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Extra-hepatic clinical manifestations in hepatitis C virus antibody carriers in Cotonou and Parakou, Benin in 2019-2020

Abstract

Introduction: Viral hepatitis C (HCV), primarily a liver disease, also has many extrahepatic manifestations (EHM). The aim of this study is to determine the prevalence of clinical EHM in patients with anti-HCV antibodies and the factors associated with them.

Method: This was a descriptive and analytical cross-sectional study. It was conducted between August 2019 and January 2020 at the University Hepatology and Gastroenterology Clinic (CUHGE) of the CNHU-HKM in Cotonou and the medical department of the CHUD-B/A in Parakou. Patients who were seen during this period and who were HCV antibody positive were included. Data collection was prospective.

Results: A total of 135 patients were included, 121 at the CNHU-HKM and 14 at the CHUD-B/A. The sex ratio was 0.7 and the mean age was 57 ± 15.8 years (ranging from 12 to 86 years).

The most common clinical HEHMs were: asthenia (32.6%); arthralgia (23.7%), type 2 diabetes (15.6%), pruritus (11.1%), myalgia (5.9%), peripheral neuropathy (2.2%), decreased visual acuity (2.2%), and glaucoma (2.2%).

There was a statistically significant association between clinical HEHMs and: age over 50 years (p=0.001); elevated AST (p<0.001) and ALT (p=0.001) aminotransferase levels, viral load, and isolated asthenia (p=0.042). There was no statistically significant link between MEH and gender, although there was a predominance of female patients.

Conclusion: Clinical MEHM associated with HCV is common. Their impact on patients' quality of life therefore warrants consideration. Such manifestations should therefore be seen as opportunities to offer hepatitis C virus screening and assess quality of life in seropositive patients.

Keywords: viral hepatitis C, clinical extrahepatic manifestations, associated factors

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Aboudou Raïmi Kpossou,[1-3] Khadidjatou Saké Alassan,[4] Rémi Zoundjihekpon,[1] Rodolph Koffi Vignon,[1,2] Comlan N'déhougbèa Martin Sokpon,[1] Vincent Zoundjihekpon,[5] Nicolas Kodjoh,[6] Jean Séhonou[1]

[1]University Hepatology and Gastroenterology Clinic, Hubert Koutoukou MAGA National Hospital and University Centre (CNHU-HKM), Benin
[2]Faculty of Health Sciences, University of Abomey-Calavi (UAC), Benin
[3]Calavi International Hospital Centre (CHIC), Abomey-Calavi, Benin
[4]Internal Medicine Department, Borgou-Alibori Departmental University Hospital Centre (CHUD-B/A), Benin
[5]Hepatology, Gastroenterology and Geriatrics Department, Olomouc University Hospital, Czech Republic
[6]National Hepatitis Control Programme (PNLH), Benin

Correspondence: Dr Aboudou Raïmi KPOSSOU, University Hepatology and Gastroenterology Clinic, Hubert Koutoukou MAGA National Hospital and University Centre (CNHU-HKM), Cotonou, Benin, Tel 0022966181939

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Introduction

Viral hepatitis is a major public health problem worldwide. Today, the estimated number of deaths attributable to viral hepatitis is on the rise. Together with tuberculosis, this disease is one of the two leading causes of death from infectious diseases worldwide, with 1.3 million deaths per year for each of the two conditions.[1] Chronic infection with the hepatitis C virus (HCV), defined as the presence of HCV RNA in the blood, affects more than 71 million people and is responsible for 400,000 deaths per year.[2] Approximately 1.75 million new cases of HCV infection were estimated worldwide in 2015.[3] In West Africa, all fifteen ECOWAS member states have a prevalence of viral hepatitis C greater than or equal to 1%.[4] In French-speaking sub-Saharan African countries, there are no data on the prevalence rates of hepatitis C in the general population. The available data are fragmentary and concern blood donors and certain risk groups. In Benin, the overall seroprevalence of hepatitis C virus infection in the entire population screened in 2016 was 1.5% (42 people tested positive out of 2,809).[5]

Extrahepatic manifestations of hepatitis C virus infection must be recognised and understood due to their high frequency and polymorphism. Cryoglobulinaemic vasculitis is the most severe and most common form. On the one hand, 55 to 95% of patients with symptomatic mixed cryoglobulinaemia (MC) have anti-HCV antibodies in their serum. Conversely, prospective follow-up of cohorts of HCV-infected patients has shown the presence of MC in 36 to 55% of cases.[6] Neurological manifestations are present in 9 to 45% of cryoglobulinaemic patients.[7-9] They manifest as encephalopathy, convulsions, cerebral vasculitis with cerebral infarcts and cranial nerve involvement.[10] There is also impairment of higher functions, including cognitive and attention disorders, which may or may not be associated with depression or chronic fatigue syndrome.[11]

