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SEROPREVALENCE OF HIV INFECTION IN PATIENTS WITH POSITIVE SYPHILIS SEROLOGY

SİFİLİZ SEROLOJİSİ POZİTİF HASTALARDA 'HIV' SEROPREVALANSI

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ABSTRACT

Objective: The aim of the study was to investigate Human Immunodeficiency Virus (HIV) seroprevalence in patients with positive syphilis serology.

Materials and methods: 105 (8.4%) samples, which were found positive with the rapid plasma reagin (RPR) and/or the Treponema pallidum hemagglutination assay (TPHA) tests, were also tested with the anti-HIV-1/2 quick test (INSTI HIV1/HIV2 Antibody Test, Bartel Inc. USA) for the detection of HIV, any sample that gave positive result, was submitted to enzyme linked immuno-sorbent assay (ELISA) (Behring Diagnostics, Marburg), and then western blot (WB) (HIV BLOT 2.2, Diagnostic Biotechnology Ltd. USA) as confirmatory test. The samples with positive results were also tested with the Serodia Treponema pallidum particle agglutination (TP.PA) (Serodia-TP.PA, Fujirebio Inc., Japan); the Murex Syphilis ICE (ICE), IgG+IgM (ELISA), (ICE Syphilis Detection Pack, Murex Biotech Limited, Dartford, UK); the Enzywell TP (TP), IgG+M (ELISA) (Diesse, Sienna, Italy); the Captia Syphilis-M (CS-M) (IgM) (ELISA) (Captia™Syphilis-M, Trinity Biotech plc, Ireland) and the fluorescent treponemal antibody absorption assay (FTA-abs) tests (Mastaflour™-FTA-ABS, Mast Diagnostics, UK) as other specific treponemal tests.

Results: Two RPR positive TPHA negative patient sera were found as HIV seropositive with the ELISA and WB tests. Additionally, in these samples all other specific tests as the TP.PA, ICE, TP, CS-M and the FTA-abs tests were found as negative. So, these two anti-HIV positive sera were evaluated as biologic false-positive (BFP) reaction of syphilis. Non of the sera with positive syphilis reaction was found as positive for anti-HIV reaction.

Conclusion: Because patients who have acquired a sexually transmissed disease (STD) have demonstrated their potential risk for acquiring HIV infection all patients with syphilis serology positive should be counseled concerning the risk of HIV.

Key words: Syphilis serology, HIV seroprevalence, BFP reaction.

ÖZET

Amaç: Sifiliz serolojisi pozitif sonuç veren hastalarda 'Human Immunodeficiency Virus' (HIV) seroprevalansının araştırılmasıdır.

Gereç ve yöntem: 'Rapid plasma reagin' (RPR) ve/veya 'Treponema pallidum hemagglutination assay' (TPHA) testleri ile pozitif sonuç vermiş 105 (%8,4) serum örneği, HIV-1/2 hızlı test (INSTI HIV1/HIV2 Antibody Test, Bartel Inc. USA) ile test edilmiş, pozitif sonuç veren serumlar ile 'enzyme linked immuno-sorbent assay' (ELISA) ve doğrulama testi olarak 'western blot' (WB) testleri yapılmıştır. Pozitif sonuç veren örnekler treponemal testler olan 'Serodia Treponema pallidum particle agglutination' (TP.PA) (Serodia-TP.PA, Fujirebio Inc., Japan); 'Murex Syphilis ICE' (ICE), IgG+IgM (ELISA), (ICE Syphilis Detection Pack, Murex Biotech Limited, Dartford, UK); 'Enzywell TP' (TP), IgG+M (ELISA) (Diesse, Sienna, Italy); 'Captia Syphilis-M' (CS-M) (IgM) (ELISA) (Captia™Syphilis-M, Trinity Biotech plc, Ireland) ve 'fluorescent treponemal antibody absorption assay' (FTA-abs) (Mastaflour™-FTA-ABS, Mast Diagnostics, UK) ile de test edilmiştir.

