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Current Issues in Clinical and Laboratory Diagnosis in Malaria

Adeola Orogade
Ahmadu Bello University Teaching Hospital, Shika Zaria
Nigeria

Diagnosis is not the end, but the beginning of practice. ~Martin H. Fischer

1. Introduction

Malaria is a protozoan infection (Najera &Hempel, 2006 as cited in Okwa & Ibidapo, 2010) with protean manifestations in the human species (Mohaptra, 2002; Murthy, 2000; Talib, 1996) causing nearly one million deaths mainly in African children and decreasing gross domestic product by as much as 1.3% in countries with high disease rates (World Health Organization [WHO], 2010). Approximately half of the world's population is at risk of malaria and in 2008; malaria was present in 108 countries and territories of the world (WHO, 2010). The most specific at risk population groups include young children in stable transmission areas, non immune pregnant women, semi immune pregnant women irrespective of HIV status, people with HIV/AIDS, international travelers to malaria endemic from non endemic areas as well as immigrants from endemic areas and their children living in non endemic areas returning to their home countries to visit friends and relatives (WHO, 2010).

Making a diagnosis requires careful clinical examination and laboratory investigation. Whereas malaria could be over diagnosed in endemic areas, (Ammah et al, 1999; Gwer et al, 2007; Hussain et al, 2009; Rehlis & Kurczewska, 2001; Rougemont et al, 2003; Smith et al, 1994;) in the non endemic areas a high index of suspicion is usually required (Berrang –Ford et al, 2008). However, in the most vulnerable: neonates, under fives, (Dzeing-Ella et al 2005) pregnant women, the elderly and non immune(Sengoz inan et al,2010) who may develop potential life threatening complications of *falciparum* malaria, it is important in most cases to make a rapid, accurate diagnosis to ensure prompt treatment. WHO recommends that before giving treatment, clinical malaria should be confirmed by parasite –based diagnosis. Treatment given solely on the basis of symptoms (presumptive diagnosis and treatment) should only be considered when a parasitological diagnosis is not possible. In 2008, 33 of 43 malaria endemic countries in the African region and 45 out of 63 countries in other regions were reported to have developed a policy of parasitological testing of suspected malaria cases in persons of all ages. However, policy development has not matched actual practice. Parasitological test for suspected malaria cases is carried out in less than 20% of individuals living in 21 of the highest disease burden countries.(WHO, 2010).

Moreover, the field of malaria diagnosis is rapidly expanding and bringing to fore hitherto unidentified issues both clinically and in the laboratory. Malaria, once thought to be rare in the newborn (Molyneux, 1989) has in recent times been increasingly reported (Falade et al, 2007; Ibanesebor, 1995; Kamwendo et al, 2002; Lamikanra,1993; Lehner & Andrews, 1988; Muktar et al, 2006; Olowu et al, 2000; Opare,2010; Runsewe –Abiodun et al, 2006; Sowunmi et al, 1996) Incidences range from 0.3 to 33%in these areas (Fisher, 2003) and has brought into question the extent of protection for the baby in the face of maternal placental infections such as HIV. Malaria infection is also described in the first 6 months of life which may be clinically indistinguishable from common bacterial and viral infections (Orogade, 2006).The use of clinical algorithms proposed for malaria diagnosis and their role as predictors for morbidity and mortality are being investigated (Tabitha et al, 2005). With the introduction of rapid diagnostic tests (RDTs) for diagnosis in malaria, there should be less need for presumptive diagnosis based solely on clinical features in high burden areas. However, there is a growing need to monitor and assess the performance of the RDTs in face of varied availability of RDTs and their low specificity and sensitivity in mixed malaria parasite infections. This chapter reviews these current issues in malaria diagnosis and discusses their implication for prompt malaria identification and treatment which are key aspects of the WHO policy and strategy for global malaria control.

