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Currently Observed Trend in the Resistance of Malaria to Artemisinin Based Combination Therapy in Nigeria – A Report of 5 Cases

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Authors' contributions

This work was carried out in collaboration between both authors. Author GSW did the study design and wrote the protocol. Author AAO did the statistical analysis and literature searches while analyses of study were done by both authors. Both authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Malaria is a life threatening disease caused by parasites transmitted through the bite of an infected female mosquito. About 3.2 million (about half of the world's population) are at risk of malaria; it affects all age group from young to old. Between 2002 – 2015, Sub-Saharan Africa was home to 88% of malaria cases and 90% of malaria deaths most of which were under-five years old. *Plasmodium falciparum* – transmitted by female Anopleles mosquito (one of the five parasites that cause malaria in humans) is the most prevalent malaria parasite in the African continent and is responsible for most malaria-related deaths globally [1].

Artemisinin-based combination therapy (ACT) resistance is rare in Sub-Saharan Africa. The World Health Organization (WHO) identifies monitoring and surveillance using day – 3 parasitaemia post treatment as the standard test for identifying suspected artemisinin resistance [2]. Early treatment failure due to possible ACT resistant *Plasmodium falciparum* has been identified in 5 cases across different age group, race, sex and gender. All cases managed showed significant clinical and parasitological responses to further treatment with combined Artesunate (intravenous) and Arthemeter (intramuscular), Arthemeter only (IM) or Artesunate tablets.

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This study seeks to emphasize the need for a re-evaluation of the malaria treatment protocol and to throw more light on the increasing resistance of *Plasmodium falciparum* to the commonly used Artemisinin – based combination therapy agents in Nigeria.

Keywords: Artemisinin based combination therapy; malaria; artesunate; resistance; arthemether; Nigeria.

1. BACKGROUND

The Artemisinin based combination therapy has been the bed rock of treatment of uncomplicated malaria for about a decade replacing the monotherapy which proved resistant and ineffective overtime. The current UK guidelines recommend the use of Atovaquone-proguanil (Malarone), Artemether- Lumefantrine and oral quinine sulfate and doxycycline or clindamycin for pregnant women [3]. Atovaquone-proguanil has been one of the principal treatments of acute malaria in France for over a decade. In a prospective observational study of 553 cases of visitors and travelers to France already infected with *Plasmodium falciparum* from West Africa and Asia, had malarone administered as first line treatment; and it was observed that 469 (85%) of these cases were symptom free by day 3 and all patients showed negative parasitaemia by day 7 [4]. A similar finding was seen in Denmark amongst 50 adults who came in from West African countries, they were effectively treated with Malarone with negative malaria parasite tests seen a week after treatment with no recrudescence [5]. In a review of the morbidity and mortality caused by malaria in Africa between 2000 and 2015, UNICEF reported a decrease in the mortality rate by 60% and incidence by 37% globally. This success rate was partly attributed to provision of insecticides treated nets in Africa and more significantly to the use of ACT as the recommended treatment for uncomplicated *Plasmodium falciparum* malaria [6]. It was also observed that Arthemether-lumefantrine was highly effective in the treatment of uncomplicated malaria in Southwestern Ethiopia as 83.1% of patients were symptom free by day 3 [7]. According to a study done in Kolkata, India in 2013, the ACTs were used as first line treatment of malaria in 117 districts which represented more than 90% of the reported cases [8].

2. CASE PRESENTATION

This report identifies resistant *Plasmodium falciparum* malaria to Artemisinin based combination therapy in Abuja, Nigeria.

