

Extra-Hepatic Biological Manifestations in Hepatitis C Virus Antibody Carriers in Cotonou and Parakou (Benin) in 2019-2020

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Abstract

Introduction: Viral hepatitis C, essentially a liver disease, can be accompanied by clinical and biological extra-hepatic manifestations. The aim of this study was to determine the prevalence of biological extrahepatic manifestations in patients with hepatitis C virus (HCV) antibodies and the factors associated with them. **Methods:** This was a descriptive and analytical cross-sectional study. It took place between August 2019 and January 2020. Data collection was prospective. All patients with a positive anti-HCV antibody in the gastroenterology departments of CNHU-HKM and CHUD-B/A who had given their consent were included. Extrahepatic biological manifestations, including cryoglobulinemia, were investigated in each patient. **Results:** A total of 135 patients with chronic hepatitis C were included, 114 at CNHU-HKM and 21 at CHUD-B/A. The sex ratio was 0.73. The most common extrahepatic biological manifestations were cryoglobulinemia (23/90 *i.e.* 35.6%), thrombocytopenia (10/56 *i.e.* 17.9%) and renal failure (26/58 *i.e.* 44.8%). There was a statistically significant association between cryoglobulinaemia and peripheral neuropathy ($p < 0.038$). There was also a statistically significant association between cryoglobulinaemia and C viral load ($p < 0.001$), with those with a detectable viral load more likely to have positive cryoglobulinaemia. Similarly, genotype 1 pa-

tients had a greater risk of developing cryoglobulinaemia ($p < 0.001$). There was also a statistically significant association between thrombocytopenia and hepatomegaly ($p = 0.048$). However, there was no statistically significant association between age, sex, alcohol consumption and cryoglobulinaemia or thrombocytopenia. **Conclusion:** Biological extra-hepatic manifestations in chronic hepatitis C are frequent. This raises the question of their possible impact on patients' quality of life, and the value of offering hepatitis C virus screening to patients presenting with such manifestations.

Keywords

Viral Hepatitis C, Cryoglobulinaemia, Thrombocytopenia, Benin

1. Introduction

Viral hepatitis is a major public health problem worldwide. In 2024, it was estimated that viral hepatitis was responsible for 1,426,070 deaths a year worldwide, including 1,172,604 from viral hepatitis B (VLB) [1], and 253,466 from viral hepatitis C (VHC) [2], a figure higher than that attributable to HIV/AIDS (1 million) or tuberculosis (1.3 million). Chronic hepatitis C virus (HCV) infection, defined as chronic carriage of HCV RNA in the blood, affected 50,648,211 people [2]. It is estimated that there will be 1,036,807 new cases of chronic HCV infection worldwide in 2024 [2]. In West Africa, an estimated 1% of the population are chronic carriers of hepatitis C [2]. The data available on the prevalence of hepatitis C in sub-Saharan countries is fragmentary and concerns blood donors and certain at-risk groups. In Benin, the latest estimates for 2024 gave a national prevalence of 1%, representing approximately 111,332 people [2].

For a long time, hepatitis C was regarded by doctors as a disease of the liver alone. However, those affected have always mentioned problems not directly related to the liver. Even today, many people are afraid to mention these problems for fear of not being listened to, or because they are unaware that they may be repercussions of their hepatitis. Three out of four people with hepatitis C experience at least one extra-hepatic symptom. Several extrahepatic manifestations (EEM) can be observed in the various types of hepatitis. Approximately 50% of chronic carriers of the hepatitis C virus (HCV) have a positive mixed cryoglobulinemia (MC); more than one out of three people with hepatitis C experience at least one extra-hepatic symptom. These MEHs are often the main reason why patients consult a doctor [3].

Haematological damage is classified as a blood disorder, generally expressed as haemolytic anaemia, agranulocytosis or thrombocytopenia. Neurological manifestations occur in 9% to 45% of cryoglobulinemic patients [3]-[5]. They manifest as encephalopathy, convulsions, cerebral vasculitis with cerebral infarctions and damage to the cranial pairs [6]. There is also impairment of higher functions, including cognitive and attention problems, which may or may not be associated

with a depressive syndrome or chronic fatigue syndrome [7]. There are many types of kidney damage. Glomerular nephropathy is the most common form. They may be responsible for proteinuria and haematuria, and are often associated with arterial hypertension or renal failure of varying severity over time. Arthralgias are the most frequent joint symptoms; they are non-deforming and predominate in the hands and knees. They occur in 25% of patients, with or without myalgias, cramps and uncontrolled movements of the legs and hands [3].

