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Original Article

Prevalence and Factors Associated with Human Parvovirus B19 Infection in Sickle Cell Patients Hospitalized in Tanzania

Florence Urio[1,2], Humphrey George[1*], Furahini Tluway[2], Thomas B. Nyambo[1], Bruno P. Mmbando[2,3] and Julie Makani[2,4].

[1] Department of Biochemistry, Muhimbili University of Health and Allied Sciences, Dar es salaam, Tanzania.
[2] Sickle Cell Programme, Department of Haematology and Blood Transfusion, Muhimbili University of Health and Allied Sciences, Dar es salaam, Tanzania.
[3] National Institute for Medical Research, Tanga, Tanzania.
[4] Department of Haematology and Blood Transfusion, Muhimbili University of Health and Allied Sciences, Dar es salaam, Tanzania.
* Diseased

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Abstract. Background: The distribution of human parvovirus B19 (HPV B19) infection is ubiquitous and occurs worldwide. The virus has high tropism to red blood cells progenitor`s cells leading to temporary infection of bone marrow and transient arrest of erythropoiesis. People with frequent episodes of hemolytic anemia including sickle cell disease (SCD) and thalassemia are at increased risk of infection. This study aimed at assessing prevalence and factors associated with HPV B19 infections among hospitalized SCD patients.
Methodology: This was a cross-sectional hospital-based study among SCD patients hospitalized at Muhimbili National Hospital. HPV B19 was detected using RT-PCR. Hematological and Chemistry tests were done using Sysmex XT2000i and Chemistry analyzer respectively.
Results: A total of 329 SCD patients, median age 15 years (interquartile range 7-22 years) were tested for HPV B19. The prevalence of HPV B19 was 29%. In multivariate logistic regression model, HPV B19 infection was associated with pain (OR=4.28, 95%CI: 1.20–15.19; p=0.025), low neutrophil counts (OR=0.57, 95%CI: 0.35–0.92, p=0.022) and MCH (OR=0.92, 95%CI: 0.85–0.99; p=0.033). Individuals infected with HPV B19 had slightly higher prevalence of severe anaemia (30.4% vs. 20.3%, p=0.054) and HIV infection (6.0% vs. 2.1%, p=0.083) in the univariate analysis. Considering the effect of HPV B19 virus on spleen, aplastic anemia and platelet counts in SCD patients, our study did not find any association with these parameters (p=0.244; p= 0.205 and p=0.567 respectively).
Conclusion: The prevalence of HPV B19 among hospitalized SCD patients at MNH was high. SCD patients with HPV B19 were more likely to present with pain, low neutrophils levels, and MCH. HIV infection might be associated with a high risk of HPV infection in SCD patients; however, this requires further investigation.

Keywords: Human Parvovirus B19; Sickle cell disease; RT-PCR

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Correspondence to: Florence Urio, Department of Biochemistry and Sickle Cell Programme, Muhimbili University of Health and Allied Sciences P. O. Box 65001, Dar-es-Salaam, Tanzania. Phone: +255716894860 Email: flosu28@gmail.com

Background. Parvovirus B19 is a small, single-stranded DNA virus of family parvoviridae and genus Erythrovirus which shows tropism to bone marrow and has been implicated in erythema infectiosum and other hematological disorders.[1,2] The virus has high tropism towards red blood cells (RBCs) progenitors.[1-3] Sickle cell disease (SCD) patients are at high risk of infection due to an increase in RBC progenitor division; this is for compensating the deficiency of circulating RBC which is a common feature in SCD.[4]

Infection with human parvovirus B19 (HPV B19) is relatively common, mildly contagious, occurring sporadically or in epidemics. It has been estimated that the peak incidence of infection occurs in children between 6 and 14 years old. The most common route of transmission appears to be through respiratory droplets because HPV B19 DNA has been found in respiratory secretions at the time of viremia. Transmission is mostly common occurs by close contacts from person to person. The rate of transmission is almost 50% in household contact, but it varies from 10% to 60% in school and daycare exposure.[1]

HPV B19 is of interest because it causes transient aplastic anemia in SCD and is mostly associated with hemolytic disease.[5] HPV B19 is currently considered a disease of public health importance, particularly among patients with SCD. Prevalence of severe anemia in non-SCD patients with Parvovirus B19 has been reported previously to be 2.7% in Kenya and 30.2% in Papua New Guinea (PNG).[4,6] A prevalence of 23.3%, 27.3% and 32.1% in non SCD with aplastic anemia were also reported in Northern Nigeria, India and Brazil respectively.[5,7,8] However, a prevalence of 37.6% was reported in SCA population in Eastern Saudi Arabia.[1]

Several complications have been associated with HPV B19 like erythema infectiosum; arthropathy; transient aplastic crisis; chronic red cell aplasia; papular, purpuric eruptions on the hands and feet ("gloves and socks" syndrome); and hydrops fetalis. It is thus important that like many other diseases, HPV B19 should be clearly understood in its virology, pathogenesis, clinical manifestation, diagnosis, laboratory management, and its epidemiology for proper prevention and control. While there is adequate information from developed countries, there is currently no information on the prevalence of HPV B19 and its associated factors in SCD in Tanzania.

