Relationship Between Genotypes of Hepatitis C Virus and the Progression to Cirrhosis in Chronic Hepatitis C Patients

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Objective: To assess the influence of the identified genotype on the stage of liver fibrosis at hepatitis C identification and at the 5 years follow up.
Methods: In our retrospective study we enrolled 126 patients with Hepatitis C admitted to the Gastroenterology Unit at the Nouvel Hopital Civil in Strasbourg, France between October 2006 and December 2011. All patients had detectable serum HCV-RNA and had not been transplanted during the 5 years surveillance period. The data collected were analyzed with GraphPad Prism Demo for descriptive and inferential statistics and with StatMate2Demo for power analysis.
Results: In our retrospective study we enrolled 126 patients. Genotype distribution was as follows: genotype 1a, n=23 (18.25%); genotype 1b, n=48 (38.10%); genotype 2, n=17 (13.50%); genotype 3, n=18 (14.29%) and genotype 4, n=20 (15.86%). Fibrosis at diagnosis and follow up was not influenced by the genotype (odds ratio ranging from 0.395 to 5.147 but with a 95% CI below 1), except genotype 1b (odds ratio 2.093 [1.008; 4.348] at follow up).
Conclusions: There is no association between a particular HCV genotype and the fibrosis stage as defined by transient elastography.

Keywords: fibrosis, genotype, HCV, cirrhosis, fibroscan

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Introduction

Hepatitis C virus (HCV) is estimated to affect approximately 200 million people worldwide with a global prevalence of 3% [1]. More than 80% of patients with HCV infection progress to chronicity, 20–30% of patients with chronic HCV infection progress to cirrhosis in 10 to 20 years, which in turn is associated with an increased risk of hepatocellular carcinoma [2].

Virological studies have identified six genotypes (1–6) of HCV and various subtypes [3].

The most prevalent genotype worldwide is genotype 1 (1a and 1b), subtype 1b having the highest prevalence in Europe. Genotypes 5 and 6 are less frequent.

HCV RNA testing, HCV genotyping and staging of liver disease are essential for diagnosis and HCV treatment. The liver biopsy is the gold standard in assessing the liver fibrosis in patients with chronic HCV infection. Several types of fibrosis classifications are now available for non-invasive fibrosis tests (Fibrotest, Fibroscan, FibroMeter), the most important of which is detailed fibrosis class classifications [4,5]. Recently, non-invasive methods (transient elastography, serological markers) have been used for identifying patients with mild fibrosis and cirrhosis, but their accuracy less reliable in discriminating moderate and severe fibrosis. The European Association of the Study of the Liver hepatitis C virus clinical practice guidelines 2011 recommended that transient elastography could be used to asses liver fibrosis in patients with chronic hepatitis C [6]. Transient elastography is a simple, non-invasive and effective method to assess liver fibrosis by measuring liver stiffness [7].

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Material and methods

Our study is a retrospective one enrolling 126 patients with Hepatitis C admitted to the Gastroenterology Unit at the Nouvel Hopital Civil in Strasbourg, France between October 2006 and December 2011.The inclusion criteria were: detectable serum HCV-RNA, patients aged above 18 years, clearly identified genotype, a 5 years follow up, fibrosis evaluation by transient elastography at identification and follow up, viral load, general biochemistry done on a regular basis. The exclusion criteria were: liver transplantation during the surveillance period and missing follow up sessions.

All laboratory tests were performed for each patient on enrolment. They were measured using commercially available assays. HCV genotype was determined by Bayer Trugene HCV 5'NC sequence and NS5B Applied Biosystems 3130 and classified according to Simmonds' classification system. Serum viral load was determined by quantitative reverse transcription polymerase chain reaction with Abbot real-time PCR from 2008 on and by signal amplification on the branched DNA probe (Bayer bDNA Quantiplex 3.0) until 2008.

For the fibrosis identification and evaluation we used the transient elastography method (FibroScan® Echosens,

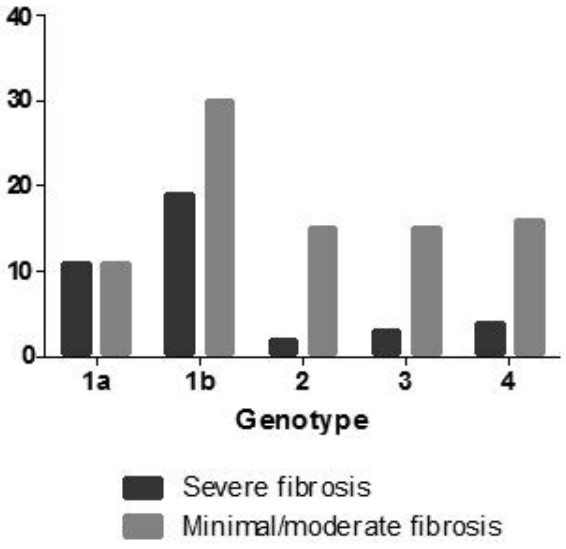

Fig. 1. Distribution of severe and minimal to moderate fibrosis on identification

