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HIV AND MALARIA CO-INFECTION IN INDIA

SHANKARKUMAR U.*, SHANKARKUMAR A. AND GHOSH K.
National Institute of Immunohaematology, 13th Floor, K.E.M.Hospital, Parel, Mumbai – 400012, MS, India
*Corresponding author. E-mail: shankar2kumar@rediffmail.com, Mobile: 09321042920

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Abstract- Background: Conflicting reports exist regarding the HIV-1 infection on the risk of malaria. A transient almost one-log elevation in HIV viral load occurs during febrile malaria episodes; in addition malaria is enhanced in HIV infected patients. HIV and malaria co-infection might also have facilitated the geographic expansion of malaria in HIV prevalent areas. We prospectively studied malaria patients for HIV infection from Mumbai. **Materials and Methods**: A total of 171 malaria patients and 28749 normal voluntary blood donors studied for their HIV status. On microscopical examination of blood, all patients showed a ring form of *P.falciparum*. Blood screened for HIV-1&2 antibodies by micro well ELISA using Enzaids & J Mitra kits followed by confirmation using Western Blot (Innogenetics, Belgium) analysis. **Results**: Thirteen malaria patients (7.6%; Odds ratio= 4.45; P value <0.0001) and 521 blood bank donors found to be HIV reactive. Among the 13 HIV reactive patients, we found that eight patients (4.6%) who were Elisa borderline reactive and western blot positive (p24) due to cross-reactive antibodies. Five Malaria patients (2.9%) found to be HIV-1 positive by ELISA and Western Blot confirming co-infection. **Conclusion**: It seems that our findings suggest that HIV-1 and Malaria co-infection is associated with severe malaria in hyper endemic countries like India.
Keywords: Malaria, HIV-1 co-infection, Mumbai, Western India

Introduction

Malaria is endemic in many areas of India and repeated infections with Plasmodium falciparaum and P.vivax occur. Moreover, P.vivax can exit in its exoerthrocytic form as lypnozoites unless eradicated by primaquin and many cause recurrent febrile episodes. Malaria parasitemia differs in instances of asymptomatic and clinical malaria and the degree of parasitemia may influence the pathological and biochemical presentations in this patients[1,2]. Influence of Therapy to avoid HIV on malaria infection is controversial. Available studies have limited sample sizes and failed to demonstrate any association of malaria with HIV among hospitalized patients from areas with stable malaria transmission[3]. It has been postulated that HIV infection alters clinical presentation of malaria [4]. Further, treatment failure of anti-malarial is reported in HIV positive patients[5, 6] which also has been contradicted [5-7]. Fever, a major manifestation present not only in HIV positive individuals, is malaria due to infection but also because of many other common infections. An immune reconstitution syndrome along with adverse effects of antiretroviral drugs and other medicines lead to a febrile illness too. The fact that people in malaria endemic areas may have asymptomatic malarial parasitemia further complicates the diagnosis of febrile illness in malaria HIV co-infected patients.

More than 90% of acute malaria infections worldwide found in tropical Africa account for a majority of deaths, including children less than 5 years. Survivors suffer chronic immune activation on repeated infection with increased susceptibility even in HIV negative individuals[8]. High prevalence of HIV in Africa aggravates it to greater extent. Malaria increases HIV viral load as much as 10-fold, increasing contagiousness of HIV infected persons and affecting the population epidemiology dynamics [9]. Individuals in malaria endemic areas have a higher probability of sexual contact with persons who are infected with both malaria and HIV, with high viral load. Models of malaria HIV interaction estimate a threefold increase in HIV transmission in malaria endemic populations and increased malaria transmission due to HIV co infection[9].various reports state that malaria is a powerful stimulator of the immune system and the subjects exposed to malaria frequently show enhanced immunoglobulin levels and accelerated IgG production. Others have also reported that malaria infection might have an adverse effect on HIV infection both by stimulating T cell turnover and by impairing T cell cytotoxic function.

Our current understanding of the human immune response to malaria and HIV leads us to expect that either infection might influence the clinical course of the other. Many other types of infections are associated with at least a transient increase in HIV viral load. Hence, it is logical to expect malaria to do the same and potentially to accelerate HIV disease progression. On the other hand, the control of malaria parasitemia is immune

mediated, and this prevents most malarial infections from becoming clinically apparent in semi-immune adults in endemic areas. The immune deficiency caused by HIV infection should, in theory, reduce the immune response to malaria parasitemia and therefore increase the frequency of clinical attacks of malaria.

