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Recent Progress in the Pathophysiology and Diagnosis of Imported Malaria. Review article

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I. Introduction

Malaria is caused by obligatory intracellular parasites belonging to the Plasmodium genus.. Even though there are more than 120 species of Plasmodium, only five—*P. falciparum, P. vivax, P. ovale, P. malariae*, and *P. knowlesi*—are known to infect humans. P. falciparum is the most prevalent and causes over 90% of malaria-related deaths .The transmission occurs through the bite of a female *Anopheles* mosquito, which acts as a vector for the disease. Although extremely rare, human-to-human transmission can happen by organ transplants, blood transfusions, needle stick injuries in medical facilities, or vertical transmission from mother to child. The parasite enters red blood cells, or erythrocytes, and multiplies there over the course of its intricate life cycle. The parasite directly consumes the infected erythrocyte's hemoglobin to obtain energy and necessary metabolites. Three unique morphological stages—the ring, trophozoite, and schizont stages—can be seen under a microscope as the erythrocyte matures. The parasites that cause malaria periodically invade and re-invade areas in red blood cells lead to an exponential growth in the number of infected red blood cells, which causes the fever, headache, rigors, and nausea that are typically associated with malaria.(1)

Keywords: Plasmodium, Imported malaria, Severe malaria, Malaria transmission, Rapid diagnostic test. Molecular diagnosis.

Epidemiology

Worldwide malaria cases increased to 247 million in 2021 from 245 million in 2020 and 232 million in 2019, respectively. Disruptions in malaria control efforts during the COVID-19 epidemic were blamed for the recent upswing. *P. falciparum*, the parasite that causes over 90% of malaria cases, is found in the African Region. Conversely, only 2 % of malaria cases worldwide are caused by *P. vivax*. In endemic locations where both species coexist, the prevalence of *P. vivax* infections has been rising while that of *P. falciparum* cases has been declining, despite lower relative numbers. Malaria-related deaths were predicted to account for between 568,000 and 625,000 deaths in 2019–2021. The majority of fatal instances involved youngsters under the age of five and were brought on by *P. falciparum*.(2)

Pathophysiology and Microbiology.The two hosts that the Plasmodium species uses to complete its life cycle are vertebrates and mosquitoes.

Humans are infected when Plasmodium sporozoites migrate from infected Anopheles mosquito's salivary glands into dermis through mosquito bite.

Sporozoites move to the liver in a matter of minutes to hours, where they develop into liver-stage schizonts. Typically, the hepatocytic schizont stage lasts between two and ten days. Between 2,000 and 40,000 merozoites are produced by each liver schizont, and these are released into the bloodstream to infiltrate red blood cells. Merozoites develop into trophozoites and then, in the end, into blood-stage schizonts in erythrocytes. By releasing an increasing number of merozoites, the schizonts prolong an asexual cycle and increase the overall number of parasites within their human host. However, some trophozoites do not go through an asexual stages, and instead give rise to the sexual stage known as gametocytes, which is infectious to mosquitoes. Gametocytes will produce zygotes in the gut of the mosquito after being consumed by another feeding mosquito during a later bite, and fresh parasites will move to the salivary glands of the mosquito to complete the cycle.(3.4)

Differences in the geographic distribution and clinical presentation of different Plasmodium species are caused by genetic and physiological variations. The majority of severe and fatal cases of malaria are caused by *P. falciparum*, a parasite that produces special proteins that are expressed on the surface of infected erythrocytes and promote their adhesion to platelets, endothelium, and uninfected erythrocytes. In the clinical setting, this phenomenon encourages the sequestration of parasites, obstruction of microcirculation, hypoxia of tissue, and

lactic acidosis.([5.6.7.8)] P. falciparum can be momentarily removed from the peripheral circulation by infected red blood cell binding or sequestration, which results in low-grade parasitemia that is occasionally undetectable on blood smears and presents a diagnostic challenge.[(9)]

