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The role of cell mediated immunity in reactivation of latent Varicella-Zoster virus

***Zainab A. Tolaifeh[1] , Mohammed K. Alhattab[2], Habeeb S. Naher[3]**

[1]University of Babylon, College of Science for Women, Department of Biology/Iraq
[2]University of Babylon , College of Medicine, Department of Dermatology / Iraq
[3]University of Babylon , College of Medicine Department of Microbiology/ Iraq

Abstract : Background:Varicella-Zoster virus the same virus that causes chicken pox . After an attack of chickenpox (varicella), the virus lies dormant (asleep) in the nerve tissue. The cell mediated immunity plays a role in suppressing the virusand therefore a decline in this immunity allows the virus to resurface from latency.
Objective: An evaluation of function of some immune cells in patients with herpes zoster.
Methods: Fifty patients with herpes zoster attending Marjan Hospital in Babylon – Iraq, and thirty healthy control were subjected for this study. Serum samples were collected from patients and from healthy control. All samples were investigated for measuring the level of CD4,CD8 by ELISA to investigate their role in the immune-regulatory mechanisms involved in reactivation of latent VZV.
Results: There is significant rise in the levels of CD8 (21.42±5.43)ng/ml of shingles patients when compared with the healthy control group(19.11±3.29) ng/ml, while the levels of CD4 were significantly lower in patients (6.70± 0.97) ng/ml when compared with healthy control group (9.36±2.02) ng/ml.
Conclusions: CD4 cells have the main role in suppressing of VZV reactivation, and people with low CD4 counts have a higher risk than the general population.
Keywords : Varicella ,Herpes zoster, Latency, Cellular immunity.

Introduction:

Varicella –Zoster virus (VZV) is member of *herpesviridae* family, highly contagious, which infects most of world's people. It causes two clinically major infections: chicken pox (varicella) and shingles (herpes zoster)[1,2]

VZV causes primary infection as varicella, at which time latency is established in the neurons of the dorsal root ganglia or ganglia of the cranial nerves. Reactivation produces herpes zoster infection (HZ), commonly called shingles. [3]Varicella is resulted from first infection of Varicella zoster virus. In immunocompetent person, varicella is insignificant disease, with lesion development ending within seven days[4]. When immune reactions act to remove reproducing virus in varicella, but not all virus was cleared at this interval, with some supposed to contact nerve axons in a skin, enabling passage to neurons in sensory ganglia, where the virus is capable to create lifelong hidden infection [5].

VZV can reactivate in approximately 10 - 20% of cases, during life reasons shingles, also called zoster or herpes zoster[6,7].

VZV-specific cell mediated immunity may limit reactivation of latent VZV in sensory neurons and prevent the development of HZ by inhibiting the spread of VZV infection from these neurons. VZV-specific CD4+ and CD8+ T-cells are both involved, but CD4+ T-cells appear predominant[8]. The cell mediated immunity plays a role in suppressing the virus, and, therefore, a decline in this immunity allows the virus to resurface from latency [9,10].

With advancing age or immunosuppression, cell-mediated immunity to VZV declines and virus reactivates to cause shingles(herpes zoster) which is often complicated by chronic pain (postherpetic neuralgia), cranial nerve palsies, zoster paresis, meningoencephalitis and cerebellitis, myelopathy, vasculopathy and multiple ocular disorders. VZV reactivation also produces chronic radicular pain without rash (*zoster sine herpete*).

This relationship with age has been demonstrated in many countries,[11-14]and is attributed to the fact that cellular immunity declines as people grow older[15,16].

VZV-specific T-cell immunity is elicited by primary VZV infection and is required for the resolution of varicella. Memory CD4 and CD8 T cells that recognize VZV proteins remain readily detectable in younger adults, in whom herpes zoster is relatively rare . Strong memory-T-cell immunity to VZV may reflect either the extent of the initial expansion of VZV-specific T cells elicited during primary infection or periodic boosting on exposure to varicella or on abortive, subclinical reactivation[17-19].

Materials and Methods

Three ml of vinous blood were collected from studied group (fifty cases of herpes zoster infection were identified in patients admission to Marjan hospital in Babylon – Iraq, and about thirty healthy persons), the age of two groups range (14-80) years. Blood samples left in the room temperature at 30 minutes. Then serum was separated by centrifuge at the 4000 rpm for 5 minutes. The sera samples stored at -20c in deep freeze unit [20]until used for ELISA assay.

Enzyme Linked Immunosorbent Assay (ELISA) was used to evaluate the levels of CD4 and CD8 (Elabscience).

Results and Discussion

After primary infection, the immune response includes VZV-specific antibody and T cell-mediated immunity (CMI), which are important for recovery from varicella. T cell responses are essential to control latent VZV in the sensory ganglia. T-cell immune suppression is associated with worsened recurrent infection. A lack or a declining level of CMI to VZV has been associated with a higher risk of development of herpes zoster [21,22].Cellular immunity of the host is crucial in defense. Antibodies cannot reach viruses multiplying within cells. The herpesviruses utilize a great deal of cell-to-cell spread, which is why cellular immunity is critical for host defense against these viruses.