However, as research evidence emerged from sub-Saharan Africa in the 1980s and 1990s, it soon became clear that malaria is not a typical opportunistic infection. In fact, the interaction between HIV and malaria has proved to be remarkably subtle, and it is only in the past few years that a clearer picture of this association has begun to emerge. The current study describes the occurrence of malaria and HIV co-infection in hospitalized malaria adult patients of malaria in Mumbai.

Materials & Methods

One hundred and seventy one malaria patients with high-grade fever (38-45^{0}C) for three to eight days admitted in the medicine ward of KEM hospital at Mumbai enrolled in the study. Five ml blood collected aseptically at the time of admission for full blood count, Erythrocyte sedimentation rate (ESR), peripheral smears, thick and thin films for malaria parasite (examined by two experts for confirmation of species). The serum separated and stored in – 20^{0}C. These patients were confirmed for the malarial *P.falciparum* parasite in peripheral blood smears and the density showed varied numbers (<1% - 5%). These malaria patients tested for HIV-1&2 antibodies by two independent ELISA assays (Enzaids & J Mitra kits) and confirmed by Western blot assay (Innogentics, Belgium) following the kit manufacturers protocol. The controls were normal blood bank volunteer donors who tested for HIV-1&2 antibodies by ELISA kits confirmed by western blot. The local ethical committee approved the study.

Results

Our results showed that 13 (7.6%) out of 171 malaria patients and 521 (1.81%) out of 28749 blood bank donors were HIV-1 &2 seroreactive (Table: 1). Five (38.46%) of the 13 malaria patients were confirmed to have HIV-1 infection, eight (61.5%) of the 13 malaria patients were showed borderline ELISA reactive results and indeterminate status on western blot analysis (Table: 2). Our results of Malaria and HIV-1 co-infection were highly significant.

Discussion

Infection with HIV-1 causes progressive cellular immunosuppression, and any resulting impairment in the immune response to malaria might be associated with failure to prevent infection or to suppress parasitemia and clinical disease[10]. However, laboratory-based studies have found that although some components of the human immune response to Plasmodium falciparum are modified by HIV-1, others are unaffected.[11] On the other hand, P falciparum has been shown to stimulate HIV-1 replication through the production of cytokines (interleukin-6 and tumor necrosis factor-alpha) by activated lymphocytes [12]. *P. falciparum* also increases the potential reservoir for HIV in the placenta by increasing the number of CCR5+ macrophages[13].An important study from Malawi showed that HIV-1 plasma viral loads were significantly higher in patients with malaria infection than in those without, and these levels remained higher for up to 10 weeks after treatment[14]. The increases in viral load were greatest in those with clinical malaria, high levels of parasitemia, and relatively high CD4 counts. Studies report that malaria may speed the progression of HIV disease, and this is supported by a study from Uganda showing increased CD4 cell decline associated with episodes of malaria despite prompt treatment[15]. However, the true clinical impact of malaria on HIV progression remains to be determined.[16] Evidence indicates an interaction between HIV-1 and malaria in pregnancy, causing more peripheral and placental parasitemia, higher parasite densities, malaria that is more clinical, more anemia, and risks of adverse birth outcomes increased.[17] HIV-infected women remain susceptible to the effects of malaria whether or not they are pregnant. Placental HIV-1 viral load increased in women with placental malaria, especially those with high parasite densities.[18] However, the effect of malaria on mother-to-child transmission of HIV is unclear because published studies to date have given conflicting findings.[18-21] It has been suggested that the discrepancy might be due to variations in maternal immunocompetence. That is, immunocompromised mothers have deranged chemokine and cytokine profiles, less protective immune responses, and consequently higher parasite densities and viral loads, leading to an increased risk of mother-to-child transmission of HIV[22].

Studies in men and nonpregnant women show that the underlying epidemiology and intensity of malaria transmission seem to be critical for determining the consequences of co infection. In areas of stable malaria, transmission is intense and continuous, although seasonal variations may occur. Immunity develops early in life, and young children and pregnant women are at greatest risk of morbidity and mortality from malaria. In these areas, HIV-related immunosuppression may increase rates of malaria infection and clinical malaria disease, but does not increase the rates of severe or complicated malaria[23]. Relative risk for parasitemia and malarial fever increase with decreasing CD4 count and increasing viral load. These findings suggest that HIV infection not only may interfere with parasite control, but also, perhaps more important, may cause the loss of antitoxic immunity, which protects persons with parasitemia from clinical disease. In regions of unstable malaria, transmission is intermittent and less predictable, and epidemics may occur. The disease burden is similar in all age groups because preexisting ant malarial immunity is limited. As a result, malarial fever rate as a direct function of parasite transmission rate. Thus, HIV co infection has its impact on disease presentation, with an increased risk of complicated and severe malaria and death[24]. Studies of malaria and HIV interactions in

children living in areas of stable malaria epidemiology have been inconclusive.[25] A study in rural Kwazulu-Natal, an area of unstable malaria, reported that HIV-infected children were more likely to experience severe disease, coma, and death.[26] More data are required to document any significant malaria and HIV interactions in children.

