Research Article
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Extrahepatic manifestations of chronic hepatitis B at the Centre National Hospitalier et Universitaire Hubert Koutoukou Maga in Cotonou in 2017

Abstract

Introduction: Extrahepatic manifestations (EEM) are frequently encountered in chronic viral hepatitis. The aim of this study was to determine the prevalence of MEH in chronic viral hepatitis B (CVH) and to identify factors associated with these manifestations.

Materials and methods: This was a descriptive and analytical cross-sectional study conducted from May 15 to August 31, 2017. Data were collected prospectively on the basis of the results of clinical examinations and paraclinical examinations of patients with HVB who consulted us during this period.

Results: A total of 121 patients with HVB were included. Of the 121 patients with HVB, MEH was found in 103 patients (85.1%). These MEH were clinical (MCEH) in 86 patients (71.1%), and biological (MBEH) in 57 patients (47.1%). The main MCEH were asthenia (58.7%), arthralgia (27.3%), dermatological manifestations (17%) and paresthesias (12.4%). Biological manifestations included renal impairment (33.8%) and thrombocytopenia (25.6%). None of the factors studied was associated with the presence of extrahepatic clinical manifestations of HVB. However, age and antiviral treatment were associated with the presence of renal involvement (p= 0.011).

Conclusion: MEH was present in the majority of chronic HVB carriers, and was dominated by asthenia. However, no factor was associated with the presence of extrahepatic clinical manifestations; whereas age and antiviral treatment were associated with the existence of an extrahepatic biological manifestation.

Keywords: hepatitis B, extrahepatic manifestations, associated factors, Cotonou

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Comlan N'dehougbèa Martin Sokpon,[1] Aboudou Raimi Kpossou,[1] Rodolphe Koffi Vignon,[1] Akanni Prudence Olou,[1] Nicolas Kodjoh,[2] Jean Séhonou[1]

[1]Clinique Universitaire d'hépato-gastroentérologie, Centre National Hospitalier et Universitaire Hubert Koutoukou MAGA (CNHU-HKM), Cotonou, Benin
[2]National Hepatitis Control Program, Ministry of Health, Cotonou, Benin

Correspondence: Dr Sokpon CN Martin, Clinique Universitaire d'hépato-gastroentérologie, CNHU-HKM Cotonou, Tel 0022961003550, Email msokpo@yahoo.fr

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Introduction

Viral hepatitis is a major public health problem worldwide. In West Africa, hepatitis B is highly endemic, with a prevalence of over 8%.[1] In the sub-Saharan states of French-speaking Africa, there is a lack of data on hepatitis B prevalence rates in the general population. Available data are fragmentary and concern blood donors and certain at-risk groups. In Benin, the prevalence of hepatitis B and hepatitis C among blood donors were estimated at 9.9% and 4.12% respectively, meaning that around 1,400,000 people are infected.[2] Today, it is estimated that viral hepatitis is responsible for 1.45 million deaths a year worldwide, a figure higher than that attributable to HIV/AIDS (1.3 million) or tuberculosis (1.3 million).[3]

For a long time, hepatitis was considered by doctors to be a disease of the liver alone. However, those affected had always mentioned disorders not directly related to the liver. In fact, three out of four sufferers present at least one Extra-hepatic symptom.[3] Several extra-hepatic manifestations can be observed in viral hepatitis. In the case of hepatitis B, a number of extrahepatic manifestations may occur during the natural history of the disease. The main Extra-hepatic manifestations are generally grouped into 2 type's manifestations: periarteritis nodosa (PAN) and extra membranous glomerulonephritis (GEM).[4] HBV is responsible for 20-50% of PAN. This is a severe disease which, alongside general manifestations such as fièvre, myalgias and abdominal pain, includes neurological, cardiac, renal and cutaneous multivisceral involvement responsible for a non-negligible early mortality of 10-30%. GEM is the most frequent form of HBV-related renal damage. In highly endemic areas, hepatitis B is the most frequent cause of GEM.

In Africa, and particularly in Benin, very few data are available to date, enabling us to assess the extent of extra-hepatic manifestations. This justifies the importance of this preliminary study, the aim of which was to determine the prevalence of MEH found during chronic viral hepatitis B (CVH) and to investigate the factors associated with these manifestations at the national hospital and university center in Cotonou, Benin.

