Original Research Report

Prevalence of *Treponema pallidum*, Hepatitis B Virus and Hepatitis C Virus Infection in Non-hemophiliac Patients Infected with Human Immunodeficiency Virus in Japan

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Objective : We investigated the prevalence of viral infection with syphilis, hepatitis B virus (HBV) and hepatitis C virus (HCV) among human immunodeficiency virus (HIV)-infected patients. Several reports have analyzed these prevalence in Europe and America, but few reports have examined prevalence of syphilis and hepatitis in HIV-infected patients in Japan.

Materials and Methods : Seroprevalence of *Treponema pallidum* hemagglutination (TPHA), hepatitis B surface antigen and anti-HCV antibodies were examined in 116 HIV-infected non-hemophiliac Japanese adults (110 men, 6 women). As controls, we randomly selected 116 HIV-negative general checkup patients in Juntendo University Hospital, age- and sex-matched to HIV-infected patients.

Results : Sixty TPHA-positive patients were HIV-positive (42.1%). Only 1 HIV-negative patient was TPHA-positive (0.9%). TPHA-positive results were significantly more frequent in the HIV-positive group than in the HIV-negative group ($P < 0.0001$). However, no differences between HIV-positive and -negative groups were seen for HBV or HCV. Among HIV-TPHA-double-positive patients, 83.3% were men who have sex with men.

Conclusion : The ratio of TPHA-positive patients among HIV-positive patients was significantly high. Syphilis is an important indicator to find HIV infection.

Key words : HBV, HCV, *Treponema pallidum*, HIV, Japan

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Introduction

The morbidity rate of human immunodeficiency virus (HIV) is increasing worldwide. Although sexually transmitted infection (STI) in HIV-infected patients such as chlamydiosis, amebic dysentery and human papilloma viruses are well known, syphilis and viral hepatitis are less well-recognized by general physician in Japan.

Syphilis is a common STI caused by spirochetes of *T. pallidum*. The World Health Organization (WHO) has reported that up to 1.4 million cases of syphilis exist worldwide, with more than 90% occurring in developing countries[1,2]. Several reports have indicated that in HIV-positive patients, syphilis infection itself may be at higher risk for syphilis relapse than among HIV-negative patients[3–7]. Determining the prevalence of positive results for *Treponema pallidum* hemagglutination (TPHA) in Japanese HIV patients and identification of their features is thus important. The present study analyzed routes of HIV infection and CD4 cell counts.

The importance of the prevalence of hepatitis virus co-infection in HIV-infected patients has recently been recognized. Hepatitis viruses may lead to faster progression to liver cirrhosis and increase the risk of antiretroviral therapy-induced hepatotoxicity in HIV-infected patients. However, few reports have examined the prevalence of hepatitis B virus (HBV)-HIV co-infection in Japan.

The present study analyzed the prevalence of syphilis, HBV and hepatitis C virus (HCV) in HIV-positive Japanese from 2002 April to 2007 April. We hope this report will provide useful information on HIV-infected patients in Japan.

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Materials and Methods

This study was performed at Juntendo University Hospital in Tokyo, Japan. For HIV testing, our laboratory follows WHO testing strategies. Between April 2002 and April 2006, a total of 164 new HIV-infected patients were treated in our hospital. We retrospectively reviewed their records and selected 116 Japanese non-hemophiliac patients (110 men, 6 women). Results for TPHA, HBV-Ag and HCV-antibody at the first medical examination were retrospectively examined. As controls, we randomly selected 116 HIV-negative general checkup patients in Juntendo University Hospital, age- and sex-matched to HIV-infected patients. Informed consent was obtained from all patients prior to inclusion in the study.

The details of patients are shown in Table 1. The most common routes of HIV infection were homosexual contact (58.6%), followed by heterosexual contact (34.5%). No intravenous drug abuser was reported. Median age of HIV-positive patients was 38.3 years, compared to 37.8 years for HIV-negative controls.

Tests for HIV antibody, TPHA, hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb) were performed by chemiluminescence enzyme immunoassay (CLEIA). Comparison of proportions between HIV-infected and non-infected individuals was performed using Fisher's exact probability tests. Values of $p < 0.05$ were considered statistically significant.