2.1 Case 1

A 43 year old Caucasian male, resident in Nigeria for 2 years but on vacation to Europe for one week. While in Europe, he developed fever with chills and headaches on Nov 1, 2016. His blood was examined for Malaria parasite following the advice of his general practitioner. He was found to have ring forms of Plasmodium in the red blood cells. He was immediately commenced on Tabs Malarone 4 tablets as a single dose daily for 3 days. Compliance to medication was adequate. He felt slightly better after completion of the drugs. But on arrival to Nigeria 5 days following treatment, he experienced body weakness, fever and headaches. A repeat thick and thin smear was done revealing the presence of malaria parasites. He was placed on Tabs Artesunat 12 tablets for five days (4 tablets on the first day and 2 tablets daily for 4 days). The symptoms were significantly reduced on the third day after treatment. A post treatment test done after 7 days of completion of treatment was negative.

2.2 Case 2

A 39 year old Caucasian male resident in Abuja for about 3 years was rushed into the clinic with a history of generalized body weakness, fever and yellowness of the eyes. He had received a 3 day course of Coartem (Arthemeter/Lumefantrine). He experienced no relief of the symptoms. On examination, he was pale, febrile T- 40℃, icteric, organs were not palpably enlarged. Malaria parasite antigens were tested applying the Malaria Antigen Rapid Diagnostic Test Kit. Also thick (Giemsa stained) and thin (Leishmann stained) films of the patient were observed. Microscopic examination of the films revealed the presence of ring forms of *Plasmodium falciparum* and antigens of this parasite were also detected in the kit. Complete Blood Count (thrombocytopenia – 46 x 10^9/L, White blood cell count and Hemoglobin were within normal range, other parameters were also normal); Liver Function Test was also within normal range; Hepatitis B test was negative. He was commenced on IV Artesunate 2.4 mg/kg at

0 hours, 12 hours and 24 hours and fever controlled with appropriate antipyretic.

After completion of the intravenous Artesunate, he was immediately commenced on a 5 day course of intramuscular Arthemether given as a dose of 3.2 mg/kg stat and 1.6 mg/kg daily for 4 days. He was symptom free after 72 hours of commencing treatment. A repeat test done after 7 days of completion of treatment was negative for *Plasmodium falciparum*.

2.3 Case 3

Female, 27 year old Nigerian, resident in Abuja, suffered from fever with chills on alternate days, worse at night and headaches. She visited the clinic 5 days after the onset of symptoms. A thick (Giemsa stained) and thin (Leischmann's stained) was done and a rapid kit test for *Plasmodium falciparum* antigen was also performed and both were positive. She was commenced on a 3 day course of Malarone 4 tablets once a day for 3 days. There was strict compliance and adherence to medications. She experienced a transient relief of the symptoms for about 2 days but symptoms re-occurred with worsening of body pains and fever. A repeat Malaria test done confirmed the presence of Malaria parasite. She was commenced on IM Arthemeter for 5 days at 3.2 mg/kg stat and 1.6 mg/kg daily for 4 days. She was symptom free after completion of the injections and a post treatment test done 2 weeks after was negative.

2.4 Case 4

Female, 3 year old Caucasian resident in Nigeria for two years was brought by her parents with history of high fever for 5 days, transiently relieved by syrup Ibuprofen. Temperature was 40℃, no other significant examination findings. Malaria parasite antigens were tested using the Malaria Antigen Rapid Diagnostic Test Kit, also, thick (Giemsa stained) and thin (Leishman stained) films of the patient were observed. Microscopic examination of the films revealed the presence of ring forms of *Plasmodium falciparum* and antigens of this parasite were also detected in the kit.

She was commenced on Syrup Arthemether/ Lumefantrine 20/120 mg taken at 0 hours, 8 hours, 24 hours, 36 hours, 48 hours and 60 hours. The fever subsided significantly after treatment. However, high fever reoccurred 9 days after. A repeat Malaria test was done and showed parasitaemia of the red blood cells. She was commenced on IM Arthemeter for 5 days at a dose of 3.2 mg/kg stat and 1.6 mg/kg daily for 4 days. Symptoms resolved and a repeat Malaria test done one week following treatment was negative.