These extra-hepatic manifestations may develop independently of liver damage. In some cases, they may be life-threatening or, failing that, disabling, and in such cases may affect patients' quality of life [8].

In Benin, a study by Olou *et al.* of 15 patients with hepatitis C showed a 100% prevalence of MEH [9]. The present study looks at extrahepatic biological manifestations (EEM) in a wider population.

The aim of the study was to determine the prevalence of biological extrahepatic manifestations in patients with anti-HCV antibodies and the factors associated with them.

2. Methods

This was a descriptive and analytical cross-sectional study. It took place between 02 August 2019 and 31 January 2020. Data collection was prospective. The target population consisted of all patients admitted for consultation in the CUHGE and followed up for documented viral hepatitis C, whether on treatment or not, and those followed up in the internal medicine department of the CHUD Borgou for hepatitis C. Patients with anti-HCV antibodies who had given informed consent and whose medical records were complete (medical observation, paraclinical examinations) were included in the study.

In this study, the analysis focused on three main extrahepatic biological manifestations, considered as dependent variables: cryoglobulinemia (immunological manifestation), thrombocytopenia (haematological manifestation), and renal failure (renal manifestation).

Patients had their creatinemia measured in mg/l. Glomerular filtration rate (GFR) was calculated using the modified MDRD formula in ml/min/1.73 m². The degree of renal impairment was based on the GFR value:

- ≥90: no renal impairment
- 60 - 89: mild renal impairment
- 30 - 59: moderate renal impairment
- 15 - 29: severe renal failure
- ≤15: end-stage renal disease

Thrombocytopenia was defined by platelet count below 150 G/L.

The independent variables were sociodemographic (age; sex; marital status; occupation and level of education), clinical (lifestyle habits including alcohol consumption; history of HCV, HIV, cirrhosis, HCC; general condition with WHO performance index, BMI; physical signs (notably hepatocellular insufficiency,

portal hypertension, jaundice, ascites); biological signs (liver function with PT, ASAT, ALAT, alpha-fetoprotein, platelets, liver fibrosis with FIBROTEST®; virology (anti-HCV Ac; HCV viral load, HCV genotype), ultrasound : liver size (hepatomegaly or not); liver parenchyma (normal - steatosis - cirrhosis - nodular); echogenicity (homogeneous or heterogeneous).

The data were cleaned and coded, then entered into the EPI data v4.4.2.1 software. Analysis was performed using SPSS 21 French version and Epi-Info 7.1.0.6. The study of associated factors was structured as a univariate and multivariate analysis. In the univariate analysis, comparisons of the frequency of the dependent variables were made according to the independent variables, using Pearson's uncorrected Chi-2 tests and Fisher's exact test for small numbers (theoretical numbers less than 5).

The different variables associated with the dependent variables at the 5% or 20% risk in the univariate analysis were entered into a top-down logistic regression model. Adjusted ORs with their 95% confidence intervals were generated to quantify the strength of the associations. The difference in comparisons was considered significant for all p-values < 0.05.

Although the total study population included 135 patients with anti-HCV antibodies, the sample sizes used to calculate the prevalence of the various extrahepatic biological manifestations varied depending on the availability of biological tests in the medical records. Cryoglobulinemia could only be investigated in 90 patients, thrombocytopenia in 56 patients with recent platelet counts, and renal failure in 58 patients who had undergone a complete renal assessment. These variations are mainly due to missing data and the uneven availability of specific tests in the context of limited resources, rather than to an analysis of predefined subgroups.

From an ethical point of view, prior informed consent was obtained from the patients, as well as administrative authorisation from the hospital directors and heads of department concerned. Data were collected and processed in strict confidence.

3. Results

Our study involved 135 patients with positive anti-HCV antibodies, including 114 at the CNHU-HKM (Cotonou) and 21 at the CHUD Borgou/Alibori (Parakou).