Malaria and HIV-1 are two of the most common infections in sub-Saharan Africa and, to a lesser extent, in other developing countries. An increased prevalence of malaria and increased parasite density in HIV-infected individuals could lead to increased malaria transmission affecting both HIV-positive and -negative individuals.[23,26] (This assumes that the frequency, duration, and density of gametocytemia rise in parallel with asexual parasitemia, which is currently unproven.) The increased risk of clinical malaria in HIV-positive subjects could increase the burden on clinical services in areas where HIV-1 is prevalent as observed in the present western Indian study.

The population-attributable fraction of adult malaria due to HIV-1 would be expected to rise in parallel with HIV-1 prevalence. In a region with an increased HIV-1 prevalence of 30%, such as parts of southern Africa, the population-attributable fraction could reach 20% for parasitemia and 35% for clinical malaria. However, malaria tends to affect mainly children, men and pregnant women, especially in rural areas, whereas HIV is more common among sexually active adults in urban centers.

Conclusion

It seems that our findings suggest that HIV-1 infection is associated with severe malaria in hyperendemic areas. Further, the study suggests that the fraction of febrile illness attributable to malaria is lower in HIV positive adults. HIV testing should be conducted in malaria patients as an evaluation for febrile illness. Malaria infection and fever rates increase in areas of stable transmission, especially for individuals with low CD4 counts or high viral loads. In areas of unstable transmission, HIV is associated with more severe disease and death. Antimalarial therapy appears to be less effective in HIV-infected than in uninfected adults because of more rapid reinfection. In pregnant women, HIV is associated with more episodes of malaria, more fever, and more adverse birth outcomes. In the other direction, malaria up-regulates HIV transcription transiently during acute episodes and increases the rate of CD4 decline. Still in India, we need to address several unanswered questions, such as

1. Whether the current HIV epidemic is affecting malaria control programs in Africa and India,
2. Whether improved clinical management of malaria in HIV-1-infected subjects (eg, avoidance of mosquito bites or chemoprophylaxis) slows the progression of HIV disease.
3. Whether acute malaria episodes accelerate clinical HIV disease progression and increase transmission.
4. We also need more information about pharmacokinetic interactions between antimalarials and antiretroviral drugs in areas with higher malaria prevalence.

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Table 1- HIV testing in Malaria patients and Normal blood bank donors from Mumbai, India

Patient status	Malaria Patients	Blood Bank Controls						
	N =171	N =28749						
	PF%(N+)	PF%(N+)	OR	Ki2	EF	95% CI	P value	
Total HIV Reactive	7.60 (13)	1.81 (521)	4.45	28.331	0.0582	2.51-7.901	<0.0001	**
Malaria HIV co- infection	2.92 (5)	0 (0)	1899.4	680.12	0.0291	104.53-34512	<0.0001	**
(N+) Number positive								
Ki2=Chi-square with Yates correction								
PF(%) phenotype frequency percentage								
OR=Odds ratio								
EF=Etiological fraction	** highly Significant P value							
95% CI = 95% confidence Interval								

Table 2-ELISA And Western Blot Results of the HIV -1 positive Malaria patients

ID	First	Second	Western Blot results										Remarks
N=171	ELISA	ELISA	P17	P24	P31	gP41	P51	P55	P66	gP120	gP160	gP36	HIV-1
1	2.022	1.708	1+	3+	2+	2+	4+	1+	3+	1+	1+		Positive
2	0.497	0.055											
3	2.496	1.642		4+	2+	1+	3+	1+	3+	1+	1+		Positive
4	0.558	0.129		1+									
5	0.212	0.011	1+	1+									
6	2.422	1.446	2+	4+	1+	3+	3+		3+	1+	1+		Positive
7	1.721	1.453	1+	4+	2+	2+	4+	1+	4+	1+			Positive
8	0.226	0.092	1+	1+									
9	0.336	0.020	1+	2+									
10	0.424	0.115	1+	2+									
11	0.230	0.028		1+									
12	2.171	1.264		2+	1+	1+	3+	1+	3+	1+	1+		Positive
13	0.321	0.040		4+									

1+ (weak Positive), 2+ (Moderate Positive), 3+ and 4+ (Strong Positive)
8 out of 13 patients first ELISA positive second one Negative
5 patients were both ELISA positives and confirmed in Western Blot for HIV-1