The present study aimed at assessing the prevalence of HPV B19 infection and associated factors among hospitalized SCD patients and its possible impact on hematological parameters, biochemical parameters [Alanine Aminotransferase (ALT), Aspartate transaminase (AST), Bilirubin (direct and total) and Lactate dehydrogenase (LDH)] and clinical parameters.

Methodology. *Study Area*. The study was conducted at Muhimbili National Hospital (MNH). MNH is a National referral hospital located in Dar es Salaam; it receives referral cases from all over Tanzania. About 4,000 cases of SCD patients are seen at MNH annually.[9]

Study Population. This was a nested study investigating factors associated with severe anemia among patients admitted at Muhimbili National Hospital.[10] The study population was hospitalized SCD patients with various complications between February and April 2016. Patient care and management for recruited study population is well described in the published protocol by Tluway et al.[10] Inclusion criteria were: 1) aged between 0-45 years 2) confirmed SCD-(SS/Sβ^{O}) by High-Performance Liquid Chromatography (HPLC), and 3) hospitalized at MNH during the study period. Patients on hydroxyurea, those who had received blood transfusion within the past four weeks and re-admission within the past four weeks were excluded from this study.[10] The study was granted ethical approval by Muhimbili University of Health and Allied Science (MUHAS) Institutional Review Board. This work was part of a study for the Master of Science in Biochemistry.

Laboratory procedures. Venous blood samples were collected from the antecubital or femoral vein in EDTA tubes. Hemoglobin level (g/dl), red blood cell (RBC) counts (x10^6/µl), mean cell volume (MCV) (fl), mean cell hemoglobin (MCH) (pg), reticulocyte count (%), white blood cell (WBC) count (x10^3/µl) and platelet counts(x10^3/µl) were determined by automated hematology analyzer (Sysmex XT 2000i Kobe, Japan). Whole blood was collected in serum tubes and was used for microbiology (HIV Test, which was performed according to the National HIV Rapid Test Algorithm and Parasitology), Alanine Aminotransferase (ALT), Aspartate transaminase (AST), Bilirubin (direct and total) and Lactate dehydrogenase (LDH) were done using a chemistry analyzer (Roche Cobas integral 400plus) and Malaria test was performed using Malaria rapid diagnostic kit.
Buffy coat was collected by spinning the EDTA blood at 3000rpm for 10 minutes, then were separated to obtain plasma and buffy coat and was stored in graduated cryopreserve tubes. The DNA extraction was performed with QIAamp DNA Min kits, (Germany), HPV B19 DNA viral detection was undertaken using in-house optimized TaqMan real-time PCR machine and primers designed for the study.

Data Analysis. Data were entered into a MySQL database and analyzed using STATA version 11 (Stata Corp, College Station, TX). Description of the study participants was summarized by proportions for categorical variables, while continuous variables were presented as means with standard deviations. The mean

differences of continuous variables between groups were compared using the independent t-test. Proportions were compared using the Chi-square test or the Fisher exact test. All estimates were presented within 95% confidence intervals, and p-value less than 0.05 was deemed significant.

Results. Three hundred and twenty-nine (329) hospitalized SCD patients fulfilled the inclusion criteria and were enrolled in the study; their median age was 14 years (IQR 7–22years). HPV B19 viral DNA was detected in 94 (28.6 %) patients of whom males were 51 (54.2%). The median age for hospitalized SCD patients with HPV B19 was 15 years (IQR; 7-22), and there was no statistically significant difference in HPV status within age groups.

Table 1A. Patients characteristics associated with Parvovirus B19 among hospitalized SCD patients (N=329).

