Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.09.006

Evaluation of levels of (VZV IgG, IL 21, IL - 23 and PLG) among patients with shingle in Thi-Qar Province

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Submitted: 08 February 2023; Accepted: 22 March 2023; Published: 06 April 2023

ABSTRACT

With age, cell-mediated immunity is known to decrease as part of immunosenescence which renders old people more susceptible to cancer and previously encountered infectious diseases such as VZV, Eventually, older people are more susceptible to complications. This research reveals the level of interleukin profile (IL 21 and IL - 23) and assessed the level of VZV IgG antibodies and checking level PLG that reflect cell mediate and humoral immunities in patients with herpes zoster as an attempt to predict the complications of reactivation of the virus. According to the findings of this research, the titer of VZV IgG antibody and serum levels of cytokines IL-21 and IL-23 increased significantly in HZ patients compared to the control group, while HZ patients' plasma plasminogen levels dropped in comparison to the control group.

Keywords: *Herpes zoster, VZV, cytokines, plasminogen*

INTRODUCTION

Herpesviruses are among the most successful viruses in the human population and are exceptionally efficient in establishing persistent infections. The Varicella-zoster virus (VZV) is ubiquitous, highly contagious, highly infectious neuropathic human DNA alpha-herpesvirus which acts as causative agent for two clinically different diseases: chickenpox (varicella), acquired via the respiratory mucosa during primary infection and results in a secondary disease potentially life-threatening called herpes zoster (HZ), or shingles [1]. One in five people worldwide may contact VZV at some stage in their lives, and about one-third of those infected will go on to develop HZ [2]. Following chickenpox, the virus becomes latent in cells of the cranial nerve, dorsal root ganglia, and adrenal glands when adequate levels of VZV-specific T cells (CMI) and VZV-specific antibodies that sustain latency are present. The immunosuppression due to aging, infections (such as AIDS or COVID-19) cancer, or drugs, may reactivate VZV usually with spread of the along the sensory nerve to the dermatome resulting in HZ most often in the trunk or face [3]. VZV can also disseminate centrally, causing encephalopathy and myelopathy with or without the zoster rash. In the aged, it is more likely to cause post-herpetic neuralgia, vasculitis, renal, and gastrointestinal complications. Other risk factors for HZ, in addition to advanced age, include genetic predisposition, feminine sex, white ethnicity, physical or mental stress, and immunosuppression, HZ causes significant morbidity as age-dependent manner the incidence of HZ ranges from 1.2 to 3.4 per 1000 people per year in younger adults to 3.9-11.8 per

1000 people per year in patients who are elderly (i.e., those who are over 65) or those who have cancer. [4], worse than that, by the age of 14 years, 95 % of children were seropositive for VZV [5]Unfortunately, HZ reactivation has been listed as a potential side effect following COVID-19 immunization [1].Unknown immunologic mechanisms allow VZV to resist immune clearance, which regulates VZV delay. In addition to primary human perineurial cells, fetal lung fibroblasts, cerebral vascular adventitial fibroblasts, and vascular smooth muscle cells, VZV can infect a variety of other cell types and cause the release of a number of proinflammatory cytokines [6]. Herpes viruses are extremely common in humans, primarily because of their extraordinary capacity to modulate host immune responses, ability to establish life-long latency, and possessing a species-specific cytokine profile. [7]. The adaptive immune system has undergone numerous alterations, such as a decrease in naive T cells, an accumulation of terminally differentiated senescent T cells, changes in cell signaling, and metabolic abnormalities, and functional exhaustion, may occur due to the depressed cell-mediated immunity with ageing. These changes may all contribute to immune impairment in the elderly. [8]. Given the obvious clinical severity and complications of this disease, the need is great for biomarkers that contribute to early diagnosis, risk classification, and outcome prediction that will help elucidate the mechanisms underlying their clinical development. Consequently, to more accurately describe the pathogenic process in HZ patients this study aimed to assess the humeral and cellular immunity characteristics in HZ patients to get knowledge which might be facilitate the stimulation a T cells response by one or other cytokine phenotypes in elderly HZ patients.

METHODS

70 non superinfected. non immunosuppressant medication or steroid taking HZ patients that attended to Nassiriah governorate public and private clinics were recruited in this study. The control group comprised of 30 healthy individuals With similar age groups and free from infectious or inflammatory disorders. We evaluated the serum level of interleukins (21, and 23) in addition to the concentrations of PLG proteins and VZV IgG antibodies for both cohorts.

