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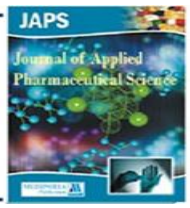

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Seroprevalence of Ig G and Ig M Antibodies in Individuals with Herpes Simplex Virus -1 &2 Infection in HIV Positive and Negative Individuals of South Indian Population

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ABSTRACT

The seroprevalence of HSV type 1 and 2 both in HIV positive and negative individuals of south India was studied. A comparative analysis was made to study the IgG and IgM antibodies to both types of HSV and the age and gender based distribution of HSV. IgG antibodies were more in HIV positive patients than the IgM antibodies. HSV-1 was more in HIV negative men and in HIV positive men, HSV was predominant than in women. Co infection with both HSV types was more in men. Either HSV-1 or 2 or both were predominant in HIV positive persons of 30 yrs or above than in those below 30 years. HIV negative patients showed high HSV-1 in the age group of 30 and above and high HSV-1 and 2 co infection was found in the age group below 30 yrs. HSV-2 was equally prevalent in both groups. This study helps in the earlier detection of HSV antibodies, which would be useful in immunoprophylaxis.

Keywords: Seroprevalence, Herpes Simplex Virus, HIV, Antibodies, South Indian Population.

INTRODUCTION

Herpes Simplex Virus (HSV) infection is known to be common, but estimates of its prevalence vary widely, depending on the patient population that is studied and the diagnostic methods used (Becker *et al.*, 1985; Johnsen *et al.*, 1990). Initial HSV-infection often occurs during childhood, with infection typically developing as a result of direct inoculation of infected droplets from orolabial or nasal secretion onto susceptible mucosal surfaces. HSV has a great impact on human health globally due to its high prevalence, successful sexual transmissibility rate, association with Immuno compromised patients, and ability to cause recurrent disease. Early studies used clinical history, viral cultures, and nonspecific antibody testing to determine the prevalence of infection, but this results in an underestimate of infected patients (Koutsky *et al.*,1992) Type-specific antibody testing allows accurate identification of persons infected with HSV-1 or HSV-2 (Ashley *et al.*,1988). Herpes Simplex Viruses are the most common cause of genital ulcer disease worldwide (Schomogyi *et al.*, 1998). Genital herpes is the most frequent sexually transmitted disease (STD) among persons seropositive for the human immunodeficiency virus (HIV) (O'Farrell *et al.*, 1994) and most persons seropositive for HSV type 2 (HSV-2) have an intermittent reactivation of the virus on mucosal surfaces (Augenbraun *et al.*, 1995; Schacker *et*

al., 1998). In addition, disruption of the epithelial barrier and inflammation of HSV genital ulcers appear to increase the risk of HIV transmission. Acute or reactivated HSV infection may stimulate HIV replication, leading to the progression of HIV disease (Heng *et al*., 1994). Studies to determine the seroprevalence of HSV have been conducted largely in several special populations (Nahmias *et al*., 1990; Kulhanjian *et al*., 1992; Siegel *et al*., 1992; Koutsky *et al*., 1990; Mele *et al*., 1988; Gibson *et al*., 1990). On the other hand, HIV-induced immunosuppression results in alterations in the natural history of HSV. More severe HSV outbreaks and more frequent viral shedding are common in persons coinfected with HIV and HSV compared with those without HIV infection. The treatment of HSV can be more challenging in HIV-infected patients.

