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Research Article

HDV Coinfection Rates in Moroccan Chronic Hepatitis B Patients

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Abstract

The infection of Viral Hepatitis D (HDV) is life-threatening due to the chronically infected hepatitis B virus carriers which lead to the sudden acute hepatitis or severe chronic active hepatitis. Thus, an active surveillance of these patients with HDV co-infection is an important step to reduce the risk of hepatitis clinical complications. At present, we aimed to update the Moroccan sero-prevalence for HDV in these individuals and determine the status of hepatitis in chronic HBV carriers.

Methods: A one year follow-up was performed for 280 chronic HBV carriers and all patients were young-adults and adults. The anti-HDV antibodies (Total IgG and IgM Abs), while HBeAg and anti-HBe antibodies were additionally assessed by DiaSorin. The HBV-DNA levels were measured by Cobas Ampliprep Cobas TaqMan 48: KIT CAPA-G/CTM HBV V2.0 72 TESTS CE-IVC. The HDV-RNA detection and/or viral load quantification were performed in France in Avicenne laboratory of virology, as it has been described by Lunel-Fabiani.

Results: Only 2 (0.8%) individuals among chronic HBV infected individuals had been in contact with hepatitis D virus and have anti-HDV antibodies and both were HDV-RNA negative while 278 (99.2%) had a negative serology anti-HDV antibodies. 98% of chronic HBV individuals were HBeAg-negative with very low DNA HBV levels and five patients had "isolated anti-HBc" profile carriers with low DNA HBV levels. Two patients with a positive HBeAg had elevated ALT with higher HBV DNA loads.

Conclusion: A low prevalence of HDV in Moroccan chronic HBV carriers was demonstrated by this study, while 35% of patients with negative HBeAg were established as inactive carriers.

Background

The average rate of Hepatitis B Surface Antigen (HBsAg) was estimated with less than 2% across the country during the last decade [1,5] while Chronic Hepatitis B (CHB) infection is considered to be an intermediate public health burden in Morocco [2]. The dominant genotype was defined as genotype D [4,6-8] and D7/subtype ayw 2 was found in 70.8% [9,10]. This D genotype was shown to be associated with precore mutations, negative HBeAg, development of Hepatocellular Carcinoma (HCC) and cirrhosis developing in older individuals [4,11,12].

In Morocco, infection is higher among adults especially in age group older than 40 while the exposure to HB Virus (HBV) was found in high-risk groups (sexually active heterosexuals and people having dental cures) [13]. The chronic carriage in Morocco is most likely the result of sexual activity and parenteral exposure as these risk groups were defined sensitive to HBV infection. On the other hand, progression to the most severe form of chronic hepatitis in many Hepatitis B Surface Antigen (HBsAg)-positive patients was shown to be associated with a co-infection of a virus-like delta agent or Hepatitis Delta Virus (HDV) initially detected in 1977 in hepatocytes of patients with chronic HBV infection [14]. The HDV is transmitted percutaneously or sexually through contact with infected blood or blood products and chronic HBV carriers are at risk for infection with HDV. The latter is life-threatening of chronically infected HBV-carriers which leads to fulminant acute hepatitis or severe chronic active hepatitis, often progressing to cirrhosis [15]. Thus, an active surveillance of patients with chronic HBV infection and HDV co-infection should be an important step to reduce the risk of HCC in the region.

No data are available up to now concerning this infection in our country except for an old study reported in 1987 by Rioche and his co-authors [16], which stated that Morocco is a country of low endemicity of HDV infection in chronically infected HBsAg positive patients. In the present study, we were interested at describing delta co-infection in CHBV carriers. We examined the prevalence of serum anti-delta antibody among 280 HBsAg patients taking into consideration some variables such age, gender, sexual behaviors, dental cures and Alanine Aminotransferase (ALT). Data from HbeAg and anti-Hbe antibodies were available from 117 patients and are included in the present study to determine their chronic HBV infection status.

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Table1: Baseline characteristics of patients.

variable	Caractéristiques
Age*	42.13 ± 12.5
Sex§	
M	201(71.8 %)
F	79 (28.2 %)
Statut des patients§	
Externes	208(74 %)
Hospitalisés	72 (26 %)
Sérologie HVD§	
Négative	278 (99.2%)
Positive	2 (0.8%)
Coïnfection virale§	
HCV	Néant
HAV	Néant
HIV	Néant

*Exprimé en moyenne ± ecart-type

§Exprimé en effectif (pourcentage)

Results

Among 280 chronic HBV patients in our study, 201 men (71.8%) and 79 women (28.2%) with an average age of 42.64 +/- years. HBeAg-negative patients is the majority of adults with chronic HBV (99%) and with a relatively lower DNA load (usually <20000 UI/ml) and lower levels of ALT (32.3+/-10.5 U/L). All patients have been under Antiretroviral Therapy (ART) with Tenofovir monotherapy. The HDV infection was detected in two patients (0.8%) by a positive HDV serology while 278 (99.2%) had a negative serology. The HBV genotyping was detected for both patients with HBV / HDV co-infection, both of which have a D-genotype. The first patient had low levels of serum HBV DNA (<20 IU / ml), the second patient had a high level of viral load of HBV (33 600 IU / ml). Both patients had anti-HBc (HBcAc) positive antibodies (Tables 1 and 2).

