DIAGNOSTIC DILEMMA: IS IT SEVERE MALARIA?

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Abstract

Symptoms of altered consciousness, respiratory distress, and the inability to sit up unaided (prostration) indicate a medical emergency and are the symptoms of malaria. Malaria is severe when background immunity is low; optimal outcome for severe malaria requires accurate diagnosis followed by treatment and supportive care. However, clinically differentiating severe malaria from other serious medical emergencies is difficult.

The gold standard for diagnosing malaria is demonstration of parasite in thick and thin Giemsa stained smears of peripheral blood. Successful treatment and prognosis depends on identifying the species and measuring its concentration. However, unreliable laboratory support can lead to health-care workers treating for malaria after either not ordering a smear, or ignoring a negative smear.

The adjunctive use of rapid diagnostic tests for malaria will improve the diagnostic capacity of health centers to confirm or rule out the diagnosis of malaria, particularly in areas of lower malaria transmission. When both light microscopy and rapid diagnostic tests fail to confirm malaria, other infective causes should be considered.

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Introduction

Every year malaria infects about 500 million humans worldwide and is said to cause between 1 and 3 million deaths. Nearly 3 billion humans live in areas where malaria is prevalent.(1) Deaths from severe malaria are usually from Plasmodium falciparum infections in humans with limited background immunity: infants and children under 5 years of age, especially in sub-Saharan Africa, travelers, and migrant workers. Asymptomatic (sub-clinical) malaria is common among older children and adults living in regions with continuous high levels of transmission: at lower altitudes in the humid tropics. Infected mothers confer passive immunity to neonates; however this protection lasts only about 9 months. From 9 months to about 5 years of age children are susceptible to severe malaria and may develop profound anemia, hypoglycemia, and seizures.

A community-based survey of households in 3 districts in Togo showed that 62% of children 9 months to 5 years of age were infected with malaria parasites, and 21.7% of these children had moderate to severe anemia (hemoglobin < 8 $g.dL^{-1}$).(2) Mortality from malarial infection, when plotted against age, has a U shaped curve. The mortality of malaria is greater in children 0 to 5 years of age and in adults in areas with lower malaria transmission.(3)

Reducing malaria morbidity and mortality requires attention to primary, secondary, and tertiary prevention; each form is defined as follows:

1.Primary prevention protects healthy humans from contracting the disease. Attempts include chemoprophylaxis of travelers, the drainage of standing water, the use of mosquito larvacides, spraying programs, insecticide treated nets, and repellents.

2.Secondary prevention is the early detection and treatment of humans who have contracted the disease and who can infect others.

3.Tertiary prevention is the long-term management of humans with disease complications.

Secondary prevention of morbidity and mortality from severe malaria involves accurate diagnosis and early, appropriate treatment. Severe malaria syndromes may include other manifestations: central nervous system dysfunction, circulatory collapse, severe anemia, metabolic acidosis, septicemia, acute renal failure, coagulation disorders, pulmonary edema, hepatic dysfunction, and hypoglycemia. Accurate diagnosis of the etiological agent, whatever it may be, is critically important. Much of the overall mortality attributed to malaria may result from the misidentification of malaria as the etiological agent. Other etiological agents mimic or complicate the severe malaria syndrome, including the following:

1.Anemia or other causes

2.Viral infections: dengue fever, Epstein Barr Virus (infectious mononucleosis), Parvovirus B19, echoviruses, dengue fever, viral gastroenteritis,

viral hepatitis, viral meningitis, and HIV/AIDS

3.Other parasites: trypanosomiasis

4.Rickettsia and rickettsia-like diseases: s Babesiosis, Ehrlichiosis, and typhus

5.Bacterial infections such as pneumonia, bacterial endocarditis, bacterial meningitis, leptospirosis, and typhoid fever

6.Toxic crises such as insecticide poisoning by cholinesterase inhibitors

Treatment requires timely use of anti-malarial therapy and careful management of the hypoglycemia, fluid and electrolyte disturbances, profound anemia, seizures, acute renal failure, pulmonary edema, hepatic dysfunction, sepsis, and bleeding disorders that may co-occur in severe malaria.

