



Epidemiological and Clinical Factors Associated with Spontaneous Clearance of Hepatitis C Virus

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ABSTRACT

BACKGROUND

The risk of chronicity is high after acute hepatitis C. The infection remains limited and spontaneously resolves in an average of 30% of subjects. Such subjects are considered recovered and do not require any medical care. This study aims to evaluate the epidemiological and clinical factors associated with spontaneous viral clearance.

METHODS

We conducted a descriptive retrospective study on patients' files managed for a positive hepatitis C serology who benefited from the research of serum viral RNA by molecular biology

RESULTS

The study collected 429 usable files. The mean age of the patients was 50.21 years, and the sex ratio was 0.98. Spontaneous viral clearance was estimated at 17.2%. The univariate analysis showed that clearance was significantly greater in subjects under the age of 50 years, patients without type 2 diabetes, patients co-infected with hepatitis B virus, patients with transfusion, and those diagnosed fortuitously. Multivariate analysis confirmed the relationship between diabetes and the circumstances of the diagnosis. The relationship in the case of hepatitis B co-infection was very close to the statistical significance level ($p=0.055$).

CONCLUSION

The presence of hepatitis B co-infection in patients with positive hepatitis C serology predicts a high probability of having spontaneous clearance. However, advanced age and the existence of a history of blood transfusion, type 2 diabetes or suggestive signs of liver damage are associated with persistent viremia

KEYWORDS:

Hepatitis C virus; Spontaneous clearance; Diabetes; Diagnostic circumstances; Hepatitis B co-infection

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INTRODUCTION

LiHepatitis C virus (HCV) is a hepatotropic virus that can cause serious chronic infections in humans. Virus contamination results from exposure to blood that occurs during blood transfusion (become less frequent since the systematic screening of blood donors), risky medical care (during hospitalization, surgery, endoscopic exploration, etc.), traumatic sexual intercourse, injection drug use, or from mother to child. The distribution of viral hepatitis C (VHC) is ubiquitous; about 130 to 150 million people are chronically infected. The most affected regions are Africa, Central Asia, and East Asia. In Algeria, the prevalence of anti-HCV antibodies in the general population is on average 1%.^{1,2}

After an acute VHC infection, the risk of progression to chronicity is approximately 60-85%. The infection is limited and spontaneously progresses to resolution in 30% of the subjects. This healing is affirmed by the presence of HCV antibodies and the absence of serum viral RNA. Such subjects are considered cured and do not require medical treatment.

Spontaneous viral clearance (SVC) usually occurs within 3 to 12 months of infection (16.5 weeks on average). According to a meta-analysis that included six studies involving 998 individuals, the occurrence of SVC in the 3, 6, 12, and 24 months after infection was 19.8%, 27.9%, 36.1%, and 37.1%, respectively.^{3,4}

The asymptomatic nature of acute VHC makes its diagnosis difficult and its evolution poorly studied. Factors associated with SVC are poorly understood; however, several factors appear to be involved: host factors such as sex and immune response (T lymphocyte response: CD4 + T lymphocytes as key regulators and CD8 + T lymphocytes as major antiviral effectors), viral factors such as genotype, and genetic factors such as genotype of interleukin-28B and some alleles of the HLA system.^{3,5,6,7,8,9,10}

SVC is rare but possible in the chronic hepatitis phase.¹¹ It has been reported following liver transplantation, development of hepatocellular carcinoma, or stopping immunosuppressive therapy. It has also been reported during pregnancy, after superinfection with hepatitis B virus (HBV)^{12,13,14,15} and after immune restoration in patients infected with human immunodeficiency virus (HIV).^{10,16,17,18}

The objective of this study is to look for epidemiological and clinical factors that may be associated with SVC in Sétif, Algeria.

MATERIALS AND METHODS

We conducted a retrospective descriptive study on patient files treated in the Department of Infectious Diseases of the University Hospital of Setif-Algeria, between January 2000 and December 2019, for a positive hepatitis C serology and benefited from serum viral RNA research by molecular biology. An undetectable serum viral RNA was checked regularly by a second sample 2 to 3 months later.

As this is a retrospective study, authorization to access the files was obtained from the head doctor of the Department.

All the data collected from the files were initially entered in Excel, and statistical analyses were performed using SPSS software for Windows version 18.0 and considered:

- A descriptive study of all the epidemiological and clinical variables available in the files:
 - o Sex
 - o Age at the time of discovery of positive HCV serology
 - o Medical history
 - o Potential contamination factors: transfusion, surgery, endoscopic exploration, similar case in the family surrounding, blood exposure accident (BEA), tattooing or scarification, intravenous drug addiction, and dental care.
 - o Associated co-morbidities: diabetes, arterial hypertension, chronic hemodialysis, thyroid disorders, coinfection with HBV and/or HIV, overweight, consumption of alcohol and/or tobacco, etc.
- We excluded 45 files due to two or more missing data
- An analysis of the factors associated with an SVC in univariate then in multivariate by logistic regression. The statistical test was Chi-square for percentages. Odds ratios (OR) are shown with 95% confidence intervals (CI); the significance threshold was set at 5%. The variables included in multivariate analysis are those with a significant relationship in univariate analysis.

