RESEARCH LETTER

Artemisinin Partial Resistance in Ugandan Children With Complicated Malaria

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.

Editorial

Supplemental content

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).

Table 1. Clinical Features of Malaria Complications in Study Participants[a]

Clinical feature	No. (%) (N = 100)
Hematologic	
Severe malarial anemia (Hb <5 g/dL, parasitemia >10 000/μL)	9
Anemia (Hb 5-6 g/dL), admitted for potential transfusion	13
Neurologic	
Cerebral malaria	4
Multiple convulsions (>2 per 24 h)	8
Prostration	1
Kidney	
Serum creatinine >3 mg/dL	1
Acute kidney injury[b]	42 (58) (n = 73)
Blackwater fever[c]	10
Other clinical findings	
Hyperpyrexia (axillary temperature >39.5 °C)	19
Systolic hypotension (SBP <70 mm Hg)	1
Jaundice[d]	6
Unable to take oral food or medications	26
Persistent parasitemia and fever despite prior antimalarial drugs	9
Laboratory findings	
Hyperparasitemia[e]	22

Abbreviations: Hb, hemoglobin; SBP, systolic blood pressure.

[a] For tests not conducted in the full study cohort, the total number tested is listed. Some children had multiple complications of malaria.

[b] Kidney Disease Improving Global Outcomes (KDIGO) criteria.

[c] Tea-colored urine.

[d] Jaundice at clinical examination.

[e] Parasite density greater than 100 000/μL.

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).

Table 2. Parasitologic and Clinical Outcomes in Study Participants

Outcome	Full cohort (N = 100)[a]	*Pfkelch13* wild type (n = 90)	*Pfkelch13 A675V* (n = 8)
Parasite clearance half-life, mean (SD), h[b]	3.3 (1.7)	3.2 (1.5)	4.9 (2.3)
Artemisinin partial resistance, No. (%)[c]	11 (11)	8 (8.9)	3 (37.5)
Early treatment failure, No. (%)[d]	2 (2)	1 (1.1)	1 (12.5)
Malaria recrudescence, No. (%)[e]	10 (10.3) (n = 97)	9 (10.1) (n = 89)	1 (12.5)

[a] *Pfkelch13* wild type (n = 90), *Pfkelch13 A675V* (n = 8), and *Pfkelch13 C469Y* (n = 2).

[b] Estimated time for parasite density to decrease by 50%.

[c] Parasite clearance half-life greater than or equal to 5 hours.

[d] Persistence of *Plasmodium falciparum* parasitemia greater than or equal to 72 hours after initial treatment.

[e] Polymerase chain reaction–adjusted 28-day recrudescence (clinical malaria within 28 days of treatment or asymptomatic parasitemia on day 28).

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.

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