3.1. Sociodemographic and Clinical Characteristics of the Study Population

The mean age was 57 ± 15.8 [12, 86] years. The study population consisted of 78 women (57.8%), giving a sex ratio of 0.73. Married patients accounted for 83/135 (61.5%). The majority of patients had at least secondary education 105/135 (77.8%). Civil servants were the most represented 56/135 (41.5%) (**Table 1**).

The main clinical signs presented by the patients were asthenia in 38.6% (34/88) and arthralgia in 30.7% (27/88).

Table 1. Socio-demographic characteristics of the study population (N = 135).

	n (%)
Age	
0 - 19	1 (0.7)
20 - 29	12 (8.9)
30 - 39	10 (7.4)
40 - 49	14 (10.4)
50 - 59	22 (16.3)
60 - 69	48 (35.6)
70 - 79	23 (17.0)
80 - 89	5 (3.7)
Gender	
Female	78 (57.8)
Male	57 (42.2)
Marital status	
Married	83 (61.5)
Widowed	28 (20.7)
Single	17 (12.6)
Divorced	12 (8.9)
Level of education	
Higher	51 (37.8)
Secondary	54 (40.0)
Primary	17 (12.6)
No education	13 (9.6)
Occupation	
Public sector	56 (41.5)
Liberal	42 (31.1)
Housewife	23 (17.0)
Craftsman	9 (6.7)
Student	3 (2.2)
Pupil	2 (1.5)

3.2. Profil Des Manifestations Extra-Hépatiques Biologiques

Of the 135 patients, cryoglobulinemia was detected in 90. It was positive 32 times out of 90, or 35.6%. The other extra-hepatic biological manifestations were thrombocytopenia in 10 out of 56 patients (17.9%); and renal failure in 26 out of 58 patients (44.8%) (**Table 2**).

Table 2. Biological characteristics.

	n (%)
Genotype (N = 135)	
2	39 (28.9)
1	35 (25.9)
Indeterminate	16 (11.9)
Detectable viral load (N = 135)	90 (66.7)
Hepatic cytolysis	
ASAT > 40 IU/L (N = 135)	52 (38.5)
ALAT > 40 IU/L (N = 135)	46 (34.1)
Hepatic fibrosis	
Fibrotest ≥ F2 (N = 135)	23 (17.0)
APRI ≥ 2 (N = 135)	4 (3.0)
Haematological	
Anaemia (N = 135)	13 (9.6)
Thrombocytopenia (N = 56)	10 (17.9)
Low TP (N = 135)	7 (5.2)
Cryoglobulinemia (N = 90)	32 (23.7)
Renal failure (N = 58)	26 (44.8)

3.3. Factors Associated with Extrahepatic Biological Manifestations

- Factors associated with the presence of cryoglobulinaemia in HCV carriers

There was a statistically significant association between cryoglobulinaemia and viral load ($p < 0.001$), with those with a detectable viral load more likely to have positive cryoglobulinaemia. The same is true between cryoglobulinaemia and genotype, with a higher risk of genotype 1 patients developing cryoglobulinaemia ($p < 0.001$). There was also a statistically significant association between cryoglobulinaemia and peripheral neuropathy ($p < 0.038$). However, there was no statistically significant association between age and cryoglobulinaemia ($p = 0.302$), sex and cryoglobulinaemia ($p = 0.659$) or alcohol consumption and cryoglobulinaemia ($p = 1.000$). The same was true between: cryoglobulinaemia and age ($p = 0.302$); cryoglobulinaemia and sex ($p = 0.659$); cryoglobulinaemia and fibrosis ($p = 0.634$); cryoglobulinaemia and steatosis ($p = 0.292$) (**Table 3**).

Table 3. Factors associated with cryoglobulinaemia.