CD4 (cluster of differentiation 4) is a glycoprotein found on the surface of immune cells such as T helper cells, monocytes, macrophages, and dendritic cells. CD4+ T helper cells are white blood cells that are an essential part of the human immune system. They are often referred to as CD4 cells, T-helper cells or T4 cells. They are called helper cells because one of their main roles is to send signals to other types of immune cells, including CD8 killer cells, which then destroy the infectious particle.

If CD4 cells become depleted, for example in untreated HIV infection, or following immune suppression prior to a transplant, the body is left susceptible to a wide range of infections that it would otherwise have been able to fight. Shingles occurs commonly in HIV-infected patients and sometimes is the initial sign to the underlying immunodeficiency[23,24].

An increasing number of atypical presentations have been reported, demonstrating the wide spectrum of VZV-induced skin manifestations. These manifestations include acute herpes zoster, *zoster sine herpete*, chronic zoster, and disseminated zoster. The clinical polymorphism of herpes zoster reactivation may be dependent on the patient's age, variations in immune status, prior treatment, and VZV gene expression. Increased incidence of zoster has been described in patients with low CD4 cell counts[25,26]. Because of their

decreased cell-mediated immunity, immunocompromised patients are at an approximately 20-fold increased risk for zoster than age-matched control patients[27].

Immunocompromised patients may develop several episodes, atypical manifestations, or increased severity of herpes zoster [28]. Disseminated visceral disease, diffuse cutaneous dissemination, chronic hyperkeratotic skin lesions, acyclovir resistance, bullous ecthymatous zoster, lichenoid reactions, and follicular herpes zoster have been reported in immunocompromised persons[29-33].

Multidermatomal zoster in HIV-infected patients has been diagnosed at a lower CD4 level than zoster involving a single dermatome[34].

The activation of virus could be due to reduction of VZV-specific T-cells (CD4+T lymphocytes), that keep the virus latent and prevent the reactivation occur back with aging or in the causes of immune compromised[35].

T helper cell CD4 induced the production of pro- inflammatory cytokines which have role in acute phase of HZ infection such as IL-2, IL-6, IL-12 and INFα,γ[36].

In this study, we found that the mean± SD of serum level of CD4ng/ml in shingles patients and control group was (6.70± 0.97 and 9.36±2.02) ng/ml respectively. The results in figure **1** show a significant decrease ($p<0.01$) in serum level of CD4 of shingles patients group compared to serum level of CD4 in control group. This results agree with the results of study had been done by [37] which revealed a significant decrease in the percentage of CD4 lymphocytes in each patient group as compared with normal controls ($p < 0.01$).

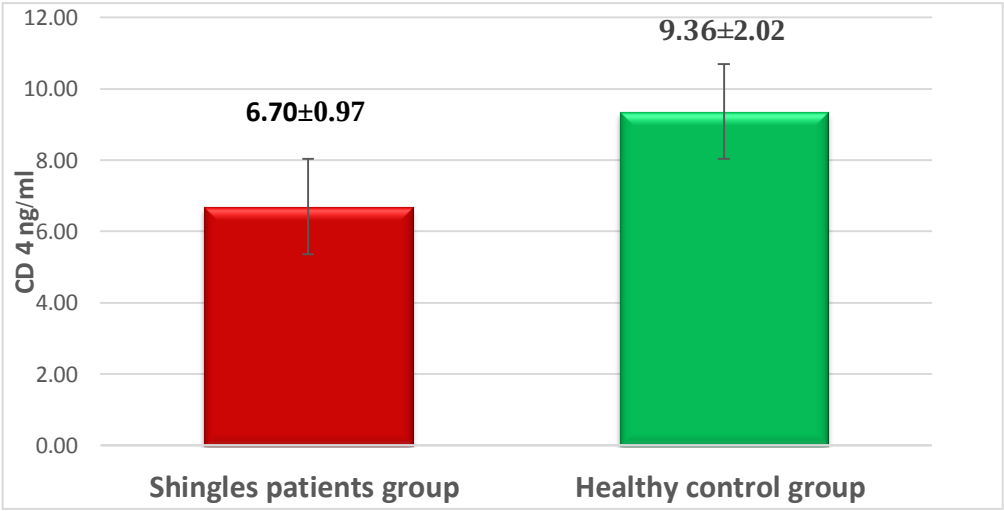


Figure 1: Distribution of patients and control by CD4 ng/ml.

Table (1): Effect of Varicella zoster virus infection on CD4 level in patients and control according to the age .

Age categories	Group	CD4ng /ml(Mean± SD)	P-value
1-20 year	Control	11.18±0.9	0.002*
	Patients	7.40±0.7	
21-40 year	Control	11.33±1.4	0.000*
	Patients	7.12±1.1	
41-60 year	Control	8.59±0.5	0.000*
	Patients	6.69±0.9	
61-80 year	Control	7.23±1.1	0.05*
	Patients	6.24± 0.7	

***significance (P ≤ 0.05)**

As shown in table **1**, the patients of age category (61-80) have low level of CD4 than other age categories.

