Hepatitis C of Genotype 2 : The Role of Medical Invasive Exams

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Abstract

***Background and Aim* : Hepatitis C virus genotype 2 is the third in order of frequency in Belgium. The aim of this study was to better define the genotype 2 carriers' epidemiology characteristics.**

***Methods* : In a database comprising 1726 viremic hepatitis C virus patient from the south part of Belgium, the files of 98 genotype 2 carriers were reviewed.**

***Results* : There was a strong association between genotype 2 and the mode of transmission. The rate of contamination by invasive medical exams was very high (23%), and statistically different from the one of the others genotypes. Eligibility for antiviral therapies and the rate of sustained viral response were high.**

***Conclusion* : HCV genotype 2 was highly associated with transmission by invasive medical exams.** (Acta gastroenterol. belg., **2011**, 74, **277-280**).

Key words : hepatitis C, genotype, nosocomial transmission, epidemiology.

Introduction

Hepatitis C virus is a major public health problem world-wide and the World Health Organization estimates that 3% of the world population is infected with the hepatitis C virus (HCV). In Europe, 5 million people are HCV carriers, the prevalence ranges from very low (< 0.1%) in United Kingdom and Scandinavia, to low (0.1-0.5%) in the rest of Western Europe and moderate (0.6%) in Southern Europe (1). In a sample of the general population in Belgium, the seroprevalence was 0.87% (2).

More than 70% of newly infected patients progress to chronic infection with its attendant complications of cirrhosis, liver failure and hepatocellular carcinoma (3). Furthermore, the health-related quality of life is significantly compromised in persons with chronic HCV, compared with the general population (4).

HCV is classified into six major genotypes and several subtypes based on the nucleotide sequence homology (5). Genotypes differ from each other by more than 30% over the complete virus genome. These virus types are each comprised of several more closely related subtypes that vary by more than 20%, while within each subtype variation is less than 10%. With longitudinal studies that give a rate of substitution of 1.5 to 2 10-3 per site per year, it was estimated that the divergence of genotypes occurred at least 500-2000 years ago, whereas thef divergence of subtypes has been proposed to derive from 100 to 300 years (6).

Genotype identification is very important for different reasons.

It is known that the prevalence and incidence of HCV genotypes vary significantly among geographical areas (7). Genotype 1 is distributed world-wide and is the predominant genotype found in Europe and in the United States, followed by genotypes 2 and 3. Genotype 4 is the principal type in North and Central Africa and in the Middle East. Genotypes 5 and 6 are rare, and are predominantly found in a specific geographical area : genotype 5 is always a minor component of the HCV population, except in South Africa or in some particular areas ; and genotype 6 is mainly observed in South East Asia (7).

Genotype is the most important predictive factor of response to therapy, and in many cases, determines the duration of treatment (8).

In addition, a statistical association exists between genotype and mode of transmission (9,10 and 11). Genotype 3 and 1a are more frequent in younger patients contaminated by intravenous drug use whereas genotype 1b and 2 are widely dominant among older patients with a history of blood transfusion. Genotype 4 is described in three different populations in the Southern part of Belgium (patients of African origin, European drug users and European non drug users, mostly of Italian origin) (12). Genotype 5 is associated with patients contaminated by transfusion (13,14).

In addition to its role as an epidemiologic marker, genotyping has thus an important role in the day-to-day clinical management of chronic HCV infection, and its prognosis.

In spite of its importance in our populations, genotype 2 has not been very well studied. We aimed to better determine the epidemiological characteristics and eligibility to treatment of this subgroup of patients.

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Material and methods

Study population

In a retrospective analysis from 1992 to 2002, 1726 consecutive patients were found HCV-RNA-positive by polymerase chain reaction (PCR) in the Centre of Molecular Diagnosis of University Hospital of Liege, Belgium. These patients had been addressed to the teaching hospital or nearby hospitals either to confirm the diagnosis of hepatitis C by PCR or for a pre-treatment evaluation. In this series, genotypes were known for 829 patients. Among them, 98 patients were infected with genotype 2. A questionnaire was sent to the treating physicians and their files were reviewed to collect information about age, gender, ethnic origin, risk factors for HCV acquisition, results of liver biopsy (Metavir score), rate of patients eligible for therapy, rate of sustained viral response when treated and rate of human immunodeficiency virus (HIV) co-infection.

This study was approved by the Ethics Committee of the University of Liege, Belgium.