	Cryoglobulinaemia				p
	Yes		No		
	N	%	n	%	
Age					0.302
<50	5	25.0	15	75.0	

Continued

≥50	27	38.6	43	61.4	
Gender					0.659
Male	12	32.4	25	67.6	
Female	20	37.7	33	62.3	
Alcoholism					1.000
Yes	2	33.3	4	66.6	
No	25	34.2	48	65.8	
HYPERTENSION					0.141
Yes	18	46.2	21	53.8	
No	13	26.0	37	74.0	
Diabetes					0.360
Yes	4	36.4	7	63.6	
No	27	34.6	51	65.4	
Cryoglobulinemic syndrome					0.143
Yes	2	100	0	0.0	
No	28	32.9	57	66.1	
Peripheral neuropathy					0.038
Yes	1	33.3	0	0.0	
No	30	35.3	57	64.7	
Asthenia					0,710
Yes	10	30.3	24	64.3	
No	21	38.9	33	61.1	
Arthralgia					0.297
Yes	11	40.7	16	37.0	
No	20	32.8	41	54.1	
Myalgia					0.597
Yes	2	40.0	3	60.0	
No	27	33.3	54	66.7	
Dry syndrome					0.069
Yes	0	0.0	0	0.0	
No	31	35.6	66	64.4	
Pruritus					0.561
Yes	3	27.3	8	72.1	
No	28	36.4	49	63.6	

- Factors associated with thrombocytopenia in HCV carriers

There was a statistically significant association between thrombocytopenia and hepatomegaly ($p = 0.048$) (**Table 4**).

Table 4. Factors associated with thrombocytopenia in anti-HCV carriers.

	Thrombocytopenia				p
	Yes		No		
	N	%	n	%	
Gender					0.198
M	12	66.7	6	33.3	
F	32	82.1	7	17.9	
Cirrhosis					0.117
Yes	1	33.3	2	66.7	
No	42	80.8	10	19.2	
BMI					0.230
Lean	1	50.0	1	50.0	
Normal	26	83.9	5	16.1	
Overweight	7	58.3	5	41.7	
Obese	10	83.3	2	16.7	
Hepatomegaly					0.048
Yes	4	33.3	8	66.7	
No	1	33.3	2	66.7	
TP					0.337
<70	4	57.1	3	42.9	
≥70	30	78.9	8	21.1	

- Factors associated with renal failure in HCV patients

There was no statistically significant association between renal failure and the parameters studied (age, clinical manifestations, stage of progression, treatment) (Table 5).

Table 5. Factors associated with renal failure (RF) in anti-HCV carriers.

	RF				p
	Yes		No		
	n	%	n	%	
HTA					0.279
Yes	20	69.0	9	31.0	
No	16	55.2	13	44.8	
Diabetes					0.332
Yes	10	76.9	3	23.1	
No	26	57.8	19	42.2	

Continued

Asthenia					0.857
Yes	12	60.0	8	40.0	
No	20	62.5	12	37.5	
Arthralgia					0.747
Yes	8	66.7	4	33.3	
No	24	60.0	16	40.0	
Myalgia					0.514
Yes	2	100.0	0	0.0	
No	29	59.2	20	40.8	
Cirrhosis					0.769
Yes	10	55.6	8	44.4	
No	21	61.8	13	38.2	
Age					0.505
≤50	6	50.0	6	50.0	
>50	30	65.2	16	34.8	
Treatment					1.000
Yes	4	66.7	2	33.3	
No	28	60.9	18	39.1	

4. Discussion

Of the 135 patients, probably mixed cryoglobulinemia was detected in 90 patients. It was positive in 32 of the 90, *i.e.* 35.6%. A study carried out by Eloumou *et al.* in Cameroon in 2019 on the detection of cryoglobulinaemia and associated factors in 116 patients with HCV reported a prevalence of 52.57% [10] whereas Kahloun *et al.* reported a prevalence of 9% [11]. There was a statistically significant association between cryoglobulinaemia and peripheral neuropathy ($p < 0.038$). This significant association observed is clinically relevant. It can be explained by the pathophysiological mechanisms of cryoglobulinemic vasculitis, characterized by immune deposits in the vessels, which cause peripheral nerve ischemia. Cryoglobulins, often linked to chronic HCV infection, precipitate in the vessel walls when exposed to cold, leading to vasculitis with manifestations such as asthenia, arthralgia, and purpura. Cryoglobulinemic vasculitis mainly affects small and medium-sized vessels, affecting the skin, kidneys, and nerves. This neurological involvement is well described in the literature as one of the most common and debilitating extrahepatic manifestations of HCV-associated cryoglobulinemia [12] [13].