Methods

This was a descriptive and analytical cross-sectional study, with prospective data collection, covering the period from May 15 to August 31, 2017. It took place in the university clinic of hepato-gastroenterology (HGE) of the CNHU-HKM. The study population consisted of adult patients (at least 18 years of age) admitted for consultation in the department and who were being followed up for documented viral hepatitis B, whether on treatment or not. The sample was obtained by consecutive and systematic recruitment of patients who met the inclusion criteria during the study period. Patients with hepatitis B-hepatitis C co-infection were not included. Data were collected using a questionnaire, on which variables relating to questioning, physical examination and paraclinical examinations were recorded. Dermatological lesions had already been identified in some patients treated in the dermatology department. Extrahepatic manifestations were investigated both clinically and biologically.

The clinical manifestations sought were as follows:

I. General manifestations: asthenia was selected in patients who complained of it.

II. Rheumatic manifestations: arthralgia and myalgia.

Arthralgia was considered in all patients who complained of joint pain in at least one of the following joints: shoulders, elbows, wrists, interphalangeal joints, metacarpophalangeal joints, knees, metatarsophalangeal joints and spine.

Myalgia was considered in patients complaining of diffuse muscle pain or aches.

I. Dermatological manifestations sought were: pruritus, prurigo, cutaneous lichen planus, oral lichen planus, chronic urticaria, purpura, pityriasis, psoriasis, porphyria cutanea tarda, erythema nodosum, periarteritis nodosa.

Lesions such as pruritus, chronic urticaria, prurigo, purpura and pityriasis were easily recognized in patients who were seen with them.

The cases of lichen planus found were taken into account in patients followed by dermatologists and in whom the diagnosis had been retained.

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

I. Ophthalmological manifestations: xerosis (dry eyes)

II. Neurological manifestations: paresthesia

III. Other clinical manifestations: xerostomia (dry mouth).

The biological manifestations sought were:

Renal manifestations

Patients had their creatinemia measured in mg/l. Glomerular filtration rate (GFR) was calculated using the modified MDRD formula (Modification of diet in renal disease: used to estimate glomerular filtration rate from creatinine levels) in ml/mn/1.73m2. The degree of renal impairment was determined according to the GFR value: ≥ 90: no renal impairment; 60-89: mild renal failure; 30-59: moderate renal failure, 15-29: severe renal failure; ≤ 15: end-stage renal failure.

Hematological manifestations: thrombocytopenia.

Only thrombocytopenia was included among the hematological disorders. Thrombocytopenia was considered in patients with a platelet count of less than 150 G/L.

Data were cleaned and coded, then entered into EPI data 3.1. Analysis was performed using SPSS 21 French version and Epi-Info 7.1.0.6. Qualitative variables were expressed as percentages with their 95% confidence intervals; quantitative variables as mean and median, depending on whether the distribution was normal or not. Pearson's chi - 2 tests and Student's t test were used according to the type of variable. For the various associations, the significance threshold was 5%.

Results

Characteristics of the study population:

One hundred and twenty-one presented with viral hepatitis B only. There were 84 men and 37 women (sex ratio= 2.27). Mean age was 42.51 ± 11.60 years, with extremes of 18 and 74 years. Cirrhosis was present in 15.7% of patients. Only one patient was co-infected with HIV and HBV. With regard to liver biology, prothrombin levels (PT) were measured in 88 patients, and were low in 14.8%. The mean PT was 88.6 ±13.7. Cytolysis tests (alanine aminotransferase or ALT and aspartate aminotransferase or AST) were performed in 108 patients. The mean ASAT level was 50.4 ± 35.0 IU/L, and the mean ALAT level was 50.1 ± 39.6 IU/L. Platelets were measured in 116 patients, with an average of 193.0 ± 69.3 G/L. Liver fibrosis was assessed by FIBROTEST® in 84 patients. A fibrosis stage of F4 corresponding to cirrhosis was found in 13 patients (15.5%), while fibrosis ≤ F1 was noted in 21 patients (25%). Analysis of virological characteristics in 106 patients who underwent viral replication testing revealed that 9.1% of patients were positive for HBeAg. In 90 patients who underwent quantitative HBV DNA PCR, it was detectable in 52.9% (n=64) of patients. The mean was 23,477,964 ±128,554,362 IU/ml. The main ultrasound abnormality in the study population was hepatomegaly, observed in 21.2% of patients. The majority of patients included were at the stage of chronic non-cirrhotic liver disease (84.5%), some of whom were on tenofovir therapy (47.1%).