Characteristics	Parvovirus B19		Test statistics (P-value)
	Positive: N = 94 N (%)	Negative: N = 235 N (%)	
Socio-demographic			
Sex (Male)	51 (54.2)	114 (48.5)	χ^2=0.886 (0.346)
Age group (years) (0-5 yrs)	16 (17.0)	47 (20.0)	χ^2=0.385 (0.535)
Clinical parameters			
Fever	50 (53.2)	111 (47.8)	χ^2=0.76 (0.382)
Pain	86 (91.5)	193 (83.2)	χ^2=3.735 (0.053)*
Severe anemia	28 (30.4)	46 (20.3)	χ^2=3.721 (0.054)*
Jaundice	7 (7.4)	21 (9.1)	χ^2=0.219 (0.639)
Pallor	88 (93.6)	206 (88.0)	χ^2=2.250 (0.134)
Malaria	3 (3.3)	18 (8.2)	χ^2=2.377 (0.123)
Spleen	8 (8.51)	12 (5.11)	χ^2=1.363 (0.244)
HIV Status	6 (6.0)	5 (2.1)	Exact test (0.083)

*Marginally significant

Table 1B. Patients characteristics associated with Parvovirus B19 among hospitalized SCD patients (N=329).

Characteristics	Parvovirus B19		Test statistics (P-value)
	Positive: N = 94 N (%)	Negative: N = 235 N (%)	
Biochemical parameters (Means±SD)			
Log (Lactase dehydrogenase (units/L))	6.37±0.55	6.38±0.60	t=0.148(0.883)
Log (Bilirubin direct (mg/dl))	2.29±0.91	2.28±0.86	t=0.055 (0.956)
Log (Total bilirubin (mg/dl))	3.16±1.02	3.21±0.87	t=0.409 (0.683)
Log (Alanine aminotransferase (units/L))	2.74±0.81	2.69±0.87	t=0.459 (0.647)
Log (Aspartate transaminase (units/L)	3.86±0.66	3.84±0.67	t=0.298 (0.766)
Hematological parameters (Means±SD)			
Log (White blood cells (x10^3/µl))	2.87±0.48	2.93±0.49	t=0.909 (0.364)
Log (Reticulocytes, %)	2.21±0.87	2.32±0.70	t=1.173 (0.242)
Log (Neutrophils, x10^9/µl)	2.12±0.77	2.29±0.66	t=1.827 (0.069)
Log (Lymphocytes, x10^9/µl)	1.52±0.77	1.62±0.79	t=0.869 (0.193)
Log (Platelets, x10^3/µl)	5.70±0.58	5.68±0.67	t=0.169 (0.567)
Hemoglobin, g/dl	6.03±2.04	6.36±1.53	t=1.590 (0.113)
Red blood cells, x10^6/µl	2.44±0.88	2.46±0.76	t=0.215 (0.415)
Mean cell hemoglobin, pg	25.35±4.83	26.28±4.09	t=1.640 (0.102)
Mean cell volume, fl	78.43±11.35	79.49±10.14	t=0.771 (0.441)

The **tables 1A** and **1B** show that pain (p=0.053), severe anemia (p=0.054), neutrophil counts (p=0.069) and HIV infection (p=0.083) are features that are marginally associated with HPV B19 infection. However, results from multivariate logistic regression model of variables with P<0.2 show that HPV B19 infection was associated with pain (OR=4.28, 95%CI: 1.20–15.19; p=0.025), neutrophil counts (OR=0.57, 95%CI: 0.35–0.92, p=0.022) and mean cell hemoglobin (OR=0.92, 95%CI: 0.85–0.99; p=0.033). Hemoglobin concentration, severe anemia (Hb<5g/dL) and HIV infections were not statistically associated with HPV B19 infections in the multivariate model, and these were excluded from the parsimonious model. Even though the HIV infection was non-significant in the multivariate model, the direction of effect was still positive (OR=1.75, 95%CI: 0.335–9.13, 0.507).

Discussion. In this study, the prevalence of HPV B19 among hospitalized SCD patients was 29%. We also found an association between HPV B19 with pain, severe anemia, HIV infection, mean cell hemoglobin, and neutrophil counts among hospitalized SCD patients.

The prevalence reported in this study is higher than that reported in Kenya (2.7%) from 264 hospitalized non-SCD children with severe anemia and 23.3% and 27.3% from non-SCD with aplastic anemia in Northern Nigeria and India respectively.[4,5,7] However, other studies reported a higher prevalence of HPV B19, 30.2% in non SCD with severe anemia in PNG, and 32.1% in Brazil.[6,11] Eastern Saudi Arabia reported a higher prevalence of HPV B19 37.6% in SCD patients compared to this study. The latter difference may be attributed to the different SCD haplotypes found in these two countries. Another reason may be due to the age group of study participants; our study had a wider range of age group from 0 to 45 years of age whereas other studies were conducted only to children less than five years. As expected, studies done on SCD population had mostly higher prevalence compared to those done in non-SCD population because SCD patients have frequent episodes of hemolytic anemia. The prevalence of HPV B19 reported in Kenya is much lower compared to other studies due to the small number of study participants.