Results

The HIV-positive group displayed 60 TPHA-positive patients (51.7%) (Fig. 1A). Conversely, only 1 patient in the HIV-negative group was TPHA-positive (0.9%). Prevalence of TPHA-positive results was thus significantly higher among HIV-positive patients than among HIV-negative patients ($p < 0.0001$). The rate of HbsAg-positive results was 5.2% among HIV-positive patients and 2.6% among HIV-negative patients, while the rate of anti-HCV antigen-positive results was 2.6% among HIV-positive patients and 0% among HIV-negative patients (Fig. 1B). No significant differences in hepatitis

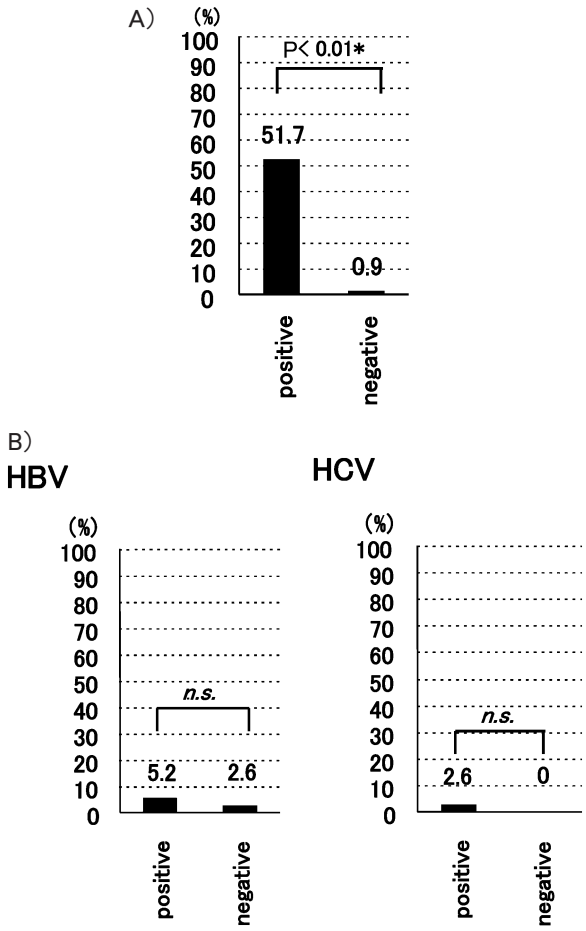

Figure 1 **A)** Prevalence of syphilis among HIV-positive and HIV-negative patients.
B) Prevalence of HBV and HCV infection among HIV-positive and HIV-negative patients.

Table 1 Characteristics of HIV-infected patients in the present study (n=116).

	HIV-positive patients	control
Age (Mean age±SD*)	38.3±11.5	37.8±7.6
Sex (n)	Male : 100, Female : 6	Male : 100, Female : 6
Route of infection (n)	MSM : 68 (58.6%) Heterosexual : 40 (34.5%) Unknown : 8 (6.9%)	
CD4 cell/μl (Mean±SD*)	339.8±287.2	

*SD, standard deviation

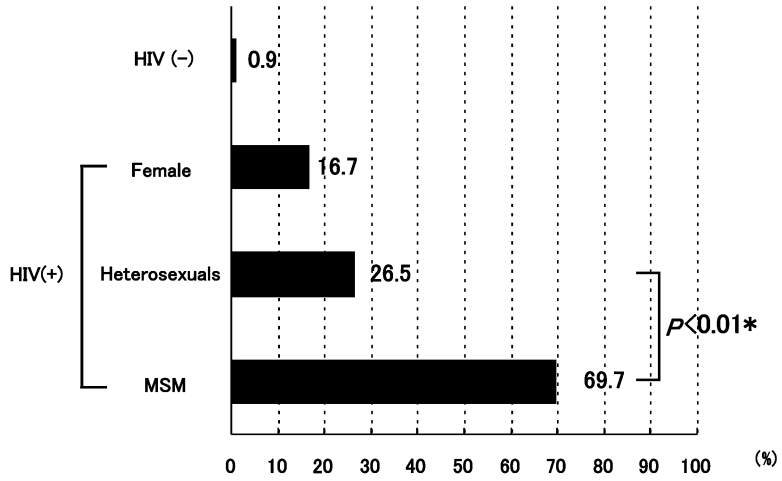

Figure 2 Prevalence of syphilis classified in HIV positive/negative patients by route of infection.

infection were identified between HIV-positive and HIV-negative patients.