Higher doses of antiviral drugs may be required, and persons infected with HIV have an increased incidence of acyclovir resistant HSV (Reyes *et al*., 1998). This appears unrelated to acyclovir exposure because resistance is found in patients with no previous exposure to acyclovir, and rates of acyclovir resistance are lower in patients taking suppressive doses of acyclovir compared with those receiving therapeutic doses of the drug (Barry *et al*.,1986; McLaren *et al*., 1983; Lehrman *et al*., 1986; Fife *et al*., 1994; Englund *et al*.,1990; Boivin *et al*., 1993). Worldwide incidence of HSV ranges from roughly 65% to 90% (Chayavichisilp *et al*., 2009). Because asymptomatic HSV-2 infections in HIV-positive persons may be associated with increased transmission of HIV and may accelerate the course of HIV disease, screening should generally be offered to patients with documented HIV and without a history of genital herpes. HSV-specific education and counseling should be provided for individuals with either HSV-2- negative or HSV-2-positive results, because HSV-2-negative, HIV-infected patients have a significantly increased risk of HSV-2 acquisition. In recent years number of sero assays have been established and introduced in the market, most of them being useful for screening of HSV (Louie *et al*., 2003; Saha *et al*., 2011). From 1990 lot of type specific assays were used for HSV screening, but those assays were unable to differentiate the HSV-1 and HSV-2 types (Bessong and Mathomu, 2010). The diagnosis of HSV presents a challenge for public health programmes and for clinicians in developing countries (Celum *et al*., 2004).

In this paper we have reported the prevalence of HSV-1 and HSV-2 in both HIV infected and uninfected individuals of South India.

MATERIALS AND METHODS

Study population

A total of 70 sera samples were included in this study. All those samples were collected in HIV and Tuberculosis clinics of the Tuberculosis Research Center and its peripheral units located at the Government Hospital for Thoracic Medicine, Tambaram, and the Government General Hospital,Chennai, Tamilnadu. Pre-test counseling was done and informed consent was obtained from all the HIV screened individuals. Out of 70 samples 35 were HIV positive and 35 were HIV negative, all with tuberculosis. The Institutional Review Board of the Tuberculosis Research Center approved the study and patients gave written informed consent for participation.

Serologic Testing

70 serum samples were tested for IgG and IgM antibodies to HSV-1 and HSV-2 infection by using ELISA kits. Out of these, 35 were already tested to be positive for HIV and 35 were negative for HIV but all were positive for tuberculosis.

RESULTS

Demographics of the study population

Out of the 107 patients who initially were approached, 70% agreed to participate. Women refused to participate more frequently than did men (25% compared with 10%, respectively. No significant differences between those patients who agreed to participate and those who refused were noted with respect to Social influence, family status, religious, age, race, insurance status, or reason for the office visit.

Seroprevalence of herpes simplex virus antibodies

31 out of the 35 HIV positive samples and 32 out of the 35 HIV negative samples tested positive for HSV antibodies. In that 34.3% of both HIV positive and negative individuals were positive for HSV-1 IgM antibodies. 80% of HIV positive individuals and 71.4% of HIV negative individuals were positive for HSV-1 IgG antibodies. 28.6% of HIV positive individuals and 17.1% of HIV negative individuals were positive for HSV-2 IgM antibodies. 60% of HIV positive and 17.1% of HIV negative individuals was positive for HSV-2 IgG antibodies (Table 1).

Table 1. HSV antibodies status between the HIV positive and HIV negative individuals.

Assay Types	Antibodies	HIV Positive samples		HIV Negative samples	
		Number Of Positives	Percentage	Number Of Positives	Percentage
HSV-1	IgM	12	34.3	12	34.3
ELISA	IgG	28	80	25	71.4
HSV-2	IgM	10	28.6	6	17.1
ELISA	IgG	21	60	6	17.1

Table 2. Gender wise distribution of HSV.

S. No	Type of Infection	Male	Percentage (%)	Female	Percentage (%)
		HIV positive individuals			
1	HSV-1	3	9.7	3	9.7
2	HSV-2	2	6.5	1	3.2
3	HSV-1&2	13	42	9	29
		HIV negative individuals			
1	HSV-1	13	40.6	6	18.8
2	HSV-2	1	3.1	1	3.1
3	HSV-1&2	7	21.9	4	12.5

Gender and Age Wise Distribution of HSV

A total of 18 men and 13 women were found to be HSV positive. 21 men and 11 women were found to be HSV negative. Individual distribution of HSV types 1 and 2 antibodies in men and women are listed (Table 2) .The type specific distribution of HSV

is given in Table 3. Nineteen individuals from ≥ 30 age group and 12 individuals from <30 age group were HSV positive. 15 individuals from ≥ 30 age group and 17 individuals from <30 age group were found to be HSV positive (Table 3). HSV –Ig G antibodies are higher than HSV-IgM in both HIV positive and HIV negative individuals.

