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CLINICAL CHARACTERISTICS AND EVOLUTION OF SYPHILIS IN 24 HIV+ INDIVIDUALS IN RIO DE JANEIRO, BRAZIL

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SUMMARY

A total of 24 patients with syphilis and HIV infection were treated from January 1997 to March 2003 at the Infectious Dermatology Outpatient Clinic of the Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil. The caseload consisted of 20 males (83.3%) and four females (16.7%), with a mean age of 38.04 years and mean T CD4+ count of 389.5 cells/mL. Syphilis was diagnosed as secondary in 16 (62.5%) patients, late latent in eight (33.3%), and tertiary in one (4.2%). Manifestations of secondary syphilis were palmar and plantar erythematopapulous cutaneous lesions in nine (37.5%), papulous exanthema in four (16.7%), patchy alopecia in 3 (12.5%) and osteochondritis in one patient (4.2%). Tertiary syphilis was characterized by verrucous lesions. Neurosyphilis was diagnosed in four patients (16.7%), with headache as the only manifestation in two patients. Drugs used in treatment included benzathine penicillin, ceftriaxone, erythromycin, and crystalline penicillin. Cure was achieved in 18 patients (75%). Five patients (20.8%) were retreated, three of whom presented a history of re-exposure. This study confirms the importance of establishing the diagnosis of neurosyphilis in patients with HIV infection, in addition to performing follow-up on treatment for syphilis.

KEYWORDS: HIV; Syphilis; Neurosyphilis; Treatment.

INTRODUCTION

The natural history of syphilis has been modified with the advent of HIV infection. Syphilis increases the susceptibility to HIV infection[2], and HIV infection can modify the clinical course of syphilis. A more rapid progression from the primary chancre to the secondary and tertiary stages, increased incidence and greater severity of neurosyphilis, and early malign syphilis have been described in patients with HIV[7,8,25,26,27,29].

Few case series reports have been published on syphilis associated with HIV infection. The current study aims to describe the clinical, laboratory, and therapeutic aspects of syphilis in individuals with HIV infection.

PATIENTS AND METHODS

This study was approved by the Ethics Committee of Evandro Chagas Clinical Research Institute (IPEC), Rio de Janeiro, Brazil and appropriated informed consent was obtained for all participants. This was a longitudinal, open, non-placebo-controlled study consisting of 24 patients with HIV infection and syphilis, treated at the Infectious Dermatology Outpatient Clinic, IPEC from January 1997 to March 2003 and followed up for a minimum of two years after treatment of syphilis. This outpatient clinic receives patients referred with HIV/AIDS that are followed up in the IPEC cohort, as well as external patients with suspected infectious dermatoses. During the study period, 474 HIV-infected patients were treated, and syphilis comprised 2.2% of the 1124 dermatological diagnoses in this group.

Diagnosis of syphilis was based on the Venereal Disease Research Laboratory test (VDRL) and fluorescent treponemal antibody-absorption (FTA-ABS) or *Treponema pallidum* hemagglutination assay (TPHA). Active infection was defined as VRDL > 1/8. Based on clinical criteria, syphilis was classified as primary, secondary, or tertiary. Asymptomatic patients with prior VDRL titers ≤ 1/8 and who evolved with increasing titers in a 12-month period were classified as early latent syphilis; individuals with more than 12 months of infection or who had no documented VDRL in the last 12 months were classified as late latent syphilis. All patients were submitted to a spinal tap. Diagnosis of certainty for neurosyphilis was based on VDRL reactivity in the cerebrospinal fluid (CSF); probable diagnosis was based on increased protein (≥ 50 mg/dL) and/or cellularity (> 5 cells/dL).

VDRL was performed at months one, three, six, nine, 12, and 24 after the completion of treatment for syphilis. The criterion of cure was a decline in plasma VDRL to ≤ 1/8. Patients who maintained high

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titers or who presented a two-to-fourfold increase in titers after an initial decline during follow-up were submitted to a new spinal tap for investigation of neurosyphilis. Cases were classified as re-infection when there was either a history of sexual exposure without condom use or the presence of primary chancre upon physical examination, and as relapse when there was no history of these data.

In the case of tertiary syphilis, the persistence of a titer after 24 months of follow-up was not classified as active disease. In the investigation of HIV infection, patients had been subjected to clinical and laboratory evaluation with routine tests including peripheral blood lymphocyte subpopulations and HIV-1 viral load every four months.

Data analysis included estimates obtained by means of relative frequencies and sample descriptive statistics (mean, median, and standard deviation).

