

Association between the occurrence of herpes zoster and various type of cellular immunity disorders in HIV/AIDS patients

Lali Sharvadze, Tengiz Tsertsvadze, Nino Gochitashvili

Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi, Georgia

ABSTRACT

We have studied the association between the occurrence of Herpes Zoster and various type/severity of cellular immunity disorders in immunocompromised HIV/AIDS patients. Besides we assessed the relationship between disease (Herpes Zoster) severity, disease duration, associated postherpetic neuralgia and CD4 counts. A total of randomly selected 154 adult, antiretroviral treatment naive HIV infected patients were enrolled in the study. These 154 HIV patients were divided into 3 groups according the range of CD4+ T cell count. 51 HIV patients (40 male, 11 female) with CD4+T cell count $<200/\text{mm}^3$ (1st group), 49 HIV patients (41 male and 8 female) with CD4+T cell count $200-500/\text{mm}^3$ (2nd group) and 54 HIV patients (42 male and 12 female) with CD4+T cell count $>500/\text{mm}^3$ (3rd group). We found that incidence of Herpes Zoster in immunocompromised HIV/AIDS patients significantly was associated with decrease rate of cellular immunity. Direct correlation between incidence and decreased CD4+ counts revealed. The disease severity and duration was associated with immunodeficiency severity. Frequency of postherpetic neuralgia - the most devastative complication of herpes Zoster was also associated with decrease of CD4+ count.

KEYWORDS: *herpes zoster, CD+T cell, HIV/AIDS, cellular immunity*

Herpes zoster (shingles) is one of two distinctive manifestations of human infection with the varicella-zoster virus (VZV), the other being varicella (chickenpox). Chickenpox is the primary infection, whereas herpes zoster represents reactivation of a previous infection. It is estimated that more than 90% of the US population has serologic evidence of VZV infection and is consequently at risk for developing herpes zoster [7].

Chickenpox is a common and generally benign illness of childhood that is characterized by an exanthematous vesicular rash. After primary infection, the virus migrates along sensory nerve fibers to the satellite cells of dorsal root ganglia where it becomes dormant. This dormancy may be permanent, or the virus may become reactivated by conditions of decreased cellular immunity, resulting in Herpes Zoster (HZ) [1]. In case of insufficiency of human immune system (HIV infection/AIDS, oncological disease, persons receiving immunosuppressive therapy and persons with primary infection in utero or in early infancy) virus reactivation occurs [13,15,6].

The host immunologic mechanisms suppress replication of the virus. Reactivation can occur if host immune mechanisms are compromised.

Upon reactivation, the virus migrates down the sensory nerve to the skin, causing the characteristic painful dermatomal rash. After resolution, many individuals (up to 20% of patients) may continue to experience pain in the distribution of the rash (postherpetic neuralgia) [9].

In addition, reactivation of VZV infection can cause a spectrum of atypical presentations ranging from self-limited radicular pain without rash to spinal cord disease with weakness [1,7].

In the United States, as many as 10,000 hospitalizations and approximately 100 deaths occur per year as a result of complications from VZV infection. Morbidity and mortality affect mostly immunosuppressed individuals, including elderly persons.

The incidence of herpes zoster increases with age [5], with approximately 10 cases per 1000 persons in adults older than 75 years [7]. The lifetime risk of a first episode of herpes zoster ranges from 10% to 20%. It is estimated

that 50% of persons who live to the age of 85 years will ultimately develop herpes zoster [10,14].

The most prominent risk factors for herpes zoster development are age and cellular immunosuppression. The level of VZV-specific, cell-mediated immunity (CMI) naturally wanes with increasing age, which likely contributes to the high prevalence of herpes zoster in older adults [7,1,2].

The incidence of herpes zoster is approximately 15 times higher in HIV-positive persons than in HIV-negative persons [7,8]. Furthermore, in hematological malignancies such as Hodgkin's disease, as many as 25% of patients develop herpes zoster during their lifetime [15]. Organ and tissue transplant patients who are undergoing immunosuppressive therapy are also at high risk for developing herpes zoster [13].

