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ORIGINAL ARTICLE

Syphilis and neurosyphilis in human immunodeficiency virus-infected patients: A retrospective study at a teaching hospital in Taiwan

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Background and Purpose: Some studies have reported that the risk factors for neurosyphilis in patients with human immunodeficiency virus (HIV) and syphilis co-infection, include CD4 cell counts ≤350 cells/μL and rapid plasma reagin (RPR) titer ≥1:32. However, neurosyphils can develop even in patients with CD4 cell counts >350 cells/μL or RPR titer <1:32. In this study, we evaluated the outcome of syphilis to treatment in HIV-infected patients, and analysed the predictors of neurosyphilis in this population.
Methods: We retrospectively reviewed medical records of HIV-infected patients with syphilis who visited the China Medical University Hospital between January 2000 and December 2009. Neurosyphilis was defined by white blood cell (WBC) counts >20 cells/μL in the cerebrospinal fluid (CSF) sample or elevated Venereal Disease Research Laboratory (VDRL) titers of the CSF samples. Treatment failure was defined as less than 4-fold decrease in the serum RPR titer at or beyond 12 months post-treatment in case of early syphilis, and, at or beyond 24 months in case of late syphilis.
Results: One hundred and twenty-one HIV-infected patients (average age, 32 years) with syphilis were included in this study. Of 63 patients who had follow-up of serologic responses, 30 (47.6%) failed to respond to treatment. CD4 cell counts ≤200 cells/μL was the indicator for treatment failure ($P = .029$). Lumbar puncture was performed in 65 patients, and 14 patients were diagnosed with neurosyphilis. At the time of lumbar puncture, 31 and 19 of the 65 patients showed CD4 cell counts of >350 cells/μL and RPR of <1:32, respectively. An HIV viral load (VL) ≥10000 copies/mL was found to be associated with the development of neurosyphilis ($P = .016$).

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Conclusion: In HIV-infected patients with syphilis, RPR titer should be evaluated more frequently when CD4 count $\leq$200 cell/μL is associated with treatment failure. Lumbar puncture for the diagnosis of neurosyphilis should be considered in patients with HIV and syphilis co-infection, even in patients with CD4 cell counts >350 cells/μL, and particularly when the HIV VL $\geq$10000 copies/mL.

Introduction

Syphilis, caused by *Treponema pallidum*, is a major health problem. This disease can mimic various infectious diseases and shows protean clinical manifestations, including genital ulcers, rashes, lymphadenopathy, and severe cardiovascular and neurologic symptoms such as paralysis and formation of gumma.[1] Although the incidence of syphilis decreased dramatically after the introduction of penicillin, it has recently increased after the advent of human immunodeficiency virus (HIV) infections.[2]

T. pallidum invades the central nervous system (CNS) early during the course of the infection; the infection may be asymptomatic or show variable expressions, ranging from headache and oculopathy to serious conditions such as cerebrovascular events and tabes dorsalis. HIV infection appears to affect the neurological involvement in syphilis and increases the risk of neurosyphilis.[3–5] The use of lumbar puncture in HIV-seropositive patients with syphilis for neurosyphilis survey is a matter of debate among clinicians. Centers for Disease Control and Prevention (CDC) recommend the criteria for the use of lumbar puncture (LP) for diagnosing syphilis in HIV-infected patients as follows: neurologic or ocular signs or symptoms, active tertiary syphilis, and treatment failure.[6,7] Some previous studies in HIV-infected patients also observed risk factors of neurosyphilis, including CD4 cell count $\leq$350 cells/μL and rapid plasma reagin (RPR) titer $\geq$1:32.[8–10] However, neurosyphilis develops even in patients who have CD4 cell counts > 350 cells/μL or RPR titer <1:32.

This retrospective study aimed to describe the clinical and laboratory features of syphilis in HIV-infected patients. In order to investigate the occurrence of neurosyphilis in patients with CD4 cell counts >350 cells/μL or RPR titer <1:32, we assessed factors that were associated with neurosyphilis in these patients.

