ABSTRACT

Background

In 1949, Haldane introduced a pioneering theory connecting red blood cell disorders such as thalassemia with resistance to malaria-an idea that has fascinated scientists ever since. Alpha thalassemia in particular, is prominent in malaria-endemic areas like sub-Saharan Africa, where it acts as both a hereditary challenge and a possible protective factor. It is believed to offer partial defense against severe malaria, potentially by boosting immune clearance, hindering parasite development, and limiting red blood cell invasion, though its complete role remains unclear. This study aimed to investigate how alpha thalassemia influences Plasmodium falciparum infections, focusing on parasite presence, immune responses, and the performance of antimalarial treatments, to fill key gaps in knowledge about the connection between alpha thalassemia and malaria.

Methods:

A cross-sectional survey involving 1,401 individuals aged 1 to 60 years was carried out across three ecological zones in Ghana. Alphα-thalassemia genotyping was performed using multiplex PCR, while Plasmodium falciparum infections were detected through rapid diagnostic tests (RDTs), microscopy and PCR. Antibody responses in symptomatic participants were evaluated using indirect ELISA. Data were analyzed statistically according to genotype, infection status, season, sex, and age using non-parametric methods. After excluding other haemoglobin disorders, a genotype-based recall study was conducted focusing on the three alpha thalassemia genotypes, utilizing synchronized cultures of the 3D7 P. falciparum strain and SYBR Green I assay to determine IC_{50} values in vitro of 9 antimalarial drugs.

Results:

The most common alpha thalassemia genotype was the wild-type (αα/αα), found in 57.8% of participants, followed by the heterozygous form (-α/αα) at 37.9%, and the homozygous mutant (-α/- α) at 4.2%. Malaria infection rate was highest by PCR (25.55%), compared to 11.28% by rapid diagnostic tests and 5.71% by microscopy. The forest zone recorded the highest malaria prevalence at 36.45%. Gametocyte carriage was observed in 2.36% of participants, with significantly higher rates in the Sahel savannah zone. Antibody responses were generally more common among individuals with malaria, with those carrying the heterozygous (-α/αα) genotype showing the strongest antibody responses overall. Significant differences in antibody levels across alpha thalassemia genotypes were noted for AMA-1, EBA-175, GLURP, MSP-1, and RH5, with EBA-175 also showing seasonal variation. Quinine and primaquine demonstrated more than 50 times greater effectiveness in individuals with the homozygous (-α/-α) genotype but artemisinin

derivatives and lumefantrine showed irregular IC_{50} patterns across genotypes, while chloroquine, amodiaquine, and antifolates were unaffected by genotype.

Conclusions:

These results contribute to the growing body of evidence supporting the concept of heterozygote advantage, showing that individuals with heterozygous alpha thalassemia not only have lower malaria parasite prevalence but also exhibit stronger antibody responses to important P. falciparum antigens. This combination of improved immune function and altered drug sensitivity suggests the value of tailoring malaria treatment based on genetic profiles. The findings emphasize the importance of incorporating genetic testing into malaria control programs, particularly in African regions where haemoglobin disorders are widespread, to enable more targeted and effective disease management strategies.