Original Article

Recurrent malaria infection in Khartoum State, Sudan

Mutasim O Ali, MD, Mamoun MA Homeida, MD FRCP, James L Bennett, PhD, Hayam Okasha, M.B.,B.S., Khairia Abdel Hamid, M.B.,B.S., Hala Elkhatim, M.B.,B.S.
Khalid Mokhtar, M.L.S.

Department of Internal Medicine
The University of Medical Sciences and Technology, Khartoum, Sudan

Abstract

Objectives
The study aimed to investigate the underlying causes of recurrent malaria infection in Khartoum State.

Methods
This study was conducted in El Haj Yousif a peri–urban area in the northeast border of Khartoum state in the period August 1998 - December 2000, it was a prospective, clinically based study. Three hundred patients presenting with recurrent malaria were studied.

Correspondent author:
Mutasim.O.Ali
E-mails: mutasim_o@hotmail.com / amst33@hotmail.com
Tel: +249-183-427765

Results
Eighty three percent of the patients were found to have P. falciparum, 10% have mixed infection (P. falciparum and P. vivax), 5% have P. vivax only and 2% of cases have P. ovale.

Conclusion
Unlike what is generally believed not all recurrent malaria in Khartoum State was due to recrudescence of the primary infection, (incomplete treatment or drug resistance or re-infection). A significant proportion was due to relapse from persistent hypnozoites (P. vivax & P. ovale) in the liver, relapses of which can be prevented by eradication of the liver hypnozoites by primaquine therapy. This was confirmed by the malaria parasite identification and count which was done on the blood samples.
Keywords: malaria, falciparum, vivax, ovale, Sudan.

Introduction
Malaria is the most important human parasitic infection with 170 million new malaria cases occurring world-wide every year along with 2 million deaths from Plasmodium falciparum. The high mortality and severe morbidity of the disease is seen mainly in Africa, Asia, and Latin America. Eighty percent of all cases occur in tropical Africa, where malaria infection accounts for 10-30% of all hospital admissions and 25% of childhood deaths\(^{(1,2)}\). In the Sudan, malaria is a leading cause of morbidity (such as renal failure, pulmonary oedema, fluid imbalance, neurological deficit, DIC) and mortality, the annual estimated number is 7.5 million cases and 35,000 deaths, accounting for 20-40% of the total outpatient attendance and around 40% of admissions (WHO-Sudan 2005\(^{(3)}\)).

The emergence of resistance of Plasmodium falciparum parasite to chloroquine resulted in an increase of morbidity and mortality in many parts of Africa\(^{(4)}\). The commonest parasite causing malaria infection in North Sudan is Plasmodium falciparum. It is generally believed that recurrent malaria in the Sudan is either due to failure of therapy or a recrudescence, defined as relapse of the primary infection because of incomplete treatment\(^{(5)}\). We postulate that relapse of the infection may be accounted for by a large percentage of recurrence. In the present study, we studied patients who presented with frequent attacks of malaria (2 or more in 6 months or 4 or more in 12 months) with the emphasis of finding out the causes.

Malaria is prevalent in Khartoum with higher transmission in the peri-urban areas like Haj Yousif (the present study area)\(^{(6)}\). Recrudescence of the primary infection of malaria, because of incomplete treatment, usually occurs in falciparum malaria infection 2-4 weeks following treatment\(^{(5)}\) while relapse from persistent hypnozoites occurs in Plasmodium vivax and Plasmodium ovale, often occurs in 3-6 weeks following the primary infection\(^{(7,8,9)}\). It thus becomes unclear if a patient fails to respond to therapy, because the treatment failed or there is a relapse from maturation of a persistent hypnozoites. In the Sudan, resistance to chloroquine is increasing in many parts of the country as reported by many researchers. Bayomi et al reported chloroquine resistance in 42% of cases in Eastern Sudan\(^{(10)}\) while Adam in the same region reported 15.4% and 61.5% treatment failure early and late respectively\(^{(11)}\). Badria et al reported 2.4% chloroquine treatment failure in a peri-urban area in Khartoum state.