RESULTS

Investigation of syphilis (Table 1): Of the 24 HIV+ patients, the majority was male (83.3%) and the mean age was 38.04 years (range 27 - 60). Syphilis was diagnosed as secondary in 15 patients (62.5%), late latent in eight (33.3%), and tertiary in one (female) patient (4.2%). Cutaneous manifestations of secondary syphilis included predominantly erythematopapulous lesions located principally on the trunk and palmar and plantar regions in nine patients (37.5%), followed by disseminated erythematopapulous infiltrative lesions observed in four patients (16.7%) and patchy alopecia in three (12.5%). In case number 2, manifestations of secondary syphilis included alopecia and osteochondritis in the left proximal sternal region, diagnosed by the presence of edema, pain, and local erythema. The patient with tertiary syphilis presented a verrucous lesion with two years' evolution located on the left forearm (case 15).

In five individuals (20.8%) (cases 2, 8, 10, 15, 20) diagnosis of neurosyphilis was established by VDRL reactivity in the CSF; and in eight individuals (33.3%) the possibility of neurosyphilis was raised on the basis of increased protein (cases 16 and 24), cellularity (cases 21 and 23), or both (cases 1 and 6). Headache was the only symptom present in two patients (cases 8 and 20).

In patients with secondary and latent syphilis without neurosyphilis, benzathine penicillin 7.2 million units IM was the drug of choice. Erythromycin was used in one patient who presented allergy to penicillin. Both possible and confirmed neurosyphilis were treated with crystalline penicillin 18 to 24 million units or ceftriaxone 1 to 2 g/day for 14 days. The patient with osteochondritis received oral prednisone associated with the treatment for syphilis, with remission of the clinical syndrome.

Table 1
Clinical, laboratory and treatment data of syphilis in HIV+ individuals

Case	Sex	Age	CD4	Syphilis	Liquor parameters			Neurosyphilis	Treatment	VDRL	
					VDRL	Cells	Protein			Baseline	Follow-up
1	M	28	267	S.S.[1]	negative	16	75	P[5,6]	Cf[7]	1/128	(-)
2	M	36	623	S.S.[1]	¼	1	60	C[4]	Cf[7]	1/32	1/8
3	M	50	528	S.S.[1]	negative	2	20	absent	Bp[8]	1/128	1/2
4	M	36	549	S.S.[1]	negative	3	30	absent	Bp[8]	1/32	(-)
5	M	35	501	S.S.[1]	negative	1	33	absent	Bp[8]	1/512	1/2
6	M	37	365	S.S.[1]	negative	13	60	P[5,6]	Cf[7]	1/256	1/128
7	M	29	636	L.L.S.[2]	negative	5	65	P[5,6]	Cf[7]	1/32	1/16
8	F	34	10	S.S.[1]	1/1	12	77	C[4]	Cp[10]	1/256	1/16
9	M	45	375	S.S.[1]	1/1	4	25	C[4]	Bp[8]	1/256	cure
10	M	36	262	S.S.[1]	negative	not done	163	P[6]	Cf[7]	1/4096	1/8
11	M	35	242	L.L.S.[2]	ngative	3	20	absent	Bp[8]	1/64	cure
12	M	42	183	L.L.S.[2]	negative	3	20	absent	Bp[8]	1/32	(-)
13	M	39	806	L.L.S.[2]	negative	3	26	absent	Bp[8]	1/32	(-)
14	M	27	182	S.S[1]	negative	4	20	absent	E[9]	1/64	cure
15	F		413	T.S.[3]	¼	4	76	C[4]	Cp[10]	1/512	1/128
16	F	44	27	L.L.S[2]	negative	2	60	P[6]	Cf[7]	1/32	1/32
17	M	32	1382	S.S.[1]	negative	1	60	P[6]	Cf[7]	1/512	1/32
18	F	32	824	L.L.S.[2]	negative	5	25	absent	Bp[8]	1/512	cure
19	M	31	162	L.L.S[2]	negative	3	20	absent	Bp[8]	1/32	(-)
20	M	40	41	S.S.[1]	1/1	not done	not done	C[4]	Cf[7]	1/512	(-)
21	M	41	404	L.L.S.[2]	negative	2	60	P[6]	Cf[7]	1/256	1/128
22	M	32	430	S.S.[1]	negative	3	34	absent	Bp[8]	1/16	(-)
23	M	60	287	S.S.[1]	negative	77	5	P[5]	Cp[10]	1/1024	1/8
24	M	44	618	S.S.[1]	negative	4	60	P[6]	Cf[7]	1/32	1/1