2. Clinical features in malaria

2.1 Newborn

2.1.1 Prevalence of congenital malaria

Congenital malaria is defined as the presence of malaria parasites in the peripheral smear of the newborn within the first week of life (Mc Gregory, 1986). It had been thought to be rare due to the known effectiveness of placental barrier but recent reports from malaria endemic areas of incidence in small numbers were made. In a national multicenter study carried out to determine the epidemiology of congenital malaria in Nigeria (Falade et al, 2007), 1,875 babies were assessed within the first 4 hours of life for parasitemia using freshly prepared Giemsa kept at pH 7.2 to stain conventional thick and methanol fixed thin blood smears. A prevalence of 5.1% of patent parasitemia was obtained. It was observed that the mean parasite density in these neonates was low (8-200/µl) as was also reported in an earlier study by Mc Guiness et al (1998). In about two thirds of these babies with parasitemia observed in the first 4 hours of life there was spontaneous parasite clearance by the second day of life, while 33.7% of them persisted and babies became symptomatic within the first 3 days postpartum.

2.1.2 Relationship between malaria in pregnancy and congenital malaria

Antepartum maternal and placental parasitemia have been identified as consistent risk factors for congenital malaria (Orogade et al 2004,2008). Neonates in these studies who had peripartum malaria parasitemia had a 20 fold increased risk of infection. In Papua New Guinea, Lehner et al(1990) observed that where there was a maternal antepartum parasitaemia of 29.4%, there were corresponding cord and neonatal blood parasitemia of 14.6% and 7.7%. They found a significant correlation between anti malarial IgG antibodies in paired maternal and cord blood which indicated transplacental transfer. Using the PCR

methods, Kamwenedo et al (2002) also working in Malawi had demonstrated that cord blood genotypes were a subset of the maternal and placental blood. An issue of current interest relating to the integrity of the placenta has been the role of HIV infection. In several recent studies (Steketee,2004; Ticconi et al, 2003; van Ejik et al, 2003; Verhoeff et al, 1999;), it has been found that HIV impaired the ability of pregnant women to control malaria parasitemia. Results from these studies showed that HIV-infected women experienced consistently higher prevalence of peripheral and placental malaria (summary relative risk = 1.58 and 1.66, respectively), higher parasite densities, and more febrile illnesses, severe anemia, and adverse birth outcomes when compared with HIV-uninfected women, particularly in multigravidae. Thus, HIV alters the typical gravidity-specific pattern of malaria risk by shifting the burden from primarily primigravidae and secundigravidae to all pregnant women.

2.1.3 Implication for malaria prophylaxis in pregnancy

Maternal, especially perinatal malaria is a significant risk factor for congenital malaria. Intermittent preventive therapy (IpT) is recommended by WHO for pregnant women and infants in areas of high transmission in Sub Saharan Africa with stable malaria transmission who are particularly vulnerable to the consequences of malaria. This prophylaxis when adequately taken as two doses at least one month apart substantially reduces both maternal and neonatal morbidity and mortality related to malaria. However, the progress report on malaria prevention (WHO, 2010) indicates that coverage with Intermittent Preventive treatment for pregnant women (IPTp) has remained far below the target levels. Thirty three out of 43 endemic countries in Africa had adopted the IPTp programme by 2009. Only 55% of all women attending antenatal clinics received the second dose of IPTp and since not all women attend antenatal clinic, household surveys in some countries report 2.4% to 62% with an overall weighted average of 12% received the second dose of therapy. This presents a picture that calls for urgent action to reduce maternal malaria and its consequences.

2.1.4 Major clinical features in congenital malaraia

The major clinical features in congenital are fever within the first 24 hours of life, refusal to suck and anaemia (Orogade et al, 2008). Fever is the most consistent feature while some other studies have described hepatosplenomegaly, jaundice, irritability. These are indistinguishable from features commonly seen in neonatal septicaemia. The implication of this is that every febrile neonate born to a mother who is epidemiologically vulnerable for malaria should be screened for malaria as well as other bacterial and viral infections.

