ORIGINAL ARTICLE

Status of immunity against PVB19 in HIV-infected patients according to CD4+ cell count, and antiretroviral therapy regimen groups

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ABSTRACT

Background: Human Parvovirus B19 (PVB19) is among the aetiology of aplastic crisis in human immunodeficiency virus (HIV)-infected patients. Several studies have indicated the importance of an infection agent in bringing about complications in immuno-compromised patients. The current study aims to determine the seroprevalence of IgM and IgG antibodies to PVB19 among HIV-positive patients and its association with clinical and epidemiological factors. **Materials and Methods:** In a case control study, 90 HIV-positive patients were compared with 90 sex and age matched healthy controls in terms of anti-PVB19 IgG and IgM along with other primary clinical and laboratory features. **Results:** The overall prevalence of positive anti-PVB19 IgG among HIV patients and controls were 81.1% and 28.9%, respectively ($P < 0.001$). None of the subjects showed positive results for anti-PVB19 IgM. Patients with $CD4^+$ cell count <200 showed higher seroprevalence of positive anti-PVB19 IgG which did not reach statistically significant. However, anti-PVB19 IgG seropositivity differed significantly between HIV patients on different regimens of antiretroviral therapy (ART) ($P < 0.05$). **Conclusion:** Immunity against PVB19 is more prevalent among HIV-positive patients compared to healthy controls. However, positive HIV status is not associated with acute PVB19 infection. The presence of anti-PVB19 IgG does not necessarily protect the body from further complications like anaemia. Given the results of the study, AIDS patients are recommended to undergo screening for parvovirus antibody in order to prevent complications like aplastic anaemia.

Key words: ART regimen, human immunodeficiency virus, immunity, parvovirus B19

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INTRODUCTION

Viral co-infections in human immunodeficiency virus (HIV)-positive patients and acquired immunodeficiency syndrome (AIDS) are the major health concerns worldwide. As a result of interaction between HIV status and other viral infections, changes in severity or the natural progress of both infections may occur. However, opportunistic infections are the leading cause of hospitalization and morbidity among HIV-positive patients lead to significant mortality in this population.[1-3]

As an aetiology for erythema infectiosum (fifth disease) in children, human parvovirus B19 (PVB19) primarily infects erythroid progenitors and could develop an aplastic crisis in patients already under haematological stress.[1-3] However, this does not confine to the red blood cells, as by gradual spreading, PVB19 infection may also cause other manifestations such as febrile arthropathy in adults.[4,5] The transient infective episode may resolve in patients who are otherwise healthy; however, in those suffering from impaired cellular and humoural immunity, persistent replication of the virus may ultimately lead to chronic aplasia of red blood cells.[6] Infection with HIV is an important cause for such a scenario.[3] On the other hand, haematopoiesis is impaired in HIV-positive patients due to chronic disease-related anaemia or administration of antiretroviral therapy (ART).[7,8] Although life-long immunity occurs following acute infection with PVB19, a sufficient immunity may not confer in immune-deficient HIV-positive patients.[9,10] In addition, of the many causes of anaemia in HIV-positive patients, infection with PVB19 is a treatable one.[11] Therefore, timely diagnosis of PVB19 infection could clinically benefit the patients. With respect to the epidemiological variation [12,13] and in regard to the

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limited number of studies performed in Iran, the present study was designed to determine the seroprevalence of anti-PVB19 IgG and IgM among HIV-infected Iranian patients.

MATERIALS AND METHODS

One hundred and eighty consecutive patients attending High-risk Behaviour Centre in Imam Hospital were included. Patients under the age of 15 years, with known malignancy, on corticosteroid regimen and pregnant women were excluded. Patients with confirmed diagnosis of HIV infection with western blotting, polymerase chain reaction (PCR) and serology testing were considered as the case group. Controls were sex- and age-matched healthy subjects with negative HIV test results. The study was conducted in a university hospital in Tehran, Iran, between January 2012 and September 2012. Research Ethics committee of the Tehran University of Medical Sciences approved the study protocol. Written informed consent was obtained from each participant before enrolment in the study.

Blood samples were obtained from the peripheral veins, then centrifuged and stored at −20°C. Enzyme-linked immunosorbent assay (ELISA) was performed using the EuroImmune Kit (Medizinisch Labordiagnostika AG, Germany) for the determination of serum levels of anti-PVB19 IgG and IgM. According to the manufacturer's instructions, the cut-off ratios were defined by extinction of calibrator 3. The ratio <0.8, 0.8 < ratio < 1.1 and ratio >1.1 were considered negative, borderline and positive, respectively. The upper reference limit of the assay to identify non-infected patients, recommended by EuroImmune, was 5 IU/ml. The lower limit of IgG and IgM anti-PVB19 were 0.1 IU/ml with a ratio of 0.1. $CD4^+$ and $CD8^+$ cell counts were also determined by flowcytometer (PARTEC, Japan) and haemoglobin level was measured using Sysmex-xt 1500 (Sysmex Corporation, Chuo-ku, Kobe, Japan).