The patients' blood samples were taken on the day of their visit to the dermatologist clinic, which is typically at the start of the acute phase of the HZ. 5 ml of blood were drawn from a peripheral vein, put in a blood collection container with EDTA, and delivered as quickly as possible to the lab. Centrifuging the blood at 1000rpm for five minutes, and the serum plasma is collected and the stored at -8C till the analysis date. The research ethics committee board of Thi-Qar governorate health office approved this protocol. The informed consent was applied from all patients and controls group members For evaluation of different serum proteins ELISA tests were used: Antibodies (Abs) against VZV were quantified using an in-house enzyme-linked immune sorbent assay (ELISA). 96 well high-binding Costar® plates ELISA (IL 21, IL - 23) tests (Corning Inc., Kennebunk, ME USA) according to manufacturer’s instructions and results are reported in International Units (IU)/mL Plasma levels of Plasminogen (PLG) and were determined by ELISA .

RESULTS

from 1st September till end of December 2022, 70 patients presenting with HZ were included in the registry. The patients' median age was 51.9 ± 14.3 years. (range 15 – 82 years). 63% Patients over the age of 50 (44/70) of all patients, with (48.5%)34/70 being female. Between the HZ patients and control groups, the average age did not vary statistically significantly. A small percentage of patients had immune-declining diseases present at the time of testing, for example, diabetes mellitus in 15.7%, high blood pressure in 2.7%, bronchial asthma in 1.5%, or DM+BP in 1.5%. The thoracic area was where skin lesions were most frequently found (31%),, sacral to lumbar accounted for 18.3%; and 15.5% of cases respectively, HZ involved the area cervical, upper back and abdomen; as 12.7,11.3% and 7% respectively 2.8% of patients presented with HZ ocular lesion.

Cytokine profiles

Depending on clinical progress or exacerbation, the cytokine expression patterns in HZ patients changed. Comparing HZ patients to healthy controls, there was a substantial increase in the levels of circulating IL-23 and IL-21. The difference between the control group and patients with herpes zoster infection in terms of these cytokines' blood levels are shown in Fig. 1B,C, indicating that the production of these cytokines in the HZ group is significantly greater than that of the control group. In general, patients under the age of 50 had slightly greater levels of cytokines than patients over the age of 50.

IgG titer

In comparison to the control group, patients with herpes zoster had a considerably higher for VZV IgG antibody titer at($P<0.0001$) (Fig 1 A). As a result, the reactivation of the VZV and the appearance of the HZ lesions increased the number of antiviral antibodies.

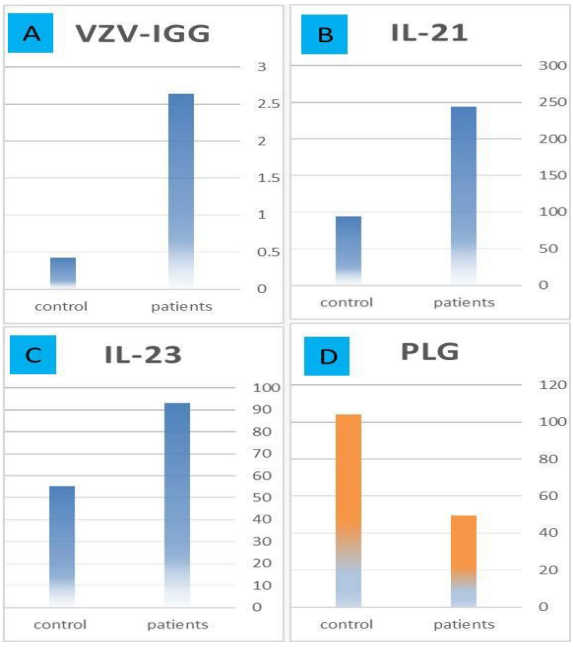


FIG 1: The mean values of (A)VZV IgG,(B) IL-21,(C) IL-23, and(D) PLG concentrations (pg/ml) in individuals with herpes zoster (n = 70) and control group n = 30, including x ±SD.

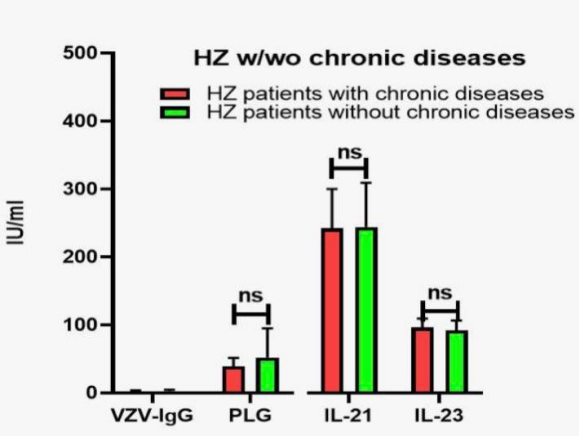
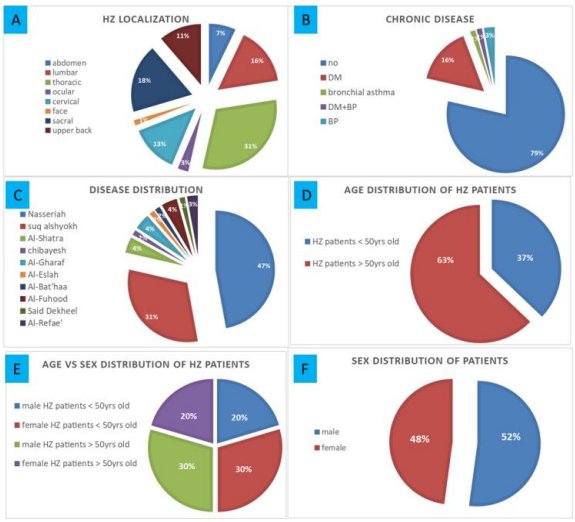


