Original Article

Herpes Zoster as a Useful Clinical Marker of Underlying Cell-mediated Immune Disorders[+]

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Abstract

Introduction: The objective of this study was to determine the necessity of further evaluation of patients presented with herpes zoster (HZ) to the Emergency Department for the underlying decreased cell-mediated immunity. Materials and Methods: The data of 132 adult patients presenting with HZ to the Emergency Department were collected from the computerised database of Akdeniz University Hospital. The following data were recorded: demographic data and underlying diseases during onset of HZ and laboratory results (white blood cell counts, blood glucose levels). Results: There were 132 patients with HZ in the study period. The mean age of patients was 52.98 ± 18.91 years (range, 14 to 96) and 53% (70 patients) were male. Of the study patients, 70.5% (93 patients) were over 45 years old. Eight (6.1%) patients had been diagnosed to have a malignancy, 18 (13.6%) had diabetes mellitus and 3 (2.3%) patients had undergone organ transplantation during their admission. Malignancy, diabetes mellitus and organ transplantation prevalence in the HZ group was significantly higher than the whole Emergency Department population. Conclusions: Our results indicate a relationship between the presence of HZ and increasing age and cell-mediated immunosuppressive disorders in Emergency Department patients over the age of 45 years. HZ should be considered as a clinical marker of cell-mediated immunosuppressive disorders, particularly in elderly patients.

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Key words: Cell-mediated immunity, Emergency department, Immunosuppression

Introduction

Herpes zoster (HZ) occurs when latent virus in the dorsal-root ganglia becomes reactivated and causes a vesicular and often painful rash with a dermatomal distribution. The rash may be followed by severe neuralgia that lasts for weeks or even months. An unknown triggering mechanism possibly caused by declining or impaired cell-mediated immunity results in a reactivation of zoster.[1]

The annualised incidence of HZ is about 1.5 to 3.0 cases per 1000 persons.[2,3] Increasing age is a key risk factor for the development of HZ. The incidence of HZ among persons older than 75 years old exceeds 10 cases per 1000 person years.[2] The other well defined risk factor for HZ is altered cell-mediated immunity. Patients with neoplastic diseases (especially lymphoproliferative cancers), those receiving immunosuppressive drugs (including corticosteroids), and organ-transplant recipients are under increased risk for HZ.[4]

HZ occurs frequently in immunocompromised patients, such as the elderly and those with lymphoproliferative malignancies, AIDS, diabetes and in transplant recipients.[2,5-10] Although HZ is referred as a predictor for suppressed cell-mediated immunity, the evidence is scarce. If it is a clinical marker of immunocompromisation, this should indicate the need for further research.

The objective of this study was to determine the necessity of further evaluation of patients presented with HZ to the Emergency Department (ED) for the underlying decreased cell-mediated immunity.

Materials and Methods

Patients

The data of all patients over 14 years old presented with HZ (ICD-10 codes B02.0-B02.9) to the ED from December 2001 to August 2005 were collected from the computerised database of Akdeniz University Hospital. One hundred and fifty-three thousand patients were admitted to the ED during the study period. There were 132 patients with HZ in the study period.

ED revisits with HZ were excluded. All charts were

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reviewed. The following data were recorded:

1. Demographic data (sex and age)
2. Underlying diseases during the onset of HZ
3. Laboratory results (white blood cell counts, blood glucose levels)

3a. A random plasma glucose at or above 200 mg/dL was accepted as high.

3b. An abnormal absolute neutrophil count value contains fewer than 1500 cells per mm^3.

The diagnosis of HZ was not based on diagnostic procedures. Patients were also categorised into 3 groups according to their ages: 14 to 45 years, 46 to 65 years and over 65 years.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows version 10.0. Two group comparisons for categorical variables were performed using chi-square. If one of the expected values was smaller than 5, Fisher's exact test was used. *P* values less than 0.05 were considered statistically significant.

Results

A total of 132 patients with HZ presented to the ED during the study period. The mean age of patients was 52.98 ± 18.91 years (range, 14 to 96) and 53% (70) were male (Table 1).

The most common affected anatomic site was the trunk (87 patients; 65.9%) followed by the face (27 patients; 20.4%) (Table 1). There was no statistically significant difference in the frequency of dermatomal distribution among the different age groups and between the cell mediated.

Of the study patients, 70.5% (93 patients) were over 45 years old. Past medical history revealed malignancy in 8 (6.1%), diabetes mellitus in 18 (13.6%), and organ transplantation in 3 (2.3%) patients. One hundred and fifty-three thousand patients were admitted to the ED during the study period. The prevalence of malignancy, organ transplantation and diabetes mellitus among the whole ED population during the study period was 1.83% (n = 2800), 0.25% (n = 382) and 1% (n = 1530), respectively. The prevalence of HZ was 0.86% (Table 2).

Malignancy, diabetes mellitus and organ transplantation prevalence in the HZ group was significantly higher than the whole ED population. Table 2 shows the prevalence in 2 groups – the HZ group and the whole ED population – and *P* values of 2 group comparisons (Table 2).

