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Prevalence and Predictors of Viral Hepatitis D Co-Infection in Chronic HbsAg Carriers

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Abstract

The characteristics of viral hepatitis B and D co-infection are poorly documented in Chad. The aim of our study was to determine the prevalence of HBV/HDV co-infection and the characteristics of this co-infection. **Materials and Methods:** This was a retrospective study including all patients with chronic HBsAg carriers referred in our department from January 2014 to December 2018. Non-inclusion criteria were: absence of anti-HDV testing, presence of anti-viral hepatitis C or Human Immunodeficiency Virus antibodies or excessive alcohol consumption. The variables studied were age, sex, blood transaminase level, HBV DNA level, HDV RNA level, and liver fibrosis and activity score (Actitest Fibrotest). The prevalence of HDV and the characteristics of HDV/HBV co-infection were determined. **Results:** During the study period, 403 patients were seen in these two hospitals for chronic HBsAg carriage. Of these, 378 (75%) had performed the anti HDV assay. Anti-HDV antibodies were positive in 53 patients (14%). In multivariate analysis, HBV/HDV co-infected patients were less frequently HBeAg positive (5.4% *vs.* 28.1%; p = 0.0001), older (35 years *vs.* 32 years; p = 0.001), and more frequently had significant necrotic-inflammatory activity (3.9% vs. 3.2%; p = 0.031) compared with mono infected patients. Neither gender (76.9% male vs. 77.4% male; p = ns), nor viral load (median 530 IU/ml vs. 195 IU/ml; p = ns), nor significant liver fibrosis (35.1% vs. 47.1%; p = ns), nor transaminases (median 26 vs. 32 IU/ml) were different with mono infected patients. **Conclusion:** VHD is common in Chad. It is associated with increased hepatic necrotic-inflammatory activity.

Keywords

Viral Hepatitis D (Anti VHD Ac), Prevalence, Favouring Factors,

Necrotic-Inflammatory Activity, Chad

1. Introduction

Viral hepatitis B is endemic in Sub-Saharan Africa where it constitutes a public health problem [1] [2] [3] [4]. It is responsible for the majority of cirrhosis and primary liver cancers [1] [5] [6] [7]. It can be associated with co-infections including hepatitis delta virus (HDV). HDV is a defective virus whose replication cycle requires the presence of HBV [8]. This virus is also endemic in several regions of the world [7] [9] [10]. Its presence seems to increase the histological lesions of HBV [6]. The prevalence of this association and its characteristics are not well known in Africa [8] [11]. Testing for hepatitis D virus through its marker, anti-HDV antibodies (anti-HDV antibodies), is not common practice in Chad due to the lack of knowledge of many practitioners, the technical difficulties of measuring anti-HDV antibodies, and cost of this test. The aim of this study was to determine the prevalence of anti-HDV antibodies in chronic hepatitis B virus carriers and evaluate the biochemical, virological and histological characteristics of this co-infection.

2. Materials and Methods

This is a retrospective study including all outpatients from two hospitals of N'Djamena seen in gastroenterology consultation from January 2014 to December 2018. All chronic HBsAg carrier patients were included. The criteria for non-inclusion were: absence of anti-HBV antibody testing, presence of anti-viral hepatitis C or Human Immunodeficiency Virus antibodies or excessive alcohol consumption. The variables studied were age, sex, blood transaminase level, HBV DNA level, HDV RNA level, and liver fibrosis and activity score. Liver fibrosis was assessed by Actitest Fibrotest*. All serologies were performed with an ELISA test (Vidas), HBV viral loads (reverse transcriptase PCR linearity range 1000 to 10.000000) and HDV (Cobas 8800 Roche real-time PCR) quantification range 10 to 1.0000000). Biochemical activity was defined by an alanine amino transferase level higher than 40 IU/ml performed on a VIDAS machine. We determined the prevalence of anti-HDV antibodies in all included patients. Then, a comparison was made between HBV and HDV mono- and co-infected patients on demographic (age and sex) and biological (viral load, transaminases, HBeAg, fibrosis stage according to METAVIR) parameters in uni and multivariate analysis by logistic regression.