Bulgular: RPR testi pozitif ve TPHA negatif sonuç veren iki örnekte anti-HIV hem ELISA hem de WB testleri ile pozitif olarak saptanmıştır. Bu serumlar ile ayrıca yapılan TP.PA, ICE, TP, CS-M ve FTA-abs testleri de negatif so-

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nuç vermiştir ve RPR ile elde edilen pozitif sonuçlar, biyolojik yalancı pozitif (BYP-BFP) reaksiyon olarak değerlendirilmişlerdir. Sifiliz serolojisi pozitif olan hiçbir serum örneğinde anti-HIV antikorları saptanmamıştır.
Sonuç: Seksüel yolla bulaşan hastalığa (STD) sahip hastalar, aynı yolla bulaşan HIV infeksiyonunu kazanma riskini taşıdıkları için sifiliz serolojisi pozitif hastalar HIV riski yönünden araştırılmalıdır.
Anahtar kelimeler: Sifiliz serolojisi, HIV seroprevalansı, BYP-BFP reaksiyon.

INTRODUCTION

The incidence of syphilis has increased significantly during the last decade, along with that of other sexually transmitted diseases (STDs) that include Human Immunodeficiency Virus (HIV) (8,30,40). Syphilis as well as other genital ulcer diseases may increase the risk of the acquisition and transmission of HIV, but also individuals with non-ulcerative STD are at increased risk for acquiring HIV since risk factors for acquiring STDs are similar, coinfections are common (1,13,25,28). Nontreponemal serologic tests for syphilis measure antibodies against cardiolipin-lecithin-cholesterol antigens. Biologic false-positive (BFP) reactions may occur transiently because of acute febrile illnesses, pregnancy, or immunization while persistently false-positive tests have been associated with collagen vascular diseases, injecting drug use and other hypergammaglobulinemic states (12,31). An unusually high incidence of biologic false-positive test results of syphilis in patients with HIV infection has been discussed (2,9,20,21,33). Syphilis serologic tests may not be a sensitive marker of prior syphilis infection in individuals with HIV infection, and it has been reported that syphilis shows atypical clinical and serological courses in HIV infected patients. Also loss of reactivity to treponemal tests is reported to occur in up to 38% of symptomatic HIV seropositives while none of the HIV seronegative individuals lost reactivity to a treponemal test. The molecular basis of the antibody/antigen reactions is not yet known(11,18,32,34,36).

The main aim of the study was to investigate HIV seroprevalence in patients with positive syphilis serology. It was also to have in account the possibility of false-positive result for Rapid Plasma Reagin (RPR) test in anti-HIV positive patients.

MATERIALS and METHODS

Serum collection: 1246 sera from patients attended Department of Microbiology and Clinical Microbiology, Istanbul Faculty of Medicine, during the period 1997-1998 (April) have been screened. All sera were tested by the Rapid Plasma Reagin (RPR) (RPR carbon, Reactivos spinreact, Gerona) and the Treponema pallidum Hemagglutination Assay (TPHA) (Microsyph™-TP 200, Shield diagnostics, U.K.) for serodiagnosis of syphilis. All samples which have positive result with the RPR and/or TPHA tests were stored at –70∞C.

Tests: The RPR test was performed qualitatively. Typically, a quantitative TPHA is performed at a unique serum dilution of 1: 80. All reactive samples were subsequently tested to determine the end dilution titers by the 1: 10240. Additionally, all 105 serum samples which were positive with the RPR and/or TPHA tests were tested with anti-HIV-1/2 quick test (INSTI HIV1/HIV2 Antibody Test, Bartel Inc. USA), single use rapid assay for the detection of antibodies to Human Immunodeficiency Virus Type I and II (HIV-1/2). Any positive results were submitted to enzyme-linked immunosorbent assay (ELISA) (Behring Diagnostics, Marburg). The positive result of one sample was confirmed with Western Blot (WB) confirmatory test (HIV BLOT 2.2, Diagnostic Biotechnology Ltd. USA). It has been also tested further by the Serodia Treponema pallidum Particle Agglutination (TP.PA) (Serodia-TP.PA, Fujirebio Inc., Japan); the Murex Syphilis ICE (ICE), IgG+IgM enzyme immunosorbent assay (ELISA) (ICE Syphilis Detection Pack, Murex Biotech Limited, Dartford, UK); the Enzywell TP (TP), IgG+M (ELISA) (Diesse, Sienna, Italy); the Captia Syphilis-M (CS-M) (IgM) (ELISA) (Captia‘Syphilis-M, Trinity Biotech plc, Ireland), and the Fluoressent Treponemal Antibody absorption (FTA-abs) assay (Mastaflour‰-FTA-ABS, Mast Diagnostics, UK) which detects both IgG and IgM for the presence of antibodies reacting with specific Treponema pallidum antigens. All tests were performed and evaluated according to the manufacturers instructions. Additionally, just after the period, another patient serum with anti HIV (+) by ELISA and WB was also tested with the RPR, TPHA, TPPA, ICE, TP, CS-M, and FTA-abs tests for serodiagnosis of syphilis.

