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Diagnosis of Malaria – Status of Malaria Rapid Diagnostic Test

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Abstract

Malaria is the most important parasitic disease of humans. Cochrane Review support the World Health Organization (WHO) guidelines for malaria treatment which recommend that in all settings clinical suspicion of malaria should be confirmed by parasitological diagnosis using microscopy or Malarial Rapid Diagnostic Test (MRDT). Microscopic diagnosis sensitivity requires expertise and may not be feasible in developing countries in endemic areas and hence MRDT may complement this test. As declared in the World Malaria report 2013 there has been increased use of MRDT which reflect that this test is being taken seriously for diagnostic and management. With every diagnosis test there are lacunae which must be reviewed before interpretation of result. A rapid diagnosis test may be used in endemic areas because it is cost effective, so that rational treatment would be given and hence prevent drug resistance as well as reduce the economic burden.

Keywords: Malaria; MRDT; pHRP-2; pLDH; LAMP; Immuno chromatographic

Introduction

Globally an estimated 3.4 billion people are at risk of malaria. WHO estimates that 207 million cases of malaria occurred globally in 2012 (135–287 million) and 6,27,000 deaths (4,73,000–7,89,000) [1]. Detection of parasites in blood is a gold standard for diagnosis of malaria where patients present with clinical manifestation of malaria. For such a large population suffering from malaria, WHO malaria global programme recommends the use of Malaria Rapid Diagnostic Tests (MRDTs) which are able to detect malarial specific protein antigens and enzymes [2,3]. MRDT can also be easily deployed in field at large scale for treatment strategy.

Detection of malarial parasites by MRDT for diagnosis

Malaria is caused by five species of parasite that affect humans, and all of these species belong to the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. Of these, P. falciparum and P. vivax are the most important. Current MRDTs are based on detection of 3 different types of Plasmodium antigen. The first is Plasmodium Histidine Rich Protein-2 (pHRP-2), which can be specific to *P. falciparum* (PfHRP-2) or *P. vivax*. The second is Plasmodium Lactate Dehydrogenase (pLDH), which can be specific to *P. falciparum* or *P. vivax* or be a variant that is common to all Plasmodium species (pan specific). The last is Plasmodium aldolase, which is pan specific. By combining detection of these 3 antigens on an Immune Chromatographic Strip (ICS) assay, MRDTs can detect any malaria species: *P. falciparum* alone, *P. vivax* alone or any combination thereof [4].

Accuracy of MRDT

Anti-PfHRP-2/Anti-Plasmodium aldolase has shown 95-97% sensitivity for *P. falciparum*, 87-100% for *P. vivax* and 62% *for P. ovale*/ *P. malariae* with specificity of 99% for all plasmodium species. pLDH is 87-96% sensitivity for *P.falciparum*, 85-96% for *P. vivax* and 57% for *P. ovale* and 47% for *P. malariae* with specificity of 99-100% for all plasmodium species [5,6]. However the sensitivity of above tests drops when parasitemias is <100/μL [5]. High levels of *P. falciparum* parasitemia may give false-positive results with pLDH assays designed to detect *P. vivax* [7]. There are variants of P. falciparum in South America which cannot be detected as they lack the antigen and hence the result will be false negative [8,9]. Cross-reactions with some assays occurs with rheumatoid factor or other circulating auto-antibodies [10,11]. MRDTs cannot be used to determine the magnitude of parasitemia which is important indicator of disease severity and for periodically monitoring to ensure adequate response to therapy.

Easy Handling and Cost Effectiveness

Rapid diagnostic tests detect malaria antigen in a small amount of blood, usually 5–15 μL, by immunochromatographic assay with monoclonal antibodies directed against the target parasite antigen and impregnated on a test strip. The result, usually a colored test line, is obtained in 5–20 min [12]. MRDTs require no capital investment or electricity, are simple to perform, reproducible and are easy to interpret. Hence with early diagnosis and prompt treatment reduces morbidity and mortality from the disease.

Clinical Utility of MRDT for Treatment

In tropical countries there are various other diseases mimicking as malarial fever eg. Dengue, leptospirosis, enteric fever; the positivity of MRDT aids in delineating the disease. Hence it limits treatment to patients who have malaria and no other febrile illnesses. The restricted use of effective anti-malarial treatment will decrease the consumption of unnecessary use of anti-malarial drugs and decrease the economic burden. Moreover it will prevent drug resistance where due to widespread empiric use of chloroquine-based therapy, it is no longer safe and effective. Artemisinin combination therapy are expensive drug and can be used judiciously in malarial patient and prevent drug

resistance [2]. WHO recommends for such malaria diagnostic tests before starting the treatment where such tests are available. Being rapid test *P. falciparum* malaria is distinguished which the more life is threatening and warrants prompt treatment. Detection of *P. ovale* or *P. vivax* malaria will ensure that malaria is radically cured. Mixed infections which are also seen can be easily identified and treatment tailored accordingly. The sensitivity and specificity pattern of MRDT will help in epidemiological studies for different geographical distribution. Few cautions should be considered in interpretation of MRDT in endemic areas where reinfection are common or infection can be due to other causes. pHRP-2 antigen is not cleared from blood and persists for few weeks after treatment so MRDT should not be used for treatment monitoring. Although pLDH and aldolase are cleared quickly from blood after treatment, with clearance of asexual parasite forms, gametocytes still persist and the test may remain positive hence should not be used to monitor response to therapy [13]. In pregnancy MRDT have been used with peripheral and placental blood specimens for the detection of malaria in pregnancy with variable outcomes [14]. As discussed earlier, severity of malaria depends on parasitemia. However in people with antimalarial immunity residing in endemic areas may present with asymptomatic parasitemia while in people with no antimalarial immunity and undetectable parasitemia will have severe malaria and it may be missed by MRDT whose sensitivity will fail [15]. Otherwise would happen that MRDT may be positive due to antigenemia and confirming the diagnosis of malaria where blood smears may be negative.

Conclusion

Rapid, accurate, and accessible detection of malaria parasites has an important role in diagnosis and in promoting more cost-effective use of increasingly costly drugs and preventing drug resistance. In endemic where there is lack of good-quality microscopy Malarial Rapid Diagnostic Tests (MRDTs) can potentially provide accurate diagnosis to all populations at-risk. No doubt that the number of MRDT delivered by National Malaria Control Programmes (NMCPs) has increased rapidly, from less than 200000 in 2005 to more than 108 million in 2012 [16]. A new commercial molecular assay based on Loop-Mediated Isothermal Amplification (LAMP) is also being assessed for field use to overcome the pitfalls of present diagnostic test [17].

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