Immunosenescence is the natural decline in T-cell function with age[38,39]. Advancing age with the accompanying decline in VZV responder T-cell frequency is the single most important factor influencing VZV reactivation in otherwise healthy individuals [40,41].

Even transient stress-induced immunosuppression[42] or trauma [43]can reactivate the VZV. Therefore, the most likely link between a waning immune system and shingles is a lack of virus clearance during episodes of virus reactivation.

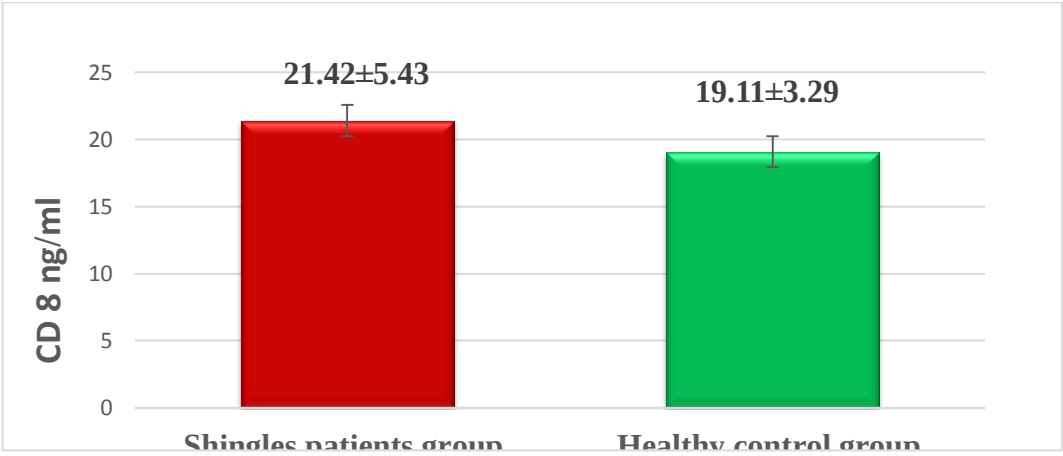
CD8 or cluster of differentiation 8 are transmembrane glycoproteins which assist as co receptors to T cells receptors. Similar to the (TCR), CD8 fixes to Major histocompatibility complex molecules, then was particular to MHC protein Class I[15]

The co receptors CD8 are principally uttered onto cytotoxic T cells however could too presented onto natural killer Cells , dendritic cells and cortical thymocytes.

CD8 cells act a vital function in virus elimination plus to CD4 which have role in both latent and activated form of virus[44]. Where these cells can recognize the mediated proteins that express by VZV during it latency in ganglion nerves for that cells mediated immunity (CMI) can limit the replication and spread of VZV with nerves and not to reactivation [45].

Several earlier studies differs among in their results about the effect of activated transcription factors and the role of their gene expression on the Th1 cells (CD4 and CD8 cells) during the infection of shingles, some of studies reported that Th1 cells decreased and it is assumed the shingles incidence, whereas other studies stated the reverse [46].

In this study, we found that the mean± SD of serum level of CD8 ng/ml in shingles patients and control group was (21.42±5.43 and19.11±3.29) ng/ml respectively. The results in figure **2** show the difference was statistically significant higher in patients than control ($p < 0.01$).



***significance (P < 0.01)**

Figure(2) Means difference of CD8ng/ ml level between shingles patients group and control group.

Table (2): Effect of Herpes virus infection on CD8 level in patients and control according to the age.

Age categories	Group	CD8ng /ml(Mean± SD)	P-value
1-20 year	Control	19.33±0.3	0.003*
	Patients	22.11±0.7	
21-40 year	Control	18.7±1.6	0.01*
	Patients	19.95±1.4	
41-60 year	Control	18.81±1.4	0.07
	Patients	22.38±8.1	
61-80 year	Control	20.80±5.7	0.07
	Patients	21.43± 2.9	

***significance (P ≤ 0.05)**

Shingles may be happen in people with normal or increased CD8 cells VZV develops many mechanisms to evade human immune system, either by remaining dormant into ganglia, thus limits an expression of proteins of virus . In that phase VZV does not duplicate however recalls the ability for return to infectious nature in some time, or by down regulating an expression of antigen of major histocompatibility complex class I onto the superficial of septic cell, indications reduction into superficial appearance of its proteins therefore limits the performance of viral peptides to Cytotoxic T cell that finally lead to emission from lysis through virus-infected cell.

In study done by[47] that revealed, patients with HIV who infected with shingles had a considerably larger Mean (+ / - SD) advance into CD8 cells number than healthy control.

Statistical Analysis

Data were analyzed statistically by using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).The normal distribution was conformed correlation analysis, independent t-test was used to estimate differences between two groups in continuous variable. Result are reported as mean and standard deviation (mean±SD) unless otherwise indicated. A p-value of ≤ 0.01 was considered as a lowest limit of significant[48].

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