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A Consequence of the Syphilis Epidemic Among Men Who Have Sex With Men (MSM): Neurosyphilis in Los Angeles, 2001–2004

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Objectives: **To describe the epidemiology and clinical findings of neurosyphilis (NS) cases diagnosed during the current syphilis epidemic occurring predominantly among men who have sex with men.**

Methods: **Syphilis cases reported to the health department were reviewed for diagnosis of NS, cerebrospinal fluid venereal disease research laboratory results, and/or treatment for NS.**

Results: **During 2001–2004, 7083 cases of syphilis were diagnosed in Los Angeles. One hundred nine cases of confirmed or probable NS occurring among persons aged 19 to 65 years were identified during this period (1.5%). Symptomatic NS was present in 1.2% of reported syphilis cases (86 of 7083). NS cases were inclusive of 71 (65%) men who have sex with men. Forty-two (49%) of the symptomatic NS cases occurred during secondary (N = 28) or early latent (N = 14) syphilis. Sixty-eight percent (N = 74) of the NS cases were human immunodeficiency virus (HIV)-positive. The estimated incidence of symptomatic NS among HIV-infected persons with early syphilis was 2.1% as compared with 0.6% among HIV-negative persons.**

Conclusion: **Providers should maintain a high index of suspicion for NS among patients with syphilis, particularly those with HIV infection.**

MANY LARGE URBAN AREAS in the United States are experiencing increases in syphilis rates among men who have sex with men (MSM). Human immunodeficiency virus (HIV) coinfection ranges from 48% to 75% among these cases.[1–5] Neurosyphilis (NS) diagnoses have likewise increased, with many affected persons experiencing significant and sometimes persistent manifestations, particularly those with HIV infection.[6,7]

National surveillance programs do not track trends in NS, thus increasing numbers of this serious manifestation may occur with minimal public health knowledge or response during periods of increased syphilis morbidity. Some public health surveillance programs have traditionally considered NS as a late manifestation of syphilis infection and thus not counted codiagnosis of NS with early syphilis (ES) in order to prioritize field investigation. However reports of NS occurring during early stages of syphilis have increased during the period of increasing HIV rates[8] and MSM syphilis epidemics[6,7] indicating the need for better surveillance of this manifestation of syphilis to inform populations at risk. Providers caring for persons with syphilis with or without HIV infection should be aware of the clinical manifestations and current NS screening recommendations to provide adequate care to persons at risk. Public health departments in areas of high syphilis morbidity among MSM should consider the need for heightened surveillance for this manifestation of syphilis.

Because of local field reports of large numbers of syphilis patients experiencing neurologic sequelae during an epidemic of syphilis occurring mainly among MSM in Los Angeles, we performed medical chart reviews to evaluate the epidemiology, clinical presentations (symptomatic vs. asymptomatic), and laboratory findings of NS cases.

Methods

Syphilis is a reportable infectious disease in California. Medical providers as well as laboratories are required to report cases of syphilis within 24 hours of diagnosis or receipt of positive laboratory result. Based on standardized annual surveys, laboratory reporting of ES cases in Los Angeles County during the years 2002–2004 was 100% (http://lapublichealth.org/std/reports.htm). To identify NS, syphilis cases and positive laboratory values reported to the health department were reviewed for diagnosis of NS, positive and negative cerebrospinal fluid (CSF) venereal disease research laboratory (VDRL) results, and/or treatment for NS. Syphilis cases with available nonreactive CSF VDRL results were reviewed for symptoms of NS and elevated CSF leukocyte counts and protein levels.

Medical chart review was performed for all confirmed and probable cases using a standardized data extraction form to collect data regarding clinical symptoms, laboratory values, treatment information, syphilis stage, and reason for performing a lumbar puncture. Demographic information was obtained from health department databases and medical chart review and included race/

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A portion of this dataset was used in a multi-city analysis of neurosyphilis incidence. This analysis was published in: Centers for Disease Control and Prevention. Symptomatic early neurosyphilis among HIV-positive men who have sex with men—Four cities, United States, January 2002–June 2004. MMWR Morb Mortal Wkly Rep 2007;56:625–628.

ethnicity, age, stage of syphilis, HIV status, and sexual orientation. NS cases older than 65 and congenital syphilis cases were not included in this review to better define NS occurring as a result of the ongoing ES epidemic among MSM.

Medical records were reviewed from the site of the NS diagnosis and/or the site where the patient received clinical follow-up. The diagnosing provider was discerned from the reporting form. The medical record reviews were performed by an infectious disease physician and/or 4 public health nurses. All completed forms were reviewed by the infectious disease physician.