2.2 Zero – Five months

2.2.1 Trend of malaria parasitaemia with age

There have been variable findings in prevalence of malaria parasitemia in this age group, ranging from 0% in children less than 3 months (Okwa, 2000) to 17.2 % in the first six months of life (Orogade, 2006) and 27.1% in a similar series by Afolabi et al (2001). Age specific parasite rates showed a sharp drop in frequency of parasitemia from first to second week of life (Orogade, 2006), but this gradually increases with age till the sixth month of life. This initial sharp drop has been attributed to spontaneous clearance of parasites which

occurs in some babies at this time. It is noteworthy that about one fifth of all parasitemia occurs in the first month of life. The neonatal age group in this study formed a large burden of the disease prevalence. Mothers who were gravida 1-2, who did not utilize chemoprophylaxis in pregnancy and had education ranging from none to primary school level were important as risk factors for malaria parasitemia in this age group. These same risk factors have also been identified especially in malaria endemic regions where women in their first two pregnancies who develop maternal parasitemia have been identified as high risk for maternal anaemia and fetal complications such as fetal wastages, still births, premature deliveries and low birth weight in the newborn babies. In this study parasitemia documented in the first week of life would likely have resulted from congenital acquisition as prevalence of 9.31% obtained closely compares to the recent congenital malaria reports

There is an average low mean parasite density rate of 64.82 ± 50.61/μL (Orogade, 2006)and this does not vary with age groups, χ2 (Bartlett's test) = 6.09, p=0.29. The mean Haematocrit is also significantly lower than controls low at 35.62 ± 7.09.%. Analysis of variants revealed a significant positive correlation between the mean haematocrit and malaria parasitemia.

 Use of malaria prevention was 93.6% and this had a significant impact on reduction of parasitemia. Of the methods used for malaria prevention, window/door net screening and insecticides sprays were the most common. Less than half of mothers used bednets for their babies and only 7(2.8%)of these were insecticide treated bednets. Other non conventional methods used were local chemicals (*ota pia-pia*) sprayed on floors and walls in the rooms where the children slept. This apparently significantly reduced parasitemia where it was used one and half fold. Of all the babies seen only 47.4% were being exclusive breast fed.

Beyond the neonatal period, the use of malaria prevention methods in particular *ota pia-pia* were significant for protection against malaria. *Ota pia-pia* which was used in 13.37% of cases seems to have been quite effective. This is a locally prepared chemical which when sprayed on floors and walls in the rooms are effective anti vector agents. However, the exact chemical compositions of these chemicals are yet to be fully analyzed and the safety of their use is not documented. Moreso, their potential harmful effects to the newborn and infant are unknown. Insecticide treated bednets have been introduced in Nigeria as an effective measure of malaria prophylaxis. However Orogade (2006) revealed a very poor utilization of this proven effective measure. Bednets, which has been a preventive measure of long standing use was utilized for less than half of the babies. There was rather more common use of window/door net screens as well as insecticide sprays which have also been known and in use for several years but which are not as effective.

There was low educational status in more than a third of the mothers and this affects how well informed the mothers would be especially about health preventive matters. This less popular use of bednets as well as the level of health information the mothers may comprehend could explain the poor use of treated bednets. Socioeconomic status of families, though not investigated in this study has been found to be a reflection of the choice of malaria preventive measures, in this region. Socioeconomic status determines the economic power to sustain the preventive measure chosen, so cheaper, locally made and available means would be more acceptable.

2.2.2 Clinical effects of parasitemia

The major clinical symptoms apart from fever were cough, diarrhea generalized rash, excessive crying and vomiting (Afolabi, 2001; Orogade, 2006). All these symptoms are non specific but had about one half to two fold occurrence in children with malaria than in others without malaria parasitemia. Fever however seems to be the most constant factor even in the older infant and children. The babies had a low mean temperature of 37.7°C ± 0.58 and respiratory distress with respiratory rate of 45.66 ± 21.6 cycles/minute. Dehydration, palmar pallor, jaundice and hepatomegaly were the commonest signs though not of significant relationship. Palmar pallor is not a good indicator of anaemia $\chi2 = 1.24$, p= 0.264. The children with parasitemia had relatively low grade fever with mean temperatures of 37.7 ± 0.58 and tachycardia, mean pulse rate of 137.67 ± 9.94..Overall most of the clinical features were non-specific and could not be attributable to only malaria. Malaria in the children aged 0-5 months though the prevalences and parasite densities are lower, yet it produces significant morbidity in the children. Prevention of malaria in the pregnant women by chemoprophylaxis is still an area that requires focus and advocacy and public enlightenment on the use of insecticide treated nets for more widespread use is needed.