RESULTS

During the study period, 105 (8.4%) sera out of 1246 have been found positive with the RPR and/or TPHA tests. Thirty eight (36 %) of them were obtained from women, 67 (64 %) were from men. All these 105 sera were tested with Anti-HIV-1/2 quick test screening for serodiagnosis of acquired immunodeficiency syndrome (AIDS). Only one patient’s serum (0.95%) with the RPR test positive and the TPHA test negative was found as HIV seropositive with the ELISA and then with the WB tests. When this serum was investigated in detail, with the TPPA, ICE, TP, CS-M, FTA-abs tests for serodiagnosis of syphilis, it was found that all tests were negative. So RPR test result was concluded as biological false-positive (BFP) reaction (40). Just after this evalution, another patient’s serum with anti-HIV (+) by ELISA and WB tests was evaluated as BFP reaction, because of positive RPR but negative TPHA, TPPA, ICE, TP, CS-M, FTA-abs tests results. All together, two anti-HIV positive sera were found as BFP. These two patients were heterosexual man and had clinical manifestation of AIDS who were on treatment.

DISCUSSION

Treponema pallidum and HIV are both sexually transmitted agents of infectious diseases with epidemiological similarities, and therefore co-infect the same host (26). The presence of genital ulcerative disease is also an important risk for the acquisition of HIV infection because of providing a possible portal of entry or exit for HIV (27,35). For women with genital ulcers, a 3.3-fold increase in the risk of acquiring HIV has been shown

in Kenya (19). In a study about correlation between syphilis and HIV infection, it is reported that whether the prevalence of lower genital tract infections among HIV-seropositive women's was higher than among high-risk HIV-seronegative women, and syphilis was more prevalent among HIV-seropositive women (8% vs. 6%) (4). The elevated risk of HIV-1 infection among patients with syphilis supports the hypotesis that syphilis enhances the sexual transmission of HIV-1 (24,29). In another study, in the summary of the experience with baseline STDs among high-risk youth with and without HIV infection from US, they screened for syphilis and found totally 28/334 (8.3%) HIV infected and 6/157 (5%) HIV uninfected adolescents (aged 12-19 years) by RPR or by history, as a result syphilis was more common among HIV infected than HIV uninfected (38). In another study in which 8932 cornea donors were screened, 103 (1.15%) had reactive screening for syphilis serology and 35 (0.39%) were HIV-1 seropositive. No donor with positive syphilis serology by the Venerial Disease Research Laboratory (VDRL) or RPR and FTA-abs or microhemagglutination-Treponema pallidum was also HIV-1 seropositive (10). Additionally, it is reported that, HIV-positive donors had an increased risk for being positive for syphilis antibodies (28). According to our results, poor correlation between positive syphilis serology and HIV seroprevalence has been found.

HIV infection may modify the clinical presentation (15), or course of syphilis (23). The relationship between HIV clinical disease stage and syphilis serology is unclear. The situation is further complicated by high VDRL titers in HIV patients leading to the prozone phenomenon (16). A study performed among 4863 patients, confirmed that BFP reactions are more common in HIV-positive patients, 4% versus 0.8% of HIV-uninfected patients (31).

