performed before antiviral treatment was taken as the reference point. Analysis of patient
characteristics was limited to patients residing in the Alpes-Maritimes area (defined as the French Department of Alpes-Maritimes). Risk factors associated with fibrosis severity were analyzed for patients whose liver biopsy slides were interpretable.

Statistical analysis

A home-built software written in Builder® C+C language operating on Windows® was used to handle data and control data quality. The chi square test was used for qualitative variables and Student’s t test for quantitative variables with an alpha risk at 5%. Annual progression of hepatic fibrosis was calculated according to the method described by Poynard et al. [1]. The odds ratio method with 95% confidence intervals was used to search for factors associated with fibrosis severity (F0-F1-F2 versus F3-F4) after adjustment for duration of infection using a logistic regression model. Statistical analyses were performed with SPSS software.

Results

Characteristic features of the patient population living in the Alpes-Maritimes

According to the last census in 1999, there were 1,011,866 inhabitants (474,543 men and 537,323 women) in the Alpes-Maritimes. Age distribution was 21% under 20 years, 50.2% aged 20-59 years, 27.7% aged over 59 years. Mortality was 11.6%.

A total of 1,056 patients were included in the study between January 1st 1997 and December 31st 1998. Among these patients, 924 (515 men, 409 women, mean age 44.9 ± 12.9 years) resided in the Alpes-Maritimes and 72.5% were born in France. Among the patients residing in the Alpes-Maritimes, 474 (51.3%) were cared for at the Nice University Hospital, and 450 (48.7%) elsewhere (3.8% in a general hospital and 44.9% in private practices).

Intravenous drug abuse was the leading cause of suspected contamination (30.1%) (figure 1), followed by blood transfusion products (28.2%), nosocomial contamination (3.1%), and occupation contamination (0.4%); 3.0% of the patients lived in contact with an HCV-positive patient. No mode of contamination could be identified in 31.5% of the patients.

Viral genotype was determined in 529 patients. Genotype distribution was: 1a (26.8%), 1b (35.3%), 2a (7.2%), 2b (0.4%), 2c (0.4%), 2f (0.4%), 3a (21.9%), 4 (5.9%) and 5 (1.5%). Among transfusion patients, genotype 1b was found in 52.5%; among drug abusers, 38% had genotype 1a and 37.4% had genotype 3; 6.1% of the patients had HIV co-infection. Among patients with no identified risk factor, genotype distribution was: 1a (25.5%), 1b (45.0%), 2a (7.8%), 2b (0.8%), 2c (0.8%), 2f (0.8%), 3a (13.2%), 4 (3.7%) and 5 (2.3%).

At the time of the liver biopsy, consumption of alcohol was ≤10 g/day in 77% of the patients while 7.2% of the patient consumed at least 50 g per day. Excess alcohol consumption was predominantly observed in men (91.5%).

Liver fibrosis

The METAVIR score was recorded in 991 patients and could not be determined in the other 65 due to insufficient biopsy material. The fibrosis severity according to the METAVIR classification was: F0: 10.8%; F1: 53.7%; F2: 15.9%; F3: 14.7% et F4: 4.9%.

The presumed date of contamination could be identified in 584 patients (55.3%). The mean annual rate of progression of fibrosis was 0.140 METAVIR fibrosis units (95%CI [0.122-0.159]). Median annual rate was 0.083 METAVIR units.

At univariate analysis, male sex, age at contamination ≥30 years, age at liver biopsy ≥40 years, presence of elevated aminotransferases at the time of the liver biopsy, alcohol consumption ≥50 g/d, and longer duration of infection were significantly associated with greater risk of severe fibrosis. Patients infected with genotype 1a had less severe fibrosis than those infected by other viral genotypes (table I).

At multivariate analysis, after adjustment for duration of infection, independent risk factors associated with fibrosis severity were: age at contamination ≥30 years (OR: 3.9; 95%CI: 1.7-9.3), genotype other than 1a (OR: 3.3; 95%CI: 1.2-9.2) and alcohol consumption ≥50 g/d (OR: 2.9; 95%CI: 1.0-8.4) (table II).

Management of patients with chronic hepatitis C who had a liver biopsy

Among the patients whose date of contamination could be determined, contamination occurred later in women than in men (30.0 ± 12.0 versus 27.6 ± 1.4 years, P = 0.02). Mean duration of disease from presumed date of contamination to first HCV serology was 12.4 ± 7.8 years. This was longer in women than men (13.5 ± 8.1 versus 11.6 ± 7.3 years, P = 0.006). Liver biopsy was performed a mean 1.5 years after discovery of HCV seropositivity, i.e. 14 years after the presumed date of contamination. This delay however, varied according to age: 2.6 years for patients under 30 and 8 months in those over 60 (figure 2).

Compared with patients managed outside the Nice University Hospital, those managed at the Nice University Hospital were younger (46.4 ± 12.8 years versus 43.6 ± 12.8 years, P < 0.001), consumed less alcohol (3.0% versus 10.8% with a
consumption ≥ 50 g/day, P < 0.001) and were more often intravenous drug abusers (21.3% versus 38.4%, P < 0.001).

Discussion

These data were collected over a period of 2 years in patients with chronic hepatitis C who had had a liver biopsy. Such data cannot provide disease incidence or prevalence but they are helpful in establishing characteristic features of the population under active management with hepatic biopsy in the Alpes-Maritimes region as well as the modalities of management. This population, while not representative of all patients with HCV infection, is however representative of those attending consultations and under treatment with laboratory follow-up tests. The results presented here must be considered with the usual reservations concerning the methodology of this type of study founded on voluntary participation of the different practitioners. Complete data collection from all practitioners cannot be guaranteed. Complete data collection was however achieved for the University Hospital because the number of hepatic biopsies reported here corresponds to the number of clinical files recorded in the hospital pathology department.