Kamini (2001) reported that, in Sudan, as a whole, 5-10% of malaria infections were due to Plasmodium vivax, with the remainder being due to Plasmodium falciparum\(^{(12)}\). Recently, it has been noted in a survey that Plasmodium ovale and Plasmodium vivax infections are seen in Khartoum dwellers at a rate of 150/1000. However, it is not very clear from that study if these infections were contracted locally or immigrated with the patients from other areas of the Sudan.

The present study attempted to find out the following: (a) if recurrent infections due to Plasmodium ovale and/or Plasmodium vivax were a cause of recurrence of fever in patients with recurrent malaria or (b) if those infections were contracted locally or immigrated with the patients from different parts of the Sudan.

Material and methods

Study site and population
EL Haj Yousif is a peri-urban area in the North-East border of the capital. Houses are of traditional mud and brick construction. The area is over populated by many tribes from different parts of the Sudan. Virtually
all tribes are represented, but the main are Mahas, Shaigia, Gaalyeen, Hafonians, and/or Dongolians from North Sudan and Dinka from South Sudan, displaced as the result of the civil war (1983-2004) were also studied. The population size is around 500,000. Most of them were of low-moderate socioeconomic status. There are about 10 health centres and one governmental hospital beside many private clinics and private hospitals. This study was conducted in a consultant private clinic between August 1998 - December 2000. The study is a clinically based prospective study where 2000 patients with clinical symptoms of fever and laboratory confirmed malaria infection, were seen in the period between August 1998 – December 2000. Out of the 2000 patients seen 300 had recurrent attacks and were included in this study. All of them received adequate doses of chloroquine in the previous attacks (chloroquine then was widely used). For the purpose of this study, recurrent attacks of malaria were defined as:

a) 2 or more attacks in 6 months, or
b) 4 or more attacks in one year.

Parasitological Diagnosis:
All laboratory tests were done by the same technician specialized in malaria parasite detection selected from the Central Quality Control Laboratory, Khartoum. The malaria parasite identification and count was done on blood samples, obtained by pin prick method from the thumb of all the 300 patients using standard slide method (13,14). The test included:

a) The thick Giemsa stained blood film for malaria consisting of 20 layers of red blood cells (standard slide).
b) The thin Giemsa stained (after fixation with alcohol) blood film for malaria consisting of one layer of red blood cells (standard slide).
c) The count, which is a reflection of the degree of parasitaemia in the blood (15,16). A standard formula is used for the purpose of malaria parasite count (15).

Patients with detectable blood stages of the parasite were given chloroquine tablets or injections (25mg base/kg in divided doses) (17), followed by primaquine (0.25mg base/kg daily for 14 days) (18) to clear liver stages of Plasmodium vivax or Plasmodium ovale.

The attack rate is defined as the number of clinically detected episodes of malaria in one year. For the purpose of this study, the following definitions were considered:

a) High attack rate = more than 6 in one year.
b) Moderate attack rate = 5 - 6 in one year.
c) Infrequent attack rate = less than 5 in one year.

Results
The geographic origin of the study population was as follows: 40% were from Khartoum, 29% from Al Gezira, 20% from the South, 6% from the North, 4% from the East and 1% from the West, all patients presenting with recurrent attacks of malaria from outside Khartoum were referred from the different areas mentioned above (1-15 days of their presentation in the clinic) for consultation and treatment for malaria. The distribution of the different species of malaria in the study population (the 300 patients) presenting with recurrent attacks of malaria is shown in Fig. 1.

Fig. 1: Shows the distribution of the different species of malaria in the study population (300)
The number of recurrent attacks per year for Plasmodium falciparum and Plasmodium vivax is shown in Fig. 2.