We report no evidence of an association between the HPV B19 infection and age, although the trend indicated an increase in the risk of infection with increasing age; this is contrary to finding reported by Iwalokun et al.[12] Transmission of HPV B19 was reported to occur frequently in a school-age child.[13]

HPV B19 infection is known to induce acute splenic sequestration crisis (ASSC).[14] The risk of developing ASSC is mostly for infants and toddlers with SCD, who produce sickled red blood cells and have not yet developed splenic infarctions and organ complexities. In our study, we observed no association between HPV B19 and spleen size. Our study population had a majority of children between the ages of 11-20 years. Only 5% of children below five years had HPV B19 infection. The small sample size of children below five years could explain the lack of association between HPV B19 and spleen size. Patients with chronic hemolytic anemia such as SCD tend to have transient aplastic crises due to acute infection of HPV B19. They may have life-threatening anemia due to the shortened red cell survival.[15] Aplastic anemia has been shown to mainly affect the pediatric age group with the median age of onset of 8 years, and it is very rarely seen after the age of 15 years in SCD patients.[16] In this study, we did not find an association between HPV B19 with aplastic anemia. 7% of the HPV B19 positive SCD patients had aplastic anemia. The smaller sample size of the pediatric age group patients could explain the lack of association between these two parameters. We recommend further studies with larger sample size of pediatric age group SCD patients to evaluate this association.

This study found that HPV B19 was associated with low levels of neutrophil counts and severe anemia. However, in the multivariate model, the association was more evident with low levels of neutrophil counts and mean cell hemoglobin but not severe anemia. Our findings are similar to previous studies performed by Whitley et al., who conducted an epidemiological study of HPV B19 in children with SCD; he reported an association with low levels of neutrophils.[17] A study by Sakai et al. also suggested that HPV B19 virus may not have a direct effect on the low levels of neutrophils but which instead is due to secondary removal and consumption of leukocytes.[18] We did not observe an association between HPV B19 with platelets counts in SCD patients. This may be because leukocytopenia and thrombocytopenia sometimes do occur in addition to erythrocytopenia to patients with HPV B19.[19] Our study did not find a statistically significant difference in red blood cell count between HPV B19 positive and negative population. Wildig et al. conducted a study on SCD patients with HPV B19 and reported an association with hemoglobin.[6] We expected to find an association with hemoglobin due to the pathogenesis of the disease but did not find an association in this study.

Our findings showed that hospitalized SCD individuals with HIV infection are more likely to be infected with HPV B19. Although the association was not significant because of low statistical power, further investigation with a larger sample size is required to evaluate the association. It has been postulated that mechanism involved in the persistence of HPV B19 in HIV patients may be due to lack of production of anti-parvovirus antibody, possibly secondary to a basic defect in antigen presentation by the macrophages or by dysfunctional T cells.[20] Previous studies have shown persistent HPV B19 infection to be an important factor

in the development of chronic anemia in HIV-infected individuals.[21] There is a hypothesis that immune suppressed people with HPV B19 infection may be infectious for long periods;[21] however, there is limited information on this hypothesis, and hence, more research is required.

In our study, SCD patients with HPV B19 had more painful crises (4 times more) compared to those without HPV B19. At variance with the cases reported by Smith-Whitleyet et al.,[22] and by others,[23] the pain crises, in our circumstances, were not related to aplastic episodes and bone marrow necrosis.

This study has some limitation, including the exclusion of SCD patients on HU and those that were readmitted within the past four weeks. Including this group could have removed any bias and estimated the actual prevalence of HPV B19 in SCD patients. MNH is a national referral hospital where most patients are referred from peripheral facilities. Therefore, our study site may be a limitation, as most of these patients would have received interventions before reaching MNH.

Conclusions. This study has highlighted the prevalence of HPV B19 among hospitalized SCD patients at MNH. The prevalence was 29%. Further research is required to evaluate the clinical and laboratory factors on a larger study population. Furthermore, the prospective follow-up to evaluate outcome would be of great value as this would assist in understanding the complications that arise in SCD individuals with HPV B19 infection. In turn, this would improve the care and management of SCD individuals.

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Contributions. HG participated in designing the study, data collection, data analysis and wrote the first draft of the manuscript; FU assisted in designing the study, participated in data analysis and wrote the manuscript; FT designed the research, collected data and reviewed the manuscript; BPM analyzed the data, interpreted results and participated in writing the manuscript; TBN reviewed the manuscript. JM designed the research and reviewed the manuscript. All authors have read and approved the final manuscript.

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