The main skin symptom is vascular purpura, which is present in 30 to 100% of symptomatic CM patients.[7,8,12] Arthralgia is the most common joint symptom, non-deforming and predominantly affecting the hands and knees. It is reported in 25% of patients, with or without myalgia, cramps and uncontrolled movements of the legs and hands. These extrahepatic symptoms may develop independently of liver damage. In some cases, they can be life-threatening or, failing that, disabling and impairing patients' quality of life.[13] However, little data is available on these EHDs EHMs in Benin.

The aim of this study is to determine the prevalence of clinical EHDs EHMs in patients with anti-HCV antibodies and the factors associated with them.

Methods

This was a descriptive and analytical cross-sectional study with prospective data collection. It was conducted between 1 August 2019 and 31 January 2020 at the University Hepatology and Gastroenterology Clinic (CUHGE) of the Centre National Hospitalier

Universitaire-Hubert Koutoucou Maga in Cotonou and the medical department of the Centre Hospitalier Universitaire Départemental-Borgou/Alibori in Parakou.

The study population consisted of all patients admitted to the CUHGE of the CNHU-HKM in Cotonou for documented viral hepatitis C, whether undergoing treatment or not, and those followed up in the internal medicine department of the CHUD Borgou for hepatitis C. Patients who were HCV antibody positive (by ELISA serology) and who gave their informed verbal consent were included.

The variables studied were the extrahepatic clinical manifestations of hepatitis C. The clinical manifestations investigated were as follows:

A. General manifestations: asthenia was recorded in patients who complained of it.

B. Rheumatic manifestations: arthralgia and myalgia

a) Arthralgia was recorded in all patients who complained of joint pain in at least one of the following locations: shoulders; elbows; wrists; interphalangeal joints; metacarpophalangeal joints; knees; metatarsophalangeal joints; and spine.

b) Myalgia was recorded in patients complaining of diffuse muscle pain or aching muscles.

I. The dermatological manifestations investigated were: pruritus, prurigo, cutaneous lichen planus, oral lichen planus, chronic urticaria, purpura, pityriasis, psoriasis, late cutaneous porphyria, erythema nodosum and periarteritis nodosa.

i. Lesions such as pruritus, chronic urticaria, prurigo, purpura and pityriasis were easily recognised in patients who presented with them.

ii. Cases of lichen planus were taken into account in patients followed by dermatologists and in whom the diagnosis had been confirmed.

iii. More complex dermatological lesions found and not identified by dermatologists were not taken into account.

A. Ophthalmological manifestations: xerosis (dry eyes)

B. Other clinical manifestations: xerostomia (dry mouth)

Data collection was carried out through interviews with thorough physical examinations, followed by blood tests where necessary. After collection, the data was cleaned and coded, then entered into EPI data v4.4.2.1 software. Analysis was performed using SPSS 21 French version and Epi-Info 7.1.0.6 software.

Administrative authorisation was obtained at both centres prior to the start of the study. Data were collected and processed in complete confidentiality, and storage and processing were carried out anonymously and securely.

Results

The study involved 135 patients who tested positive for anti-HCV antibodies, including 114 at CNHU-HKM (Cotonou) and 21 at CHUD Borgou/Alibori (Parakou).

Sociodemographic and clinical hepatic characteristics of the patients included

The mean age was 57 ± 15.8 years (range 12 to 86 years). The study population consisted of 78 women (57.8%), giving a sex ratio of 0.7. Married individuals accounted for 83/135 (61.5%). The majority of patients had at least a secondary education level 105/135 (77.8%). Civil servants were the most represented 56/135 (41.5%) (Table 1). In most subjects, HCV infection was asymptomatic and was discovered either during routine screening (46.7%) or during the investigation of another disease (39.3%). Hypertension (HTN) and diabetes were the most common comorbidities, occurring in 43.7% and 15.6% of patients, respectively. Ten of the 135 patients (7.4%) were co-infected with hepatitis B virus (HBV), while 2 patients (1.5%) were co-infected with human immunodeficiency virus (HIV); 2.2% of patients had a history of stroke.