Prevalence of extrahepatic manifestations in chronic hepatitis B

Of the 121 patients with viral hepatitis B, 85.12% (n=103) had at least one MEH. These MEH were classified into clinical and biological manifestations.

Clinical manifestations were present in 71.1% (n=86) of patients. These manifestations were dominated by asthenia (58.7%) and rheumatic manifestations (35.5%). Arthralgia was the predominant rheumatic manifestation. Dermatological symptoms were dominated by pruritus (12.4%) and neurological symptoms by paresthesia (12.4%) (Tables 1, 2 and 3).

Table 1 Distribution according to extra-hepatic clinical manifestations

Extra-hepatic clinical manifestations	HVB (N = 121)	
	Numbers (n)	Frequency (%)
General (asthenia)		
No	50	41.32
Yes	71	58.68
Neurological (paresthesia)		
No	106	87.6
Yes	15	12.4
Rheumatological (arthralgia and/ or myalgia)		
No	78	64.46
Yes	43	35.54
Dermatological		
No	100	82.64
Yes	21	17.36
Ophthalmological (xerosis)		
No	113	93.39
Yes	8	6.61
Other damage (xerostomia)		
No	113	93.39
Yes	8	6.61

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Table 2 Distribution of patients by type of rheumatic disease

Types of Damage Rheumatic	HVB (N = 121)	
	Numbers (n)	Frequency (%)
Arthralgia		
No	88	72.73
Yes	33	27.27
Myalgia		
No	93	76.86
Yes	28	23.14

Table 3 Patient repairs by type of dermatological damage

Types of Damage Dermatological	HVB (N = 121)	
	Numbers (n)	Frequency (%)
Pruritus		
No	106	87.6
Yes	15	12.4
Chronic urticaria		
No	117	96.69
Yes	4	3.31
Purpura		
No	119	98.35
Yes	2	1.65
Cutaneous lichen planus		
No	117	96.69
Yes	4	3.31
Oral lichen planus		
No	120	99.17
Yes	1	0.83
Pityriasis		
No	119	98.35
Yes	2	1.65
Prurigo		
No	119	98.35
Yes	2	1.65

The biological manifestations sought were renal and hematological impairment (renal failure and thrombocytopenia). These biological manifestations were dominated by renal impairment (33.9%) and hematological impairment (25.6%) (Table 4).

Table 4 Population distribution by type of extrahepatic biological damage

Types of Events Biological	HVB (N = 121)	
	Numbers (n)	Frequency (%)
Renal		
No	67	55.37
Yes	41	33.88
No research	13	10.74
Hematological (thrombocytopenia)		
No	85	70.25
Yes	31	25.62
No research	5	4.13

Factors associated with extrahepatic manifestations in patients with HBV

None of the factors studied was associated with the presence of extrahepatic clinical manifestations of HBV. However, age was significantly associated with renal involvement, and the frequency of renal involvement was significantly higher in the [50 - 80] bracket, i.e. 51.6% (p=0.011) (Table 5).

Table 5 Factors associated with renal impairment in patients

Variables	Kidney damage			Total	p-Value
	No (n/%)	No research	Yes (n/%)		
Age					
[0 - 50[	57 (63.33)	8 (8.89)	25 (27.78)	90	0.011
[50 - 80[	10 (32.26)	5 (16.54)	16 (51.61)	31	
Treatment					
No	33 (51.56)	12 (18.75)	19 (29.69)	64	0.01
Yes	34 (59.65)	1 (1.75)	22 (38.60)	57	

In the study population, thrombocytopenia was significantly associated with male gender (p=0.032); cirrhosis (p=0.0428); obesity (p=0.001); IHC (p=0.03); low PT (p= 0.002); and hepatomegaly (p=0.013) (Table 6).