RESULTS

The study collected 429 usable files. Descriptive analysis of the population studied found a mean age of 50.21 years [4 to 86 years old], a median of 52 years old, and a sex ratio, males to females, of 0.98. The discovery of HCV was fortuitously made by routine blood tests (preop-

Table 1: Variables associated with spontaneous viral clearance in univariate analysis

Variables		Spontaneous viral clearance: N (%)	No spontaneous viral clearance: N (%)	OR [IC à 95%]	p (X2)
Age at the time of diagnosis (years old)	< 50	43 (22.6)	147 (77.4)	1.96 [1.18-3.26]	0.006 (6.92)
	> 50	31 (13.0)	208 (87.0)		
Diagnostic circumstances	Fortuitous	71 (21.3)	262 (78.7)	8.40 [2.58-27.32]	<1/1000 (17.28)
	Presence of suggestive signs of liver injury	3 (3.1)	93 (96.9)		
Type 2 diabetes	Yes	8 (8.6)	85 (91.4)	0.39 [0.18-0.83]	0.007 (6.22)
	No	66 (19.6)	270 (80.4)		
Blood transfusion	Yes	33 (23.4)	108 (76.6)	1.84 [1.10-3.07]	0.014 (5.57)
	No	41 (14.2)	247 (85.8)		
HBV co-infection	Yes	10 (38.5)	16 (61.5)	3.31 [1.44-7.62]	0.007 (8.73)
	No	64 (15.9)	339 (84.1)		

erative, pregnancy, employment, etc.) or screening around a case in 333 patients (77.6%); the diagnosis was made on clinical or paraclinical signs suggestive of liver injury in 96 patients (22.4%). Decompensation of cirrhosis revealed the disease in 27 patients.

Iatrogenic risk factors were frequent and varied in patients: surgery (264 patients), blood transfusion (141 patients), previous hospitalization (311 patients), endoscopy (120 patients), BEA (34 patients), scarification or tattooing (109 patients), intravenous drug abuse (4 patients), risky sexual behavior (9 patients), and dental care (366 patients from 391 data collected). The presence of VHC in the family surrounding was found 23 times, and only three partners had a positive HCV serology.

Co-morbidities were frequent and sometimes multiple in the same patient. Arterial hypertension (165 cases), type 2 diabetes (93 cases), chronic hemodialysis (74 cases), thyroid disorders (37 cases), bronchial asthma (32 cases), and overweight estimated by a body mass index (BMI) greater than 25 kg/m² (131 cases from 293 data collected). Alcohol and tobacco consumption were found in 12 and 65 cases, respectively.

26 patients had positive HBs Ag, and four patients were

infected with HIV. No patient had HCV-HBV-HIV co-infection or syphilis serology positive.

Other pathologies such as respiratory diseases, hematological diseases, or inflammatory diseases were found in 86 patients.

The SVC rate was estimated at 17.2% (74 cases) with a 95% CI of [14.0-20.7]. Univariate analysis showed that SVC is significantly greater in subjects less than 50 years of age, patients without type 2 diabetes, patients co-infected with HBV, people receiving transfusions, and those diagnosed fortuitously (table 1). No association was found for the other variables.

Multivariate analysis confirmed the relationship of SVC with the circumstances of diagnosis and diabetes. The relationship with HBV co-infection was very close to the significance level: $p=0.055$ (table 2).

DISCUSSION

To the authors' knowledge, this is the first study assessing the factors associated with SVC after HCV contamination in Algeria.

Several results characterize our study: besides the importance of iatrogenic risk factors in our region, their

Table 2: Variables associated with spontaneous viral clearance in multivariate analysis

Variables	B	S.E	Wald	Df	Sig.	Exp (B)
Age at the time of diagnosis	.292	.282	1.070	1	.301	1.339
Diagnostic circumstances	1.968	.609	10.453	1	.001	7.158
Type 2 diabetes	.833	.417	3.982	1	.046	2.299
Blood transfusion	-.211	.279	.570	1	.450	.810
Coinfection VHB	-.861	.449	3.677	1	.055	.423
Constant	-3.212	.829	14.995	1	.000	

multiplicity in the same patient is frequent. Indeed, among 264 patients who underwent surgery, 109 patients were transfused, and 82 patients underwent endoscopic exploration, but intravenous drug addiction (a major risk factor in high-income countries and increasingly common in low- and middle-income countries^{5,19,20}) has only been found in four patients. This means that the fight against transmission in health care remains a key element in the elimination of the disease in our region.