Secondary syphilis[1]; late latent syphilis[2]; tertiary syphilis[3]; LLS; Confirmed neurosyphilis (CSF = reactiveVDRL)[4]; Possible neurosyphilis > 5 cells/dL[5]; Possible neurosyphilis protein > 50 mg/dL[6]; ceftriaxone[7]; Benzathine penicillin[8]; Erythromycin[9]; Crystalline penicillin[10]

Investigation of HIV infection: In the epidemiological classification, 17 (70.8%) and seven (29.1%) of the patients belonged to the homo/bisexual and heterosexual exposure categories, respectively. The mean CD4 T lymphocyte count was 389.5 (range 10 - 1382) cells/mm^3 (Table 1) and the mean HIV viral load was 194,790 (range < 80 to 800,000) copies/mL. Twenty patients (83.3%) were using anti-retroviral drugs according to regimens from the Brazilian Ministry of Health guidelines. Mean time from beginning of follow-up of HIV infection to diagnosis of syphilis was 47.5 months (range: 2 to 168 months). In four individuals (16.7%) (cases 1, 8, 10, and 15), diagnosis of HIV infection was made after diagnosis of syphilis. We observed a higher mean VDRL titer (median 1:1081) and lower CD4+ T lymphocyte count (median 276.20 cells/mm^3) in the patients with confirmed neurosyphilis as compared to those without neurosyphilis [median VDRL 1:142.67 ($p < 0.00$) and median CD4+ T lymphocyte 511.92 cells/mm^3)($p < 0.01$)].

Follow-up: At the end of 24 months of treatment for syphilis, 17 patients (70.8%) presented clinical and laboratory cure and seven patients (29.1%) persisted with titers classified as active infection (cases 6, 7, 8, 15, 16, 17, and 21). In three of these patients there was a history of re-infection (cases 7, 17, and 21), one of whom with palmar/plantar erythematopapulous lesions (case 17). Seven patients were submitted to a repeat spinal tap. Three patients presented alterations in the CSF (increased protein in cases 7 and 17 and increased protein and cellularity in case 21); crystalline penicillin was initiated in cases 7 and ceftriaxone in cases 17 and 21. Two patients were treated with benzathine penicillin (cases 6 and 16) and two (cases 8 and 15) were maintained in follow-up, since the serum titers were declining. In case 8, the laboratory criterion for cure occurred four years after the initial episode.

In the follow-up of patients treated for the second time, coincidentally the two patients that presented a history of re-exposure before the re-treatment (cases 17 and 21) presented an increase in the post-treatment VDRL titers. These patients reported a new history of re-exposure, and one of them presented an inoculation chancre on the penis in addition to palmar/planter papulous lesions (case 17). The spinal tap showed normal CSF in case 17 and increased protein in case 21, and the two patients were treated with benzathine penicillin and ceftriaxone, respectively.

DISCUSSION

The caseload presented an increased frequency of secondary and latent syphilis, the most common clinical presentations in the presence of HIV infection[5,27]. Likewise, the presence of multiple genital ulcers and concurrent primary and secondary stages (diagnosed in one case) are observed more frequently in HIV+ individuals[24,25]. Immunological alterations induced by HIV could account for the rapid dissemination of treponemes from the primary lesion and the early appearance of secondary lesions. Cutaneous manifestations were those classically described[17]. However, the florid clinical picture frequently called our attention in this series, consistent with reports by other authors in relation to the manifestations of secondary syphilis in association with HIV infection[13]. Bone alterations, although rare, can be present in secondary syphilis, as observed in one case of osteochondritis. Sporadic cases of cranial and ulnar osteitis have been described in HIV+ patients[11,14].

Diagnosis of neurosyphilis in patients with HIV infection is still a challenge, because VDRL sensitivity in the CSF is low, and the increased protein and cellularity can result from the HIV infection itself in the central nervous system[22]. Studies with more sensitive techniques such as polymerase chain reaction (PCR) for the detection of *T. pallidum* have demonstrated low sensitivity and a lack of correlation between positive PCR findings in the CSF and the clinical and serological diagnosis of syphilis[9,20]. Because of the greater severity with which neurosyphilis can evolve in these individuals, cases classified as possible neurosyphilis (alterations in CSF proteins and/or cellularity) were treated with treponemicidal drugs that penetrate the CSF.

Neurosyphilis was diagnosed in 20.8% of the case series or 25.0% if we include CSF alterations. A previous study showed a prevalence rate of 23.5% [3] for neurosyphilis in HIV-positive patients as compared to 10.0% in HIV-negative patients[16]. More recent studies have confirmed that titers greater than 1/32 are predictive of neurosyphilis, regardless of the clinical stage of syphilis and presence or absence of HIV infection[20]. Furthermore, co-infection with HIV and *T. pallidum* constitutes a threefold risk when the CD4+ T lymphocyte count is below 350 cells/mm^3 [(21)]. Except for one patient, all the others in the current sample presented high titers as described in HIV infection[10].