The most common malarial parasite outside of Africa in tropical and subtropical areas is *P. vivax*. Its restricted distribution across Africa is thought to result from a decreased expression of the Duffy antigen on African erythrocytes, a blood group antigen that *P. vivax* frequently uses for erythrocyte entry but is not required.[(2,10).] Furthermore, *P. vivax* exhibits a strong affinity for reticulocytes. *P. vivax* causes a much lower degree of parasitemia than other Plasmodium species due to a small number of reticulocytes in peripheral circulation, although it causes a higher systemic inflammatory response than *P. falciparum*.[(11,12).] Months or even years after the original inoculation, *P. vivax* and *P. ovale* both produce dormant liver-stage hypnozoites, which result in recurrent episodes of parasitemia. *Plasmodium malariae* is the type of malaria that has the lowest mortality rate and the lowest risk of severe illness, at about 2%. Rare side effects include respiratory and renal insufficiency, as well as severe anemia.[(13).] The majority of human cases of *P. knowlesi*, a simian malaria parasite endemic to Southeast Asia, have been reported from Malaysia. Long-tailed and pig-tailed macaques are the typical hosts, but humans can also contract the infection if bitten by a mosquito that has eaten a macaque's food. As of yet, no human-to-human transmission has been documented. The incidence of *Plasmodium knowlesi* has been increasing recently, despite ongoing success in eliminating other Plasmodium species that were circulating in Southeast Asia.[(14,15.16).] Since *P. knowlesi* resembles *P. falciparum* and *P. malariae* under a microscope, *P. knowlesi* malaria cannot be diagnosed using this method.[(17).] Nested polymerase chain reaction (PCR) can be used to make a conclusive diagnosis, but its application is limited to areas with low resources. In regions where *P. knowlesi* is endemic, falciparum malaria can be ruled out using rapid diagnostic tests (RDTs). Therefore, after ruling out falciparum malaria on RDTs, it is advised to presumably treat for *P. knowlesi* in cases originating from endemic areas for these parasites. [(18,19).]

Immunity and Transmission

The degree of an illness is significantly influenced by innate and adaptive immunity, as well as certain genetic factors. The degree of parasitemia, age of the host, immune response, effects of chemoprophylaxis, and treatment duration all generally influence the severity of malaria .[(20)] A protective factor against *P. vivax* in the African population is the lack of the Duffy antigen, as previously mentioned among significant hereditary factors. Certain hemoglobinopathies also show promise in the fight against malaria. Sickle cell trait and sickle cell disease carriers usually do not experience a significant illness from falciparum malaria, even though they are just as susceptible as those without sickle cell disease. Less convincing evidence also points to hemoglobin E disease, thalassemias, ovalocytosis, and glucose-6-phosphatase (G6PD) deficiency as protective factors against malaria [(4,21,22).] .Residents of hazardous areas gradually acquire immunity through repeated exposure. Because of this, endemic areas tend to have a higher proportion of milder and asymptomatic cases in adults, with severe disease affecting mostly infants and young children.[(3,4).] It was once thought that the risk of developing a severe disease was lowest in populations with the highest transmission, and that the risk of developing a severe disease was highest in populations with low-to-moderate transmission.[(23).] Travelers who are not immune to dangerous regions are therefore highly susceptible to severe disease because they do not have a prior immune system. Recent research, however, has revealed that this relationship is more nuanced. First, because many people with submicroscopic parasitemia are asymptomatic or only mildly ill, it is difficult to accurately estimate the prevalence of malaria in a given population.[(24.25).] Moreover, it is possible for a parasite to exist in multiple clones within a single host at the same time, and sequencing techniques are required to monitor newly acquired genotypes [(26, 27).] Finally, a high degree of infectivity is not always indicative of a parasitemia. For instance, a study conducted in Ethiopia revealed that just 15% of people with *P. falciparum* and 35% of those with *P. vivax* infections were contagious [(28).] These and other elements lead to uncertainty about the true burden of malaria, routes of transmission, and immunity.

The clinical manifestation of uncomplicated malaria

Depending on the Plasmodium species, the incubation period can vary from 7 to 30 days. *P. falciparum* infections have shorter incubation periods, *while P. malariae* infections have longer incubation periods. 95% of people experience symptoms within six weeks of exposure [(4).] Some people living in endemic areas may experience the disease as "asymptomatic," meaning they have no symptoms at all when parasitemia is present. The term "chronic" malaria is preferred by some experts over "asymptomatic" malaria because of the long-term harm that untreated cases can cause [(29).] Fever, the defining characteristic of malarial illness, is synchronized with the parasites' periodic release during erythrocyte schizont rupture. The febrile response is triggered by inflammatory cytokines such as interleukins, complement factors, prosta-glandins, tumor necrosis factor, and other pyrogenic factors once the parasites are released into the bloodstream [(5, 30)] The typical clinical course consists of periods without symptoms interspersed with episodes of fever. There are three stages to a typical febrile malarial paroxysm. The rigors and cold feeling are the hallmarks of the first stage, which is called the cold stage.