The importance of co-morbidities is linked to the type of study (real-life data). Among 163 patients with arterial hypertension in this series, 58 had diabetes, and 49 were receiving chronic hemodialysis. This element leads to more severe disease and may hamper therapy in viremic patients.

The circumstances of the diagnosis (fortuitous in more than ¾ of the patients) and the lower age at the discovery of the disease (less than 50 years old) are common during VHC. They are due to the silent nature of the disease over several decades.²¹

The prevalence of SVC estimated at 17.2% with a 95% CI [14.0-20.7] appears smaller than the reported mean (30%), but it remains within the range theoretically reported,²¹ for example, Alter had reported a rate of 14% while Rodger had found a rate of 46%.^{22,23}

The majority of factors associated with SVC found in our study are in agreement with the literature:

SVC and epidemiological factors

Most studies report that women are more likely to clear the virus spontaneously than men. This finding has not been explained yet^{3,4,5,10,24} However, some studies have found a result similar to ours (lack of relationship between

sex and SVC).²⁵ Hormonal genetic variations appear related to SVC. A Chinese study evaluated the consequences of genetic variants of the estrogen receptor α (ER α) on the course of the disease and found that the genotype “ESR2 rs4986938 AA” of ER α would be associated with SVC.²⁶

As this is a retrospective study unable to study the age of contamination, we studied the age at the time of the diagnosis of the infection. The results of a greater SVC in case of early discovery of a positive serology ($p=0.006$; OR: 1.96 [1.18-3.26]) in the univariate analysis could be correlated with the results of prospective studies, which had found that the probability of an SVC was higher when the contamination was early.^{3,25} Other studies have shown that the risk of cirrhosis is more important when contamination occurs in old age.²⁷ Similarly, the natural history of HCV explains the positive relationship found between diagnostic circumstances and SVC (only three cases were not viremic among symptomatic patients: $p<0.001$). It is well established that clinical signs regress and transaminases become normal after virus elimination.²¹

Regarding the mode of contamination, a significantly greater SVC in transfused patients found in the univariate analysis should be interpreted with caution because of the retrospective nature of the study and the multiplicity of risk factors in the population studied. Indeed, among 141 patients transfused, 135 had at least two risk factors, and 109 had three or more factors. The result found in multivariate would be more probable. We did not find any study comparing SVC according to the modes of contamination in the literature; the percentage of SVC after transfusion is usually between 15% to 20%.^{28,29,30} while a study carried out on women contaminated after injection of anti-D found a significantly higher rate (45%).³¹

SVC and clinical factors

HBV/HCV co-infection is not rare in areas where HBV endemicity is high due to the same modes of transmission. A greater SVC in the case of HBV co-infection ($p=0.007$ in univariate and $p=0.055$ in multivariate analysis) has also been reported by several studies. It would be due to mutual interference. There is probably a biological interaction between HBV and the response of specific HCV T cells leading to the production of interferons that could trigger a suppressive effect on HCV infection.^{3,14,15,25,32}

In contrast, in the case of HIV co-infection, there is a deleterious influence of HIV on liver disease leading to a rapid progression of liver damage and an increase of HCV viral load. SVC is not frequent, and viremia increases gradually as advancing immunosuppression.^{24,33,34} A few cases of SVC in chronic HCV have been reported after immune recovery under antiretroviral therapy.^{16,17,18,35} The small number of HIV-infected patients of our series does not allow us to draw any conclusions. Also, in hemodialysis patients, SVC is not usual and occurs in approximately 5% of cases. This is due to a failure of the adaptive immune system, such as the absence of significant responses of T cells and antibodies.^{8,36,37,38}

The first descriptions of diabetes/HCV association date back to the 1990s. Several studies from different parts of the world have reported that HCV can contribute to the development of diabetes mellitus. A higher prevalence of type 2 diabetes was observed in patients infected with HCV than in those with other forms of chronic hepatitis. Rouabhia found a higher prevalence of type 2 diabetes in VHC compared with VHB (39.1% vs. 5%; $p<0.0001$). The course of the infection in cases of diabetes is characterized by advanced lesions of fibrosis and cirrhosis.^{39,40} This explains our result; only 8.6% of diabetics against 19.6% of non-diabetic patients had spontaneously eliminated the virus ($p<0.05$).

CONCLUSION

In patients with positive HCV serology, The presence of hepatitis B co-infection in patients with positive hepatitis C serology predicts a high probability of having spontaneous clearance. However, advanced age and the existence of a history of blood transfusion, type 2 diabetes or suggestive

signs of liver damage are associated with persistent viremia.

The fight against iatrogenic transmission of HCV remains essential for the elimination of the disease in our country.

Despite the positive results of this retrospective study, prospective studies analyzing all the factors (host, viral, and genetic factors) are needed in order to overcome the shortcomings of retrospective studies represented mainly by a lack of several data in the files.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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