CLINICAL AND VIROLOGICAL CHARACTERISTICS OF HIV-1 POSITIVE PATIENTS WITH DELTA HEPATITIS

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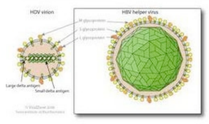
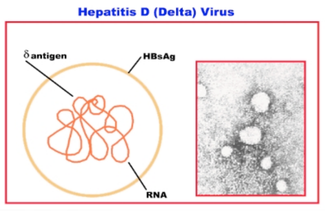
Background

Hepatitis D virus (HDV) or delta hepatitis is a defective single stranded RNA virus that requires hepatitis B surface antigen envelope (HBsAg) for replication and transmission.

HDV infection as been mainly studied in HIV negative patients, while data on HIV-1 positive patients are limited.

We investigated the virological pattern as well as biochemical and clinical features of liver disease and immune status in HIV-1 positive patients with delta hepatitis. Their clinical characteristics were compared with those of anti-HDV negative, hepatitis B surface antigen (HBsAg) positive/HIV+ patients.





Methods

Patients

This retrospective observational study examined demographic, clinical, therapeutic information and laboratory data retrieved from the database of the Division of Infectious Diseases of the San Raffaele Hospital (CSLHIV Cohort), Milan, Italy.

Data were collected for each HIV-1 infected/HBsAg positive patient at last visit available in 2017.

The CSLHIV Cohort was approved by the ethics committee of the San Raffaele Hospital.

At their first visit the patients provide written informed consent for scientific analyses of their data.

Statistical analysis

Results for continuous variables were reported as median [interquartile range (IQR)].

Characteristics of HIV-1 positive patients were compared using the Pearson's chi-square or Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. Potential determinants for HDV positivity were examined by applying multivariate regression model.

All statistical tests were two-sided at the 5% level ($p \leq 0.05$).

Results

Detection of anti-HDV

Among **78** HBsAg+ HIV-1 infected patients tested for anti-HDV for whom were available clinical data, **59** were anti-HDV negative (HDV-, 75.6%) and **19** were anti-HDV positive (HDV+, 24.4%).

Clinical characteristics of HDV+ patients and HDV- patients are depicted in Table 1

Univariate analysis

1. Male gender dominating in these two groups.
2. HDV frequency extremely high in intra venous drug users (IVDU) respect to patients sexually exposed to the virus (P<0.001).
3. HDV+ patients had higher alanine amino transferase levels (ALT) than HDV- patients (P=0.021).
4. Liver stiffness measured by transient elastography and expressed by kilopascal (KPa), resulted higher in anti-HDV+ subjects respect to HDV- ones (P=0.001).
5. Higher degree of fibrosis (assessed by transient elastography according to metavir score) was found in HDV+ patients (P=0.001).
6. HDV+ patients were less often HBeAg positive than HDV- patients (5.9% and 43.6%, respectively, P=0.004).
7. Antibodies against HCV (anti-HCV) were more frequently detected in HDV+ than in HDV- patients (68.4% and 22.0%, of anti-HCV positivity respectively, P<0.001)

Table 1 Characteristics of HDV+ and HDV- patients

	Overall	HDV+ No pts=19	HDV- No pts=59	P
Gender males/females	71/7	17/2	54/5	1.000
Age	51.0 (48.0-55.3)	53.0 (50.0-55.0)	51.0 (46.0-56.0)	0.151
Risk factor for HIV-1 IVDU/sexual/unknown	17/39/22	11/4/4	6/35/18	<0.001
Years of HIV infection	21.2 (14.4-27.8)	25.5 (23.0-30.5)	18.5 (11.5-25.7)	0.002
Years of ART	17.0 (9.1-20.7)	20.6 (16.9-23.7)	14.7 (7.3-19.4)	<0.001
CD4 T cells number/mm^3	698 (426-857)	535 (245-854)	750 (482-867)	0.151
ALT° IU/L	34.(26-56)	51 (28-88)	32 (22-46)	0.021
Transient elastography (KpA)	7.2 (4.6-11.7)	9.6 (7.2-14.1)	5.9 (3.8-8.3)	0.001
Fibrosis degree F0-F2 vs F3-F4 (N 58)	41/17	No pts=18 9/9	No pts=40 32/8	0.020
HBeAg-pos/neg(N72)	25/47	1/16	24/31	0.004
HIV-RNA* positive/negative	7/71	3/16	4/55	0.352
HIV-RNA load, copies/mL	164 (60-5569)	352 (-)#	112 (59-4218)	0.400
HBV-DNA pos/neg (N 74)	19/55	No pts.=17 4/13	No pts.=57 15/42	1.000
HBV-DNA load IU/mL	10 (10-15)	10 (10-42)	10 (10-19)	0.754
Anti-HCV pos/neg	26/52	13/6	13/46	<0.001
HCV-RNA pos/neg	8/18	1/12	7/6	0.030
HCV-RNA load IU/mL	114527 (401-446430)	173575 (-)##	55478(362-1830824)	1.000
FTC or 3TC /TDF+FTC°°	12/65	8/10	4/55	0.001

