Fetal hemoglobin modifies the disease manifestation of severe *Plasmodium falciparum* malaria in adult patients with sickle cell anemia.

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Sickle cell anemia (SCA) and *P. falciparum* malaria are two major public health problems in the state of Odisha, India. The prevalence of sickle cell gene in the western part of Odisha is 13.1%,1 *P. falciparum* contributes 23% of cases and 15% of malaria related deaths in India. Various African studies have showed that, even though SCA protects from *P. falciparum* infection, the risk of severe illness and death due to malaria is higher.2,3 Though several factors are responsible for the disease severity in *P.* *falciparum* malaria in patients with SCA, it was recently found that fetal hemoglobin (HbF), a normal hemoglobin usually found higher in patients with SCA had a negative epistatic interaction with HbS during protection against malaria.4 The role of HbF against *P. falciparum* malaria in cases with normal hemoglobin genotypes has been widely studied and found to be protective against severe disease manifestation. So it is necessary to study this association in region with high prevalence of sickle cell gene and high endemicity of *P. falciparum* malaria. This study aims to find out the effect of HbF level on the clinical manifestation of severe *P.* *falciparum* malaria in patients with SCA.

This prospective study was undertaken at the Sickle Cell Clinic and Molecular Biology Laboratory, Veer Surendra Sai Institute of Medical Sciences and Research, Burla, Odisha, India. Forty six adult patients with SCA along with severe *P. falciparum* malaria admitted in the Department of Medicine of this institute were included in this study. The mean age of patients was 25.4±8.8 years (range, 17 to 60 years) with 58.7% (27/46) being males. The hemoglobin variants including HbF was estimated by Cation-Exchange high performance liquid chromatography (CE-HPLC) using Variant II - 𝛽 thalassemia short program (Bio-Rad laboratories, Hercules). The mean % HbF level was found to be 18.5±6.5 %; ranging from 9.1 to 29.0 %.

 The severity of malaria was defined by WHO guideline in 2010 [5]. The severity due to malaria was defined by the presence of single or multiple complications. Cerebral malaria, severe malarial anemia, jaundice, acute renal failure and/or hepatopathy were considered as the major clinical symptoms of the patients. Among the various clinical symptoms, the incidence of cerebral malaria was 37.0% (17/46) followed by severe malarial anemia (21.7%, 10/46). Episodes of vaso-occlusive crises were observed in 50.0% of cases. Death was recorded in 9 patients including 6 females. There were multiple complications responsible for mortality in these patients. The comparison of % HbF level in patients with varied number of complications they had, revealed that the mean % HbF levels increased with the number of clinical complications in the patients. The mean increase in the % HbF level was 15.7±4.0, 18.0±4.0, 18.9±6.1 and 20.8±1.2 respectively in patients with single, two, three and four complications. Further linear regression analysis between total hemoglobin level and % HbF level in the patients elucidated an inverse relationship (*r*, -0.356; *p*, 0.015), which indicates that patients with higher % HbF level had lower total hemoglobin level.

In another comparison, we found that there was an increasing trend in the % HbF level in patients with severe malarial anemia compared to patients without it. A similar trend was observed in patients with cerebral malaria. The mean % HbF level also significantly increased in patients who died compared to patients who survived (*p*, 0.01). The % HbF differences in the patients with severe malarial anemia, cerebral malaria and fatality has been illustrated in Figure 1.

From the three factors above, which are associated with severity and mortality due to *P. falciparum* malaria in patients with SCA, it was revealed that HbF has a negative role in protection against severe disease manifestation. Though, HbF in SCA is found to be supportive in reducing episodes of vaso-occlusive crises and requirements of blood transfusion,6 the protection afforded by HbS against severe malaria reduced with increased % HbF level. This study supports the hypothesis of negative epistatic interaction between HbS and HbF in reduction of protection against severe malaria by Mmbando et al.,4 Following this hypothesis, the use of hydroxyurea (a drug which increases HbF levels) in patients with SCA remains unanswered in malarial endemic regions like ours. A large cohort study in a malaria endemic region is essential to elucidate a conclusive result on association of HbF and use of hydroxyurea in patients with SCA.

**Conflict of interest statement:**

We declare that we have no conflict of interest.

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**Figure 1.** Comparison of % HbF level in patients with severe *Plasmodium falciparum* malaria with different clinical manifestation.

A. HbF level in death patients; B. HbF level in survived patients; C. HbF level in patients with cerebral malaria; D. HbF level in patients with no cerebral malaria; E. HbF level in patients with severe malarial anemia; F. HbF level in patients with no severe malarial anemia. The line joined the median value in each category.