Predictive and diagnostic value of VZV infections in HIV patients: Clinical and laboratory cross-correlations between VZV and HIV infections

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Abstract

Background: People with healthy immune system can be exposed to certain viruses, bacteria, or parasites and have no reaction to them-but people living with HIV/AIDS can face serious health threats from what are known as "opportunistic" infections (OIs), including VZV , HSV and CMV. These infections are called "opportunistic" because they take advantage of their weakened immune system, and they can cause devastating illnesses. It is possible that we may have underestimated the association of opportunistic infections with subsequent VL elevation and CD4+T cell count decline. However, we already know that there is an association between people having had an opportunistic illness and short- and long-term effects on HIV RNA VL and CD4+ cell count.

Objectives: To assess the predictive and diagnostic value of VZV infections in HIV patients, the clinical and laboratory cross-correlations between VZV and HIV infections.

Patients/Methods: Two thousand one hundred eighteen (2118) HIV- positive patients were included in this study. These patients were hospitalized in a Specialized Infectious Disease Unit of "A. Sygros" Hospital from 1/1/1988 up to 31/12/2010 (over 23 years). They were classified based on demographic data (age, gender and source of infection) and characteristics of the VZV infection (history of the HZ infection, clinical picture of VZV after the diagnosis of HIV infection and recurrence rates). All these findings were correlated with CD4+ cell count and HIV RNA VL.

Results: Out of the 2118 HIV-positive patients, 317 patients (15%) presented with VZV (varicella or Herpes Zoster). The overall patients follow-up was 23 years (1.007, 33 person/years). Twenty-eight (28) patients of the 317 (8, 8%), had VZV history prior to HIV diagnosis. In 32 patients (~10%), relapses of VZV were referred. The primary attack of VZV and its relapses were associated with low levels of CD4+ cells (<100). However, the difference in counts of CD4+ between HZ first attack and its relapses was statistically borderline non-significant (p=0.051).

Conclusions: The VZV infection is associated mainly with progressed immuno-suppression. (Infection lowers CD4 count and the lower CD4 count means a weaker immune system.) This important finding shows the opportunistic character of VZV infections. Different opportunistic infections are associated, at their onset, with significantly different HIV RNA levels, regardless of CD4 count and ART.

Introduction

More than 95% of adults (aged >20 years) born in the United States have immunity to varicella, the vast majority due to primary VZV infection. Reactivation of latent VZV results in herpes zoster (or shingles). A person's lifetime risk for herpes zoster is 15% to 20%, with the highest incidence occurring in the elderly and immunocompromised individuals, like people taking immunosuppressive drugs, chemotherapy due to malignancy or having HIV. The incidence of herpes zoster is >15-fold higher for HIV-infected adults than for age-matched controls. Herpes zoster can occur in HIV-infected adults at any CD4 T lymphocyte (CD4) cell count, but frequency of disease is highest with CD4 counts of <200 cells/μL. Antiretroviral therapy (ART) has not been shown to reduce the incidence of herpes zoster in adult populations: in fact, rates appear to be higher in the period immediately after initiation of ART. Most herpes zoster-related complications in HIV-seropositive patients, including disseminated herpes zoster, recurrent, necrotic, hemorrhagic, bullous and systemic involvement, occur in patients with CD4 counts of <200 cells/μL. The CNS is the primary target organ for herpes zoster dissemination in patients co-infected with HIV. Various VZV-related neurologic syndromes occur in HIV-infected patients, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.

Sample and methods

The sample of our study, included HIV positive patients of the Specialized Infectious Disease Unit of "A. Sygros" Hospital, from 01/01/88 to 31/12/2010 (23 years). We have recorded 2118 seropositive individuals, of whom 317 developed VZV infection which manifested

as either Herpes Zoster (HZ), mainly, or varicella. We have studied the possible VZV history, the time of VZV appearance after diagnosis of HIV infection, the VZV forms (e.g. disseminated HZ, recurrent HZ, HZ encephalomyelitis, unilateral HZ involving multiple dermatomes), the CD4+ count and the HIV- RNA load, at the first attack of HZ and its relapse.

In similar studies, VZV infection in HIV positive patients is associated with underlying immunodeficiency. If you're beginning HIV testing or treatment, you'll learn to keep a sharp eye on your viral load and CD4 count. These two counts speak volumes about your HIV and immune system health. They alert the immune system to invading viruses (like VZV HSV, CMV) and bacteria. They provide important information on virus progression, therapy response, and help determine whether to begin HIV treatment.

Results

We have recorded 2118 HIV-positive patients that were hospitalized in a Specialized Infectious Disease Unit of "A. Sygros" Hospital from 1/1/1988 up to 31/12/2010 (over 23 years).