2.3 Six months – Five years

2.3.1 Clinical features of complicated and uncomplicated malaria

In the areas of stable malaria transmission, this group of children are the most affected in morbidity and mortality. Reporting the findings of severe malaria in Gabonese children, children Dzeing-Ella et al (2005) observed that most children with severe malaria are under 5 years old. Commonest features were anaemia, respiratory distress, cerebral malaria hypoglycaemia. Anaemia was commoner in children under 18 months of age, while cerebral malaria was commoner above 18 months. Poor prognostic factors were coma, hyperlactaemia and hypoglycaemia. Another study reporting uncomplicated malaria in febrile under 5 years children (Ikeh & Teclaire, 2008) showed prevalences of about 52.2% and the most common presentation was fever. Most of the children within this age group at are various levels of developing immunity and yet have parasite rates that could range from 80-90%. This explains their potential to develop severe malaria.

2.3.2 Use of clinical algorithms and predictors for malaria morbidity and mortality

Development of clinical algorithms were initially done as guidelines to ensure that the young child at risk of potentially fatal diseases were identified and received prompt attention and commenced some management at the community level. In this guideline, the Integrated Management of Childhood Diseases [IMCI], children under 5 years of age, living in areas of high malaria endemicity were to be treated for malaria if they presented to a health facility with fever, temp >37. 5°C. Studies by Tabitha et al (2005) found in a study that using a set of symptoms and signs with highest sensitivity and specificity and comparing these to parasitemia, a significant proportion of patients would have been sent home untreated. This tendency increased with increasing age. In situations as alluded to by the report of Khan et al (2005), the other issue was that often there were co-morbidities in febrile illness in some communities. Simply using algorithms for treatment of malaria might also lead to delay in treatment of other equally life threatening infections like Enteric fever which

was commonly observed in their study. Algorithms on the one hand may lead to wastefulness of treatment supplies and on the other hand endanger lives for other possibly life threatening conditions.

2.4 School aged 5-12years

2.4.1 Asymptomatic malaria parasitemia and its implication for malaria control

The school aged child in an area of high endemicity typically has malaria parasite prevalence rates of up to 75%. Despite this high rates of parasitemia, theses children largely remain asymptomatic, having developed sufficient immunity which is both antiparastic and antitoxic to keep them from having clinical infection (Bruce Chwatt et al as cited by Orogade et al, 2002). In their study, Orogade et al (2002) also observed that these asymptomatic children had high levels of gametocytaemia (65%). Possible association between asymptomatic parasitemia and the utilization of vector control measures were analyzed. Vector control measure utilization was strongly related and inversely associated with the rates of ASMP. The estimation of ASMP is therefore recommended for use as an index for evaluation of malaria vector control programmes.

3. Laboratory diagnosis in malaria

3.1 Role of presumptive versus laboratory diagnosis for treatment

The policy and strategies for Malaria control by the WHO hinges on Malaria prevention, diagnosis and treatment. Diagnosis of malaria has been a challenge in both endemic and non endemic countries alike: the former having overdiagnosis with consequences of wastage of resources for treatment, excessive drug pressure and antimalarial drug resistance and the latter under diagnosis or even missed diagnosis which in some cases lead to malaria mortality. Gwer et al (2007) in an over view of problems associated with overdiagnosis in severe malaria identified the unavailability and unreliable parasitological confirmation of parasitemia as the greatest challenge in endemic countries.