**Discussion**

This study demonstrates that recurrent malaria attacks is frequent with Plasmodium vivax (53% high attack rate) but occurs less frequently with Plasmodium falciparum (20% high attack rate). Plasmodium vivax is known to result in relapses if the hypnozoite stage is not treated. Recurrence of fever with Plasmodium falciparum may be due to inadequate treatment or re-infection. The number of clinically detected episodes of malaria per year was compared between Plasmodium falciparum, the commonest species and the only species reported until recently in Khartoum, and Plasmodium vivax the commonest cause of relapsing recurrent attacks of Malaria. We attempted to calculate the morbidity in each case. It was found that the attack rate was either high or moderate in 100% of the cases of Plasmodium vivax, while in Plasmodium falciparum high and moderate rates were reported in only 32% of patients. Therefore, although it is reported by other workers that malaria induced by species other than Plasmodium falciparum is milder\(^{13,14}\) with less complications and severe malaria with complications such as cerebral malaria occur with Plasmodium falciparum, patients with Plasmodium vivax infection tend to have frequent relapses of malaria as shown from this study, thus affecting patients productivity and well-being.

In the last few years, there were concerns among the health professionals in Sudan about malaria treatment and chloroquine resistance. The Federal Ministry of Health recommended the withdrawal of chloroquine as an anti-malarial in Khartoum State and the whole of Sudan\(^{15}\). In this study, we provide evidence that not all recurrences were due to drug (chloroquine) resistance, as reported by many researchers in different parts of the Sudan including Khartoum\(^{10,11}\). Some of these infections have been shown in this study to be due to relapses of liver hypnozoites of Plasmodium vivax or Plasmodium ovale species. In fact, some authors reported 15% of Plasmodium ovale and Plasmodium vivax in Khartoum state. If clinicians are not aware of this fact many such cases can be missed as recrudescence due to inadequate chloroquine response, especially when inadequate laboratory investigations were done. Thick and thin films and the parasite count should be performed to identify the species in order to avoid the vicious cycle of treatment and retreatment.

In the last two decades, mass displacement of people from the different parts of the Sudan especially the South to the capital has resulted in the alteration of the epidemiology of many diseases including malaria. Some of the malaria species which were not recognized in Khartoum early on, were probably imported by those displaced people. In the 300 patients studied, only 40% were from Khartoum while 60% came from various parts of Sudan, indicating that probably the majority of cases of relapses...
were coming from outside the city\textsuperscript{(4)}. The possibility that patients coming from outside contracted the infection in Khartoum is unlikely because they came from their homes for treatment of an attack, however these Plasmodia of vivax and ovale may soon become endemic in Khartoum. In addition, these patients have only spent 1-2 weeks in Khartoum while the incubation period for the naturally occurring malaria is 13-28 days\textsuperscript{(16)}. So, if they were missed and entered an environment for transmission especially during the rainy season of the year, these parasites could become more prominent in Khartoum in the future. On the other hand, eradication therapy is easy and safe. What is missed is the professional and public awareness. Moreover, this study showed that in a total of 17\% of patients the recurrent malaria was due to either Plasmodium falciparum or mixed Plasmodium vivax and Plasmodium falciparum (10\%). Mixed Plasmodium falciparum and Plasmodium vivax infections, were reported by many researchers from Southwest Nigeria and Thailand\textsuperscript{(17,18,19,20,21,22,23)}. Many studies from the same areas showed mixed complicated co-infections with P. falciparum and P. vivax malaria\textsuperscript{(24,25,26,27,28,29)}. These cases would have been missed as chloroquine resistant malaria or recrudescence, resulting in the spread of these infections in the community with progressive increase in the magnitude of the problem of endemicity of relapsing malarials in Khartoum. This problem could be prevented if physicians would stop treatment based exclusively on clinical presentation and/or the thick blood film for malaria alone. Patients should have at least their thick and thin blood film examined before giving any treatment. Moreover, improving public awareness with respect to avoidance of self medication would help. Training of laboratory technicians in proper preparation and reading of thick and thin blood film for malaria is very crucial in the Sudan where malaria is a major health problem. Therefore, we conclude that in patients presenting with frequent attacks of malaria in Khartoum state, the possibility of Plasmodium vivax or Plasmodium ovale malaria should be considered and primaquine should be used.

\textbf{Acknowledgement}

This study was supported by a grant from the Faculty of Medicine Research Board The Academy of Medical Sciences & Technology (AMST)(2004).

\textbf{References:}