Laboratory Methods

Qualitative HCV-RNA was assessed by nested PCR between 1992 and 1995, by Amplicor HCV test (Roche Laboratories, Basel, Switzerland), version 1.0 until 1998, and then version 2.0). Genotypes were determined using the LIPA-HCV test from Innogenetics (Zwijnaarde, Belgium) and viral load by Amplicor HCV monitor test, version 2.0 (Roche). All procedures were performed and results interpreted according to the manufacturer's recommendations.

Statistics

Continuous variables were analysed by Student's unpaired t-test. Categorical variables were tested by the chi-square test, Mann-Withney test and Kologorv-Smirnov test. Results were considered significant at the classic level of 5%.

Results

Among the 829 patients with an identified genotype, 98 patients were infected with the genotype 2. Genotype 1 was found among 510 patients (61.5%), genotype 3 among 116 patients (14%), genotype 4 among 85 patients (10.3%), genotype 5 among 13 patients (1.6%) and genotype 6 among only two patients (0.2%).

Characteristics of patients with genotype 2 (Table 1)

The mean age at the diagnosis was 48 +/- 15 years. 53 patients were female ; 45 were male. Mode of contamination was known for 88 patients. The main mode of contamination was nosocomial : 31 patients had received blood transfusion (31%), 23 patients had a history of medical invasive exam (23%), with 18 urological interventions in the same unit (18%), six surgical interventions (6%) and three contaminations to health care workers, some of them with combined risk factors. Seven patients were drug users (7%), and the mode of transmission was unknown for 11 patients (sporadic cases) (11%). There was no HIV co-infection.

Table 1. — **Clinical and epidemiological characteristics of 98 patients with genotype 2**

Characteristics	n	%
Age	48 +/- 15	
Sex		
Male	45	(46)
Female	53	(54)
Ethnic Group		
African	16	(16)
European	82	(84)
Risk Factors		
Transfusion	31	(31)
Urological	18	(18)
Surgical	6	(6)
Health Care Workers	3	(3)
IV Drug Use	7	(7)
Unknown	21	(21)
Sexuel	1	(1)
Vertical	0	
HIV co-infection	0	
Hepatic biopsy n= 39		
F0-F2	33	(85)
F3-F4	6	(15)
Treatment		
Treated	37/51	(73)
Untreated	14/51	(27)
Transplantation	1	(6)
Viral response	25/37	(68)
Subtypes		
2a-2c	68	(69)
2a	10	(10)
2	14	(14)
2a-2c and 2b/ ?	2	(2)
2b	3	(3)
2a-2b	1	(1)

A liver biopsy was performed for 43 patients (82%) ; a fibrosis score was known for 39 patients. Six had an advanced fibrosis (Metavir score of F3-F4).

The treatment was described in 51 files. Thirty seven patients (70.5%) were treated, either with pegylated interferon or non pegylated interferon, often associated with ribavirine. 68.5% patients developed a sustained viral response (defined as undetectable viral load 6 months after the end of the treatment) (24 of the 35 patients who had a complete treatment and follow-up). One patient was transplanted. From these 24 patients, 13 patients had a fibrosis score (Metavir) of F0, 4 patients a fibrosis score of F1, 1 patient was F3, three patients were F4 and the fibrosis score was not determined in three patients.

Subtypes were very heterogeneous, but with a majority of genotype 2a-2c : 68 patients had a genotype 2a-2c (69%) ; 10 patients had a genotype 2a (10%) ; 14 patients had a genotype 2 (14%) ; one patient had a genotype 2a-2c and 2b (1%) ; three patients had a genotype 2b (3%) ; one patient had a genotype 2a-2c and

Table 2. — **Comparison of 98 genotype 2 carriers' epidemiological parameters with those of 1726 hepatitis c virus patients**

Characteristics	Genotype 2 n = 98	Patients HCV n = 1726	P
Age	48 +/- 15	47 +/-17	NS
Sex			
Male	45 (47%)	917 (53%)	NS
Female	53 (53%)	808 (47%)	NS
Risk factors			
Transfusion	31 (31%)	399 (23%)	= 0,05
Medical invasive exams	23 (23%)	97 (5,6%)	< 0,001
Surgical	6.1 (6%)	9 (0.52%)	< 0,001
Dialysis	0	32 (1,9%)	NS
Sexual	1 (1%)	20 (1%)	NS
Vertical	0	4 (0,23%)	NS
IV Drug Use	7 (7%)	254 (14%)	< 0,05
Date of Detection	1998 +/- 3	1998 +/- 3	
Locality			
4000	16 (17%)	455 (28%)	< 0,05
4800	28 (30%)	260 (16%)	< 0,05