Qualitative variables were expressed as percentages, quantitative variables as their mean with standard deviation. The viral load was also presented in logarithm with its mean and standard deviation. The chi-square test was used to compare percentages, the Student's t test for means. The 5% threshold was used to define the p significance level.

The study complied with the Declaration of Helsinki (ethical clearance to be requested).

3. Results

During the study period, 403 patients were seen in these two hospitals for chronic HBsAg carriage. Of these, 378 (75%) had an anti-HBV antibody test. Two had positive HIV serology and four had positive HCV antibody. Ninety-three patients did not have an HDV antibody test. These patients were significantly younger, had positive HBe antigen and higher necrotic-inflammatory activity. Of the 378 patients, 53 were anti-HDV antibody positive, a prevalence of 14%. Table 1 summarizes the characteristics of the study sample.

Table 1. Characteristics of the sample.

Variables	Overall sample
% male	233/303 (76.6%)
Mean age ± standard deviation	36.4 ± 11.6
Biochemical activity (n = 259)	71 (27.4%)
Mean ALT	43.3 ± 111
Mean GGT	43.4 ± 52.4
HBeAg positive (n = 278)	15 (5.4%)
HBV DNA <10 (n = 280)	12.9% (n = 36)
HBV DNA ≥2000 IU/ml	30.4% (n = 85)
Mean Log10 viral load B (IU/ml)	7.4 ± 3.7 (0 - 20)
Anti-HDV antibodies positive	14% = 53)
Mean Log10 viral load D	10.8 ± 5.4 (0 - 10)
Histological activity	
F ≥ 2	64 (43.8%)
A ≥ 2	21 (14.1%)
A or F ≥ 2	43.8% (n = 67)
METAVIR score	
Fibrosis stage	
0	52 (34%)
1	37 (24.2%)
2	30 (19.6%)
3	16 (10.5%)
4	18 (11.8%)
Activity stage	
0	72.5% (108)
1	13.4% (20)
2	6.7% (10)
3	7.4% (11)

In multivariate analysis (see Table 2), HBV/HDV co-infected patients were less often HBeAg positive (5.4% vs. 28.1% p = 0.0001), older (35 years vs. 32 years; p = 0.001) and more frequently had significant necrotizing-inflammatory activity (3.9% vs. 3.2%; p = 0.031). Neither gender (76.9% male vs. 77.4% male; p = ns), nor viral load (median 530 IU/ml vs. 195 IU/ml; p = ns), nor significant liver fibrosis (35.1% vs. 47.1%; p = ns), nor transaminases (median 26 vs. 32 IU/ml) differed from infected mono-infected patients (Table 3).

Table 2. Characteristics of co-infected versus mono-infected patients.

Variables	Anti-HDV antibodies		
	Positif (n = 53)	Négatif (n = 325)	p
% male	46 (86.8%)	244 (75.1%)	ns
Mean age ± standard deviation	41.1 ± 9.3	35.6 ± 11.7	ns
Biochemical activity (n = 259)	14 (41.2%)	57 (25.3%)	0.06
Mean ALT	46.5 ± 39	42.8 ± 118	0.06
Mean GGT	65 ± 71	40 ± 48	0.03
HBeAg positive (n = 278)	4 (12.9%)	11 (4.5%)	ns
Anti HBe positive (n = 371)	44 (91.7%)	310 (96%)	ns
HBV DNA < 0 (n = 280)	7	29	ns
HBV DNA ≥2000 IU/ml	13 28.3%	72 30.8%	ns
Mean Log HBV DNA	6.74 ± 3.3	7.58 ± 3.7	ns
Histological activity (n = 153)			
F ≥ 2	16	48	
A ≥ 2	7	14	
A or F ≥ 2	17 (65.4%)	50 (39.4%)	0.018
METAVIR score			
Fibrosis stage (n = 153)			0.024
0	7 (26.9%)	45 (35.4%)	
1	3 (11.5%)	34 (26.8%)	
2	4 (15.4%)	26 (20.5%)	
3	5 (19.2%)	11 (8.7%)	
4	7 (26.9%)	11 (8.7%)	
Activity stage			0.026
0	12 (48%)	96 (77.4%)	
1	6 (24%)	14 (11.3%)	
2	3 (12%)	7 (5.6%)	
3	4 (16%)	7 (5.6%)	

Table 3. Factors associated with hepatitis D antibody positivity.