The hot stage follows, which is characterized by a fever that can occasionally reach 40–41 °C, along with malaise, headache, nausea, vomiting, myalgia, and possibly seizures, especially in young patients. Lastly, the sweating phase, during which the fever lowers, completes the paroxysm [4, 31].The length of febrile episodes was traditionally linked to distinct species, despite being an uncommon observation. *P. falciparum, P. vivax, P. ovale*, and *P. malariae*, therefore, cause malarial paroxysm every 48 hours ("tertian" fever), and every 72 hours ("quartan" fever) [31, 32]. The results of a physical examination are typically nonspecific and can include jaundice, lethargy, anorexia, pallor, petechiae, or mild abdominal pain. Compared to adults, children are more likely to present with splenomegaly and hepatomegaly [33].

Laboratory diagnosis of uncomplicated malaria

A complete blood count, metabolic panel, liver panel, coagulation panel, plasma lactate level, arterial blood gas analysis, urinalysis, and chest imaging should be done on all patients who present with feverish illness in the context of suspected malaria. Diagnostic procedures unique to malaria are covered separately. Laboratory abnormalities include mild-to-moderate anemia, elevated liver enzymes, mild coagulopathy, elevated blood urea nitrogen, elevated creatinine, and 60–70% of cases of thrombocytopenia (though rarely significant enough to cause bleeding in an uncomplicated disease) [33, 34]. It is generally advised to obtain blood cultures and a urine culture upon admission due to the documented cases of invasive bacterial infections in malaria. While the risk of concurrent bacteremia in malaria-endemic areas has been demonstrated to be significant in children [35,36], it has been found to be significantly less significant in adult returning travelers [37, 38].

Severe Malaria

The World Health Organization (WHO) defines severe malaria as having two or more of the following complications:, impaired consciousness, severe physical deconditioning, hypoglycemia, severe anemia, renal impairment, hyperbilirubinemia, pulmonary edema, significant bleeding, shock, and high parasite density, when one or more of these complications occur without an alternate cause [39 ,40] .Living in non-endemic areas, reaching extreme age limits, being pregnant, and having compromised immune system are risk factors for severe malaria [3, 4, 34]. Adults are more likely to experience acute renal failure and pulmonary edema, while children are more likely to experience seizures, hepatosplenomegaly, and severe anemia [39, 41] Most severe cases are caused by *P. falciparum*, which does this by rapidly expanding its parasite biomass, sequestering infected erythrocytes, obstructing microvascular flow, activating endothelial cells, and causing subsequent damage to organs [3, 4, 6, 10, 32]. Although cerebral malaria has not been documented to date, it is widely acknowledged that *P. knowlesi* may cause severe disease through comparable mechanisms [42]. Since *P. vivax* does not typically cause sequestration, the pathogenesis of severe malaria caused by this parasite is poorly understood [3, 5, 43]. Severe malaria is a group of several clinical syndromes.

Cerebral malaria

Cerebral malaria (CM), defined as a clinical condition with a score of less than 11 on the Glasgow Coma Scale, is characterized by a symmetrical, diffuse, and potentially reversible encephalopathy that arises from parasite sequestration in the brain vasculature [44]. Although there may be some degree of blood-brain barrier dysfunction, parasites cannot cross the blood-brain barrier [45]. On imaging, brain edema is frequently discovered. When malarial retinopathy is present, the diagnostic sensitivity and specificity of CM are increased by 90% and 95%, respectively, resulting in retinal hemorrhages and patchy retinal whitening [46, 47]. If a lumbar puncture is done, elevated opening pressure and nonspecific cerebrospinal fluid analysis are observed in CM.Similar clinical presentations require clinicians to rule out meningitis and meningoencephalitis when considering CM. It is common for survivors to experience neurological sequelae, which can include blindness, hemiplegia, ataxia, epilepsy, and long-term cognitive impairments [48].