Materials and methods

Subjects

In this study, we included patients diagnosed with HIV infection and syphilis between January 2000 and December 2009 at China Medical University Hospital (CMUH), a teaching hospital in mid-Taiwan. The patient's charts were reviewed to collect data for variables such as sex, age, status of diagnosis of syphilis, comorbidity, syphilis stage, cutaneous manifestations, treatment plan, history of sexually transmitted diseases, serum RPR titer, and serum titer for *Treponema pallidum* hemagglutination (TPHA). We also reviewed neurological symptoms (photophobia, cranial nerve abnormalities, neuropsychiatric abnormalities, focal neurologic deficits), and cerebrospinal fluid (CSF) characteristics (white blood cell (WBC) count, red blood cell (RBC) count, percentage of monocyte, protein levels, and glucose levels), age of the patient at the time of HIV infection, HIV transmission route, sexual behavior, CD4 cell counts, viral load (VL) of HIV, HIV stage, receipt of highly active antiretroviral therapy (HAART), opportunistic infection (OI), and HIV-associated malignancies.

Patients with early syphilis received at least one dose of weekly intramuscular (IM) injection of 2.4 million units of benzathine penicillin G (BPG), those with late syphilis received three weekly IM injections of 2.4 million units BPG, and those with neurosyphilis received intravenous (IV) aqueous crystalline penicillin G, 18–24 million units daily, for 10–14 days followed by three weekly IM injections of 2.4 million units BPG.[6,7] Whether to perform the lumbar puncture in patients with syphilis was decided by the treating physicians.

Definitions

The diagnosis and stages of syphilis were based on the Case Definitions for Public Health Surveillance.[11] Treatment failure was defined as less than 4-fold decrease in the serum RPR titer at or beyond 12 months post-treatment in case of early syphilis, and, at or beyond 24 months in case of late syphilis.[6,7] Early syphilis included primary, secondary, and early latent syphilis. Late syphilis included late latent and syphilis of unknown duration. Neurosyphilis was defined as CSF WBC count >20 cells/μL or elevated Venereal Disease Research Laboratory (VDRL) titers of the CSF samples.[6,11–13] For RPR titer, TPHA titer, CD4 cell counts, and HIV VL, only data collected within 90 days before or after the lumbar puncture were used. HAART was defined as concomitant use of 3 antiretroviral drugs. To evaluate the effect of HAART, the HAART-positive group included patients who had HAART for a duration of 6 months or more before the diagnosis of syphilis. The clinical categories for HIV infection was based on 1993 revised classification system.[14] Cases were excluded if the CNS infections were not caused by syphilis or if they had concurrent CNS infections.

Laboratory methods

We used ^{BD}Macro-Vue™ RPR Card Tests, 18 mm Circle Qualitative and Quantitative, (Becton Dickinson, U.S.,

Puerto Rico) to determine serum RPR, and, FTI-SERODIA -TPPA (Fujirebio Inc., Taiwan) to determine serum TPHA. The CSF VDRL test was performed by using BD VDRL Antigen (Becton Dickinson, U.S.A.). CD4 and CD8 cell counts were performed using Cytomic FC500 system (Beckman Coulter, Miami, USA). HIV VL was determined using the system of COBAS AmpliPrep/COBAS HIV-1 (v1.0, Roche, Switzerland).

Statistical analysis

Continuous variables were analysed using the student's *t* test. Categorical data were analysed by the chi-square test. Multivariable analysis was performed with logistic regression. A 2-tailed *P* value < 0.05 was considered statistically significant. All the statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; Chicago, IL, USA).