HIV infection may affect the serological response to syphilis, which may be either enhanced or decreased (5,42). In a study, 5% of the samples gave false positive and high titer results with VDRL in HIV (+) males (7). In another study, it is reported that nonspecific screening methods, and perhaps even the specific treponemal tests, are not enough to exclude syphilis in HIV-infected individuals because of false-reactions, and suggest that to apply Western-blot to investigate the inconsistencies for syphilis (14). In another study, it is reported that in 7 cases both HIV and RPR were positive, but 5 of them were negative by FTA-abs, so 5(1.4%) were evaluated as BFP reaction (6). Additionally, it is reported that serological findings (both RPR and TPHA) may be altered in the presence of HIV infection (9).

It is concluded that the Captia Syphilis G enzyme immuno assay (EIA) were of similar specificity and sensitivity in HIV-positive patients as a marker of past syphilis in HIV infected patients (41). In our phenomenon, in two sera with HIV-positive RPR test was reactive, but TPHA and other treponemal tests done were non-reactive. This might account for nonspecific immunoglobulins that could react with the RPR test, or might diminished response of antibodies to various treponemal antigens. It is reported that non-specific screening methods, and perhaps even the specific treponemal tests are not enough to exclude syphilis in HIV-infected individuals (9). On the other hand, it is reported that, HIV-positive donors had an increased risk for being positive for syphilis antibodies (28). In a study, about correlation between syphilis and HIV infections of 8932 cornea donors screened, 103 (1.15%) had reactive screening for syphilis serology and 35 (0.39%) were HIV-1 seropositive. No donor with positive syphilis serology by VDRL or RPR and FTA-abs or microhemagglutination-Treponema pallidum was also HIV-1 seropositive (10).

According to our results, poor correlation between positive syphilis serology and HIV seroprevalence had been found. The main reason of this is that HIV seroprevalence was low in Turkey especially at that period when the study samples were collected. It is reported that anti-HIV seroprevalence was 0.001% in 1.773.943 donors between1987 and 2003 (17). Another reason may be that sera with positive syphilis serology were not collected from high-risky individuals for HIV, such as males who have engaged in homosexual activity and intravenous drug users. For example, there is a reported rate of 6% for anti-HIV1/2 in intravenous narcotic addicts (39).

In summary, all syphilis patients should be counseled concerning the risk of HIV because patients who have acquired an STD have demonstrated their potential risk for acquiring HIV infection. For that reason, it is recommended that all patients with syphilis positive sera have to be investigated for HIV and all patients who have HIV positive sera have to be investigated for syphilis (3,4,22,37).

REFERENCES

1. Assefa A, Rahlenbeck S, Molla K, Alemu S. Seroprevalence of HIV-1 and syphilis antibodies in blood donors in Gonder, Ethiopia, 1989-1993. J Acquir Immune Defic Syndr 1994; 7: 1282-1285.
2. Augenbraun MH, DeHovitz JA, Feldman J, Clarke L, Landesman S, Minkoff HM. 1994. Biological false-positive syphilis test results for women infected with human immunodeficiency virus. Clin Infect Dis 1994; 19: 1040-1044.
3. Cohen MS. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. Lancet 1998; 3515-3517.
4. Cu-Uvin S, Hogan JW, Warren D, Klein RS, Peipert J, Schuman P, Holmberg S, Anderson J, Schoenbaum E, Vlahov D, Mayer KH. Prevalence of lower genital tract infections among human immunodeficiency virus (HIV)-seropositive and high-risk HIV-seronegative women. HIV Epidemiology Research Study Group. Clin Infect Dis 1999; 29: 1145-1150.
5. Dada AJ, Ajayi AO, Diamondstone L, Quinn TC, Blattner WA, Biggar RJ. A serosurvey of Haemophilus ducreyi, syphilis, and herpes simplex virus type 2 and their association with human immunodeficiency virus among female sex workers in Lagos, Nigeria. Sex Transm Dis 1998; 25: 237-242.
6. Fermández Soncira MJ, Fajardo M, Mufloz Criado S, Nufloz Bellido JL, Garcia-Rodriguez JA. Relationship between HIV and syphilis in prisoners (abst no P835). p 201. In program and abstracts of the International Congress of Sexually Transmitted Diseases, 19-22 October, Sevilla-Spain,1997.
7. Flichman JC, Casiro A, Chuluyan JC. Serological response to Treponema pallidum infection among HIV positive and HIV negative. (abs no P817). p198. In program and abstracts of the International Congress of Sexually Transmitted Diseases, 19-22 October, Sevilla-Spain, 1997.
8. Fullilove RE, Fullilove MT, Bowser BP, Gross SA. Risk of sexually transmitted disease among black adolescent crack users in

