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Molecular studies on clinically severe *Plasmodium vivax* infections

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Severe clinical cases exclusively associated with *Plasmodium vivax* are increasingly being reported worldwide with complications like renal failure, jaundice, acute respiratory distress syndrome, cerebral malaria, seizures, anemia, thrombocytopenia, pulmonary edema, splenic rupture and death. Emergence of *P. falciparum* like severity in *P. vivax* and its pathogenesis has been speculated to be linked to increasing chloroquine resistance (CQR). Two main transporters studied with regard to CQR in *P. vivax* are *P. vivax* chloroquine resistance transporter, *pvcr-t-o*; and the *P. vivax* multidrug resistance transporter, *pvmdr1* which are orthologous to the *pfcr-t* and *pfmdr1* genes respectively. Even though these transporters are not established as molecular markers for CQR, they have a speculated role in CQR of *P. vivax*. Further, it has been demonstrated that the clinical severity in *P. vivax* could be associated with increased expression levels of parasite transporter genes likely to be involved in CQR i.e. *pvcr-t-o* and *pvmdr1*. In this study, relative expression levels of *pvcr-t-o* and *pvmdr1* genes were analyzed in severe and non-severe *P. vivax* cases compared to a non-severe control group. *P. vivax* positive isolates were classified as severe and non-severe according to the WHO guidelines for severe malaria. Transcription analysis of drug resistance genes was carried out for severe and non-severe *P. vivax* isolates by real-time PCR normalized to β -tubulin; the endogenous gene. The severe *P. vivax* isolates were found to have higher expression levels of the drug resistance genes (*pvcr-t-o* and *pvmdr1*) as compared to the non-severe *P. vivax* infections. Increased expression levels of CQR transporters in severe infections indicate their role in the changing pathogenesis of *P. vivax* that can no longer be considered benign. It brings to light how genes linked to the emerging CQR in *P. vivax* might impart virulence to vivax malaria making them excellent genetic markers for disease severity.

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