Disease surveillance, data collection, evaluation, and analysis are ongoing public health surveillance activities and thus are not subject to review by institutional review boards or HIPAA regulations.

Case Definition

Confirmed NS was defined as a case of syphilis at any stage in which a reactive VDRL from the CSF was obtained. A probable case of NS was defined as syphilis of any stage with a negative CSF VDRL and both an elevated CSF protein (>50 mg/dL) or CSF leukocyte count (>5 cells/μL) in the absence of other known causes of these abnormalities, and clinical symptoms or signs consistent with NS in the absence of other known causes for these clinical abnormalities.[9] Cases that were defined and reported by the medical provider as NS, and that did not meet criteria for confirmed or probable cases were not included in this review.

ES consisted of all reported primary, secondary, and early latent syphilis cases. The diagnosis of primary syphilis was made by the presence of 1 or more ulcers at the site of exposure and the demonstration of exposure to *Treponema pallidum* by a reactive serologic test for syphilis. Secondary syphilis was diagnosed by the presence of characteristic dermatologic lesions and a reactive nontreponemal test (titer ≥1:4). The diagnosis of early latent syphilis was made in asymptomatic persons with evidence of having acquired the infection within the previous 12 months demonstrated by 1 or more of the following: documented negative test or a 4-fold or greater increase in titer of a nontreponemal test or a history of symptoms consistent with primary or secondary syphilis, a history of sexual exposure to a partner who had independently confirmed ES, or had their only possible exposure during this time period. The diagnosis of late latent syphilis was made in asymptomatic persons with evidence of having acquired the infection >12 months previously. The diagnosis of syphilis of unknown duration was made in asymptomatic persons when the date of infection could not be established as having occurred within the previous year and the patient's age was between 13 and 35 years and the patient's nontreponemal titer was ≥32.[9] Centers for Disease Control and Prevention (CDC) syphilis surveillance case definitions were used for classification of latent syphilis cases with NS as if the NS was not present to reflect the timing of NS diagnosis and duration of syphilis infection.

Laboratory Values

Public health databases were used to collect rapid plasmin reagin (RPR) and CSF VDRL titers, and syphilis confirmatory testing information. CSF laboratory values including protein, glucose, and leukocyte and erythrocyte counts were collected from public health databases and from medical chart review. HIV viral loads and CD4 counts were collected from medical chart review if they were performed within 12 months of NS diagnosis.

Data Analysis

Data were analyzed using SPSS version 12 (SPSS Inc., Chicago, IL). Univariate correlates of symptomatic infection were determined by χ^2. Statistical analysis of medians was performed using Kruskal-Wallis nonparametric test.

Denominator data for unknown HIV status and sexual orientation among total ES cases were extrapolated by multiplying the number of unknown cases by the proportion of cases with available information of HIV status and sexual orientation and adding this product back to the totals for that group.

Results

Demographics of Syphilis Cases

A total of 7083 cases of syphilis were reported to the Los Angeles County Department of Health during January 2001 to December 2004 (Table 1); 2883 of these were early cases. Of the ES cases, 1505 (52%) had primary or secondary syphilis and 1378 (48%) had early latent syphilis. One thousand eighty-two (38%) of ES cases were white, 469 (16%) were black, and 1147 (40%) were Hispanic. The ages were as follows: 81 (3.0%) <20 years of age; 647 (23%) 20 to 29 years of age, 1174 (41%) 30 to 39 years of age; and 750 (26%) 40 to 49. HIV status was available for 77% of the ES cases. Fifty-six percent (N = 1250) of these ES cases reported being HIV positive. One thousand nine hundred forty-nine (68%) ES cases occurred among MSM; 1149 (59%) of these MSM reported being positive.

Demographics of NS Cases

One hundred twenty-three cases of NS were reported during 2001–2004. One hundred nine cases of confirmed (N = 94, 86%) or probable (N = 15, 14%) NS occurred in persons <65 years of age and were identified for this review. Twenty cases of NS were identified from 2001, 21 from 2002, 37 from 2003, and 31 from 2004. The diagnosis of NS was made by the clinician in 108 (99%) of the cases. NS cases were diagnosed in various clinical settings that included: emergency department 28% (N = 31), hospital 7%

TABLE 1. Syphilis and Neurosyphilis Cases Reported to the Los Angeles County Health Department, 2001–2004

Case Description/Stage	No. Cases (%)
Total syphilis	7083
Primary	451 (6)
Secondary	1054 (15)
Early latent	1378 (19)
Late latent	3787 (53)
Latent unknown duration	413 (6)
Symptomatic neurosyphilis	86 (1.2)
Primary	0 (0)
Secondary	28 (1.9)*
Early latent	14 (1.0)*
Late latent	44 (1.2)*
Latent unknown duration	0 (0)*
Asymptomatic neurosyphilis	23 (0.3)
Primary	0 (0)
Secondary	9 (0.6)*
Early latent	8 (0.6)*
Late latent	5 (0.1)*
Latent unknown duration	1 (0.2)*

*Percent calculations performed using the total number of syphilis cases for that stage as denominator.