Table 3. — **Genotype 2 carriers' infected by medical invasive exams : epidemiological characteristics**

Parameters	EMI n = 23	Others G2 n = 75	P
Age	49	48	
Sex			
Male	9	36	NS
Female	14	39	NS
Liver Biopsy	14/15	29/37	NS
F0-F2	11/12	22/27	NS
F3-F4	1/12	5/27	NS
Treatment			
Treated	13/15	24/36	NS
Untreated	2/15	12/36	NS
SVR	7/10	17/25	NS
Subtypes			
2a	3	7	NS
2a-2c	20	47	< 0,001
Others		21	< 0,01
Locality			
Verviers	18	15	
Liège and around	5	58	< 0,001

another unidentified subtype (1%) ; and one patient had a genotype 2a-2b (1%).

Comparison of 98 genotype 2 carriers' epidemiological parameters with those of 1726 hepatitis C virus patients

Epidemiological parameters of 1726 hepatitis C virus patients have been described previously (13) and are reminded in the Table 2.

The characteristics of the 98 genotype 2 carriers did not differ from those of the 1726 patients of the whole series as far as age and gender were considered. Among the genotype 2 carriers, however, there was a higher rate of nosocomial contamination. The risk factor of contamination by transfusion was higher among genotype 2 carriers. Moreover, medical invasive exams rate was significantly higher among genotype 2 carriers. Surgical transmission was also found more often among genotype 2 carriers. The proportion of intravenous drug users was less among genotype 2 carriers. There was no significant difference for the others risk factors : sexual or vertical transmission. There was no significant difference concerning date of detection between the two series.

Geographical distribution was also analysed, by using the postal code. There was a significant difference, in the province of Liege : in the city of Verviers, the prevalence was higher (30%) than in the others cities of the province (17%).

Nosocomial transmission was higher in genotype 2 carriers, especially for invasive medical exams. Therefore, we analysed the characteristics of patients infected with genotype 2 and contaminated by medical invasive exams, versus patients with genotype 2 contaminated by other modes of contamination (Table 3). There was no phylogenic analysis performed, but medical invasive exams contamination were significantly associated with subtype 2a-2c ($p < 0.001$), and with the city of Verviers ($p < 0.001$).

A multivariate analysis was performed for the mode of contamination, to determine the main associated factor. This analysis confirmed that medical invasive exams were significantly associated with genotype 2.

Discussion

Genotype 2 is the third most frequent genotype in our countries (12%), after genotype 1 (61.5%) and genotype 3 (14%) (12). These data are similar to others studies for infected patients in Benelux (12%) (15).

In our study, most of the patients were treated by an association of nonpegylated interferon and ribavirine. A high sustained viral response rate (67.5%) was found. This rate was similar to the one of the literature for the same regimen of treatment (usual in before) (16).

Moreover, eligibility for antiviral therapies was very high (72.5%), which is much more than what was described in our general HCV population (41%) (17). This can be explained by the better results expected in genotype 2 patients, in comparison with other genotype carriers. The lower rate of drug users among genotype 2 patients may be another explanation.

This study showed the predominance of contamination with medical invasive exams (mainly urological procedures) in our population of genotype 2 infected patients. This mode of contamination was suspected by the hepatologist based on the typical medical history of the patient and the exclusion of other modes of transmission. This is an illustration of the persistence of iatrogenic transmission of the virus C during the last twenty years, as demonstrated by several publication elsewhere (18-28). Concerning the transmission by

urological procedures in our study, it seems that the contamination were related to the use of the same contrast medium vial for several patients during the realisation of intravenous pyelography (the short catheter connected with the vial, and changed after each procedure, being too short to avoid blood flow reflux in the vial). In fact, some patients developed acute hepatitis C a few weeks after this procedure. By this way, the responsibility of this technique was suspected. A few years later, patients were seen with chronic hepatitis C, medical history of urological procedure, and no other risk factors. The reason why the contamination occurred mainly with genotype 2 remains indeterminate. De Ledinghen described in 2005 a similar situation : patients were contaminated during sclerotherapy of varicose veins by a same physician who used a single vial for multiples patients (29-30). Whether the genotype 2 could resist longer than other genotype is a question that could be raised, but without having found concluding arguments in the literature.

The main message of this study is that poor infection control techniques in some subregions can have a sufficient magnitude to change significantly a whole population epidemiology.

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