Demographic characteristics and the clinicopathologic data including $CD4^+$ cell count, $CD8^+$ cell count, types of ART regimen, serum levels of haemoglobin and anti-PVB19 IgG and IgM were compared between the 2 groups. Statistical Package for the Social Sciences (SPSS; version 16, Chicago Inc., Illinois) was used for the analysis. Chi-square test was applied to compare the qualitative variables between the groups, while independent-sample t-test and one-way analysis of variance (ANOVA) were employed to analyze the quantitative variables. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Out of 180 subjects enrolled in this study, 90 were HIV positive (case group) and another 90 were healthy HIV-negative individuals (control group). The mean (SD) age of HIV-infected patients and controls were 37.20 (10.39) and 36.30 (10.21) years, respectively. Male/female ratio was 65/25 in the case group as compared with 63/27 in the control group. There was no significant difference between the 2 groups in terms of demographic characteristics ($P > 0.05$). Of 90 HIV-positive patients, 63 (70%) had AIDS and were receiving ART therapy including Protease Inhibitors (PI), Non- Nucleoside Reverse Transcriptase Inhibitors (NNRTI), and Nucleosidase Reverse Transcriptase Inhibitors (NRTI).

Positive anti-PVB19 IgG was presented in 81.1% of HIV patients and 28.9% of controls, with a statistically significant difference ($P < 0.001$). However, no positive serology for anti-PVB19 IgM levels was found in either group [Table 1]. Table 1 showed the positive, borderline and negative test results for anti-PVB19 IgG and IgM in the case and the control groups.

Table 2 represents the status of immunity against PVB19 in HIV-positive patients according to age, sex, $CD4^+$ cell count, $CD4^+/CD8^+$ ratio, haemoglobin level, transmission route of HIV-infection, and ART regimen. Of patients on NRTI+NNRTI regimen, 83.3% (40 patients) had positive anti-PVB19 IgG serology and 16.7% (8 patients) were sero-negative. Similarly, of those receiving NRTI regimen, 75% (3 patients) had positive serological test for anti-PVB19 IgG, while there was no negative test result. Also, all patients on NRTI+PI regimen had positive anti-PVB19 IgG result. It is apparent from Table 2 that anti-PVB19 IgG seropositivity differed significantly between different groups of ART Regimen ($P < 0.05$). However, IgG seropositivity did not show statistically significant differences between different categories of other parameters.

DISCUSSION

In this study, positive anti-PVB19 IgG was present in 81.1% of patients in the case group and 28.9% of patients in the control group with statistically significant difference ($P < 0.05$). However, anti-PVB19 IgM did not differ between the case and the control groups. Anti-PVB19

Table 1: Seroprevalence of anti-PVB19 IgG and IgM among HIV patients and controls

	Case group				Control group	*P*-value
	HIV positive	AIDS	*P*-value	Total		
IgG						
Positive	70.4%	85.7%	0.233	81.1%	28.9%	<0.001
Borderline	3.7%	1.6%		2.2%	0	
Negative	25.9%	12.7%		16.7%	71.1%	
IgM						
Positive	0	0	0.533	0	0	0.155
Borderline	3.7%	1.6%		2.2%	0	
Negative	96.3%	98.4%		97.8%	100%	

Table 2: Status of immunity against PVB19 in HIV-infected patients according to age, sex, $CD4^+$ cell count, $CD4^+/CD8^+$ ratio, haemoglobin level, transmission route and ART regimen groups

	IgG				
	Positive N (%)	Borderline N (%)	Negative N (%)	Total	*P*-Value
Age					
<30	12 (63.2%)	1 (5.3%)	6 (31.6%)	19	0.35
30-40	38 (88.4%)	1 (2.3%)	4 (9.3%)	43	
40-50	14 (82.4%)	0	3 (17.6%)	17	
>50	5 (71.4%)	0	2 (28.6%)	7	
Sex					
Female	21 (84%)	1 (4%)	3 (12%)	25	0.613
Male	52 (80%)	1 (1.5%)	12 (18.5%)	65	
$CD4^+$					
<200	27 (87.1%)	0	4 (12.9%)	31	0.292
200-300	17 (73.9%)	0	6 (26.1%)	23	
300-500	20 (80%)	2 (8%)	3 (12%)	25	
>500	9 (81.8%)	0	2 (18.2%)	11	
$CD4^+/CD8^+$					
<1	69 (81.2%)	2 (2.4%)	14 (16.5%)	85	0.926
≥1	4 (80%)	0	1 (20%)	5	
Haemoglobin level					
<12	5 (71.4%)	1 (14.3%)	1 (14.3%)	7	0.79
≥12	68 (81.9%)	1 (1.2%)	14 (16.9%)	83	
Route of Transmission					
IDU	41 (82%)	0	9 (18%)	50	0.227
Sexual	22 (81.5%)	1 (3.7%)	4 (14.8%)	27	
Blood Transfer	3 (100%)	0	0	3	
Maternal	0	0	1 (100%)	1	
Unknown	7 (77.8%)	1 (11.1%)	1 (11.1%)	9	
ART Regimen					
NRTI+NNRTI	40 (83.3%)	0	8 (16.7%)	48	0.001
NRTI	3 (75%)	1 (25%)	0	4	
NRTI+PI	11 (100%)	0	0	11	