Table 6 Factors associated with thrombocytopenia in patients

Variables	Thrombopenia			Total	P-Value
	No (n/%)	No research	Yes (n/%)		
Sex					
Female	32 (86.49)	1 (2.70)	4 (10,81)	37	0.032
Male	53 (63.10)	4 (4.76)	27 (32.14)	84	
Cirrhosis					
No	76 (74.51)	3 (2.94)	23 (22.55)	102	0.0428
Yes	9 (47.37)	2 (10.53)	8 (42.11)	19	
BMI					
Skinny	1(25.00)	3 (75.00)	0 (00.00)	4	< 0.001
Regular	33 (68.75)	0 (00.00)	15 (31.25)	48	
Obesity 1	7 (70.00)	0 (00.00)	3 (30.00)	10	
Obesity 2	1 (33.33)	1 (33.33)	1(33.33)	3	
Weight	28 (80.00)	1(2.86)	6 (17.14)	35	
HIC					
No	84 (71.19)	4 (3.39)	30 (25.42)	118	0.03
Yes	1 (33.33)	1 (33.33)	1 (33.33)	3	
TP					
Low	4 (30.77)	1 (7.69)	8 (61.54)	13	0.002
Normal	58 (77.33)	1 (1.33)	16 (21.33)	75	
Hepatomegaly					
No	74 (74.75)	2 (2.02)	23 (23.23)	99	0.013
Yes	11 (50.00)	3 (13.64)	8 (36.36)	22	

Discussion

In our study, the mean age was 42.51 ± 11.60 years, with extremes of 18 and 74 years. This mean age was lower than that reported in a study on the same theme, in Turkey in 2012 (51±13 years with extremes from 18 to 78 years) by Fatih Ermis et al.[5] In our sample, there was a male predominance (69.4%) with a sex ratio of 2.27. This sex ratio was higher than that found by FATIH ERMIS et al in Turkey in 2012.[5] (sex ratio=0.48).

Extrahepatic clinical manifestations in our series were dominated by asthenia in 58.68% of cases. Asthenia is often seen as part of a chronic fatigue syndrome, and may conceal underlying depression. In the literature, chronic fatigue syndrome has been described in 35% to 67% of cases.[6,7,8]

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Whereas the rheumatological manifestations sought in our study were arthralgia and myalgia. In the literature, very few authors have studied the prevalence of arthralgia and myalgia in patients with viral hepatitis B. Lower rates than those we found had been reported by some authors. In 2003, Cacoub et al reported prevalence's of around 6% for both arthralgia and myalgia.[9] Even lower prevalences were reported by the same authors in 2005: 3% for arthralgia and myalgia.[10] Nevertheless higher prevalences were reported by AYDENIZ et al in 2010 in 36 patients with HVB: 53% for arthralgia and 58% for myalgia.[11] This difference may be related to the number of patients in this study. AYDENIZ et al had identified viral load as a factor associated with the presence of arthralgia in HVB patients (p=0.000).[11] In our series, no statistically significant relationship was found between arthralgia and viral load (p=0.1898 for HVB). This could be explained by the fact that not all patients had had their viral load tested. The main dermatological manifestation in our series was pruritus, present in 12.4% of patients. In HVB, a much lower prevalence was reported by CACOUB et al in 2003 and again in 2005 (1%).[9,10] The low prevalence reported by these authors may be linked to the type of study carried out. Both studies were retrospective. This type of study might not have enabled us to record all cases of pruritus. Indeed, patients seen in consultation do not always complain of it spontaneously, and it is not often systematically investigated in the absence of jaundice or complications of viral hepatitis. Chronic urticaria was detected in 3.3% of patients. Chronic urticaria was not associated with viral hepatitis B in our study. Acute urticaria was most often evoked. Isolated acute urticaria, or urticaria as part of the Caroli triad, can occur during the pre-icteric phase in around 15-20% of patients, one to six weeks before the onset of hepatitis, and disappears during the icteric phase.[12] The absence of cases of acute urticaria in our series would therefore be linked to the absence of cases of acute hepatitis.