Thrombocytopenia was found in 10 out of 56 patients (17.9%). In a study conducted by Sehonou *et al.* on haemogram abnormalities in patients treated for viral hepatitis B or C in a gastroenterology practice in Cotonou (Benin) in 2017, thrombocytopenia was noted in 76 patients (40%). Thrombocytopenia was 55% in patients with anti-HCV antibodies (21/38). Cacoub *et al.* in 2000 reported a preva-

lence of 17% [3] similar to that found in our series. The frequent occurrence of thrombocytopenia in patients chronically infected with HCV may be due to several mechanisms: peripheral involvement (hypersplenism, autoimmune thrombocytopenia due to anti-platelet or anti-phospholipid antibodies, HCV RNA in platelets), or central involvement (HCV RNA in megakaryocytes, malignant lymphoproliferation, decreased hepatic production of thrombopoietin [14].

Of the 135 patients, 58 underwent renal assessment. Renal failure was noted in 26 patients, representing a prevalence of 44.82%. Olou found a prevalence of 53.8% in patients with CVH. This difference may be explained by the small sample size (15 in Olou's study) [9].

Few data are available on the prevalence of renal failure in viral hepatitis C. The most commonly reported renal manifestations are cryoglobulinemic glomerulonephritis [15]. This is a membranoproliferative glomerular nephropathy. A few cases of extra-membranous, mesangio-proliferative glomerulonephritis and segmental and focal hyalinosis have been reported in non-cryoglobulinemic HCV-infected patients, raising suspicion of a possible direct role for HCV in their genesis. Renal biopsies are often performed. This was not the case in our study: biopsies are not routinely performed in Benin. Furthermore, the overall prevalence of renal failure in the general population in Benin is unknown. In Senegal it was reported by Faye *et al.* [16] in 2014 and was 37%. This prevalence in the general population is slightly lower than that found in our study in patients with viral hepatitis C. We therefore have reservations about the role of viral hepatitis C in the onset of renal failure in our patients.

Histologically, renal involvement presents as membranoproliferative nephropathy, with thrombi in the vessels (formed by precipitated cryoglobulins), as well as diffuse IgM deposits in the glomerular capillaries, with a possible progression to end-stage renal failure [13]. The absence of renal biopsies is therefore a significant limitation of this study. Histological examination would have made it possible to precisely characterize the type of nephropathy, in particular to confirm or rule out membranoproliferative cryoglobulinemic glomerulonephritis, which is classically associated with HCV. The absence of biopsies limits the possibility of establishing a formal causal link between HCV infection and the renal failure observed in our patients.

Several studies have shown that extrahepatic manifestations of HCV, such as arthralgia, chronic fatigue, or cryoglobulinemia, are associated with a significant impairment in quality of life, regardless of the severity of liver damage. Peripheral neuropathy, often a sensorimotor polyneuropathy, is a common and debilitating extrahepatic manifestation of HCV-related mixed cryoglobulinemia, manifesting as pain, paresthesia, and motor disorders. These symptoms, which are often chronic and debilitating, can significantly affect patients' physical, psychological, and social well-being, warranting comprehensive management beyond the treatment of liver damage alone. The advent of direct-acting antivirals (DAAs) has profoundly changed the management of hepatitis C. The introduction of new,

more effective and better tolerated treatments (in the case of polymorbid patients for whom interferon was contraindicated) involves the management of both liver disease and extrahepatic complications [13]. Several studies have shown that sustained virological eradication with DAAs is associated with an improvement or even resolution of many extrahepatic manifestations, including cryoglobulinemia, hematological disorders (thrombocytopenia, inflammatory or hemolytic anemia) and certain renal disorders (cryoglobulinemic glomerulonephritis or membranoproliferative nephropathies) [17] [18]. Taking into account the results of studies and the efficacy of DAAs with reduced side effects, new indications for HCV treatment promise a better future [13] [19] [20]. It should be noted that these data highlight the importance of early diagnosis and wider access to modern antiviral treatments, particularly in patients with extrahepatic manifestations.

5. Conclusion

This study showed that the extra-hepatic biological manifestations found in patients with anti-HCV antibodies were mainly cryoglobulinaemia, thrombocytopenia and renal failure. There was a statistically significant link between cryoglobulinaemia and viral load, and between cryoglobulinaemia and genotype. This raises the question of their possible impact on patients' quality of life, and the value of offering hepatitis C virus screening to patients presenting with such symptoms.

Authors' Contribution

All the authors were involved in the active writing and editing of the article. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest in this work.

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