All diabetic patients who presented with HZ to the ED were over 45 years old except 1 and also the patients with malignancy were over 45 years old except 2. However, all the patients with transplantation were under 45 years old (Table 3).

Table 1. Demographic Data of Patients Presented with Herpes Zoster (HZ)

Variable	Patients with HZ – n (%)
Sex	
Male	70 (53)
Female	62 (47)
Age group (y)	
14-45	39 (29.5)
46-65	56 (42.5)
>65	37 (28)
Distribution of skin lesions	
Trunk	87 (65.9)
Face	27 (20.4)
Pelvis	8 (6.1)
Lower extremity	7 (5.3)
Upper extremity	3 (2.3)

Table 2. Study Population

	Patients with HZ 132 (%)	All emergency visits 153 (%)	*P*
Malignancy	8 (6.1%)	2800 (1.83%)	0.003
Diabetes	18 (13.6%)	1530 (1%)	0.000
Transplantation	3 (2.3%)	382 (0.25%)	0.005

HZ: herpes zoster

None of the patients diagnosed with immunocompromised diseases had neutropenia; however, 3 of the 18 diabetic patients (16.6%) had hyperglycaemia.

Discussion

Increasing age is a key risk factor for the development of HZ. The incidence of zoster among persons older than 75 years of age exceeds 10 cases per 1000 persons annually.[3] Similar to this data, majority of the HZ patients were over 45 years old (70.5%). The prevalence of immuno-compromised situation among patients with HZ was higher than the whole ED population admitted during the study period.

HZ is a clinical presentation of zoster virus seen more frequently in immunocompromised hosts (neoplastic diseases, especially lymphoproliferative cancers; receiving immunosuppressive drugs, including corticosteroids; organ-transplant recipients; and diabetics) than in the general population.[2-4]

The precise roles of humoral and cellular immunity in protection against HZ virus infection are controversial. However, cell-mediated immunity seems to be more important than humoral immunity, probably due to the

Table 3. The Distribution of Immunocompromised Patients with Herpes Zoster According to Their Age

Age (y)	14-45	46-65	>65	Total
Malignancy	2	2	4	8
Diabetes	1	10	7	18
Transplantation	3	0	0	3
Total	6	12	11	29

spread of virus within the body which is exclusively via the intracellular route.[11,12] T-lymphocyte subsets (CD3, CD4, and CD8 lymphocytes) in peripheral blood are parameters of cell-mediated immunity. There were slight increases in the percentages of CD4 lymphocytes (helper/inducer) and highly significant increases in the percentages of CD8 lymphocytes (suppressor/cytotoxic), resulting in marked decreases in CD4/CD8 ratios in the acute phase of HZ. The percentages of CD3 lymphocytes (pan-T lymphocytes) did not differ significantly.[13] The importance of cell-mediated immunity for clearance of primary infection, prevention of recurrent infections, and reactivation of infection has been shown indirectly by increasing risk for HZ associated with cellular immune dysfunction and with waning cellular immunity in the elderly.[14]

HZ infection is usually diagnosed clinically. The most common application of laboratory testing for HZ is to confirm fatal, severe or atypical illness. HZ virus can be identified in clinical materials by culture, or indirectly by polymerase chain reaction or rapid antigen tests based on immunofluorescence techniques.[15]

An association between neoplastic disease and HZ has been recognised since 1955.[16] HZ was proposed as a marker for internal malignancy, since it is often found in association with a malignancy. A critical review of the literature revealed that when HZ and malignancy occur in the same individual, rarely does HZ precede the malignancy, but it usually follows it.[17] HZ often occurs concomitantly with various internal malignancies, most commonly haematological in origin.[17-21] In this study, HZ occurred in 2 (25%) patients who had underlying malignancies with haematological origin.

In an in vitro study, Stentz et al[22] showed that patients with diabetic ketoacidosis and hyperglycaemia have increased proinflammatory cytokines and activated CD4+ and CD8+ T lymphocytes. The diabetic state, where effective insulin concentrations are low and both glucose and free fatty acids are high, provides an environment of oxidative stress and activation of the inflammatory pathways. The mechanisms underlying insulin action, in general, or in the CD4+ and CD8+ T-lymphocytes, in particular, have not been clearly elucidated. In our study, 3 of the 18 diabetic patients (16.6%) had hyperglycaemia.

On the other hand, the factors likely to affect the HZ prevalence in diabetic patients with normoglycaemic states should be investigated. Although Najdawi et al[23] reported the prevalence of HZ in diabetic patients as 6.9%, in the present study it was 1.2%. However, diabetes mellitus prevalence in the HZ group was significantly higher than malignancy and organ transplantation.

Conclusion

Our results indicate a relationship between the presence of HZ and increasing age and cell-mediated immunosuppressive disorders in ED patients over the age of 45 years old. Consequently, HZ should be considered as an indicator of cell-mediated immunosuppressive disorders, particularly in elderly patients.

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