Other dermatological lesions found in our series, such as purpura, lichen and pityriasis, have been described in the literature as possibly associated with HBV, but their prevalence is unknown.[13] The prevalence of these lesions in patients with hepatitis C virus had been reported by some authors.[14,15,16]

Only paresthesia was sought at this level, without prejudging its location or type. It was found in 12.4% of patients. Isolated paresthesias were rarely documented in either VBH or CVH cases. They are often sought in the context of peripheral neuropathy or polyradiculoneuritis. Cacoub et al.,[10] report a 5% prevalence of peripheral neuropathy in a group of 119 patients with viral hepatitis B in 2003.[10] In our study, we looked for xerosis and xerostomia, both of which are part of a dry syndrome (Gougerot-Sjögren's syndrome). To confirm the diagnosis of dry syndrome secondary to HCV or HBV, anti-SSA and anti-SSB antibodies must be negative, and virus PCR detectable on salivary biopsies.[17,18] In our series, these tests could not be performed. In our study, xerosis and xerostomia were found in 6.61% and 26.67% of patients respectively. Dry syndrome was reported in the literature in 6%.[9,10] A definitive diagnosis of dry syndrome was not made in our study. It would have enabled us to come closer to these figures by excluding cases of xerosis and xerostomia unrelated to viral hepatitis B.

The biological manifestations most frequently described in the literature are cryoglobulinemia and autoantibody assays. Cryoglobulinemia is the main extrahepatic manifestation of viral hepatitis B and C. Its presence is thought to underlie several of the clinical manifestations mentioned above. The autoantibodies most frequently tested for are: antinuclear Ac, anti-nucleosome Ac, rheumatoid factor, anti-DNA Ac, anti-NAEA Ac, anti-histone Ac, anti-mitochondria Ac. Thrombocytopenia and renal failure have also been reported. Our study was limited to thrombocytopenia and renal failure. Thrombocytopenia was found in 25.6% of patients. In a study conducted by Sehonou et al. on haemogram abnormalities in patients followed up for viral hepatopathy B or C in a Gastroenterology practice in Cotonou (Benin) in 2017, thrombocytopenia was noted in 76 patients (40%). Thrombocytopenia was more frequent, with a statistically significant difference in HCV antibody carriers (21/38; 55%) p=0.03. These prevalences are higher than those reported in our series. This difference may be linked to the sample size of 190 patients in this study. Renal impairment was present in 38.0% of patients with viral hepatitis B. Depending on the degree of renal impairment, patients had either mild renal failure (34.3%), or moderate renal failure (3.7%). There was no severe or end-stage renal failure. Few data are available on the prevalence of renal failure in viral hepatitis B and C. The most frequently reported renal manifestations are extra-membranous glomerulonephritis, membranoproliferative glomerulonephritis and periarteritis nodosa. Renal biopsies were often performed.[13] This was not the case in our study: biopsies are not commonly performed in Benin.

In viral hepatitis B, variable prevalences of renal failure had been reported. The HARPE (hepatitis and renal parameters evaluation) study conducted in France in 2012 reported a 55.8% prevalence of renal failure (GFR below 90 mL/min/1.73m2) in a group of 230 HBV patients.[19] This high prevalence of renal failure could be explained by the high sample size of this study. Shin et al in 2015 reported a prevalence of renal failure below ours: 16.9%.[20] This difference would be related to the method used by these authors, who defined renal failure as a decrease of more than 25% in baseline GFR.

The overall prevalence of renal failure in the general population of Benin is not known. In Senegal, according to Faye et al in 2014 the prevalence was 37%.[21] This prevalence in the general population was close to that found in our study. We therefore have reservations about the role of viral hepatitis in the occurrence of renal failure in our patients.

In a uni-variate analysis, no statistically significant association was found between gender, age and the presence of extra-hepatic clinical manifestations in our study. Cacoub et al also found no association between gender, age and the presence of extrahepatic manifestations.[22]

Patients' occupation, area of residence and level of education were not associated with the presence of extrahepatic clinical manifestations. Furthermore, in France in 2005, no statistically significant association was found between ethnicity (African, Asian or Caucasian) and the presence of extrahepatic manifestations (p=1). However, the majority of patients seen in this study were Caucasian (70% of the sample).[22] In our series, alcohol consumption or HIV co-infection were not associated with the presence of extrahepatic clinical manifestations. The same results were obtained by Cacoub.[22]

No statistically significant association was found between the presence of extrahepatic clinical manifestations and platelet levels (p=0.3041); PT (p=1) and ASAT (p=0.693) and ALAT (p=0.473) values in our series.