Acute herpes zoster carries a significant public health burden. Of all patients diagnosed with acute herpes zoster, 45% report that they experience pain every day, 23% report that they experience pain the whole day, and 42% report that zoster-associated pain (ZAP) is "horrible" or "excruciating" [10]. The pain is so debilitating that patients, especially older adults, often need to be hospitalized. One study reported that the mean hospitalization rate for ZAP in patients 60 years and older is approximately 6 times higher than that seen in younger patients [4]. Furthermore, the mean length of stay for hospitalized herpes zoster patients is 12,7 days, with an estimated cost of \$12,834 per patient [11,12].

As mentioned above the Herpes Zoster and associated complications are the public health problem. It has been suggested that risk factors for Herpes Zoster are mainly cellular immunodeficiency conditions, however it need further investigations.

MATERIALS AND METHODS

We have studied the association between the occurrence of Herpes Zoster and various type/severity of cellular immunity disorders in immunocompromised patients. Besides we assessed the relationship between disease (Herpes Zoster) severity, disease duration, associated postherpetic neuralgia and CD4 counts.

A total of randomly selected 154 adult, antiretroviral treatment naïve HIV infected patients were enrolled in the study. These 154 HIV patients (123 male, 31 female) were divided into 3 groups according range of CD4+T cell count.

51 HIV patients (40 male, 11 female) with CD4+T cell count $<200/\text{mm}^3$ (1st group),

49 HIV patients (41 male and 8 female) with CD4+T cell count $200-500/\text{mm}^3$ (2nd group) and

54 HIV patients (42 male and 12 female) with CD4+T cell count $>500/\text{mm}^3$. (3rd group).

The range of patient's age was 23-55 years.

Clinical evaluation, laboratory diagnosis (HIV and Herpes Zoster), measurement of cellular (CD3, CD4, CD8, CD4/CD8, CD16, CD19 cells) and humoral (IgG, IgA, IgM) immunity, phagocyte activity of lymphocytes, circulated immune complexes were performed.

HIV infection was diagnosed by ELISA method and was confirmed by Western Blot and PCR method.

Herpes Zoster infection was diagnosed by clinical symptoms, by detection of Herpes Zoster specific IgM and IgG and for diagnosis central nervous system Herpes Zoster detection of nucleic acids in cerebrospinal fluid by Reverse Hybridization Assay (RHA) was performed.

Reverse Hybridization Assay (RHA) test principle: Parts of the viral genomes are amplified by PCR, and denatured biotinylated amplicons are hybridized with specific oligonucleotide probes, which are immobilized as parallel lines on membrane strips. After hybridization and stringent washing, streptavidin-conjugated alkaline phosphate is added and bound to any biotinylated hybrid previously formed. Incubation with BCIP/NBT chromogen yields in a purple precipitate and the results can be visually interpreted

ELISA principle: Solid phase enzyme-linked immunoassay (ELISA) based on the sandwich principle. The wells are coated with antigen. Specific antibodies of the sample binding to the antigen coated wells are detected by a secondary enzyme conjugated antibody specific for human IgM or IgG. After the substrate reaction the intensity of the color developed is proportional to the amount of IgM or IgG specific antibodies detected.

For the purpose of evaluation immune system we have studied various indices by the following methods:

1) Determination of lymphocytes and their subpopulation via monoclonal antibodies by immunofluorescent method.

For determination of percentages and absolute count of lymphocyte subpopulations specific markers were measured following the standard immunophenotyping technique. For this purpose the monoclonal antibodies reagents were used.

All samples were analyzed using a FACSCalibur flow cytometer (Becton Dickinson Immunocytometry Systems) with Cell Quest Pro software (Becton Dickinson Immunocytometry Systems) for data acquisition and analysis. Percentage and absolute count of cells expressing specific markers were measured by gating on lymphocyte populations in SSC/CD45 scatter.