317 (15%) developed VZV infection after diagnosing HIV. 28 patients (8.8%) had VZV history. 32 patients (10.1%) developed VZV relapses and in 10 patients (3.15%), extensive VZV and persistent Herpes Zoster entered the diagnosis of HIV. In all these patients (317), the median time to onset of VZV was 3.26 years (Figure 1).

Out of the 317 with VZV, 275 (86, 7%) were men, and 42 (13, 3%) women. (p=0, 99)

272 were homosexuals or bisexuals (85.5%) and 45 heterosexuals (14.2%).

The mean age was 38.05 +/- 10.53 and the follow-up time for these patients ranged from 1-276 months.

98 of 317 HIV-positive people with VZV (31%) developed co-infection with HSV and CMV. 83 patients (84.7%) developed co-infection VZV with HSV and 11 patients (11.22%) co-infection VZV with CMV. 4 patients (4,08%) had all the 3 infections at the same period of time (Figure 2).

At the first attack of HZ, the average count of CD4+ lymphocytes was quite low (344.0 +/- 254.0), fluctuating widely between 1 cell/ml to 1412 cell/ml. The median count was 297.5. This fact proves that HZ is associated with serious immunodeficiency.

At the HZ relapses (32 individuals-10.1%), the average count of CD4+ was 253 +/- 178, 8 cell / ml. The median count was 205, 0 cell/ml. However, the difference in counts of CD4+ between HZ first attack and its relapse was statistically borderline non-significant (p=0.051), although the CD4+ count continued to decline in the following HZ relapses.

At the first HZ episode, the average value of HIV RNA VL was 136 200+/- 519 400, fluctuating widely between <20 to 6.000.000 copies/ml. The median value was 19.200.

At HZ relapse (32 individuals -10.1%), the average value of HIV RNA VL was 57.390 +/- 97.700, fluctuating again widely between <20
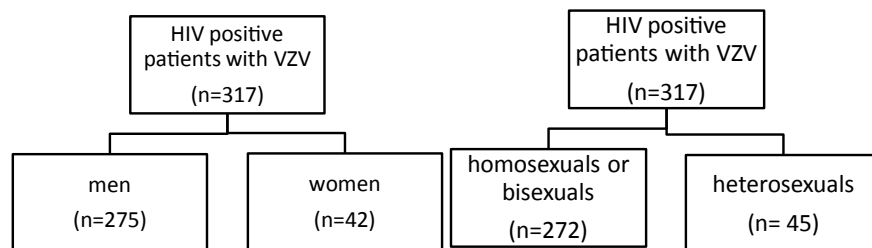

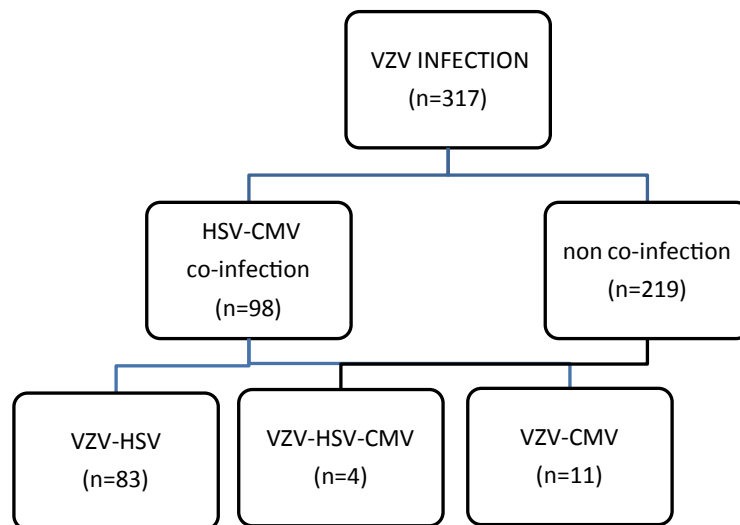**Figure 1.** Classification of HIV Positive patients.

Figure 2. HIV and Co-infections.

to 350,000 copies/ml. The median value was 5.300.

Discussion

Herpes zoster (HZ) is due to reactivation of latent varicella zoster virus (VZV), and can be a debilitating illness. Varicella-zoster virus (VZV), a neurotropic herpesvirus, is the causative agent of both varicella (chickenpox) and zoster (shingles). As with the other herpesviruses, VZV causes both acute illness and lifelong latency. Varicella usually is a benign and self-limiting illness, but can be more severe in elderly and in immunocompromised individuals, likely owing to impaired cell-mediated immunity. These individuals are at much higher risk of pneumonia and disseminated disease with visceral involvement. The incidence of HZ in the general population is around 0.15-0.33/100 person years with a higher incidence (0.5-0.9/person-years) in individuals aged 50 – 80 years.

