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Surveillance of Artemisinin Resistance Markers and Their Impact on Treatment Outcomes in Malaria Patients in an Endemic Area of South-Western Nigeria

Authors : Abiodun Amusan, Olugbenga Akinola, Kazeem Akano, María Hernández-Castañeda, Jenna Dick, Akintunde Sowunmi, Geoffrey Hart, Grace Gbotosho

Abstract : Introduction: Artemisinin-based Combination Therapy (ACTs) is the cornerstone malaria treatment option in most malaria-endemic countries. Unfortunately, the malaria control effort is constantly being threatened by resistance of Plasmodium falciparum to ACTs. The recent evidence of artemisinin resistance in East Africa and its possibility of spreading to other African regions portends an imminent health catastrophe. This study aimed at evaluating the occurrence, prevalence, and influence of artemisinin-resistance markers on treatment outcomes in Ibadan before and after post-adoption of artemisinin combination therapy (ACTs) in Nigeria in 2005. Method: The study involved day zero dry blood spot (DBS) obtained from malaria patients during retrospective (2000-2005) and prospective (2021) studies. A cohort in the prospective study received oral dihydroartemisinin-piperaquine and underwent a 42-day follow-up to observe treatment outcomes. Genomic DNA was extracted from the DBS samples using a QIAamp blood extraction kit. Fragments of P. falciparum kelch13 (Pfkelch13), P. falciparum coronin (Pfcoronin), P. falciparum multidrug resistance 2 (PfMDR2), and P. falciparum chloroquine resistance transporter (PfCRT) genes were amplified and sequenced on a sanger sequencing platform to identify artemisinin resistance-associated mutations. Mutations were identified by aligning sequenced data with reference sequences obtained from the National Center for Biotechnology Information. Data were analyzed using descriptive statistics and student t-tests. Results: Mean parasite clearance time (PCT) and fever clearance time (FCT) were 2.1 ± 0.6 days (95% CI: 1.97-2.24) and 1.3 ± 0.7 days (95% CI: 1.1-1.6) respectively. Four mutations, K189T [34/53(64.2%)], R255K [2/53(3.8%)], K189N [1/53(1.9%)] and N217H [1/53(1.9%)] were identified within the N-terminal (Coiled-coil containing) domain of Pfkelch13. No artemisinin resistance-associated mutation usually found within the β-propeller domain of the Pfkelch13 gene was found in these analyzed samples. However, K189T and R255K mutations showed a significant correlation with longer parasite clearance time in the patients ($P<0.002$). The observed Pfkelch13 gene changes did not influence the baseline mean parasitemia ($P = 0.44$). P76S [17/100 (17%)] and V62M [1/100 (1%)] changes were identified in the Pfcoronin gene fragment without any influence on the parasitological parameters. No change was observed in the PfMDR2 gene, while no artemisinin resistance-associated mutation was found in the PfCRT gene. Furthermore, a sample each in the retrospective study contained the Pfkelch13 K189T and Pfcoronin P76S mutations. Conclusion: The study revealed absence of genetic-based evidence of artemisinin resistance in the study population at the time of study. The high frequency of K189T Pfkelch13 mutation and its correlation with increased parasite clearance time in this study may depict geographical variation of resistance mediators and imminent artemisinin resistance, respectively. The study also revealed an inherent potential of parasites to harbour drug-resistant genotypes before the introduction of ACTs in Nigeria.

Keywords : artemisinin resistance, plasmodium falciparum, Pfkelch13 mutations, Pfcoronin
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