Data for a minimum of 5,000 lymphocytes were acquired.

2) Determination of A, M, G-immunoglobulins in plasma was measured using standard turbidimetric assay. Detection kit were obtained from NPO "Sinteco" (Moscow, Russia).

Samples and controls were mixed with buffer solution and adequate Ig specific antiserum. As result of immunologic reaction immune complexes were formed, which level was depended on the level of Ig in analyses. Quantity of appropriate immunoglobulins was in direct proportion to absorbance of experimental samples in the 340 nm wavelength.

3) Determination of circular immune complexes (CIC).

Level of Circulating Immune Complexes was measured using standard turbidimetric assay. Serum immune complexes were determined using precipitation by polyethylene glycol (PEG) 6000 of definite concentration, by comparing emission intensity of samples (with PEG) and controls.

RESULTS AND DISCUSSION:

Herpes Zoster occurred at all stages of HIV/AIDS, but the rate of occurrence and disease severity was depended on CD4+ count.

Out of 154 HIV/AIDS patients (with various disorders of immune system) Herpes Zoster occurred in 31 cases. The total occurrence was 20,1%.

Among 1st group of patients with CD4+ count $<200/\text{mm}^3$, the Herpes Zoster was observed in 14 cases out of 51 (27%).

Out of 14 patients with Herpes Zoster: 4 (28,5%) patients had multidermatomal Herpes Zoster with visceral organ involvement (pneumonitis, hepatitis), 5 (35,7%) patients had multidermatomal Herpes Zoster without visceral involvement, 5 (35,7%) patients had HZ meningoencephalitis.

Out of 1st group 14 patients 7 (50%) had postherpetic neuralgia with 12 months duration of pain and 5 (35,7%) patients had recurrent Herpes Zoster.

The mean duration of rash was 17-18 days.

Among 2nd + group patients with CD4+ count $200-500/\text{mm}^3$ the Herpes Zoster was observed in 10 subjects out of 49 (20%).

Among 10 patients with Herpes Zoster: 1 (10%) patient had ocular Herpes Zoster, 2 (20%) patients multidermatomal Herpes Zoster with visceral organ involvement, 5 (50%) patients had disseminated multidermatomal Herpes Zoster without visceral involvement, 1 had (10%) HZ meningoencephalitis and 1 (10%) patient had monodermatomal herpes Zoster (mild disease).

Out of 2nd group 10 patients 3 (30%) had postherpetic neuralgia and 1 (10%) patient had recurrent Herpes Zoster.

The mean duration of rash was 15-days.

Among 3rd group patients with CD4+T cell count $>500/\text{mm}^3$ the Herpes Zoster was observed in 7 cases out of 54 (12,9%).

Out of 7 patient with Herpes Zoster: 4 (57%) patients had monodermatomal Herpes Zoster without dissemination

and visceral organ involvement, 2 (28,5%) had multidermatomal Herpes Zoster without visceral organ involvement, 1 patient had ocular Herpes Zoster.

The mean duration of rash was 7 days.

Out of 3rd group 7 patients only one (14%) had postherpetic neuralgia. None of them had CNS Herpes Zoster and recurrent Herpes Zoster.

There was no significant difference of occurrence Herpes Zoster among male and female patients.

We found that incidence of Herpes Zoster in immunocompromised HIV/AIDS patients significantly was

associated with decreased rate of cellular immunity. Direct correlation between incidence rate and decreasing of CD4+ counts revealed. The disease severity and duration also is associated with immunodeficiency severity.

The direct correlation between occurrences of Herpes Zoster and humoral immunological disorders was not revealed.

Post herpetic neuralgia-the most devastative complication of herpes Zoster is also associated with decrease of CD4+ count.