Table 3. Age wise distribution of HSV in HIV positive and negative samples.

S. No	Type of infection	Gender	Age	HIV positive		HIV negative	
				Total(n) Positive	Percentage	Total (n) Positive	Percentage
1	HSV-1	Male	<30	0	0	5	15.6
			≥30	3	9.7	8	25
		Female	<30	2	6.5	4	12.5
			≥30	1	3.2	2	6.3
2	HSV-2	Male	<30	0	0	0	0
			≥30	2	6.5	1	3.1
		Female	<30	1	3.2	1	3.1
			≥30	0	0	0	0
3	HSV-1&2	Male	<30	4	12.9	5	15.6
			≥30	9	29	2	6.3
		Female	<30	5	16.1	2	6.3
			≥30	4	12.9	2	6.3

DISCUSSION

Herpes simplex virus is quite common throughout the world (Malkin *et al*., 2002). HSV causes infection in oral as well as genital area in the lesion form. Non-genital infection such as common cold sores in oral area is caused by HSV-1 (Parkes *et al*., 1991). HSV-2 typically infects the genital area and is transmittted sexually or from mother to newborn (Xu *et al*., 2002). HSV has major relationship with HIV; particularly HSV-2 is co infected with HIV and this point was supported by most of the studies.

In this paper we have reported the prevalence of HSV-1 and HSV-2 in both HIV infected and uninfected individuals of South India. The relationship between HIV infection and HSV-2 infection is of particular importance as HSV-2 is the most common cause of genital ulcers in the developing countries (Celum, 2004). General HSV screening is not recommended because there is no recommended treatment for asymptomatic HSV-2 infections, only limited evidence at this time that risk- reduction counseling or antiviral herpes suppression significantly decreases transmission of HSV or acquisition of HIV. The purpose of screening for HSV-2 is not only to identify seropositivity, but to help seropositive people identify symptoms and protect themselves from acquiring HIV and protect their partners and seronegative people from acquiring HSV-2 and/or HIV.

Until recently no commercial assays were available for detection of HSV-2 specific antibodies in human serum. The availability of HSV-2 specific serological assays offer opportunity for clinical and peripheral diagnostic laboratories to confirm a clinical diagnosis of HSV-2 infection without using relatively time consuming and relatively expensive virus isolation methods (Groen *et al*., 1998; Clemens and Farhat, 2010). With respect to technical and economical expenses, type- specific ELISAs appear to be the most suitable for screening purposes, particularly when large patient collectives are to be tested (Eing *et al*., 2002; Kumarasamy *et al*., 2008). In recent years a number of seroassays based on glycoproteins for HSV-1 and 2 have been introduced in market, most of them have proved to be highly specific and sensitive for detection of HSV-1 and 2 antibodies. Recently rapid tests are also available for detection of HSV-1/2.

In the study we have employed qualitative ELISA technique for the type-specific HSV testing; seroprevalence of HSV-1 and 2 antibodies in TB patients with or without HIV was studied. Type-specific tests with HSV-1 and 2 IgG and IgM ELISA was performed on an age and sex stratified sample of 70 sera. The prompt diagnosis of HSV infection facilitates patients' management and possible initiation of anti retro viral treatment (Burrows *et al*., 2002). Data regarding the sero prevalence of HSV-1 and, more importantly HSV-2 have been obtained. The importance of HSV infection in the present study population is also reflected in the seroprevalence. In our study, it was found that 32 out of 35 HIV negative patients and 31 out of 35 HIV positive patients had HSV infection. HSV infection was comparatively more in HIV-negative persons than in HIV-positive persons. Similar results were obtained by Behets *et al*. (1999 b). It was reported by earlier studies that 83% of HIV-1 positive persons were positive to HSV1/2 infection in Northeastern South Africa. It was also seen that infection was more in the age group of 21-35 years (Bessong and Mathomu, 2010). This data shows that the transmission rate of HSV is high and that Herpes is a life long infection. But the presence of HSV-2 antibodies in HIV-negative individuals shows that they are at a high risk of acquiring HIV at some time in the future.