The commonest symptom of malaria is fever and the subject of how many febrile episodes in susceptible populations in endemic areas even in the face of detectable parasitemia is attributable to malaria has been of immense research. Mc Guiness et al (1998) proposed some clinical case definitions for malaria in southern Ghana. Using logistic regression to model fever risk as continuous function of parasite density, fever attributable to malaria was defined by season and age groups. It was concluded that attributable fever was 51% and 22% in wet and dry seasons respectively for infants while in the children older than one year, it was higher in both seasons: 89% and 36% respectively. They also observed a lower estimated parasite density threshold for initiation of a febrile episode in infants than the older child. In another study Rougement et al (1991) working in Niger, West Africa investigated parasitemia based on 3 criteria of febrile episodes: the duration, intensity and possibility of a non malarial cause. The proportion of febrile cases attributable to parasitemia ranged from 0 to 0.92 but there was no association between parasitemia and low intensity fevers, or fever of greater than 3 days duration in the presence of an obvious non malaria cause. They however also found highly significant relationship between parasitemia and fever in the high transmission season. It seems from these studies that making a

diagnosis by clinical case definitions based on epidemiological factors may be a useful tool in areas where laboratory facilities are not always available or reliable.

However, Valerie et al (2010) again observed from studies done over 20years that there was a growing decline in malaria transmission in East Africa and a subsequent proportion of fever associated with Plasmodium falciparum. They concluded that the decline provides evidence for policy change from presumptive antimalarial therapy to laboratory diagnosis before treatment (Valerie et al 2009, 2010). Much has gone into training of personnel for laboratory diagnosis and as Ngasala et al (2008) reported on the impact of training in clinical and microscopy diagnosis of childhood malarial on prescription and health outcome: microscopy reduces prescription but there is great variation in accuracy of readings. With this observation, the caution by English et al (2009) might be only apt that rapid universal policy change that abandons presumptive antimalarial treatment for African children might be premature and in fact cause more harm than good.

3.2 Comparisons between rapid diagnostic tests and microscopy in malaria

The gold standard for malaria parasite identification and quantification has been the microscopic examination of thick and fixed thin blood smears using Giemsa stain. In cases of anticipated low malaria parasite densities, care should be taken to maintain the pH of the stain around 7 and a freshly prepared stain achieves better results (Orogade et al, 2008). Other techniques utilised to enhance microscopy include the acridine orange fluorescent technique (Keiser el al, 2002; Lowe et al, 1996; Nicholas, 1997). This has proved to be quite useful but requires the additional requirements of fluorescent microscopy. Maintenance of a good quality, effective microscopy service involves the provision of high quality supplies, reagents, microscopes as well as technical competence and an adequate work environment to prepare usable blood films (Coleman et al, 2002; Durrheim et al, 1997, Kachur et al, 1998; Kain et al, 1998; Kilan et al, 2000; Omeara et al, 2005 as cited in Bell et al, 2006).

Obstacles to lab diagnosis of malaria as have been reported in Mali (Dolo et al, 2010) are the same experience in most developing countries where malaria is endemic. These includeunderuse of laboratory diagnosis by clinicians, absence of qualified laboratory facilities in some locations, and poor continuous professional education of laboratory technicians.

Introduction of Rapid Diagnostic tests was intended to fill the need for accuracy, speed and reliability which standard microscopy has fallen short of. These are antigen detecting rapid diagnostic tests which detect the histidine rich protein 2(HRP$_2$) and Plasmodium lactate dehydrogenase(pLDH) which are usually produced during the erythrocytic cycle. Several studies have evaluated the effectiveness of these tests compared with microscopy and the results have consistently shown high sensitivity and specificity but inability to differentiate mixed infections (Chinkhumba, 2010; Gatti et al, 2007; Tomas et al, 2001). However the successful implementation of RDT has been bedevilled by poor product performance, inadequate methods to determine the quality of products and a lack of emphasis and capacity to deal with these.(Bell et al 2006) Another group (Christopher et al, 2008) described the limitations of RDTs as having: all or none test results, inability to diagnose non falciparum malaria, variable heat stability and safety risks related to blood sampling (especially HIV and hepatitis B). Also of equal concern is that negative RDT results are often ignored and patients are treated anyway.