The features of TPHA-positive patients were further investigated. More than 65% of TPHA-positive patients were identified as men who have sex with men (MSM) (Fig. 2).

Figure 2 shows the prevalence of TPHA positive patients how to infected with TPHA. The 69.7% of HIV-TPHA-double-positive patients were MSM, while 26.5% were non-MSM patients, 16.7% patients were women patients, 0.9% were HIV-negative patients.

The prevalence of TPHA was significantly high in the group of CD4 cell counts ≧200 (57.6%) compared of CD4 cell counts ＜200 cells/μl (41.9%) (p＝0.045) (Fig. 3).

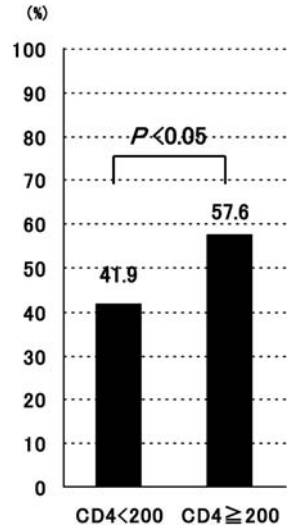

Figure 3 Differences in prevalence of syphilis among HIV patients with CD4≧200 and CD4＜200.

Discussion

We analyzed the prevalence of syphilis, HBV and HCV in HIV-positive Japanese patients who lived in Japan in our hospital. Some studies of these issues have been reported for patients in the United States, United Kingdom, India and China, but few such reports have been described in Japan.

Syphilis is also considered as an STI contracted through by blood and semen. In Japan, about 100 people are infected with syphilis annually and syphilis cases may be increasing even now. The WHO estimated that 1.4 million people worldwide were infected with syphilis in 2004, with numbers increasing each year and half of these patients displaying co-infection with HIV. Several reports have indicated that HIV-positive patients may be at higher risk of syphilis relapse than HIV-negative patients[3–7], and HIV infection may increase the frequency or accelerate the development of syphilis[8,9]. Diagnosis of syphilis usually requires positive results on both serologic tests for syphilis (STS) and TPHA, with STS usually becoming negative after therapy. TPHA remains positive for life after first infection. On the other hand, TPHA indicates positive in half patients with primary syphilis. The present study considered TPHA-positive patients as syphilis patients, although it is possible that we underestimated the prevalence of primary syphilis.

In our study, prevalence of HIV and syphilis co-infection was 51.7%, almost the same as the result obtained in a previous Japanese study[10]. However, some studies in other countries have shown lower prevalence (Table 2)[11–13]. We think that these differences of prevalence among Japan and other countries caused by the

route of infection with HIV. In this study, 58.6% (68/116) of HIV patients were MSM. In other countries, MSM population in HIV patients were less than our country[14–16]. Almost half of HIV-positive patients were co-infected with syphilis and prevalence of syphilis among HIV-positive patients in our study was significantly higher than in HIV-negative patients (Fig. 1A).

Next, we investigated the route of HIV infection to clarify patient features. MSM patients were 5-fold more frequent than non-MSM patients (Fig. 2). In Dr. Marrazzo's institution, more than half of syphilis cases in MSM are in HIV-infected men, compared to 4% of cases in heterosexual patients occurring in those with HIV infection[17]. More than 60% of MSM with syphilis in California are HIV-infected (Table 3)[8]. These data closely resembled results in this study, with high prevalence of syphilis among MSM-HIV patients. HIV screening is often not performed in TPHA-positive patients, but syphilis appears to offer an important indicator of HIV infection, particularly in the MSM population.