FIG 2: Cytokine concentrations in HZ patient and control serum). Concentration of individual cytokines composing (IL-21 and IL-23,). Graphs show median+ SD Individuals in patient and healthy groups are shown in red and green, respectively, and were grouped patients according to accompanying chronic diseases or not for this analysis. T-test. show p values n.s. not significant.

levels of PLG in patients with HZ

As a biomarker, PLG can be used to examine early HZ disease. As a result, we discovered that the expression levels of this protein compared to healthy controls, were noticeably lower. ($P < .05$)in Fig. 1D, while they were not significantly higher in HZ patients with chronic diseases in comparison to those without chronic diseases ($P >.05$, Fig. 2).



DISCUSSION

Whereas HZ is often mild in healthy young persons, it's sever in Those over the age of 65 whose level of VZV-specific cell mediated immunity is impaired (CMI) [4,5] so they are at increased risk for pain and complications may reach death. For that the most seropositive people by the time they reach puberty, will be at risk of HZ development which increases with age (particularly after 50 years of age) [5], to reach a 50% of who live to 85 years of age, up to 30% of them (especially unvaccinated persons) require hospitalization. VZV infections elicit serum specific antibody therefore, VZV IgG titer test, may be used to distinguish primary infection from reactivation or reinfection.[9]. In addition, the infection initiates specific helper and cytotoxic T cells that release cytokines, which recruit additional populations such as natural killer cells into the immune response[10]. Multiple age-related changes in repertoire of circulating HZ memory T cells have been identified in literature, but still little is known about memory T cells cytokine profile. Additionally, during infection, genes in the viral genome of herpes viruses generate a variety of cytokines and chemokine receptors. [11], to manipulate cellular chemotaxis in favor of the invasive viruses Consequently, it makes it more difficult to characterize cytokines in the context of herpes virus transmission. Characterizing cytokine, chemokine, and growth factor reactions at various phases of VZV infection may help with the creation of efficient immune-therapeutic treatments as well as vaccines. [12]. As in many of the results of previous studies [13,14,15] we obviously found significant increasing in all studied cytokine titer in HZ patients in comparison with control healthy cohorts. Our study showed that the amount of IL-21 reduced in the elderly (more than 50 years old) compared with the adults (less than 50 years), but the difference is not statistically significant. While other IL-23 did not fall with ageing. If we consider these cytokine may behave as a pro as well as an anti-inflammatory cytokine. So, they continue to be present at different ages of patients. The incidence of HZ increases with age, with an inflection point from age 50 to 80 years an average of occurrence 3 cases per 1,000 and 10 per 1,000 patient-years respectively [16]. We discovered that HZ most frequently affects the thoracic or lumbar nerve segments and the trigeminal nerve's distribution region, although other studies found ocular complications were the most common , such as [10]. Our findings revealed that the serum levels of these cytokines were significantly higher in HZ patients than in controls, confirming that humoral and cell-mediated immunity are both broadly activated during HZ. Additionally, this increase in the level of cytokines does not differ significantly depending on the patient's age or sex. Serum IL-21 and IL-23 levels were the highest of the cytokines we measured, and there was a noticeable variation between them. Age at the time of herpesvirus contraction has been proposed as a significant factor for the shaping of immune cells, and levels between patients may vary as a result. (2y versus 5y)[17]. Therefore, re-activation event of virus may depend on acute or persistent infections and age at time of primary herpesvirus infection. This in turn might affect the level of immune reactivity towards other infections or immune stimuli. as a regulator of the innate immune system, Plasminogen (PLG) encourages the phagocytosis of phagocytic cells. [18]. Therefore, it is hypothesized that as the body's immune system deteriorates, VZV will become reactivated and produce HZ. The researchers discovered that PLG proteins were significantly lower than those of healthy controls at ($P < .05$)[2], just as we discovered in our study. The information presented here may invite speculation that the order in which herpesvirus infections are acquired in early life could affect the outcome of infection.

CONCLUSION

both humeral and cell mediated immunity reactivate greatly with age against Herpes zoster virus

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