Earlier studies report that in congenital cataract persons 5.1% and 2.6% of study population were positive for IgM and IgG antibodies to HSV (Mahalakshmi *et al*., 2010). Our study showed a high prevalence rate of IgG than IgM antibodies to both HSV-1 and 2 in HIV positive patients. This suggests that antibodies to type-specific epitopes (for both gG1 and gG2) may be of particular value in immunoprophylaxis. The WHO estimated that there were 333 million infected with STDs (Arun, 2005). The high prevalence of HSV-1 and 2 antibodies irrespective of their HIV status clearly shows that most people are infected with some type of infection at least once in their lifetime. As most of them are asymptomatic during the initial stage, they remain undiagnosed for long periods of time or even throughout the life. The seroprevalence of IgG antibodies was more in HIV positive patients. HSV-1 was found to be high in HIV negative men; in HIV positive men HSV-2 was predominant than in women. Co infection with both HSV-1 and 2 was also high in men. Either HSV-1 or 2 or both 1 and 2 was predominant to HIV positive patients belonging to ≥ 30 yrs than in those below 30 yrs. HIV negative patients showed a high HSV-1 seroprevalence in age group ≥30 yrs and high HSV-1 and 2 co infection below 30 yrs. Prevalence rate of HSV-2 was equal in both age groups.

The AIDS Prevention and Control (APAC) project jointly undertaken by Voluntary Health Services (VHS) and US Agency for International Development (USAID) in a community of urban, rural adult population in Tamil Nadu state revealed that the prevalence of any STD in the study population was 15.8 percent

(Arun, 2005). HSV-2 infection being the most common STD, it is likely to be a co infection in HIV-positive patients, who are susceptible to almost all types of infection.

CONCLUSION

The present study leads to certain conclusions like infection by HSV was high in the study population and it was reflected in the seroprevalence. HSV infection was more in men than in women, particularly in those HIV-positive men belonging to ≥ 30 years of age. Infection by HSV-1 was more in HIV-negative persons of ≥ 30 years age group, and there was high HSV-1 and 2 co infections below 30 years. There is an association between infections by HIV and HSV-2, but the relationship is not yet clear. Programs for management of HIV infections should also address genital infections by HSV-2 and its transmission risk in the absence of ulcers. So detection of HSV infection in early stage is important to prevent HIV infection in future. The HIV negative patients who have tested positive for HSV-2 are in a high risk for acquisition of HIV. As HSV-2 is a risk factor for acquisition of HIV, early diagnosis of the seroprevalence of HSV-2 antigens is of prime importance. This would be of help in prevention of HIV infection to a certain level.

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REFERENCES

Arun R. Human Immunodeficiency Virus (HIV) and Sexually Transmitted Diseases (STDs). Indian Journal of Medical Research. 2005; 121:369-376.

Ashley RL, Militoni J, Lee F, Nahmias A, Corey L. Comparison of western blot and glycoprotein G-specific immunodot enzyme assay for detecting HSV-1 and HSV-2 antibodies in human sera. J Clin Microbiol. 1988; 26:662-667.

Augenbraun M, Feldman J, Chirgwin K. Increased genital shedding of herpes simplex virus type 2 in HIV-seropositive women. Ann Intern Med. 1995; 123:845-847.

Balfour HH. Herpes simplex virus resistant to acyclovir: a study in a tertiary care center. Ann Intern Med. 1990; 112:416-422.