Figure 3 shows the prevalence of syphilis-HIV co-infected patients according to CD4 cell counts. CD4 cell counts $\geq$200 cells/mm^3 were seen in 57.6% of patients. This prevalence was significantly high compared with patients showing CD4 cell counts $<$ 200 cells/mm^3 (41.9%) ($p < 0.05$). There were some reasons that the greater plevarences of CD4 cell counts $\geq$200 cells/mm^3 in co-infected patients compared to CD4 cell counts $<$ 200 cells/mm^3. MSM often examined HIV antibody test and they turn up relative early HIV. We had been continuing our research on the relationship between syphilis and MSM. But we need further evaluation for this result. Importantly, however, clinicians should be aware that HIV infection may be suggested based on checking for syphilis.

We also reported the prevalence of HBV and HCV infection in HIV-infected patients (Table 4). Worldwide, about 300 million people are infected with HBV and about 170 million people are infected with HCV. Hepatitis patients often display co-infection with HIV. Reports from Western countries have shown that an estimated 6–14% of patients with HIV have chronic HBV co-infection, and 25–50% patients have HCV co-infection[18]. In India, the prevalence of co-infection is 5–10% for HBV and 10–13% for HCV, while in Thailand HBV co-infection is seen in 25–50% and HCV in 7.8%. These represent higher prevalences than in Japan (Table 4)[19,20]. Many reports have discussed relationships between HIV and hepatitis. HBV infection in HIV-positive patients requires particular care of both HIV and HBV infection. HIV-positive subjects show higher rates of HBV chronic carriage and HBV replication and lower rates of seroconversion to anti-HBe and anti-HBs antibodies. Some authors have reported on the probability of patients with HIV and HCV co-infection displaying faster progression of hepatitis C, including rapid evolution to decompensated cirrhosis[21] or hepatic failure[22], or a lower interval from estimated time of HCV infection to cirrhosis in patients with parenterally acquired HCV[23].

We examined only HBsAg to diagnose HBV, as HBsAg indicates the state of HBV infection and is examined in our hospital as a routine procedure. In the absence of HBsAg, the presence of HBV core IgG antibody (anti-HBc) and HBV surface antibody (anti-HBs) usually indicates past resolved infection. The presence of isolated anti-HBc is often interpreted as evidence of remote HBV infection with subsequent loss of anti-HBs, but may also represent a false-positive result[24]. HCV antibody indicates past infection, so we regard HCV infection as present if HCV antibody is positive. Our study showed that the prevalences of HBV and HCV infection in HIV-positive persons were 5.2% and 2.6% respectively (Fig. 1B). These results

Table 2 Prevalence of TPHA-positive patients among HIV-positive and HIV-negative groups.

	HIV-positive (%)	HIV-negative (%)	Reference
China	10	2.4	(11)
Zimbabue	60	16	(12)
Europe and USA	14〜59	10	(13)
Japan	51.7	0.9	Present study

Table 3 Prevalence of TPHA-positive patients among MSM infected with HIV.

	TPHA (%)	Reference
California	20–50	(8)
Senegal	4.2	(15)
China	11.2	(11)
Japan	60.7	present study

Table 4 Prevalence of HBV and HCV co-infection among HIV-infected patients.

	HBV (%)	HCV (%)	Reference
Europe and USA	6〜14	25〜50	(17)
Thailand	25〜50	7.8	(19)
India	5〜10	10〜13	(20)
Japan	5.2	2.6	present study

matched theoretical results for Japan. Koike reported that approximately 20% of Japanese HIV-positive patients are infected with HCV and 6.4% are infected with HBV, but that study included hemophilia[25]. But these data in Japan were very low compared with Western countries (Table 4). Table 4 showed that the prevalence of both HBV and HCV in other countries were higher than the prevalence in Japan. The reasons of these differences are few prevalence of Maternal-fetal infection and injection drug user in Japan.

No significant differences were identified regarding the prevalence of hepatitis among HIV-positive and HIV-negative patients, possibly due to the exclusion of patients with hemophilia from this study (Fig. 1B).

The present study suggests that patients in Japan displaying TPHA-positive results have a high probability of HIV infection. Early diagnosis of HIV infection is important for both patient and public health, helping to minimize further transmission and achieving more appropriate start of antiretroviral therapy. Doctors should be careful not to miss diagnosis of HIV infection if the presenting symptoms are characteristic for syphilis.

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