Cacoub et al.,[22] found no association between hepatic cytolysis and the existence of extrahepatic clinical manifestations (ALAT p=0.983; ASAT: p=0.3574).[22] They also noted that patients with one or more extrahepatic clinical manifestations had a higher mean platelet count (215.6±72.9 G/L) than those with no extrahepatic clinical manifestations (178.8 ± 60.8 G/L), and the difference was statistically significant. (p=0.004). Similar results were noted in our

series. The mean platelet count of patients with extrahepatic clinical manifestations (196.41±64.96 G/L) was higher than that of patients without MCEH (184±78.8 G/L), but the difference observed was not statistically significant (p=0.41525).

There was no statistically significant association between the presence of extrahepatic clinical manifestations and the degree of FIBROTEST (p=0.9359). Cacoub et al.,[22] found identical results to ours, with no statistically significant association between extrahepatic clinical manifestations and patients' METAVIR score.[22]

In our study, the marker of HBV replication (HBeAg positive or negative) was not associated with the occurrence of extrahepatic clinical manifestations (p=0.9353). The same was true in the study conducted by Cacoub et al in 2005 (p=0.984).

We did not find a statistically significant relationship between HBV viral load and the presence of extrahepatic manifestations (p=0.888). This was also the case in the literature (p=0.174).[22] Furthermore, Cacoub et al., also looked for a significant relationship between extrahepatic clinical manifestations and the different HBV genotypes. The extrahepatic clinical manifestations were not significantly related to HBV genotype.[23] Genotype testing was not performed in our study. There was no statistically significant association between the presence of antiviral treatment and extrahepatic manifestations in patients with viral hepatitis B (p=0.0715).

In addition, all patients with chronic urticaria were on antiviral therapy (Tenofovir), with a statistically significant difference (p= 0.046). Treatment could be partly responsible for this dermatological manifestation. Chronic urticaria was often described as an extrahepatic manifestation,[23] and rarely as a side effect of TDF (Tenofovir Dixoploxil Fumarate): the side effects described were rushes and photoallergic reactions, not found in our series.[24,25]

There was a statistically significant relationship between the occurrence of renal failure and patient age (p=0.011). Patients over 50 years of age were the most affected. This same relationship was found by Gara et al (p=0.01)[25] and Shin et al (p=0.002).[20]

The difference was statistically significant (p=0.010), with treated patients showing more renal impairment than untreated patients. Antiviral treatment could therefore be at the root of a deterioration in renal function in our patients. However, it would be more appropriate to conduct another study to assess the renal impact of TDF in our patients, taking into account comorbidities and initial renal function. Thrombocytopenia was more frequent in men, with a statistically significant difference (p=0.0032). Thrombocytopenia was also more frequent in cirrhotic patients (p=0.0428), patients with low PT (p= 0.002) and those with hepatomegaly (p=0.013). It would rightly appear to occur preferentially in patients with deteriorating liver function. All in all, although very frequent, these extra-hepatic manifestations do not appear to be conducive to worsening liver disease. They are rarely at the forefront of the clinical picture, and rarely require specialist consultation.

Conclusion

Extrahepatic manifestations are very frequent in viral hepatitis B (85.12%), and are dominated by asthenia. However, no factor was associated with the presence of extrahepatic clinical manifestations; whereas age and antiviral treatment were associated with the existence of an extrahepatic biological manifestation, notably renal impairment. Nevertheless, this work does not prove a causal link between these extra-hepatic manifestations and the evolution or severity of viral liver disease. It could therefore be said that these manifestations do not appear to promote a worsening of liver disease. And they would rarely be at the forefront of the picture, requiring little recourse to a specialist consultation. They would therefore not, on their own, justify the initiation of antiviral treatment.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflicts of interest.

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