Table 1 Sociodemographic characteristics of patients

	Number	Perrcentage (%)
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
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 education	51	37.8
Secondary education	54	40
Primary education	17	12.6
No schooling	13	9.6
Occupation		
Public sector	56	41.5
Private sector	42	31.1
Housewife	23	17
Craftsperson	9	6.7
Student	5	3.7

Profile of clinical extrahepatic manifestations found

Among the clinical manifestations investigated, the most commonly found were general manifestations (68; 50.4%), dominated by asthenia (44; 32.6%). Next were rheumatological manifestations (42; 31.1%), particularly mechanical arthralgia (32; 23.7%). The other clinical HEHMs noted were distributed as follows: gastrointestinal manifestations 27 cases (20%), endocrine 26 (19.3%), dermatological 20 (14.8%), ophthalmological 8 (5.9%) and neurological 3 (2.2%) (Table 2).

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Table 2 Distribution of patients according to extrahepatic clinical manifestations (N=135)

	Number	Percentage (%)
General	68	50.4
Asthenia	44	32.6
Weight loss	16	11.9
Anorexia	1	0.7
Fever	2	1.5
Ophthalmological	8	5.9
Decreased visual acuity	3	2.2
Glaucoma	3	2.2
Cataract	1	0.7
Retinopathy	1	0.7
Dermatological	20	14.8
Pruritus	15	11.1
Psoriasis	1	0.7
Atypical skin lesion	2	1.5
Skin xerosis	1	0.7
Xerostomia	1	0.7
Rheumatological	42	31.1
Inflammatory arthralgia	1	0.7
Mechanical arthralgia	32	23.7
Polyarthritis	1	0.7
Myalgia	8	5.9
Digestive	27	20
Abdominal pain	12	8.9
Dyspepsia	3	2.2
Flatulence	1	0.7
Constipation	8	5.9
Neurological	3	2.2
Peripheral neuropathy	3	2.2
Endocrine	26	19.3
Diabetes	21	15.6
Dysthyroidism*	3	2.2
Goitre	2	1.5
Cryoglobulinaemia syndrome	3	2.2
Other	13	9.6
Insomnia	3	2.2
Cough	6	4.4
Dry syndrome	1	0.7
Vertigo	3	2.2

* 1 case of hyperthyroidism

Factors associated with clinical MEHM

In univariate analysis, there was a statistically significant association between age and MEHM (p=0.001); individuals aged 50 years and older had more MEHM than those younger than 50 years. However, there was no statistically significant association between other sociodemographic factors such as gender, educational level, and the presence of extrahepatic clinical manifestations (Table 3). Alcohol consumption or co-infection with HBV or HIV are not associated with the presence of extrahepatic clinical manifestations in the patients examined. However, diabetes (p=0.048) and hypertension (p=0.046) were significantly associated with MEHM (Table 4). There was no statistically significant association between clinical liver characteristics and MEHM (Table 5).

Table 3 Relationship between sociodemographic factors and clinical EHM

	EHM				p
	Yes		No		
	n	%	n	%	
Age					0.001
10 – 19	0	0	1	100	
20 – 29	9	75	3	25	
30 – 39	6	60	4	40	
40 – 49	8	57.1	6	42.9	
50 – 59	17	77.3	5	22.7	
60 – 69	44	93.6	3	6.4	
70 – 79	22	95.7	1	4.3	
80 – 89	5	100	0	0	
Gender					0.62
Male	42	75	14	25	
Female	69	88.5	9	11.5	
Level of education					0.995
Primary	13	81.3	3	18.7	
Secondary	44	83	9	17	
Higher	41	82	9	18	
No schooling	8	80	2	20	

Table 4 Relationship between antecedents and extrahepatic clinical manifestations

	EHM				p
	Yes		No		
	n	%	n	%	
HBV					0.833
Yes	9	90	1	10	
No	100		22		
HIV infection					**1**
Yes	2	100	0	0	
No	96	82.8	20	17.2	
Diabetes					0.048
Yes	21	100	0	0	
No	80	79.2	21	20.8	
Dyslipidaemia					1
Yes	2	66.7	1	33.3	
No	96	82.8	20	17.2	
hyperuricaemia					1
Yes	2	100	0	0	
No	97	82.2	21	17.8	
High blood pressure					0.046
Yes	53	91.4	5	8.6	
No	52	76.5	16	23.5	
Stroke					1
Yes	2	66.7	1	33,3	
No	98		20		
Alcoholism					**0.405**
Yes	8	100	0	0	
No	95	81.9	21	18.1	

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Table 5 Relationship between clinical hepatic characteristics and clinical MEH