TABLE 2. Demographics and Laboratory Values of Neurosyphilis Cases, Los Angeles, 2001–2004 (N = 109)

Variable	N (%) or Median (Range)		
	All Cases (N = 109)	Symptomatic (N = 86)	Asymptomatic (N = 23)
Sex			
Male	102 (94)	80 (93)	22 (96)
Female	6 (6)	6 (7)	0 (0)
Transgender	1 (0.9)	0 (0)	1 (4)
Age	41 (19–65)	42 (21–65)	39 (19–58)
Race			
White	87 (80)	64 (74)	23 (100)
Black	20 (18)	20 (23)	0 (0)
Other	2 (1.8)	2 (2.3)	0 (0)
Unknown	1 (0.9)	1 (1.2)	0 (0)
Ethnicity			
Hispanic	39 (36)	29 (34)	10 (42)
Non-Hispanic	69 (63)	56 (65)	13 (57)
Unknown	1 (0.9)	1 (1.2)	0 (0)
HIV status			
Positive	74 (68)	51 (59)	23 (100)
Negative	29 (27)	29 (34)	0 (0)
Unknown	6 (6)	6 (7)	0 (0)
Sexual orientation of male NS cases (N = 103)			
MSW	17 (17)	17 (21)	0 (0)
MSM/MSMW	70 (68)	48 (60)	22 (96)
Unknown	16 (15)	15 (19)	1 (5)
Neurosyphilis diagnosis			
Confirmed	94 (86)	71 (83)	23 (100)
Probable	15 (14)	15 (17)	0 (0)
Laboratory values			
RPR titer	1:256 (1:2–>1:2048)	1:128 (1:2–>1:2048)	1:256 (1:2–1:2048)
Cerebrospinal fluid laboratory values			
VDRL			
Reactive	92 (84)	69 (80)	23 (100)
Nonreactive	16 (15)	16 (19)	0 (0)
Not performed	1 (0.9)	1 (1)	0 (0)
CSF VDRL titer	1:4 (1:1–1:32)	1:4 (1:1–1:32)	1:4 (1:1–1:32)
Titer not performed	6 (6)	5 (6)	1 (4)
Positive CSF FTA-ABS	6 (6)	4 (5)	2 (9)
WBC count (cells/mL)	28 (0–930)	35 (0–930)	14.5 (2–203)
Protein (measure)	66 (3–730)	70 (3–730)	57 (31–185)
Glucose (measure)	54 (11–135)	54 (11–135)	54 (29–72)

MSW indicates men who have sex with women; MSM, men who have sex with men; MSMW, men who have sex with men and women.

(N = 8), private provider office 41% (N = 45) (includes HIV clinics), walk-in clinic 2% (N = 2), STD clinic 0.9% (N = 1), ophthalmology clinic 4% (N = 4), health maintenance organization 10% (N = 11), psychiatric facility 2% (N = 2), information not obtained 5% (N = 5).

The median age of NS cases was 41, 94% were male and 80% of cases were white. Of the male cases (n = 103), 71 (69%) reported having sex with other males (MSM). Thirty-seven (34%) of NS cases were classified as secondary stage, 22 (21%) as early latent stage, 49 (45%) as late latent, and 1 (0.9%) as latent unknown duration (Table 2).

NS Incidence

Reported syphilis was associated with confirmed or probable NS in 1.5% of cases (109 of 7083). Symptomatic NS was present in 1.2% of reported syphilis cases (86 of 7083). The incidence of symptomatic NS occurring during early stages of syphilis was 1.5% (42 of 2883). The incidence of symptomatic NS occurring among HIV infected and HIV noninfected persons with ES was 2.1% and 0.6%, respectively. The incidence of asymptomatic NS among HIV-infected persons with ES was 1.1%.