Results

Between January 2000 and December 2009, a total of 157 HIV-infected patients were confirmed to have syphilis. Thirty-six patients were excluded from the study, of which 75% were MSM and 22.2% presented with early syphilis. The causes for exclusion were as follows: CD4 cell counts not obtained within 90 days of lumbar puncture (n = 25), no record of RPR titers (n = 5), incomplete record of CSF data (n = 2), and tuberculosis meningitis (n = 1), toxoplasma brain abscess (n = 1), and cryptococcal meningitis (n = 2). Among the remaining 121 patients, the mean age was 32 years (standard deviation [SD], 9.72). Among the 121 patients, 49 (40.5%) presented with early syphilis: 4, 44, and 1 patient presented with primary, secondary, and early latent syphilis respectively. The most common route for HIV transmission was male homosexual contact, which accounted for 91 cases of syphilis (75.2%). Thirty-seven patients (30.6%) had taken antiretroviral therapy for more than 6 months before diagnosis of syphilis. Fourteen patients were diagnosed with neurosyphilis according to the criteria of positive results in VDRL for CSF (n = 7) or CSF WBC counts >20 cells/μL(n = 7). Two of 14 patients were asymptomatic, the others had symptoms of fever (n = 1), rash (n = 5), headache (n = 2), conscious change (n = 3), and paresis (n = 2). In 7 patients who had positive results of VDRL of the CSF samples, none of them had neurologic symptoms. Except higher percentage of a history of previous syphilis and clinical presentations in LP group (23.1% vs. 7.1%), there was no significant difference between the two groups (Table 1).

Three patients received non-penicillin treatment due to allergy; one patient with early syphilis received tetracycline and had treatment failure, the other two patients with late syphilis, who received ceftriaxone and doxycycline, had treatment success.

Follow-up serological data were not available for 58 patients; hence, these patients were excluded from the analysis of treatment outcome. Between those with follow-up and those without follow-up, there were no statistically significant differences in mean age (32.0 vs. 31.9 years), and the percentage of men who have sex with men (MSM) (74.6% vs. 62.1 %), previous syphilis (11.1% vs. 15.5%), OI (12.7% vs.10.3%), early syphilis (44.4% vs.29.3%), CD4 cell count $\leq$200 cells/μL (28.6% vs. 20.7%), RPR $\geq$1:32 (64.5% vs.

Table 1 Demographic and clinical characteristics of patients with HIV and syphilis infections

Characteristics	Total (n = 121)	LP (n = 65)	No LP (n = 56)	*P* value
Age (mean, y)	32.0	32.4	31.6	0.657
Previous history of syphilis (%)	15.7	23.1	7.1	0.001
Early syphilis (%)	40.5	38.5	42.9	0.75
RPR titer $\geq$1:32 (%)	66.1	69.8	61.8	0.129
Risks for HIV infection (%)				
MSM	75.2	75.4	75.0	0.961
Heterosexual	19.0	20.0	17.9	0.765
IVDA	5.8	4.6	7.1	0.553
Category C of HIV infection	52.9	60.0	44.6	0.337
OI (%)	12.4	15.4	8.9	0.283
HAART (%)	30.6	33.9	26.8	0.401
HIV VL $\geq$10000 copies/mL (%)	60.5	56.3	65.5	0.306
CD4 $\leq$350 cells/μL (%)	50.4	52.3	48.2	0.653
Symptoms (%)				
Asymptomatic	42.1	29.2	57.1	0.002
Fever	9.9	16.9	1.8	0.005
Rash	33.9	30.8	37.5	0.435
Genital ulcer	5.0	4.6	5.4	0.851
Lymphadenitis	2.5	1.5	3.6	0.473
Headache	10.7	20.0	0	0.0
Conscious change	5.0	9.2	0	0.02
Paresis	1.7	3.1	0	0.183

Note. LP, lumbar puncture; RPR, rapid plasma reagin; MSM, men who have sex with men; IVDA, intravenous drug abuse; OI, opportunistic infection; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus; VL, viral load.