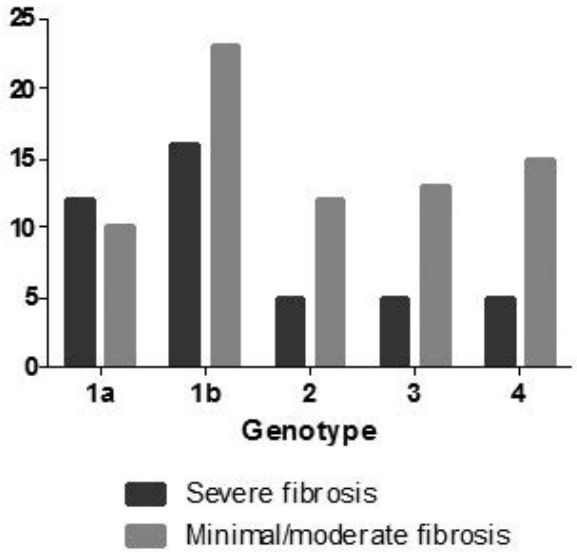

Fig. 2. Distribution of severe and minimal to moderate fibrosis at follow-up

Paris, France). We graded the fibrosis, according to METAVIR staging, into minimal to moderate (F0 to F2 staging) and severe (F3 and F4 staging).

The data collected were analyzed with GraphPad Prism Demo for descriptive and inferential statistics – odds ratio, proportions comparison, Fischer test for ordinal variables, and with StatMate2Demo for power analysis. P values below 0.05 were considered to be statistically significant.

Results

Given the number of patients included, and considering a significant variation 0.2, our study had a power of 60%. A power of 80%, for identifying a 0.1 change would require the enrolment of 500 patients. That does not mean that our study is not clinically important.

The demographic data were as follows: 67 (53.17%) males and 59 (46.83%) females with an average age of 50.15±10.55 years. Genotype distribution was as follows: genotype 1a, n=23 (18.25%); genotype 1b, n=48 (38.10%); genotype 2, n=17 (13.50%); genotype 3, n=18 (14.29%) and genotype 4, n=20 (15.86%).

Severe fibrosis was identified at diagnosis in 39 patients (30.95%) and in 53 patients (42.06%) at follow up with a p of 0.0887. The distribution of severe and minimal to moderate fibrosis as seen by FibroScan on diagnosis and follow up is depicted in Figures 1 and 2.

Table I. Odds ratio for genotype on admission and at follow-up

Genotype	On admission (odds ratio 95% CI)	At follow-up (odds ratio 95% CI)
1a	2.714 [1.059; 6.960]	1.844 [0.729; 4.659]
1b	1.805 [0.837; 3.891]	2.093 [1.008; 4.348]
2	0.259 [0.056; 1.196]	0.529 [0.174; 1.607]
3	0.400 [0.107; 1.472]	0.480 [0.160; 1.443]
4	0.507 [0.157; 1.631]	0.408 [0.136; 1.189]

The odds ratios associated with each genotype are presented in Table I.

Despite the suggestive graphic representation, there is no statistically significance associated with the genotype and the fibrosis staging, except for genotype 1b.

Discussions

The HCV genotype must be assessed prior to antiviral treatment initiation [6].

Recently, many factors have been reported to predict the outcome of treatment, such as HCV genotype, treatment duration, age and patients' gender. The serum viral load has been revealed as one of the critical predictors, despite of HCV genotype [8]. Other studies reported that the viral loads did not correlate with stage of liver disease, but these studies were conducted on small cohorts of patients or on the patients mainly infected with genotype 1b [9]. Fibrosis stages were independent of genotype of the patients; the serum viral load, aspartate transaminase (ALP), AST and bilirubin levers were significantly different among fibrosis stages [10]. But it is true that the fibrosis/cirrhosis were assessed by liver biopsy.

While a higher necro-inflamatory activity could be associated with HCV genotype 2 and with higher alanine transaminase (ALT) serum levels, no association could be proved between HCV genotype and progression of liver disease.

The study enrolling 324 patients indicates that there is no association between a particular HCV genotype and the progression to cirrhosis, and that specific genotypes are associated with distinct histopathological and biochemical manifestations although none of them is correlated with an increase of the fibrosis stage [11]. But they were using liver biopsy to fundament their research. Using transient elastography, genotype 1b seems to be more aggressive –

significantly higher incidence of fibrosis at follow up. Our findings are yet to be confirmed by prospective multicentric studies with multivariate analysis focusing on treatment. We have to emphasis that patients receiving a liver transplant in the 5 years period of follow up were excluded. Maybe the results would be different if this period of follow up would be shortened. If our results are proven to be true a change in treatment approach should be sought after.

The results of a recent prospective study conducted in a large cohort of patients with chronic liver disease showed that transient elastography (TE) is an efficient technique for the diagnosis of cirrhosis and its severity [12]. Apparently this technique replaces the liver biopsy. Further analysis of these differences will provide us with more effective treatment strategies according to HCV genotype. Maybe there is the time to change the golden standard.

TE is a relative newly acquired tool, so we are lacking studies.

Conclusion

There is no association between a particular HCV genotype and the fibrosis stage as defined by transient elastography. Further multicentric studies are needed in order to increase the power of the study, to refine the statistics and to validate our findings.

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