HIV Among Persons With NS

Seventy-four (67%) of the total NS cases were HIV positive. In comparison, the HIV prevalence in overall syphilis cases (primary, secondary, early latent, late latent, and latent unknown duration) without NS was 19%. However, HIV status was not available for 61% of overall syphilis cases. The HIV prevalence in ES cases without NS was 41%. Fifty-one (79%) of these HIV-positive NS cases were symptomatic; 23 (21%) were asymptomatic. The median viral load near the time of diagnosis was 30,165 copies/mL (range <50–>750,000); the median CD4 count was 321 cells/mm^3 (range 2–1393). Thirty (41%) of HIV-infected cases were receiving highly active antiretroviral therapy at the time of NS diagnosis (Table 3). Sixty-three (85%) of these HIV-infected cases were MSM. The median CSF white blood cell counts were significantly higher ($P = 0.01$) and the CD4 counts were significantly lower ($P = 0.01$) among symptomatic HIV-infected NS cases when compared with asymptomatic HIV-infected cases. The median viral load was somewhat higher among symptomatic HIV-infected NS cases ($P = 0.07$). There were no significant differences in serum RPR or CSF VDRL titers by highly active antiretroviral therapy status.

TABLE 3. Neurosyphilis Cases Diagnosed Among HIV-Infected Persons

Variable	N (%) or Median (Range)		
	All HIV-Infected Cases (N = 74)	Symptomatic HIV-Infected (N = 51)	Asymptomatic HIV-Infected (N = 23)
Median CD4 count (cells/mL)	321 (2–1393)	281 (2–1323)	416.5 (66–904)
Median viral load (copies/mL)	30,165 (50–>750,000)	46,000 (50–>750,000)	9057 (50–406,006)
Receiving HAART			
Yes	30 (41)	19 (37)	11 (48)
No	32 (43)	24 (47)	8 (35)
Unknown	12 (16)	8 (16)	4 (17)

Symptomatic and Asymptomatic NS

Eighty-six cases (78%) had neurologic signs or symptoms of NS. Forty-two (49%) of the symptomatic cases occurred during secondary (N = 28) or early latent (N = 14) syphilis. Among NS cases diagnosed during early stages of syphilis, 51 (86%) occurred among HIV-infected patients when compared with 23 (46%) cases diagnosed during late latent syphilis or syphilis of unknown duration.

One hundred percent of the 23 asymptomatic cases were white and HIVpositive. The median RPR value for asymptomatic cases was 1:256 (range 1:2–1:2048). Only 2 (9%) asymptomatic cases had RPR values <1:32.

Treatment

One hundred six (97%) of NS cases received treatment with a CDC-recommended or CDC recommended alternative course of therapy[10]: 88 (81%) with aqueous penicillin (PCN) G, 13 (12%) with intramuscularly procaine PCN G and 5 (5%) were treated with intravenously ceftriaxone. Non-CDC-recommended therapies included intravenously ampicillin (N = 1), 3 intramuscular doses of benzathine PCN (N = 1). One patient had no treatment information available. Thirteen of the cases that received aqueous PCN G, 2 of the cases that received procaine PCN, and 3 of the patients that received ceftriaxone received 3 intramuscular injections of benzathine PCN after the initial treatment regimen.

History of Previous Diagnosis and Treatment for Syphilis

Seventeen percent of cases (N = 19) of NS had a health department-reported history of syphilis by health department record review. Thirteen of these cases had been diagnosed and treated for syphilis within 2 years of the current NS diagnosis. Ten of these 13 were HIV positive; 6 of the 13 did not receive a recommended treatment regimen appropriate for the stage of syphilis. One of these 6 had received 1.2 million units of procaine PCN/1.2 million units of benzathine PCN (Bicillin CR).[11] Five of the 13 cases had experienced neurologic symptoms at the time of the previous syphilis diagnosis; 8 did not have neurologic symptoms. Only 3 of these 5 were treated with a CDC-recommended regimen for NS.[10] Of the 8 without neurologic symptoms, 7 (88%) had an RPR titer at the time of previous diagnosis of ≥1:32. Five of the 13 cases diagnosed and treated for syphilis within 2 years of the current NS diagnosis were suggestive of treatment failure in which they did not report additional sexual exposure (reinfection) and they received a CDC-recommended regimen of treatment appropriate for the stage of syphilis infection. All of these cases were HIV positive representing 7% of HIV-infected NS cases.

Discussion

Among overall cases of NS in this review, symptomatic NS was frequently diagnosed in early stages of syphilis with a higher incidence seen among HIV-infected persons when compared with HIV noninfected persons in Los Angeles. This review summarizes the epidemiology and clinical and laboratory findings of these NS cases diagnosed in a large urban setting during a syphilis outbreak among MSM. This review suggests the need for awareness on the part of HIV clinical providers as well as public health surveillance personnel regarding the identification and referral for diagnosis and treatment of persons at risk for NS.