Variable	p	Odds Ratio	IC Odds Ratio 95%	
			Lower	Superior
Age	ns	1.033	0.993	1.076
Sex (1)	ns	0.589	0.175	1.986
ALAT	ns	1.001	0.998	1.004
Log viral load HBV	0.013	0.676	0.496	0.920
Histological activity > 2	0.042	5.241	1.064	25.803

4. Discussion

The prevalence of anti-HDV antibodies in chronic HBV carriers was 14% in our study. Chen *et al.* in a meta-analysis and systematic review of the literature including 61 countries had noted a prevalence of 10.58% (95% CI 9.14 to 12.11) [8]. Another meta-analysis and systematic review carried out in sub-Saharan Africa showed a prevalence of 9.57%, 37.7%, in West Africa and Central Africa respectively [7]. In Cameroon, Chad's neighboring country, this prevalence varied from 6% to 17% depending on the population [12] [13] [14] [15] [16]. These figures confirm the endemic nature of this virus in this region of Africa [17] [18]. In West Africa, in Burkina Faso, Sanou *et al.* observed a prevalence of 3.4% among blood donors [11]. In the Maghreb, in Egypt, the prevalence of anti-HDV antibodies was 8% according to Fouad *et al.* [19]. In Tunisia and Libya respectively, Yacoubi and Elzouki noted a prevalence of 2% of HDV and HBV co-infection [20] [21]. In this North African region, a meta-analysis by Daw *et al.* showed a prevalence of 20% in hepatological settings and 5% in the general population [10]. Opaleye *et al.* reported a prevalence of 9% in Nigeria [9]. In America, this proportion was 8% in Brazil [22]. In Southern Europe, Odieres *et al.* reported a figure of 6% to 8% depending on the study period [23].

It is essential to search for these anti-HDV antibodies in all patients with HBV. However, this test is not feasible in Chad and is expensive. Our study shows that two factors are independently associated with this presence: a low B viral load contrasting with a high significant necrotic-inflammatory histological activity. More advanced histological lesions in case of co-infection with HDV have also been reported by other authors [7] [12] [21]; however, according to Fouad *et al.*, there was no difference [19]. Transaminases, reflecting necrotic-inflammatory activity, were higher in case of HDV co-infection in several other works [12] [21] [23] [24] [25]. In our study, transaminases were not an independent factor for the presence of HDV co-infection. The lower B viral load in case of HDV co-infection was also found by Fouad *et al.* [19]. Histological lesions were more advanced in cases of HBV-HDV co-infection [24] [26].

As the majority of patients are negative HbeAg, a low viral load could suggest an inactive carrier in the absence of liver fibrosis evaluation.

The proportion of patients who were tested for anti-HBV antibodies was 75%.

This proportion varied according to the studies. In Cameroon, Luma *et al.* reported a figure of 80% [12]. In our work, the high cost and the burden of uninsured or poor patients explain this lack of testing. The requests for HDV antibody testing were made by hepato-gastroenterologists from these two hospitals. In addition, of those who performed the assay, only 10% (n = 38) performed the VHD viral load; it was undetectable in 55.3% of them. The patients who did not perform the VHD viral load test had a different profile of HBeAg-positive chronic hepatitis than those who did perform the test or HBeAg was rarer [EASL].

5. Conclusion

HBV-HDV co-infection appears to be high in Chad. Co-infected patients have more advanced histological lesions and a low B viral load. In these patients, it is necessary to look for anti-HBV antibodies.

Limitations of the Study

Viral load, fibrosis study not performed and lack of technical facilities in Chad.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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