	EHM				p
	Yes		No		
	n	%	n	%	
Cirrhosis					0.789
Yes	4	100	0	0	
No	95	81.9	21	18.1	
Hepatocellular carcinoma					1
Yes	1	100	0	0	
No	96	82.1	21	17.9	
Hepatocellular failure					
Yes	0	0	0	0	
No	12		0		
Ascites					
Yes	1	100	0	0	
No	12		0		
Jaundice					
Yes	0	0	0	0	
No	12	100	0	0	

Discussion

In our study, a history of hypertension was found in 43.7% of subjects; 15.6% were diabetic. In 2010, Houinato et al.[14] found a prevalence of 27.9% of hypertension in the general population of Benin. Similarly, Djrolo et al.[15] reported a prevalence of 4.6% for diabetes in the adult population of Cotonou. Thus, the prevalence of hypertension and diabetes found in our series is well above that found in the general population. With regard to diabetes, the results are comparable to those of other authors. Elhawaril et al.[16] in Egypt found a prevalence of 13.84%. Similarly, Petit et al.,[17] Wang et al.[18] and Veldt et al.[19] found similar figures. Wanvoegbe et al.[20] reported a prevalence of 25% for diabetes among HCV carriers at the CNHU. This difference could be explained by the fact that diabetes was actively sought in the latter study, whereas we based our findings on medical history.

Among the clinical manifestations sought, the most commonly found were asthenia and rheumatological manifestations, particularly arthralgia. Asthenia was noted in 32.6% of patients, while rheumatological manifestations, dominated by arthralgia, were found in 23.7% of subjects. Asthenia is very often the main symptom of chronic viral hepatitis C and a frequent entry point into the 'disease', as this non-specific symptom is an indication for HCV screening and/or aminotransferase testing.[23,24] Asthenia is very often investigated in the context of chronic fatigue syndrome; it can mask underlying depression. It can have an impact on the quality of life of patients with viral hepatitis C. However, we did not have to investigate its impact on quality of life in our study.

The rheumatological manifestations mainly found in this study were arthralgia (23.7%) and myalgia (5.9%). With regard to arthralgia, prevalences similar to ours were reported in 1999 in a study of 1,614 patients by Cacoub et al. (23%)[25] and in 2001 in a study of 321 patients (19%).[7] Pruritus is the main skin symptom in chronic HCV infection.[26] This pruritus is not correlated with the presence of biological cholestasis or with treatment with interferon alpha or ribavirin. No data are available on the effect of anti-HCV treatments on the progression of this pruritus. Other dermatological manifestations include psoriasis, cutaneous xerosis, xerostomia, and atypical lesions. In univariate analysis, no statistically significant link was found between the gender of the subjects and the presence of extrahepatic clinical manifestations (p=0.620), which contrasts with the results of Cacoub et al.;[25] however, there is a predominance of females in Cacoub et al.[25] as in our series.

Furthermore, there was a statistically significant link between age and MEHM (p=0.001) in favour of advanced age ≥ 50 years. In other words, the older the patient, the greater the risk of MEHM. The patients' level of education was not associated with the presence of extrahepatic clinical manifestations, with p=0.995. These results are consistent with those found by Olou,[27] who did not observe any link between extrahepatic manifestations and level of education. In this series, alcohol consumption and HIV co-infection were not associated with the presence of extrahepatic clinical manifestations, with p=0.261 and p=0.7699, respectively. The same results were obtained by Cacoub et al.[25] (p=0.694 and p=0.131) and by Olou.[27]

The EHM more frequently found in diabetics or hypertensive patients may be linked to inactivation of critical genes such as Sirtuin 1 by the hepatitis C virus. Sirtuin 1 is critical to liver function and the prevention of diabetes and hypertension. Sirtuin 1 inactivation by HCV may be associated with EHM and diabetes in these patients with anti-HCV antibodies. Sirtuin 1 activators versus Sirtuin 1 inhibitors may need to be used to treat these patients with anti-HCV antibodies.[28-30] No statistically significant link was found between body mass index and the presence of extrahepatic clinical manifestations (p=0.656). No link was found between the presence of extrahepatic clinical manifestations and cirrhosis (p=0.781), hepatocellular carcinoma (p=0.671), hepatocellular failure (p=0.556), jaundice (p=0.556) or ascites (p=1). The relationships between these clinical data and the occurrence of extrahepatic clinical manifestations were not documented.

Conclusion

Among the clinical HEHMs investigated, asthenia was the most common, followed by arthralgia. A statistically significant link was noted between age and HEHMs in favour of the ≥50 age group, with HEHMs being more frequent in this group. MEH were also more frequent in diabetics or hypertensive patients with anti-HCV antibodies. Such manifestations should therefore be seen as opportunities to offer hepatitis C virus screening to patients.

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