Severe Anemia

Hemoglobin levels ≤ 5 g/dL in children and ≤ 7 g/dL in adults are indicative of severe anemia [39]. The pathogenesis is complex and includes immune-mediated erythrocyte destruction in the spleen, erythrocyte lysis, and bone marrow suppression brought on by inflammation.

Massive intravascular hemolysis, hemoglobinuria, and renal failure are symptoms of a phenomenon known as "blackwater fever," which is more common in people with G6PD deficiency and is associated with recurrent falciparum malaria and a history of quinine chemoprophylaxis [40]. Although the transfusion threshold is not well defined, it is usually

Severe Renal Failure

When severe malaria is present, creatinine > 3 mg/dL or blood urea nitrogen > 56 mg/dL are indicative of acute renal failure [39]. By impacting glomeruli, tubules, and the interstitial region, severe malaria exacerbates renal damage. Acute tubular necrosis is caused when renal vasculature is obstructed by parasitized red blood cells.

Pre-renal kidney injury is further complicated by hypovolemia and shock. Glomerulonephritis can be brought on by immune complex deposition and complement activation. There have also been reports of interstitial nephritis. Acidosis is further exacerbated by declining kidney function [(49)].

Recrudescence

Both *P. vivax* and *P. ovale* are known to produce hypnozoites, quiescent forms in the liver that, in the event that the initial infection is not sufficiently treated, can reappear as blood-stage forms months or even years later. It has also been reported that *P. falciparum* causes recrudescence. Although this parasite does not produce specific dormant forms, it occasionally evades treatment due to drug resistance and parasite clone sequestration [(50)].

Diagnosis

The gold standard for diagnosing malaria is still microscopy, or thick and thin smears, despite technological advancements over the last 20 years. Giemsa-stained thick smear analysis of lysed red blood cells is done to identify parasites. Speciation and description of parasite stages are possible with thin smears. To improve the diagnostic yield, two smears of each type should be performed. Repeat the smears 12 to 24 hours apart if the first set is negat ive until at least 3 sets are negative [(51)]. When the number of parasites in the sample exceeds 5–10 parasites/μl, light microscopy can accurately diagnose malaria; however, interpreters must use the same technique [(52)]. To improve the diagnostic yield, two smears of each type should be performed. Repeat the smears 12 to 24 hours apart if the first set is negative until at least 3 sets are negative [(51)]. When the parasite concentration is greater than 5–10 parasites/μl, light microscopy can accurately diagnose malaria; however, interpreters must be able to use this method [(52)]. As a result, using it has two main limitations: finding experienced laboratory staff and having enough parasite density. In order to facilitate the rapid diagnosis process, various RDTs have been created. RDTs are intended to identify pan-malarial antigens such as lactate dehydrogenase, aldolase, histidine-rich protein-2 (HRP-2) and others, as well as a falciparum-specific antigen. [(52, 53)]. All RDTs have limitations, such as the inability to identify different Plasmodium species, the inability to identify mixed infections, and the restricted capacity to track treatment response. While some studies have shown that RDTs are superior to microscopy [(54)], it is generally agreed upon to use both techniques at the same time [(52)]. Still, new RDTs are being created all the time. An ultrasensitive RDT performed better in sensitivity than a traditional RDT, as shown by a recent meta-analysis [(55)], particularly in patients who were asymptomatic and in low-grade transmission areas. Recent advances in malaria diagnosis have focused on the detection and amplification of Plasmodium nucleic acids (Table 3). As an antigen detection, it allows Plasmodium spp. directly; However, since nucleic acids can be amplified from small amounts of DNA, these methods are often much more sensitive and able to detect parasites at much lower densities. For a test to give reliable results, high sensitivity must be accompanied by satisfactory specificity to limit the number of false positives. This is a challenge for molecular methods, as small amounts of contaminating or off-target DNA can be amplified by the sample, which can alter the results. [(56)] .In addition, many molecular techniques, including polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP), and sequencing methods, provide the opportunity to gather more information about Plasmodium spp. about identification. and improve the characterization of DNA sequences and sites of interest.[(57)]

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