Oakland and San Francisco, Calif. JAMA 1990; 263: 851-855.
9. Goeman J, Kivuvu M, Nzila N, Behets F, Edidi B, Gnaore E, Van Dyck E, St Louis M, Piot P, Laga M. Similar serological response to conventional therapy for syphilis among HIV-positive and HIV-negative women. Genitourin Med 1995; 71: 275-279.
10. Goldberg MA, Laycock KA, Kinard S, Wang H, Pepose JS. Poor correlation between reactive syphilis serology and human immunodeficiency virus testing among potential cornea donors. Am J Ophthalmol 1995; 119: 1-6.
11. Haas JS, Bolan G, Larsen SA, Clement MJ, Bacchetti P, Moss AR. Sensitivity of treponemal tests for detecting prior treated syphilis during human immunodeficiency virus infection. J Infect Dis 1990; 162: 862-866.
12. Hart G. Syphilis tests in diagnostic and therapeutic decision making. Ann Intern Med 1986; 104: 368-376.
13. Hook EW 3rd. Syphilis and HIV infection. J Infect Dis 1989; 160: 530-534.
14. Horvath I, Nagy K, Scythes J, Horvath A, Notenboom R. Syphilis serology in HIV patients. (abst no P828). p199. In program and abstracts of the International Congress of Sexually Transmitted Diseases, 19-22 October, Sevilla-Spain, 1997.
15. Hutchinson CM, Hook EW 3rd, Shepherd M, Verley J, Rompalo AM. Altered clinical presentation of early syphilis in patients with human immunodeficiency virus infection. Ann Intern Med 1994; 121: 94-100.
16. Johnson PD, Graves SR Stewart L, Warren R, Dwyer B, Lucas CR. Specific syphilis serological tests may become negative in HIV infection. AIDS. 1991; 5: 419-423.
17. Kocak N, Hepgul S, Ozbayburtlu S, Altınay H, Ozsoy MF, Kosan E, Aksu Y, Yilmaz G, Pahsa A. Trends in major transfusion-transmissible infections among blood donors over 17 years in Istanbul, Turkey. J Int Med Res 2004; 32: 671-675.
18. Koneman EW, Allen SD, Schreckenberger PC, Winn WC Jr. Color Atlas and Textbook of Diagnostic Microbiology, 5th ed. JB Lippincott, Philadelphia, 1997, pp 953-981.
19. Kreiss JK, Koech D, Plummer FA, Holmes KK, Lightfoote M, Piot P, Ronald AR, Ndinya-Achola JO, D'Costa LJ, Roberts P. AIDS virus infection in Nairobi prostitutes. Spread of the epidemic to East Africa. N Engl J Med 1986; 314: 414-418.
20. Linglof T. Rapid increase of syphilis and gonorrhea in parts of the former USSR. Sex Transm Dis 1995; 22: 160-161.
21. MacLean SK, Bordón J. False-positive rapid plasma reagin tests and anti-cardiolipin antibodies. J Infect Dis 1995; 172: 905-906.
22. Madge S, Elford J, Lipman MC, Mintz J, Johnson MA. Screening for sexually transmitted diseases in an HIV testing clinic; uptake and prevalence. Genitourin Med. 1996; 72: 347-351.
23. Nandwani R, Evans DT. Are you sure it's syphilis? A review of false positive serology. Int J STD AIDS 1995; 6: 241-48.
24. Orroth K, White RG, Bakker R, Changalucha J, Serwadda D, Habbema DJF, Hayes R, Gray R. Proportion of HIV infections attributable to sexually transmitted diseases in Mwanza and Rakai-Results based on a simulation model (abst no 0730). p264. In program and abstracts of the International Society for Sexually Transmitted Diseases Research Congress. July 27-30 Ottawa-Canada 2003.
25. Podwi_ska J. Syphilis and AIDS. Arch Immunol Ther Exp (Warsz). 1996; 44: 329-333.
