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Research Letter

November 14, 2024

Artemisinin Partial Resistance in Ugandan Children With Complicated Malaria

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JAMA. Published online November 14, 2024. doi:10.1001/jama.2024.22343

Intravenous artesunate, a semisynthetic derivative of artemisinin, is the World Health Organization (WHO)–recommended treatment for malaria requiring parenteral treatment.

Malaria caused 608 000 deaths in 2022, mostly due to *Plasmodium falciparum*.[1] Artemisinin partial resistance due to *Pfkelch13* variations has been documented in East Africa in uncomplicated malaria[2,3] but not in complicated malaria. We assessed artemisinin partial resistance, *Pfkelch13* variations, and malaria recrudescence in Ugandan children with complicated malaria.

Methods

We conducted a prospective study of children aged 6 months to 12 years with complicated malaria (febrile, microscopy-confirmed *P falciparum* parasitemia with evidence of severe disease that required hospitalization) (**Table 1**) treated with parenteral artesunate followed by oral artemether/lumefantrine in Jinja, Uganda, from 2021 to 2022. Children were enrolled after written informed consent from parents. Presence of *Pfkelch13 A675V*, *C469Y*, and *R5661H* variations was evaluated and outcomes were analyzed for each variation separately. Study outcomes included parasite clearance half-life (estimated time for parasitemia to decrease by 50%), artemisinin partial resistance (half-life for parasite clearance [$t_{1/2}$] >5 hours[4]), early treatment failure (persistence of *P falciparum* parasitemia ≥72 hours after initial treatment), and polymerase chain reaction (PCR)–adjusted recrudescence (repeated clinical malaria [febrile with microscopy-positive *P falciparum* parasitemia within 28 days of treatment] or asymptomatic *P falciparum* parasitemia on day 28 after treatment, with 1 or more identical *P falciparum* genotypes during first and second episodes).[5] *P falciparum* genotypes for artemisinin partial resistance and recrudescence were determined by PCR amplification of *Pfkelch13* variations and the merozoite surface protein 2 (*PfMSP-2*) gene, respectively. Blood samples were obtained according

to WHO guidelines for parasite clearance evaluation.[5] Details of enrollment criteria, treatment, microscopy, and genotyping are provided in the eAppendix in **Supplement 1**. For statistical analysis (Stata SE version 17; StataCorp), continuous and categorical variables were compared using 2-sided *t* test and Fisher exact probability test with Woolf 95% CIs, respectively, with $P < .05$ considered significant. The study was approved by the Makerere University School of Medicine Research and Ethics Committee and Uganda National Council for Science and Technology.

Results

Of 110 enrolled children with complicated malaria, 10 were excluded (withdrawn by parents, 8; incomplete testing, 1; died before completing study, 1). Of the 100 participants in the final analysis, 47 were female. The mean (SD) age was 3.72 (2.1) years; 41 participants met current WHO severe malaria criteria,[6] with the remainder admitted for other severe complications of malaria that required hospital admission (**Table 1**).

Artemisinin partial resistance was seen in 11 study participants. Eight participants had the *A675V* variation and 2 the *C4692Y* variation; none had the *R5661H* variation. The *A675V* variation was associated with longer time to parasite clearance (mean [SD] $t_{1/2}$ for *A675V*, 4.9 [2.3] hours; for wild type, 3.2 [1.5] hours; $P = .005$) and artemisinin partial resistance (proportion with $t_{1/2}$ ≥5 hours[5]: *A675V*, 3 of 8 [37.5%]; wild type, 8 of 90 [8.9%]; odds ratio, 6.2 [95% CI, 1.2-30.6]; $P = .04$) (**Table 2**). Both patients with the *C469Y* variation cleared parasitemia rapidly (mean $t_{1/2}$, 1.3 hours). Two children with early treatment failure required prolonged artesunate therapy, 1 with *Pfkelch13 A675V* (96 hours to clearance) and 1 with wild-type *Pfkelch13* (120 hours to clearance) (**Table 2**).

Thirteen participants had a repeated clinical malaria episode despite prior documented parasite clearance. We determined the *P falciparum* genotype in 11 participants. PCR-adjusted 28-day recrudescence was 10.3% (9 clinical recrudescence and 1 day-28 asymptomatic parasitemia recrudescence out of 97 children with *PfMSP-2* genotyping). Recrudescence was not associated with carriage of *Pfkelch13* variations at enrollment (1 of 8 children [12.5%] with *A675V* variation vs 9 of 89 children [10.1%] without *A675V* variation; $P > .99$).

Discussion

This study found artemisinin partial resistance in Ugandan children with complicated malaria associated with the *Pfkelch13 A675V* variation and also found suboptimal 28-day efficacy of parenteral artesunate followed by oral artemether/lumefantrine therapy. Limitations include a small sample size and a single location for the study. Given the high morbidity and risk of death in African children with complications of malaria, additional evaluation of artemisinin resistance in children with complicated malaria is needed because confirmation of the presence of artemisinin partial resistance and clinical treatment failure may require revision of guidelines for treatment of this life-threatening condition.

Section Editors: Kristin Walter, MD, and Jody W. Zylke, MD, Deputy Editors; Karen Lasser, MD, MPH, Senior Editor.

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Article Information

Accepted for Publication: October 4, 2024.

Published Online: November 14, 2024. doi:10.1001/jama.2024.22343

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Critical review of the manuscript for important intellectual content: All authors.

Statistical analysis: Henrici, Lima-Cooper, Campino, Sutherland, John.

Obtained funding: Henrici, Campino, Opoka.

Administrative, technical, or material support: Henrici, Namazzi, Kato, Aliwuya, Pratt, Campino, Conroy, Sutherland, John, Opoka.

Supervision: Henrici, Namazzi, Campino, Conroy, Sutherland, John, Opoka.

Conflict of Interest Disclosures: Dr Henrici reported being an employee of BigHat Biosciences, a biotechnology company developing antibody therapeutics. BigHat Biosciences does not invest in or work on therapeutics for infectious diseases or pediatric populations in a way that would influence this work. No other disclosures were reported.

Funding/Support: Funding for this study was provided by the Makerere University Research and Innovations Fund and the Riley Children's Foundation.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

Additional Contributions: We thank the study participants and caregivers for their participation and the study team for their work.

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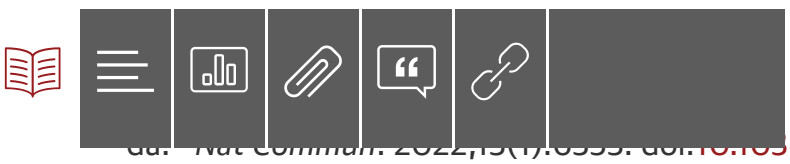

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