Barry DW, Lehrman SN, Ellis MN. Clinical and laboratory experience with acyclovirresistant herpes viruses. J Antimicrob Chemother. 1986; 18(b):75-84.

Becker TM, Blount JH, Guinan ME. Genital herpes infections in private practice in the United States, 1966 to 1981. JAMA. 1985; 253:1601-1603.

Behets FMT, Brathwite AR, Hylton-Kong T, Chen CY, Hoffman I, Weiss JB, Morse SA, Dallabetta G, Cohen MS, Figueroa JP. Genital ulcers: etiology, clinical diagnosis and associated human immunodeficiency virus infection in Kingston Jamaica. Clinical infectious diseases. 1999 (b); 28:1086-90.

Bodo RE, Lars L, Eva UL, Wali H, Wolfgang Schlumberger, Katja Steinhagen and Joachim Ewald Kuhn. Evaluation of confirmatory strategies for detection of type-specific antibodies against Herpes Simplex Virus Type-2. Journal of clinical microbiology. 2002; 40: 407-413.

Boivin G, Erice A, Crane DD, Dunn DL, Balfour HH Jr. Acyclovir susceptibilities of herpes simplex virus strains isolated from solid organ transplant recipients after acyclovir or ganciclovir prophylaxis. Antimicrob Agents Chemother. 1993; 37:357-359.

Burrows J, Nitsche A, Bayly B, Walker E, Higgins G, Kok T. Detection and Sub typing of Herpes Simplex Virus in Clinical Samples by Light Cycler PCR, Enzyme Immunoassay and cell culture. BMC microbiology. 2002; 2:12

Celum CL, Levine R, Weaver M, Wald V. Genital herpes and human immuno deficiency virus: double trouble. Bulletin of the World Health Organization. 2004; 82: 447- 453.

Celum CL. The Interaction Between Herpes Simplex Virus and Human Immunodeficiency Virus. HERPES. 2004; 11: 36-45.

Chayavichitsilp P, Buckwalter JV, Krakowski AC, Friedlander SF. Herpes simplex. Pediatr Rev. 2009; 30(4):119-29.

Clemens SAC,Farhat CK. Seroprevalence os Herpes simplex 1-2 antibodies in Brazil.Rev. Saude Publica.2010; 44(4):1-8.

Englund JA, Zimmerman ME, Swierkosz EM, Goodman JL, Scholl DR, Balfour HH. Treatment of genital herpes simplex virus infection. Ann Intern Med. 1990; 112(6):416- 422.

Fife KH, Crumpacker CS, Mertz GJ, Hill EL, Boone GS. Recurrence and resistance patterns of herpes simplex virus following cessation of$6 years of chronic suppression with acyclovir: Acyclovir Study Group. J Infect Dis. 1994; 169:1338- 1341.

Gibson J, Hornung C, Alexander G, Lee F, Potts WA, Nahmias A. A cross sectional study of herpes simplex virus types 1 and 2 in college students: occurrence and determinants of infection. J Infect Dis. 1990; 162:306-312.

Groen J, Dijk GV, Niesters HGM, Meijden VD, Osterhaus DME. Comparison of two enzyme-Linked Immunosorbent Assays and one Rapid Immunoblot Assay for detection of Herpes Simplex Virus type 2-specific antibodies in serum. Journal of clinical microbiology. 1998; 36:845-847.

Heng MCY, Heng SY, Allen SG. Co-infection and synergy of human immunodeficiency virus-1 and herpes simplex virus-1. Lancet. 1994; 343:255-258.

Johnsen RE, Nahmias AJ, Magder LS, Lee FK, Brooks CA, Snowden CB. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. N Engl J Med. 1990; 321:7-12.

Koutsky L, Ashley R, Holmes K. The frequency of unrecognized type 2 herpes simplex virus infection among women. Sex Transm Dis. 1990; 17:90-94.

Koutsky LA, Stevens CE, Holmes KK. Underdiagnosis of genital herpes by current clinical and viral-isolation procedures. N Engl J Med. 1992; 326:1533-1539.