26. Potterat JJ. Does syphilis facilitate sexual acquisition of HIV? JAMA. 1987; 258: 473-474.
27. Quinn TC, Cannon RO, Glasser D, Groseclose SL, Brathwaite WS, Fauci AS, Hook EW 3rd. The association of syphilis with risk of human immunodeficiency virus infection in patients attending sexually transmitted disease clinics. Arch Intern Med 1990; 150: 1297-1302.
28. Rahlenbeck SI, Yohannes G, Molla K, Reifen R, Assefa. Infection with HIV, syphilis and hepatitis B in Ethiopia: a survey in blood donors. Int J STD AIDS 1997; 8: 261-264.
29. Reynolds SJ, Risbud AR, Shepherd ME, Kulkarni SV, Rompalo AM, Bollinger RC, Mehendule SM. Primary syphilis, TP-HA seroconversion and the risk of HIV-1 infection in Pune, India (abst no 0554), p 200. In program and abstracts of the International Society for Sexually Transmitted Diseases Research Congress. July 27-30 Ottawa-Canada, 2003.
30. Rolfs RT, Nakashima AK. Epidemiology of primary and secondary syphilis in the United States, 1981 through 1989. JAMA 1990; 264: 1432-1437.
31. Rompalo AM, Cannon RO, Quinn TC, Hook EW 3rd.. Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. J Infect Dis 1992; 165: 1124-1126.
32. Rufli T. Syphilis and HIV infection. Dermatologica 1989; 179: 113-117 (Review).
33. Rusnak JM, Butzin C, McGlasson D, Blatt SP. False-positive rapid plasma reagin tests in human immunodeficiency virus infection and relationship to anti-cardiolipin antibody and serum immunoglobulin levels. J Infect Dis 1994; 169: 1356-1359.
34. Schofer H, Imhof M, Thoma-Greber E, Brockmeyer NH, Hartmann M, Gerken G, Pees HW, Rasokat H, Hartmann H, Sadri I, Emminger C, Stellbrink HJ, Baumgarten R, Plettenberg A. Active syphilis in HIV infection: a multicentre retrospective survey. The Germen AIDS Study Group (GASG). Genitourin Med 1996; 72: 176-181.
35. Stamm WE, Handsfield HH, Rompalo AM, Ashley RL, Roberts PL, Corey L. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. JAMA 1988; 260: 1429-1433.
36. Strobel M, Beauclair P, Lacave J. Seronegative syphilis in AIDS (letter). Presse Med 1989; 18: 1440.
37. Tramont EC. Syphilis in HIV-infected persons. In Volberding P, Jacobson MA, eds. AIDS Clin Rev, New York: Marcel Dekker, 1994, p. 61.
38. Vermund SH, Wilson CM, Rogers AS, Partlow C, Moscicki AB. Sexually transmitted infections among HIV infected and HIV uninfected high-risk youth in the REACH study. Reaching for Excellence in Adolescent Care and Health. J Adolesc Health 2001; 29:49-56. (Review).
39. Yenen OS, Badur S. Prevalence of antibodies to hepatitis C virus in blood donors and risk groups in Istanbul, Turkey. Eur J Clin Microbiol. Infect Dis 1991; 10: 93–94.
40. Yinnon AM, Coury-Doniger P, Polito R, Reichman RC. Serologic response to treatment of syphilis in patients with HIV infection. Arch Intern Med 1996; 156: 321-325.
41. Young H, Moyes A, Ross JD. Markers of past syphilis in HIV infection comparing Captia Syphilis G anti-treponemal IgG enzyme immunoassay with other treponemal antigen tests, Int J STD AIDS 1995; 6: 101-104.
42. Wagner HU, Van Dyck E, Roggen E, Nunn AJ, Kamali A, Schmid DS, Dobbins JG, Mulder DW. Seroprevalence and incidence of sexually transmitted diseases in a rural Ugandan population. Int J STD AIDS 1994; 5: 332-337.