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Abstract (poster session)

Risk co-factor in malaria drug resistance selection: frequency of CYP2C8*2 allele in Uganda

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Objectives: Plasmodium falciparum malaria is one of the leading cause of morbidity and mortality in sub-Saharan Africa and Uganda bears a particularly large burden from this parasitic infection. Unfortunately, drug resistance is a problem in the control of P. falciparum, its selection being influenced by several factors such as drug usage, transmission intensity, host immune status and pharmacokinetic. Human genetic variation could represent a further cofactor. All antimalarial drugs are metabolized by hepatic cytochrome P 450 enzymes. In particular, cytochrome P450 2C8 (CYP2C8) contributes to the hepatic metabolism of chloroquine (CQ), amodiaquine (AQ) and dapsone (DDS). This cytochrome shows a genetic variant (CYP2C8*2) associated with increased adverse side effects and with higher rate of CQ-resistant parasites in the infected host. Our aim is to describe CYP2C8*2 frequency in populations from Ugandan areas characterised by high levels of malaria transmission intensity. Methods: The samples analysed in the present study were collected during cross-sectional surveys performed during 2007 in Uganda (Karamoja and Kampala regions). A total of 262 children and adolescents had been enrolled and genotyped for the polymorphism rs11572103 (A/T). The PCR-RFLP technique was used to discriminate the wild-type (A) from the defective allele (T). Results: The frequency ± SE of the CYP2C8*2 in rural sites of Karamoja region (North-Eastern Uganda) was 0.096 ± 0.021, while was 0.132 ± 0.032 in the Kampala suburbs (central Uganda). Both the genotype distributions are in Hardy-Weinberg equilibrium, and the allele frequencies are not statistically different (Yates corrected Chi2=0.89, P=0.346). The overall CYP2C8*2 frequency in all sites was 0.105 ± 0.019. Genotype frequencies were in Hardy-Weinberg equilibrium Chi2=1.52, P=0.221). Conclusion: Our study demonstrated that CYP2C8*2 allele is present at an appreciable frequency in Uganda, an area of hyperendemic malaria transmission. Here antimalarial treatment is based on artemisinin combination therapies (ACTs), and artesunate (AS) plus AQ is used as second line ACT. Consequently, the presence of the CYP2C8*2 allele may be a potential co-factor in the onset of adverse side effects associated with AQ administration. Furthermore, we emphasize the risk related to the presence of CYP2C8*2 in selecting AQ- resistant strains, since the interplay between host and parasite genetic variation could be similar to that of CQ.