Difficulties in diagnosing severe malaria

The World Health Organization defines cerebral malaria as "the presence of an unarousable coma not attributable to other causes in a person with falciparum malaria."(4) Makani and colleagues noted that only 1% of patients admitted to treatment facilities in Tanzania with a diagnosis of cerebral malaria fulfilled the WHO criteria.(5) Only 7.5% of 199 patients had a positive malaria smear, a prevalence lower than that occurring in the asymptomatic local population (9.3%). The mortality of "cerebral malaria" in smear negative cases was higher than in cases with positive malarial smears. These authors concluded that cerebral malaria was grossly over-diagnosed, leading to the insufficient investigation and treatment of other diagnoses, with resultant increased mortality. From a prospective study, Reyburn concluded that malaria mortality in Tanzanian hospitals was overestimated by a factor of at least 2.(6)

The problem in diagnosis may stem from circular reasoning: health-care providers may order a test when they think it will be positive, and not order it when they think it will be negative. This amounts to coming to a conclusion before doing an investigation. Health officers may disregard evidence that does not support their diagnosis of cerebral malaria, and treat it anyway, often to the detriment of their patients. The routine over-diagnosis of malaria can result in chemo-resistance, over-consumption of anti-malarial agents (costly and ineffective), and underestimation of other causes.(7)

However, it would be incorrect to conclude that all of the 99% of Tanzanian patients admitted with the diagnosis of cerebral malaria who failed to meet the WHO definition did not have it. The WHO definition of cerebral malaria has high specificity but low sensitivity. Virtually everyone who satisfies the WHO diagnostic criteria will have cerebral malaria; however many who do not meet the WHO definition of cerebral malaria will also have it. Malaria may result in central nervous system symptoms that fall short of unarousable coma; such symptoms include lesser degrees of obtundation, multiple seizures, agitation, delirium, psychosis, divergent gaze, and the presence of a pout reflex. Remote hospitals and heath centers may lack the resources to rule out all of the other causes of coma. Finally, for a number of reasons, the supporting laboratory may not be able to demonstrate the presence of malaria parasite in the peripheral blood smear, even when it is the culprit. The concentration of parasites in the peripheral smear may have been below the limits of detection, having been sequestrated in organs or vascular beds or reduced by prior anti-malarial treatment. The laboratory may have misread the smear because of the inexperience of the microscopist, faulty technique, poor slides and microscopes, or degraded reagents. Finally, the laboratory may have been closed when the patient came for treatment.

Methods of Detecting Malaria

Light microscopy

The gold standard of the diagnosis of malaria is the detection, quantification, and speciation of the parasite in Giemsa-stained thick and thin smears of peripheral blood. When measured by experienced microscopists with clean slides, clean stains, good microscopes, and proper techniques, light microscopy of peripheral blood smears is both sensitive and specific. However many health centers diagnosing malaria do not consistently have these ideal conditions. Shortages of staining reagents, poor quality microscopes, improper pH or degradation of staining reagents, frequent power outages, inadequate water supply, and examination of too few microscopic fields reduce the reliability of the malaria smear. Laboratory services may not be available when the patient arrives. As a result, many health providers will treat for malaria when the malaria smear is negative, or they will not order a smear in the first place.(8)

Investigators in Thailand correctly identified the malaria infection in 10% of P falciparum cases, and in 7.1% P vivax cases. They concluded that the examination of Giemsa-stained thick and thin smears for malaria under conditions in field health centers was insensitive to detect low levels of parasitemia. Their study involved the use of expert microscopists who examined smears examined for five minutes (50 to 100 microscopic fields) with natural light and 700 x magnification-mimicking conditions that commonly exist in remote health-care centers where lack of electrical power may preclude consistent use of 1,000 power oil immersion microscopy.(9)

High technology malaria detection

Malaria can be accurately diagnosed with some lab-

oratory tests The most accurate of these involve polymerase chain reaction tests for plasmodium DNA and TaqMan real-time PCR methodology.(10,11) Laser light depolarization analysis for malarial pigment (hemozoin) in white blood cells is specific for malarial infection and has a sensitivity 80%.(12-15) However, outside of major diagnostic centers that enjoy a steady source of electrical power, rapid access to specialized supplies and teams of highly-skilled technicians, these technologies are not useful for the diagnosis of malaria.

Rapid Diagnostic Tests (RDTs) for Malaria

When resources are limited and severely ill patients need immediate treatment, diagnostic tests must be:

1.Stable at local temperature and humidity

2.>90% sensitive and specific for P falciparum

3.Functional without a reliable source of electrical power

4.Usable without highly-trained personnel

5.Usable without delicate, high-maintenance equipment

6.Quick to yield results, for effective intervention

7.Affordable and accessible by health centers in endemic areas.