This population is comparable with the French population of HCV-infected patients in reported hospital series [1]. It is noteworthy that 18.8% of the patients with a liver biopsy did not live within the French Department of Alpes-Maritimes and that 27.7% of the patients were not born in France. The modes of contamination exhibited a certain evolution of the two main routes of infection. Drug abusers predominated in our area and accounted for more patients than transfusion-related infections. This high percentage of drug abusers has also been found in recent surveys [4, 1]. These findings demonstrate a reversal in the type of contamination compared with the 1997 survey where the main mode of contamination still blood product transfusion [11]. Patients contaminated by occupational or nosocomial exposure appeared to be underestimated compared with other surveys [11]. This might be related to the relatively high percentage of contaminations of undetermined origin. A similar percentage was reported by the Côte-d’Or viral hepatitis B and C registries [6].

The genotype distribution was comparable with that previously described with a predominance of genotypes 1 and 3 [1]. Genotypes 3 and 1a occurred with equal frequency in intravenous drug addicts. Mode of contamination was not predictive of the probability of prolonged response to antiviral agents so genotype should be determined before initiating antiviral treatment [1].

Fig. 2 – Delay between HCV antibody test and liver biopsy according to the age of the patient. PBH: liver histology.

A very small number of patients (n = 45) who underwent liver biopsy had HIV co-infection. This finding was unexpected because the prevalence of HCV infection in HIV-positive intravenous drug abusers has ranged from 70 to 90% [1]. This means that care for hepatitis C with HIV co-infection still remains quite limited. Nevertheless, because HIV-positive patients can be stabilized with anti-retroviral drugs, the number of co-infected patients under clinical and therapeutic management could be expected to rise in the near future.

The median annual progression of hepatic fibrosis in our patients was lower than that reported by Poynard et al. [0.083 vs 0.133 METAVIR units] [10]. This difference is probably related to the fact that approximately three-quarters of our patients were

Table I. – Univariate analysis of predictive factors for the severity of fibrosis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95 %CI</th>
<th>P</th>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>1.58</td>
<td>1.07-2.32</td>
<td>0.01</td>
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<td>Genotype</td>
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<tr>
<td>1b</td>
<td>3.70</td>
<td>1.64-8.33</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>3.33</td>
<td>1.12-10.0</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>3.03</td>
<td>1.26-7.70</td>
<td>0.005</td>
</tr>
<tr>
<td>4, 5, 6</td>
<td>5.88</td>
<td>2.0-16.66</td>
<td>&lt; 0.001</td>
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<td>Aminotransferase levels</td>
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<td></td>
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<tr>
<td>Elevated</td>
<td>9.1</td>
<td>2.70-33.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50 g</td>
<td>3.03</td>
<td>1.61-5.88</td>
<td>&lt; 0.001</td>
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<tr>
<td>Age at contamination</td>
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<tr>
<td>≥ 30 years</td>
<td>2.44</td>
<td>1.44-4.16</td>
<td>&lt; 0.001</td>
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<tr>
<td>Age at liver biopsy</td>
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<td></td>
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<tr>
<td>≥ 40 years</td>
<td>2.63</td>
<td>1.75-3.96</td>
<td>0.001</td>
</tr>
<tr>
<td>Duration of infection</td>
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<td>≥ 20 years</td>
<td>2.79</td>
<td>1.12-6.80</td>
<td>0.02</td>
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Table II. – Multivariate analysis of predictive factors for the severity of fibrosis adjusted for the duration of infection.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95 %CI</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Genotype other than 1a</td>
<td>3.3</td>
<td>1.2-9.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Alcohol consumption ≥ 50 g</td>
<td>2.9</td>
<td>1.0-8.4</td>
<td>0.04</td>
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<tr>
<td>Age at contamination ≥ 30 years</td>
<td>3.9</td>
<td>1.7-9.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

OR: Odds-ratio; 95%CI: 95% confidence interval.
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P HCV seropositivity was long, more than 12 years. This delay was even longer in female patients. The liver biopsy was performed at a mean of 1.5 years after the discovery of HCV seropositivity. This registry did not record causes of this delay in diagnosis. Nevertheless, patient age did influence delay from discovery of seropositivity to biopsy. Indeed, this delay declined progressively with increasing age. Further efforts should be made to achieve more rapid care, particularly for young patients, early after serological diagnosis. It would also be useful, particularly with screening, to reduce the delay between presumed contamination and diagnosis of hepatitis C.

This registry also demonstrated a difference in the social and demographic characteristics of patients treated at the Nice University Hospital and those treated elsewhere. At the University Hospital, patients were younger, consumed alcohol more often, and were more frequently contaminated by use of intravenous drugs. These differences are not the same as reported by Goergebeer et al. [1] in the Côte-d’Or registry where hospitalized patients were contaminated more often by transfusion-related products and did not have an excessive level of alcohol consumption.

These above different characteristics suggest that the modes of management for patients who have had a liver biopsy are different between the University Hospital and the other facilities, particularly private practices. Thus, the facilities for alcoholism and drug abuse care at the University Hospital should be reinforced in addition to units for hepatitis C care. The fact that the number of patients can be expected to grow with implementation of screening programs emphasizes the importance of this point.

In conclusion, this registry has allowed our department to define characteristic features of patients with chronic hepatitis C who underwent liver biopsy. Delay to active management after contamination is still too long, greater than 12 years. These data have permitted a better understanding of the features of this endemic disease in order to establish a coherent healthcare policy in the Alpes-Maritimes.

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RÉFÉRENCES

ANNEXE

Hepatitis C Network
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Azur Pathology
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