REFERENCES:

1. Arvin A. Aging, immunity, and the varicella-zoster virus. *N Engl J Med.* 2005; 352:2266-2267.
2. Cohen JI, Brunell PA, Straus SE: Recent advances in varicella-zoster virus infection. *Ann Intern Med* 1999 Jun 1; 130(11): 922-32.
3. Cohen JI: Varicella-zoster virus. *The virus. Infect Dis Clin North Am* 1996 Sep; 10(3): 457-68
4. Coplan P, Black S, Rojas C, et al. Incidence and hospitalization rates for varicella and herpes zoster before varicella vaccine introduction: a baseline assessment of the shifting epidemiology of varicella disease. *Pediatr Infect Dis J.* 2001;20:641-645.
5. Donahue J, Choo P, Manson J, R Platt. The incidence of herpes zoster. *Arch Intern Med.* 1995; 155:1605-1609.
6. Friedman-Kien AE, Lafleur FL, Gendler E, Hennessey NP, Montagna R, Halbert S, Rubinstein P, Krasinski K, Zang E, Poiesz B. Herpes zoster: a possible early clinical sign for development of acquired immunodeficiency syndrome in high-risk individuals *J Am Acad Dermatol.* 1986 Jun; 14(6):1023-8.
7. Gnann J, Whitley R. Herpes zoster. *N Engl J Med.* 2002; 347:340-346.
8. *JAIDS Journal of Acquired Immune Deficiency Syndromes: Volume 37(5) 15 December 2004*
9. Jung B, Johnson R, Griffin D, Dworkin R. Risk factors for postherpetic neuralgia in patients with herpes zoster. *Neurology.* 2004;62:1545-1551.
10. Katz J, Cooper E, Walther R, Sweeney E, Dworkin R. Acute pain in herpes zoster and its impact on health-related quality of life. *Clin Infect Dis.* 2004; 39:342-348.
11. Lin F, Hadler J. Epidemiology of primary varicella and herpes zoster hospitalizations: the pre-varicella vaccine era. *J Infect Dis.* 2000;181:1897-1905.
12. Macintyre C, Chu C, Burgess M. Use of hospitalization and pharmaceutical prescribing data to compare the prevaccination burden of varicella and herpes zoster in Australia. *Epidemiol Infect.* 2003; 131:675-682.
13. Schleupen E, Korting H, Nachbar F, Volkenandt M. Molecular evidence for the existence of disseminated zoster as a distinct entity in an immunosuppressed renal transplant patient. *J Mol Med.* 1995;73:525-528.
14. Schmader K. 2001. Herpes zoster in older adults. *Clinical Infectious Diseases*; 32:1481-1486.
15. Stankus S, Dlugopolski M, Packer D. Management of herpes zoster (shingles) and postherpetic neuralgia. *Am Fam Physician.* 2000;61:2437-2444.

Взаимосвязь между частотой заболеваемости герпес зостер и степенью нарушения клеточного иммунитета у больных ВИЧ/СПИДом

Лали Шарвадзе, Тенгиз Церцвадзе, Нино Гочиташвили

Центр Инфекционных Заболеваний, СПИДа и Клинической Иммунологии,

Тбилиси. Грузия

РЕЗЮМЕ

Цель исследования - оценка взаимосвязи между частотой заболеваемости герпес зостер и степенью нарушения клеточного иммунитета у иммунокомпрометированных больных со СПИДом. Обследовано 154 нелеченных ВИЧ-инфицированных больных, которые были подразделены на 3 группы. I группа – 51 больной с CD4<200 мм³; II – 49 больных с CD4 200-500 мм³; III группа – 54 больных с CD4>500 мм³. Число клеток CD4+T измеряли методом прямой иммунофлуоресценции с использованием проточной цитометрии. Установлено, что заболеваемость герпес зостер среди иммунокомпрометированных больных с ВИЧ/СПИДом в значительной степени связано с понижением клеточного иммунитета. Обнаружена положительная корреляция между частотой заболеваемости и понижением CD4+T. Частота постгерпетической невралгии, осложнения герпес зостер, также связано с понижением уровня CD4+T.

Ключевые слова: герпес зостер, CD4+T клетки, ВИЧ/СПИД, клеточный иммунитет