2.5 Case 5

A 54 year old Caucasian resident in Abuja for over 10 years visited the clinic with a history of generalized body weakness and chills for 4 days. Malaria parasite antigens were tested applying the Malaria Antigen Rapid Diagnostic Test Kit, also, thick (Giemsa stained) and thin (Leishman stained) films of the patient were observed. Microscopic examination of the films revealed the presence of ring forms of *Plasmodium falciparum* and antigens of this parasite were also detected in the kit. He was commenced on tabs Malarone 4 tablets as a single dose, daily for 3 days. He adhered strictly to the medications. He still felt bad after completion of treatment with no relief after 3 days. A repeat malaria test still revealed presence of parasitamia on the red cell membrane. He was immediately started on a course of intramuscular Arthemether given as a dose of 3.2 mg/kg stat and 1.6 mg/kg daily for 4 days. He was symptom free after 72 hours of commencing treatment. A repeat test done after 7 days of completion of treatment was negative for *Plasmodium falciparum*.

3. DISCUSSION

Artemether-lumefantrine remains a very commonly used ACT for the treatment of uncomplicated *Plasmodium falciparum* malaria in Sub-Saharan Africa, and a pooled analysis showed a 28-day parasitological cure rate of 97% in malaria-endemic areas [2]. Also, Malarone is the drug of choice for uncomplicated *Plasmodium falciparum* in the UK and other European countries as previously discussed. Historically, Southeast Asia has been the center of the emergence of resistant malaria; however, few areas of the world are now impervious to the effects of drug-resistant malaria [9]. As of July 2016, artemisinin resistance has been confirmed in 5 countries of the Greater Mekong subregion (GMS): Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam [10].

ACT-resistant malaria is rare in Africa and even more uncommon in Nigeria, the first report was published in Ebonyi in 2013. Three cases were reported to have shown early treatment failure to

Arthemether-Lumefantrine only [2]. The five cases reported above also showed early treatment failure to both Malarone (Atovaquone/ Proguanil) and Arthemether-Lumefantrine as there was detectable parasitaemia on the red cell membrane for more than 72 hours following completion of treatment with ACT according to the WHO treatment outcomes for malaria.

Delayed parasite clearance after treatment with an ACT is of great concern. Failure to rapidly clear parasites could compromise it's use for the treatment of severe malaria [11] Also, slow parasite clearance causes more parasites to be exposed to the partner medicine alone, increasing the risk of selection of partner drug resistance; as in the cases above, we resorted to parenteral and oral Artesunate and Artemether which are currently used for the management of severe forms of *Plasmodium falciparum* malaria. Both of which have been shown to clear parasitaemias more effectively than chloroquine and sulfadoxine / pyrimethamine [12]. Oral Artesunate has also been proven to be effective in the treatment of uncomplicated falciparum malaria in areas where there is evidence of chloroquine, pyrimethamine / sulfadoxine, mefloquine and quinine resistance [13]. In the near future, these drugs too may have an increased risk of treatment failure for both the severe and uncomplicated malaria.

The purpose of this report is to re-emphasize the need for closer monitoring and surveillance for ACT resistant *Plasmodium falciparum* malaria and calls for the urgent reassessment of the efficacy of ACT.

4. CONCLUSION

The intrinsic ability of *Plasmodium falciparum* to evolve resistance to conventional antimalarial drugs is remarkable and has increased the number of deaths from malaria worldwide. It is therefore imperative that a new first line protocol for management of uncomplicated falciparum infection should be adopted in areas of resistance to the commonly used ACT. Also, in severe forms of malaria parasite infection, parenteral forms – intravenous Artesunate or intramuscular Artemether should be administered immediately, while continuing on oral medications as per protocol. Finally, there is a need to discover the genetic factors of the parasite that cause Artemisinin resistance and to identify effective markers to monitor its spread in not only Nigeria but all of West Africa; while more efforts should be made on primary prevention as regards good environmental sanitation to reduce the breeding of mosquitoes and use of insecticide treated nets amongst others.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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