Neurosyphilis in patients with HIV can by asymptomatic. However, a variety of presentations can occur. An increased frequency of ophthalmologic alterations as well as accelerated late manifestations of neurosyphilis have been described[4,15]. Two patients with confirmed neurosyphilis presented headache without an associated meningeal syndrome.

Penicillin is still the drug of choice for all cases of syphilis. In the case of neurosyphilis, IV crystalline penicillin on an inpatient basis or procaine penicillin associated with probenecid on an outpatient basis are the drugs of choice[1,30]. Probenecid is not available in our clinic. Ceftriaxone can be an alternative based on its treponemicidal activity and penetration into the CSF, having demonstrated equivalence to procaine penicillin in conjunction with probenicid in HIV+ individuals with neurosyphilis[19,28]. In our series, crystalline penicillin was offered as the drug of choice to all patients with neurosyphilis (both confirmed and possible). However, the vast majority opted for ceftriaxone since it involves a single daily dose and allows for outpatient treatment.

Although based on rather imprecise evidence, relapses (12.5%) occurred in the patients with possible neurosyphilis and who received ceftriaxone. In HIV infection, a 23% non-response rate to ceftriaxone was observed in one study in patients with latent syphilis with or without neurosyphilis[6]. MALONE *et al*.[18] described an 18% relapse rate in HIV+ individuals, with half of the cases having been treated with crystalline penicillin based on a positive VDRL in the CSF or pleocytosis. One of the questions raised is that intravenous penicillin may be ideal for the treatment of neurosyphilis or late syphilis, but that it may be suboptimal for the prevention of relapses. Although the issue is controversial, some investigators suggest adjuvant treatment with benzathine penicillin for three weeks, which is believed to act on the slowly multiplying microorganisms, thus avoiding relapses[13]. Relapses have also been related to secondary syphilis with rash or with a positive VDRL in the CSF, in most cases occurring after 12 months of treatment[10].

One (female) patient with a persistently high titer of VDRL after two years of follow-up may not have represented a case of active disease, but rather a delay in the humoral response, which can occur in HIV+ patients[17].

The majority of the cases in this series were from a cohort of HIV+ patients who were under regular clinical follow-up. However, four patients were previously ignorant of their HIV infection, thus highlighting the importance of performing HIV serology in all patients with syphilis. Syphilis constitutes an independent risk factor for HIV infection, and this risk appears to result from the break in the mucocutaneous barrier due to the presence of the genital ulcer[2].

This study demonstrated the importance of both establishing the diagnosis of neurosyphilis in patients with HIV infection as well as continued follow-up after treatment of syphilis. However, future studies should be conducted to standardize criteria for neurosyphilis as well as alternative therapeutic regimens for this disease in HIV+ individuals. Likewise, educational measures for the prevention of syphilis should be constantly reinforced in the sexually active population, without overlooking HIV patients under follow-up.

RESUMO

Características clínicas e evolutivas da sífilis em 24 indivíduos HIV+ no Rio de Janeiro, Brasil

Foram tratados 24 indivíduos com sífilis e infecção pelo HIV, de Março de 1997 a Janeiro de 2003, no ambulatório de Dermatologia Infecciosa do Instituto de Pesquisa Clínica Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brasil. Foram 20 homens (83,3%) e quatro mulheres (16,7%) com idade média de 38,04 anos e contagem média de linfócitos T CD4 de 389,5 céls/mm^3. A sífilis foi classificada como secundária em 16 pacientes (62,5%), latente tardia em oito (33,3%) e terciária em uma paciente (4,2%). As manifestações de sífilis secundária foram de lesões cutâneas eritematopapulosas em regiões palmar e plantar em nove (37,5%), exantema papuloso em quatro (16,7%), alopecia em clareira em três (12,5%) e osteocondrite em um paciente (4,2%). A sífilis terciária apresentou-se como lesão verrucosa. Cinco pacientes (20,8%) apresentavam neurossífilis, sendo a cefaléia a única manifestação presente em dois pacientes. As drogas utilizadas foram penicilina benzatina, ceftriaxone, eritromicina e penicilina. A cura ocorreu em 18 pacientes (75%). Seis pacientes (25%) foram retratados, sendo que três apresentavam história de re-exposição. Este estudo confirmou a importância de se estabelecer o diagnóstico de neurossífilis em pacientes com infecção pelo HIV, assim como de se realizar seguimento clínico e laboratorial após o tratamento da sífilis.

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