HIV binds to CD4 receptors on helper T-lymphocytes, monocytes, macrophages and neural cells. CD4 cells migrate to the lymphoid tissue where the virus replicates and then infects new CD4-positive cells. As the infection progresses, depletion or impaired function of CD4 cells predisposes to the development of immune dysfunction. The success of antiretroviral therapy (ART, formerly highly active retroviral therapy, or HAART) has revolutionized the way we think about HIV infection. Far fewer patients now progress to AIDS, which - due to the stigma surrounding the diagnosis - is increasingly being known as late-stage HIV disease. The number of circulating viruses (viral load) predicts progression to late-stage HIV disease.

Scientific studies show that in immunocompetent individuals, the first event of Herpes Zoster alerts the cell-mediated immunity, preventing in this way from following relapses of the infection. However, in HIV-positive patients and in people with other immunodeficiency (like SLE, etc.), it has been observed increased incidence of HZ, disseminated HZ, recurrent HZ, HZ encephalomyelitis, unilateral HZ involving multiple dermatomes . According to a study of Kebo et al., in 282 episodes with HZ, 5% relapsed in the first six months and 10% during the 1st year, while the corresponding rate is 1% and 4% in the general population. Incidence of HZ increases with age, along with certain conditions that impair cell-mediated immunity.

In our study, we examined 2118 people for a period of 23 years (one of the largest in overtime study) and we found 317 patients (15%) that presented VZV infection after the diagnosis of HIV. 28 patients (8, 8%) had HZ history. In 10 patients (3, 15%) the HIV diagnosis was entered due to extensive or persistent HZ. After HIV diagnosis, the mean time of onset of HZ was 3, 26 years and the median age of patients was 38, 05+/-10,53 years.

Patients who have risk behaviors of HIV infection should receive regular surveillance for undiagnosed HIV infection when they present with herpes zoster. According to a study of Lai SW, Lin CL, Liao KF, Chen WC, that was published in J Formosa Med Assoc. 2016 May, they reached the same conclusion. Some studies have revealed that herpes zoster in areas with high prevalence of HIV infection has an approximately 90% positive predictive value for underlying HIV infection.

Of the 317 seropositive patients with VZV, 275 (86, 7%) were men, and 42 (13, 3%) women. (p=0, 99), whereas 272 were homosexuals or bisexuals (85.5%) and 45 heterosexuals (14.2%). Their median age was 38.05 +/- 10.53. The follow-up time for these patients ranged between 1-276 months (1.007,33 person-years).

98 of 317 HIV-positive people with VZV (31%) developed co-infection with HSV and CMV. 83 patients out of 98 (84.7%) developed co-infection VZV with HSV and 11 patients (11.22%) co-infection VZV with CMV. 4 patients (4.08%) had all the 3 infections at the same period of time.

CD4 cells, also called T-cells, are like the alarm bells of the immune system. They alert the immune system to invading viruses and bacteria. Certain receptors on the CD4 cell make them a prime target for HIV infection. Interactions between the viral envelope glycoprotein gp120 and the cell surface receptor CD4 are responsible for the entry of human immunodeficiency virus type 1 (HIV-1) into host cells in the vast majority of cases. HIV-1 replication is commonly followed by the disappearance or receptor down modulation of cell surface CD4. This potentially renders cells non susceptible to subsequent infection by HIV-1, as well as by other viruses that use CD4 as a portal of entry. Disappearance of CD4 from the cell surface is mediated by several different viral proteins that act at various stages through the course of the viral life cycle, and it occurs in T-cell lines, peripheral blood CD4+ lymphocytes, and monocytes of both primary and cell line origin. At the cell surface, gp120 itself and in the form of antigen-antibody complexes can trigger cellular pathways leading to CD4 internalization. Intracellularly, the mechanisms leading to CD4 down modulation by HIV-1 are multiple and complex; these include degradation of CD4 by Vpu, formation of intracellular complexes between CD4 and the envelope precursor gp160, and internalization by the Nef protein. Each of the above doubtless contributes to the ultimate depletion of cell surface CD4, although the relative contribution of each mechanism and the manner in which they interact remain to be definitively established. Infection lowers CD4 count. Lower CD4 count means a weaker immune system.

A normal CD4 count ranges from 500-1,000 cells/mm³. According to AIDS.gov, a count of fewer than 200 cells/mm³ is one of the qualifications for an AIDS diagnosis.