3.3 Provision of centralised rapid diagnostic test centres for more efficient diagnosis

To ascertain some degree of quality assurance and uniformity of results there is need to develop centralised RDT centres. These centres serve for purchase, transport, storage of RDTs kits as well as provide training for personnel that administer the tests at community level. It could serve as a reference laboratory since there are more highly skilled personnel and results of tests could be ascertained. Church et al (2003), describe such a centre which has supported and facilitated the RDT programme. Bastiaens et al (2011) have described results of researches carried on at such centres which showed improved diagnosis of malaria when government policy changed to implementation of testing before treatment in malaria. However, Derua et al (2011), describe in their study the perception of the users and health service providers which were dissimilar. Whereas the clinicians and patients were satisfied with the overall performance of the labs, the laboratory personnel expressed dissatisfaction over working conditions and some details of laboratory procedures. This signal is worth more investigation across regional centres so that the efforts gained would not be undermined. There is also noted that there is need to integrate these services into existing healthcare services to ensure sustainability in the long run.

3.4 Newer microscopic techniques

Due to the limitations of the rapid diagnostic tests already noted, the RDTs are not the end in malaria diagnosis. Using Polymerase chain reaction (PCR) techniques some of the limitations have been overcome. Myjak et al (2002), describe PCR techniques that have been utilised to enhance malaria diagnosis in mixed infections and especially in patients with low parasite densities, while Patsoula et al (2003) reported a single step PCR based method to differentiate mixed infections and Ahmet et al (2010) have used nested PCR and Real-Time PCR for detection of *Plasmodium vivax.*

Reliable enumeration of malaria parasites in thick blood film using digital analysis is also described by Frean (2009).

3.5 Other non specific laboratory tests in malaria diagnosis

Some workers have identified some other non malaria haematological indicators of the diagnosis and course of malaria (Ida E et al, 2007). Such include low levels of thrombocyte, leucocytes and coagulation factors II- VII-X as well as raised levels of C-reactive protein, lactate dehydrogenase and bilirubin. It is suggested that these could serve as markers of active disease as well as for monitoring during treatment and especially so when malaria parasites are difficult to identify.

4. Conclusion

- There has been tremendous increase in research in malaria diagnosis in the last decade.
- There should be an increased awareness and identification of congenital, neonatal and early infancy malaria especially in endemic areas. This also calls for closer monitoring and care of the pregnant woman at risk of malaria infection
- Clinical algorithms for malaria diagnosis are not sensitive enough for predicting morbidity or mortality.

- Reliance on rapid diagnostic tests should be put into context. Areas with mixed malaria parasite infection would need some other confirmatory tests while in other areas, uncertain distribution of reagents and trained personnel could limit the effectiveness of RDTs in diagnosis.

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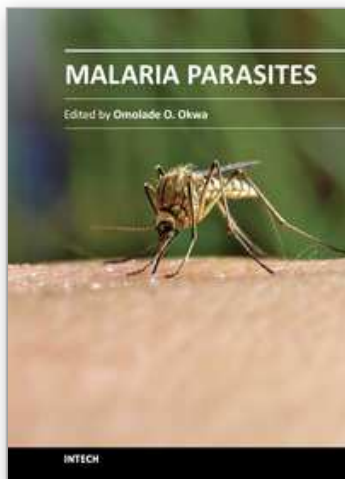
Malaria Parasites

Edited by Dr. Omolade Okwa

Malaria is a global disease in the world today but most common in the poorest countries of the world, with 90% of deaths occurring in sub-Saharan Africa. This book provides information on global efforts made by scientist which cuts across the continents of the world. Concerted efforts such as symbiont based malaria control; new applications in avian malaria studies; development of humanized mice to study P.falciparium (the most virulent species of malaria parasite); and current issues in laboratory diagnosis will support the prompt treatment of malaria. Research is ultimately gaining more grounds in the quest to provide vaccine for the prevention of malaria. The book features research aimed to bring a lasting solution to the malaria problem and what we should be doing now to face malaria, which is definitely useful for health policies in the twenty first century.

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