Rapid Diagnostic Tests (RDTs) for malaria use immunochromatographic methodologies that target either parasite lactic dehydrogenase (p-LDH) or histidine rich protein (HRP-2). P-LDH tests have fewer false positives in highly endemic areas and in post-treatment surveys. HRP-2 tests are more sensitive and can detect falciparum parasite by-products when parasite load is lower parasite.

Marx and colleagues (2005) reported a meta-analysis of studies of immunochromatographic test accuracy for the detection of P falciparum malaria in non-immune patients. Tests that targeted HRP-2 proteins were the most sensitive and specific for p. falciparum had 88-99% sensitivity and 95-100% specificity. Tests that targeted parasite LDH had similar sensitivity (79-95%) but greater specificity (98-100%). The RDTs were specific for other types of malaria but not sufficiently sensitive to recommend their current use.(16) In Thailand, the Optimal-IT (pLDH) test was reported to be 88% sensitive and 92% specific.(17) Craig, in South Africa, took blood samples having known P falciparum malaria parasite loads as determined by PCR, and diluted them with normal blood to test the sensitivity of 10 different enzyme-linked immuno-absorbent assay studies. Test sensitivities were expressed as the 50% detection rate, which is the parasite load needed for a positive test result 50% of the time. The parasite load enabling 50% test sensitivity readings ranged from 3.3 to 91 parasites per microL. This low parasitemia produces false negatives in field microscopy in many field settings. Durrheim, also in South Africa, citing the problems with the availability of accurate light microscopy, reported that the ICT test for malaria empowered field health workers to make fast, accurate diagnoses of malaria without the support of a laboratory. During an outbreak of malaria in central India, the Para-Check test was found to have high sensitivity (100%), specificity (67%), positive (94%) and negative predictive value (100%) for migrant workers, and even better performance for indigenous populations with sensitivity of 100% and a sensitivity of 97.3%.(20) The rapid The HRP-2 dip-stick assay was positive in 31 of 34 of the severe falciparum malaria cases in Addis Abbaba with sensitivity of 91.2%, specificity of 93.7%, positive predictive value (PPV) of 93.9% and negative predictive value (NPV) of 90.9%.(22)

RDTs are not a magic bullet for diagnosis of clinical malaria. When positive in a non-endemic area in a patient with fever, RDTs diagnose clinical malaria. However in areas of high malaria transmission, RDTs do not measure parasite concentrations n asymptomatic parasitemia. In combination with careful light microscopy they can help determine whether malaria is the likely cause of the patient's symptoms.(23)

Malaria is clinically significant in blood with >10,000 parasites per microL(~0.2% parasitized red blood cells). The likelihood of a severe malaria syndrome increases when $\geq$2% red blood cells are parasitized, that is, blood has $\geq$100,000 parasites per microL. The parasite concentration is estimated by counting the number of asexual parasites (non-gametocytes) in thick films fields containing a total of 200 white blood cells and multiplying by 40. This assumes a white blood cell count of 8,000. Another method to estimate parasite concentration (number of parasites per microL) is to multiply the number of parasites in 1,000 red blood cells in a thin film x hematocrit X 1,256. Hemazoin pigment in $\geq$ 5% of neutrophilic or monocytic white blood cells indicates severe malarial syndromes.

Conclusions

Health-care workers in malaria endemic areas must systematically answer 3 questions whenever they suspect severe malaria.

1.Does the patient have malaria?

2.If the patient has malaria, is it clinically significant?

3.If no to questions 2 or 3, then what caused the symptoms?

Treating severe "malaria" syndromes presumptively, without verifying its presence, or carefully addressing other potential causes of the patient's syndrome, has often been fatal. RPTs are about as sensitive as

expert light microscopy for the detection of sensitive and specific for falciparum malaria. However, these slides will not help the clinician decide whether or not the malaria is clinically relevant, particularly in areas of high transmission. When a patient either does not have malaria or it is not clinically relevant, the question becomes what has caused the symptoms. Improving the capacity of health-care workers to diagnose malaria will prolong many lives. However, improving treatment outcomes for critically ill patients in resource-limited areas requires improved reliability and availability of essential diagnostic services in the field laboratory. Basic clinical pathology is not glamorous, consequently agencies that fund health-care initiatives seldom focus on laboratory upgrades. However, I urge this focus.

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