In our study, at the first HZ attack, the mean level of CD4 lymphocytes was quite low (344.0 +/- 254.0) with mean value 297.5, fluctuating widely between 1 cell/ml to 1412 cell/ml. This fact proves that Herpes Zoster episodes are associated with serious immunodeficiency. When HZ relapsed, in 32 individuals (10.1%), the mean CD4+ count was 253 +/- 178, 8 cell/ml. The median value was 205, 0 cell/ml. The CD4+ count between first appearance of VZV and its relapse was statistically marginally non-significant. (p=0.051). However, the CD4+ count continued to decline in the following HZ relapses. (CD4<100)

In similar studies, it was found that all opportunistic infections (varicella, HZ, relapses) were associated with a gradual decline of CD4+ cells. In a Margolick study, in 859 patients, after 18 months of monitoring, a reduction in CD4 7,6µ/ l per 6 months was observed. Low circulating CD4+ cell numbers and CD4 cell dysfunction are distinguishing features of HIV-mediated disease.

Viral load is the best gauge of the level of HIV in the body. It is measured as the number of copies of HIV-1 per milliliter of blood plasma (copies/mL). According to the U.S. Department of Health and Human Services (HRSA), the lowest levels of detectable viral load are about 40-75 copies/mL. The highest measure can be over 500,000 copies/mL.

Low viral load means lower amounts of HIV activity. The goal of HIV therapy is to lower the viral load to levels below 40-75 copies/ml. It's important to know that just because viral load may fall below these
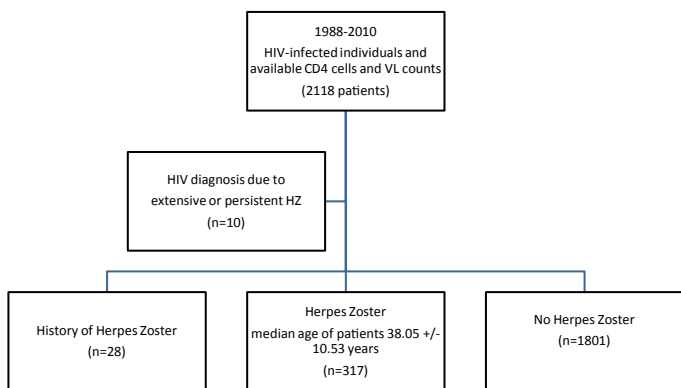
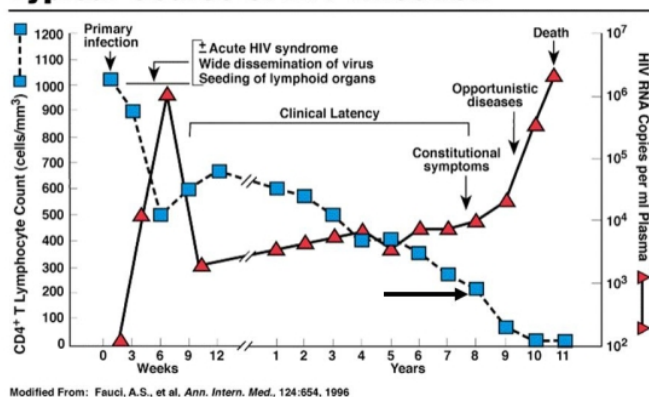**Figure 3.** VZV infection after the diagnosis of HIV.

Figure 4. Typical course of HIV infection.

levels, does not mean HIV is gone from the body.

In our study, at the first HZ attack the mean value of HIV RNA VL was 136 200 +/- 519 400 copies/ml, fluctuating widely between <20 to 6,000,000 copies/ml. The mean value was 19,200. When HZ relapsed, in 32 individuals (10.1%), the mean value of HIV RNA VL was 57.390 +/- 97.700 copies/ml, fluctuating between <20 up to 350,000 copies/ml. The median level of HIV RNA VL was 5.300 copies/ml (Figure 4).

The viral load (VL) is an independent risk factor for development of opportunistic infections. The data of several studies show a statistically significant correlation between different opportunistic infections and the HIV-RNA levels. This correlation was independent of CD4cell counts and the type of ART (therapy) [1-68].

According to our study, we should associate and adjust the antiviral therapy mainly according to the CD4 levels and not the Viral Load. CD4 count, the measure of immune system health, is the major factor in deciding whether to begin HIV therapy. Treatment guidelines recommend that therapy should begin when CD4 counts fall below 350 cells/mm³. Treatment may also be considered for patients with CD4 counts up to 500 cells/mm³ if they have a high viral load, or if they are experiencing a rapid drop in CD4 cell count.

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