Table 2 Factors influencing the treatment outcome of syphilis in 63 HIV-infected patients

Factors	Univariate			Multivariate		
	Treatment success (n = 33)	Treatment failure (n = 30)	*P* value	Odds Ratio	95% Confidence Interval	*P* value
Previous history of syphilis (%)	12.1	10.0	0.563	1.35	0.18–10.00	0.767
Early Syphilis (%)	51.5	36.7	0.236			
RPR titer ≥1:32 (%)	69.7	58.6	0.363			
TPHA titer ≥1:10240 (%)	36.4	40.0	0.961			
MSM (%)	75.8	73.3	0.825	1.19	0.34–4.18	0.785
OI (%)	12.1	13.3	0.885			
HAART (%)	21.2	33.3	0.279	2.58	0.74–9.04	0.138
HIV VL ≥10000 copies/mL (%)	66.7	51.7	0.231			
CD4 count ≤200 cells/μL (%)	18.2	40.0	0.056	4.00	1.15–13.95	0.029

Note. RPR, rapid plasma reagin; TPHA, *Treponema pallidum* hemagglutination; MSM, men who have sex with men; OI, opportunistic infection; HAART, highly active anti-retroviral therapy; LP, lumbar puncture; HIV, human immunodeficiency virus; VL, viral load.

55.4%), and HIV VL ≥10000 copies/mL (59.7% vs. 47.4%). Among 63 patients who had follow-up, 30 patients (47.6%) showed treatment failure; CD4 cell count ≤200 cells/μL, at the time of syphilis, was a predictor of treatment failure (odds ratio [OR], 4.0; 95% confidence interval [CI], 1.2–14.0; $P = .029$). No obvious associations were noted between treatment failure and syphilis stage, HIV VL, antiretroviral therapy, and opportunistic infections (Table 2). Among 24 patients who had early syphilis, but without neurosyphilis, 9 patients received1 dose IM injection of BPG and 15 patients received three dose weekly IM injection of BPG. The rate of treatment failure was 44.4% and 33.3%, respectively.

Of the 65 patients in whom lumbar puncture was performed, 31 (47.7%) had CD4 cell count of >350 cells/μL, and 19 (29.2%) had serum RPR titers of <1:32. Among the patients with CD4 cell count of >350 cells/μL, 7 (22.6%) were diagnosed with neurosyphilis, 4 showed positive VDRL of the CSF samples and 5 showed CSF WBC counts >20 cells/μL. In patients with CD4 cell count of >350 cells/μL, the predictor of developing neurosyphilis was HIV VL ≥10000 copies/mL (85.7% vs. 29.2%, OR, 35.27; 95% CI, 1.95–638.43; $P = .016$). Between the subgroups of patients with and without neurosyphilis, there were no statistically significant differences in the rate of early syphilis (57.1% vs. 45.8%) , RPR titer ≥1:32 (71.4.5% vs. 66.7%) , previous syphilis (42.9% vs. 29.2%), and serum TPHA of ≥1:10240 (71.4% vs. 50.0%) (Table 3).

In patients with serum RPR titer of <1:32, all 19 patients were presented with late syphilis. Four (21.1%) of the 19 patients were diagnosed with neurosyphilis, 1 patient had a positive VDRL titer of the CSF sample and 3 showed CSF WBC counts >20 cells/μL. In patients with serum RPR titer of <1:32, the proportion of HIV VL of ≥10000 copies/mL in patients with and without neurosyphilis was 100.0% and 57.1%, respectively ($P = .086$), and that of CD4 cell count of ≤350 cells/μL was 50.0% and 15.0%, respectively. There were no statistically significant differences in the rate of previous history of syphilis, OI, and HAART (Table 4).

Discussion

Syphilis, a common sexually transmitted disease, may occur as a co-infection in HIV-seropositive patients. Syphilis can facilitate HIV transmission, and HIV can influence the clinical features and treatment outcome of syphilis. Since the immunodeficiency is associated with a high risk of treatment failure of syphilis, especially if neurosyphils was missed, prompt diagnosis in patients with neurosyphilis is extremely important.[15–20] In the analysis of treatment outcome, CD4 cell count of ≤200 cells/μL was observed to