The majority of the symptomatic and all of the asymptomatic NS cases in this review were HIV positive and were diagnosed during early stages of syphilis. Limited studies of HIV-infected persons have reported a more rapid progression to NS during ES stages than in HIV noninfected persons.[12,13] Some clinical evidence suggests that HIV-infected persons with serum RPR titers of >1:32 and/or CD4 counts <350 may be at greater risk of having laboratory confirmed NS regardless of whether neurologic symptoms are present.[14,15] The majority of the asymptomatic NS cases in this review, all of whom were HIV positive, had RPR titers >1:32. High clinical suspicion for NS and/or CSF testing in HIV-infected patients with syphilis and neurologic symptoms is warranted regardless of stage because of the severe manifestations that may result and persist despite treatment. Routine testing of HIV-infected persons for syphilis is recommended as part of routine care with more frequent testing being recommended for HIV-infected persons engaging in sexual risk behaviors.[16] HIV providers should maintain high clinical suspicion for NS among patients engaging in sexual risk behaviors that present with neurologic symptoms.

We identified 5 HIV-infected patients that had been diagnosed and treated for syphilis within a year of presentation with NS. Data from public health investigator interviews did not indicate sexual re-exposure in these cases. These patients may have experienced treatment failure, reinfection, or perhaps may have had NS at the time of previous syphilis diagnosis but had not received CSF testing, and thus did not receive treatment adequate for NS. Some data suggests that patients with HIV infection may have a greater likelihood of treatment failure as defined by serologic criteria,[17] and clinical relapse.[18] Larger studies have not found HIV status to affect syphilis cure rates.[19,20] HIV-infected patients may have persistently abnormal CSF findings even after appropriate NS treatment when compared with HIV-negative persons.[21] Considering these findings, it is relevant to query the adequacy of current NS screening and treatment recommendations as well as whether abnormal CSF findings are related to syphilis.

Many of the asymptomatic cases were diagnosed during early stages of syphilis, reflecting the high indices of suspicion for NS by many Los Angeles HIV providers caring for patients with syphilis. Controversy persists in the diagnosis of NS because of the low sensitivity of the CSF-VDRL,[22] the difficulty in interpreting elevated CSF leukocyte counts in HIV-infected persons,[23] and the

dilemma of whether to screen for NS in HIV-infected patients with ES and without neurologic symptoms. CDC STD treatment guidelines recommend the performance of a lumbar puncture and CSF examination for patients that are HIV infected and have late latent syphilis, patients with reactive syphilis serology and neurologic symptoms and those with evidence of treatment failure.[10] These data reveal that many NS cases both symptomatic and asymptomatic were diagnosed during early stages of syphilis, suggesting the need for more formal guidance for clinicians caring for HIV-infected patients with syphilis regarding the performance of lumbar punctures in asymptomatic patients with ES.

This analysis of notifiable disease surveillance data was subject to several limitations. There was no active case finding; thus these data are subject to reporting biases. Sample selection limited our ability to identify significant correlates of NS diagnosis as we did not compare NS cases to syphilis cases without NS. Sample size limited our ability to identify significant correlates of symptomatic NS. We were not able to make predictions regarding HIV status and clinical presentations of NS as our sample was predominantly HIV positive. An underestimate of NS likely resulted from the exclusion of syphilis cases with neurologic symptoms that did not receive CSF testing (suspect cases) and late stage syphilis cases that had positive CSF findings that were not reported by the laboratory or provider. Denominator values for ES were likely underestimated as well given some cases of syphilis were not identified in early stages. Selection bias may have resulted in an overestimation of NS incidence rates if HIV-infected persons were more likely to have received a lumbar puncture. Also, asymptomatic syphilis patients may not routinely receive CSF testing thus diagnosis of asymptomatic NS reflects variation in clinical practices. Extrapolated values for HIV status and sexual orientation may have biased incidence calculations as these missing values may represent a dissimilar distribution.

These data suggest the need for providers to consider NS and the performance of a lumbar puncture in early stages of syphilis, specifically in HIV-infected patients. In addition to providers, public health departments with high rates of syphilis among MSM should consider the need for heightened surveillance for NS. Information regarding trends in this manifestation should be disseminated among providers caring for persons with syphilis and/or HIV as well as community-based organizations that provide education to persons at risk for syphilis. Prevention messages related to syphilis should include information regarding NS as a manifestation that may result in neurologic deficits.

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