Kulhanjian J, Soroush V, An D. Identification of women at unsuspected risk of primary infection with herpes simplex virus type 2 during pregnancy. N Engl J Med. 1992; 326: 916-920.

Kumarasamy N, Balakrishnan P, Venkatesh KK, Srikrishnan AK, Cecelia AJ, Thamburaj E, Solomon S, Mayer KH. Prevalence and Incidence of Sexually Transmitted Infections among South Indians at Increased Risk of HIV Infection.AIDS Patient Care STDS. 2008; 22(8): 677–682.

Lehrman SN, Douglas JM, Corey L, Barry DW. Recurrent genital herpes and suppressive oral acyclovir therapy: relation between clinical outcome and in-vitro drug sensitivity. Ann Intern Med. 1986;104: 786-790.

Louie M, Hogan C, Di Mascio M. Determining the Relative Efficacy of Highly Active Antiretroviral Therapy. Journal of Infectious Diseases. 2003; 187: 896-900.

Mahalakshmi B, Therese KL, Devipriya U, Pushpalatha V, Margarita S, Madhavan HN. Infectious aetiology of congenital cataract based on TORCHES screening in a tertiary eye hospital in Chennai, Tamil Nadu, India. Indian J Med Res.2010; 131: 559-564.

Malkin JE, Morand P, Malvy D, Ly TD, Chanzy B, Labareyre C, Hasnaoui AE, Herberg S. Seroprevalence of HSV – 1 and HSV – 2 Infection in the General Population. Sex transm Infect. 2002; 78: 201-203.

McLaren C, Corey L, Dekket C, Barry DW. In vitro sensitivity to acyclovir in genital herpes simplex viruses from acyclovir-treated patients. J Infect Dis. 1983; 148:868-875.

Mele A, Franco E, Caprilli F. Genital herpes infection in outpatients attending a sexually transmitted disease clinic in Italy. Eur J Epidemiol. 1988; 4:386-388.

Nahmias A, Lee F, Beckman-Nahmias S. Sero-epidemiological and sociological patterns of herpes simplex virus infection in the world. Scand J Infect DisSuppl. 1990; 69: 19-36.

O'Farrell N, Tovey SJ. High cumulative incidence of genital herpes amongst HIV-1 seropositive heterosexuals in south London. Int J std AIDS. 1994; 5:415-418.

Parkes DL, Smith CM, Rose JM, Brandis J, Coates SR. Seroreactive Recombinant Herpes Simplex Virus type 2 – specific Glycoprotein G. Journal of clinical Microbiology. 1991; 29: 778-781

Reyes M, Graber J, Reeves W. Acyclovir-resistant HSV: preliminary results from a national surveillance system. Paper presented at: International Conference on Emerging Infectious Diseases; March 10, 1998; Atlanta, Ga.

SahaK , Firdaus R, Santra P, Pal J, Roy A,Bhattacharya MK,Chakrabarthi S, Sadhukhan PC.Recent pattern of co infections amongst HIV sero positive individuals in tertiary care hospital, Kolkata. Virology Journal. 2011;8:116-124.

Schacker T, Hu HL, Koelle DM. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons: a double-blind, placebo-controlled trial. Ann Intern Med. 1998; 128:21-28.

Schomogyi M, Wald A, Corey L. Herpes simplex virus-2 infection: an emerging disease. Infect Dis Clin North Am. 1998; 12:47-61.

Siegel D, Golden E, Washington AE. Prevalence and correlates of herpes simplex infections: the Population-Based AIDS in Multiethnic Neighborhoods Study. JAMA. 1992; 268: 1702-1708.

Xu F, Schillinger JA, Sternberg MR, Johnson RE, Lee FK, Nahmias AJ, Markowitzz LE. Seroprevalence and Co infection with Herpes Simplex Virus type 1 and type 2 in the United States, 1998-1994. The Journal of Infectious Diseases. 2002; 185: 1019-24.