Table 2: Characteristics of patients with HBV / HDV coinfection.

	Age	Sex	HBsAg	AcHBs	AcHBcT	AcHBc IgM	HBeAg	HBeAc	PCR VHB	Stade
Patient 1	47	M	P	N	P	N	N	P	<20	surinfection
Patient 2	47	F	P	N	P	N	N	P	33600	surinfection

Patients and Methods

We developed a descriptive study where we analyzed patient data of cases collected prospectively within 5 years (January 2011 to December 2016) from a well established questionnaire. All participants were volunteers and accepted to participate in the study. They were recruited from the virology and infectious disease services of a Public Hospital, in Rabat, Morocco. The study was approved by the ethical committee of the Faculty of Medecine & Pharmacy of Rabat and all the patients gave their written informed consent.

Inclusion criteria

The 280 patients who were included in this study were chronically infected with HBV and the chronic HBV status was established by a positive HBsAg laboratory value (HBsAg + for> 6 months). They went on for at least 1 year with serum ALT levels; AST and a follow-up of viral DNA load of HBV available at least every 6 months. All patients are adult.

Exclusion criteria

We did not include hepatitis C patients, hepatitis A or VIH.

Methods

All subjects were screened for anti-HDV antibodies (Total and IgM antibodies) and HBsAg; HBeAg; AgHBc and anti-HBe antibodies were additionally assessed by DiaSorin, while the Anti-HBc antibodies were determined by commercially Immunoassay Roche Diagnostics for all patients. The HBV-DNA levels were measured by Cobas Ampliprep Cobas TaqMan 48: KIT CAPA-G/CTM HBV V2.0 72 TESTS CE-IVC. The HBV genotype was detected by using INNO-LiPA HBV assay. The HDV-RNA detection and/or viral load quantification were performed in France in Avicenne laboratory of virology, as it has been described by Lunel-Fabiani [17].

Discussion

Our results show a low rate of HDV over-infection in chronic carriers of HBV in a Moroccan population. Our study confirmed the previous results stated by Rioche and co-authors in a former study conducted in 1987 [16] which stated that Morocco is a country with low endemicity of HDV infection compared to the neighboring Mediterranean countries such as Tunisia, Mauritania where this infection constitutes a health problem [17,18,19]. Our recent data show indeed a low prevalence 0.8% of sur-infection with HDV in chronic carriers of HBV. The two patients who have an HBV / HDV over-infection have the D genotype of HBV. The genotype D is the predominant HBV genotype in all Mediterranean countries and in the Moroccan population [4,9,13] as described in previous studies. The first patient has high serum anti-IgG HVD and he sero-converted from HBeAg to anti-HBe antibody within six months of follow-up. He had undetectable serum HBV DNA levels (<20 UI/ml) accompanied by persistently normal ALT levels (approximately 34 IU/ml) within the normal range according to Papatheodoridis et al [20]. The second patient has an active liver disease but both patients had positive anti-HBc antibodies. The latter had high level of HBV (33 600 UI/ml).

These results agree with the study highlighting the HDV suppression effect on HBV replication in these patients [21-23]. Lee demonstrated that the co-infected patients had undetectable HBV-DNA viral loads and low HBV viral loads (under 100 000 IU/mL), supporting that HDV may inhibit the HBV replication [24]. In a study by Celen et al, in Turkey, they demonstrated significant association between anti-HDV positivity and the duration of HBsAg carrier status [25]. Furthermore, a marker of viral replication HBeAg was not detected in patients with the HBV/HDV co-infection. In this study, the two patients with HBV / HDV over-infection had the HBsAg, AcHBcT, HBeAc positive and AcHBs, AcHBc IgM, HBeAg negative markers: one with a positive DNA / HBV level which means hepatitis B chronic mutant early replication (Persistence HBsAg more than 6

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months) while the second patient has HBV negative viral DNA level, therefore with Hepatitis B chronic (Persistence HBsAg more than 6 months)/ Seroconversion HBe.

In our study, the low HDV endemicity can be explained by an adequate follow-up periods with a good management of chronic HBV, consequently of HDV infection rather than HBV vaccination since our patients were >30 years and the vaccination against HBV was generalized after 1999. The former establishing guidelines were strategies and tools for monitoring, preventing and controlling the viral hepatitis and for managing the capabilities, diagnostics, laboratory tests and treatment

Conclusion

This study in Morocco is the first to report the rate of co-infection of HDV/HBV in the chronically-infected HBV carriers. As compared to past three decades, our country remains a low endemic for HDV infection.

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