IgG seropositivity differed significantly between different regimens of ART ($P < 0.05$). However, IgG seropositivity did not differ significantly between different categories of other parameters.

Taguchi *et al.*, compared the seroprevalence of anti-PV B19 antibodies between HIV-positive patients, haemophilic patients and healthy population.[13] Their results showed that 96% of the haemophilic patients were positive for anti-PVB19 IgG, while non-haemophilic HIV-infected subjects demonstrated a positive rate of 50%, similar to the healthy population. In our study, however, not only the overall prevalence of anti-PVB19 was higher among HIV (81.4%) patients, the lower frequency in healthy controls was also less as compared to that reported by other studies[4,11,13]. This could point to the fact that patients with worse health status in our study would be more probable to develop co-infections. Another controversy regarding seroprevalence of PVB19 in HIV-positive patients arise from the method used in detecting the infection. While some have performed the PCR technique in detecting the DNA of PVB19,[9] others have criticized that anti-PVB19 IgG could give a higher seropositive results[14] interfering with the reported prevalence of PVB19 infection in HIV-positive patients and even healthy control population. Vernazza *et al.*, by serological assays on 100 HIV-infected patients and 30 non-infected controls reported a prevalence of 81% and 57% for anti-PVB19 IgG positive serology, which is consistent with our findings.[14]

On the other hand, similar to what observed in this study, the prevalence of acute infection with PVB19 has been reported to be low[11,13] One reason for this could be the fact that most periodically activation of latent PVB19 infection may occur during spring or summer times[15] and when this outbreak does not occur the remainder immunity of HIV-positive patients can neutralize the activity of persistent PVB19 infection preventing further development of anaemia.[14] Van Elsacker-Neile showed that there was no difference, in terms of the seroprevalence of anti-PVB19, between HIV-positive patients and healthy controls, between those with different $CD4^+$ cell counts, nor between anaemic and non-anaemic patients.[12] After detection of PVB19 DNA in only two samples with positive results of IgG, they concluded that chronic infection with PVB19 should not be considered a cause for anaemia in HIV-positive patients. In line with the previous cohort by Vernazza *et al.*,[14] in our study, lower $CD4^+$ cell count was associated with higher seroprevalance of anti-PVB19, however it did not reach statistically significant.

Naides *et al.*,[10] showed that HIV patients receiving Zidovudin but not highly responsive to the therapy may suffer from anaemia due to the persistent PVB19 infection. This would be explained by considering the fact that, anti-PVB19 IgG antibodies are unable to neutralize the persistent infection which can lead to anaemia.[6] In our study, patients receiving NRTI had the lowest seroprevalence, while patients under NRTI+NNRTI or NRTI+PI followed the next order. To our knowledge, this is the first time that a comparison has been done between different groups of ART in terms of seroprevalence of anti-PVB19 IgG. Other reports have just recommended that protease inhibitors are better tolerated by patients and would be preferred in case of disturbing anaemia.[16] However, in another study by Verrenza *et al.*, no relationship has been found between patients treated with zidovudine and those not receiving treatment in terms of seroprevalence of PVB19.[14]

This study is among the largest ones investigating the seroprevalence of PVB19 in HIV-infected patients. However, some limitations should be taken into account before extrapolating interpretation of these findings. Of these, it is worthwhile to note that quantitative measurements of PVB19 DNA by PCR would help in detecting active infection and assessing the ability of the

IgG antibodies to neutralize the infection. Furthermore, it would benefit to distinguish between the aetiologies of anaemia, which was mild in this group of patients. Another limitation is the cross-sectional feature of our study that limits the extrapolating of its results. The observed difference between varying antiretroviral regimens in terms of anti-PVB19 IgG positive results should be investigated by future studies.

CONCLUSION

Seroprevalence of anti-PVB19 IgG is different between HIV-positives patients and healthy population. However, our study did not show different IgM-positive results, suggesting that, although immunity against PVB19 is more prevalent in HIV-positive patients, positive HIV status is not associated with acute PVB19 infection.

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