Abbreviations: IVDU= intra venous drug users; pos=positive, neg=negative;
ALT= alanine aminotransferase; FTC= emtricitabine; 3TC=lamivudine; TDF=tenofovir.

Results are expressed as median (interquartile range, IQR). P-values according to Mann Whitney test or Chi-square/Fisher's exact test, as appropriate

°ALT (normal value < 35 IU/L)
*HIV-RNA positive ≥50 copies /mL
#IQR was not calculated because only 3 patients had quantifiable HIV load among anti-HDV+ patients.
##IQR was not calculated because only 1 HDV+ patient had a quantifiable HCV load.
°°One patient did not receive any treatment.

Multivariate analysis

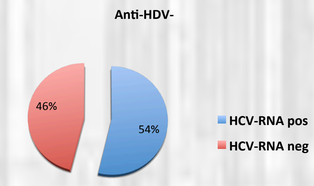
- Years of ART (OR 1.22; CI 0.986-1.43, P=0.014)
- Sexual exposure vs. IVDU (OR 0.08; CI 0.556-0.986, P=0.004)

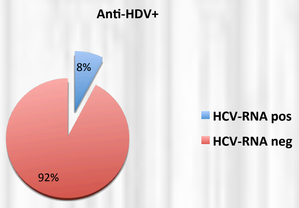
were independently associated with the risk to be anti-HDV positive.

Virologic Characteristics

No difference in **HIV-RNA and HBV-DNA** (evaluated by qualitative and quantitative assays) was found between these two groups.

HCV-RNA was more frequently found positive in HDV- than in HDV+ patients (HCV-RNA was detectable in **54.0 %** of anti-HCV+/anti-HDV- and **8.0%** of anti-HCV+/anti-HDV+ subjects, P=0.030).

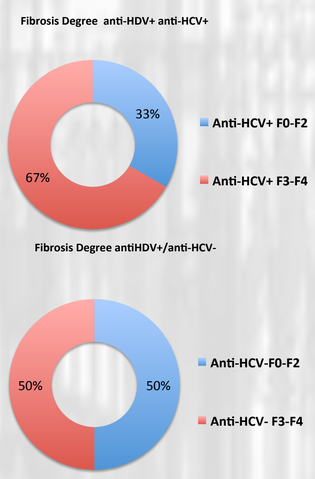




HDV-RNA qualitative assay was available in 7/19 anti-HDV+ patients and was found positive in 4/7 (57.0%) patients. In 3 patients found HDV-RNA positive, the assay was repeated in 3 subsequent serum samples with an alternance of HDV-RNA positivity or negativity.

Comparison of Fibrosis Degree between HDV+/anti-HCV+ and HDV+/anti-HCV- Subjects

Since anti-HDV+ patients had higher degree of fibrosis and were more frequently anti-HCV positive respect to HDV- patients, **we compared fibrosis degree between HDV+/ anti-HCV+ patients and HDV+/anti-HCV- subjects,** showing no difference in the fibrosis score between individuals with or without positivity for anti-HCV (F0-F2=4 patients, F3-F4=8 patients in HDV+/anti-HCV+ and F0-F2 =3 patients, F3-F4=3 patients, in HDV+/anti-HCV-, P=0.626).



Conclusions

Our study was limited by the nature of cross-sectional investigation and small sample size. So, it is possible that a number of HBsAg+ patients were not tested for anti-HDV or their data were not reported in the database. In addition, HDV-RNA assay was not performed in all anti-HDV positive patients. Therefore, we considered as HDV infected those patients with anti-HDV positivity.

We confirmed the severity of liver disease by a non invasive method (transient elastography) for assessing liver fibrosis and added information on demographic, immunological and virologic features of HIV-1/HDV+ patients, that could be taken in consideration for the management of this difficult to treat group.

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