Table 3 Risk factors of neurosyphilis when serum CD4 count was >350 cells/μL

Risk factors	Univariate			Multivariate		
	Neurosyphilis (n = 7)	Non-neurosyphilis (n = 24)	*P* value	Odds Ratio	95% Confidence Interval	*P* value
Previous history of syphilis (%)	42.9	29.1	0.495			
Early Syphilis (%)	57.1	45.8	0.598	0.99	0.04–24.21	0.993
RPR ≥1:32 (%)	71.4	66.7	0.813	0.31	0.01–10.00	0.508
TPHA ≥1:10240 (%)	71.4	50.0	0.316	11.59	0.59–227.12	0.107
OI (%)	0.0	4.1	0.583			
HAART (%)	28.6	58.3	0.827			
HIV VL ≥10000 copies/mL (%)	85.7	29.2	0.008	35.27	1.95–638.43	0.016

Note. LP, lumbar puncture; RPR, rapid plasma reagin; TPHA, *Treponema pallidum* hemagglutination; OI, opportunistic infection; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus; VL, viral load.

Table 4 Risk factors of neurosyphilis when serum RPR titer was <1:32

Risk factors	Neurosyphilis (n = 4)	Non-Neurosyphilis (n = 15)	*P* value
Previous history of syphilis (%)	0.0	33.3	0.245
TPHA ≥1:10240 (%)	0.0	21.4	0.245
OI (%)	0.0	20.0	0.33
HAART (%)	0.0	20.0	0.33
HIV VL ≥10000 copies/mL (%)	0.0	57.1	0.086
CD4 count ≤350 cell/μL (%)	50.0	15.0	0.906

Note. LP, lumbar puncture; RPR, rapid plasma reagin; TPHA, *Treponema pallidum* hemagglutination; OI, opportunistic infection; HAART, highly active anti-retroviral therapy; HIV, human immunodeficiency virus; VL, viral load.

be associated with treatment failure. This finding is similar to the observation by Ghanem et al.[21] Perhaps this is because of the immunodeficiency state induced by HIV may reduce the immunologic response to treponemal infection. Lower CD4 cell count that is associated with more severe degree of immunosuppression may increase the risk of treatment failure in HIV-infected patients who receive penicillin treatment according to the guidelines.

Although some studies have shown that CD4 cell count ≤350 cells/μL and RPR titer≥1:32 are associated with increased risk of neurosyphilis in HIV-infected patients with syphilis, neurosyphilis develops even in patients without these characteristics. In the group of patients with CD4 cell count >350 cells/μL, 7 of 31 patients were diagnosed with syphilis and HIV VL ≥10000 copies/mL was found to be associated with neurosyphilis ($P = .016$). In the setting of RPR titer of <1:32, there was a trend between HIV VL ≥10000 copies/mL and neurosyphilis, but without achieving statistical significance. Marra et al.[8] suggested that HIV-1 RNA level of >500 copies/mL is associated with neurosyphilis. Concurrent HIV infection may alter the natural history of syphilis by increasing the propensity of the disease to progress to neurosyphilis.[5] The explanations for the finding that HIV VL influences the progression to neurosyphilis are unclear and needs to be explored in prospective studies of a large sample size.

The limitations of our study were as follows: First, this was a retrospective study that was performed by review of medical records; therefore, incomplete records may have resulted in bias. Second, only 1 woman was included in this study; this factor might be related to male-predominance in the HIV-infected population in Taiwan (91.75%).[22] As a result, insufficient data were available for analysis for the female population. Third, only 63(52.07%) of the 121 patients had regular follow up of serologic responses, which may have led to a less accurate assessment of the prognosis of the infection. The poor compliance may have influenced patients' acceptance of lumbar puncture, and treatment failure maybe the result of undetected neurosyphilis. Fourth, the small numbers of the study participants limited further analysis to be performed.

In conclusion, patients with CD4 cell count of ≤200 cells/μL were at higher risk for treatment failure of syphilis, and close follow-up is needed. Diagnosis of neurosyphilis should be considered in HIV-infected patients with syphilis, even in patients with CD4 cell counts >350 cells/μL. HIV VL of ≥10000 copies/mL was associated with neurosyphilis in this population, and lumbar puncture should be performed.

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