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REVIEW ARTICLE

Invite Competition to Achieve Malaria Free World. (Keep Calm and Bat On)

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Abstract

Malaria is the most important parasitic disease of humans and often the most common cause of fever in tropics. Malaria is one of the most common treatable and preventable infectious diseases in the world. Malaria kills millions of people every year. In 2016, there were an estimated 445 000 deaths from malaria globally, compared to 446 000 estimated deaths in 2015. Most of these deaths are in the poorest regions of the world. The presence of multi-organ dysfunction adversely affects prognosis. The key elements of malaria control are effective drug treatment, deployment of insecticide treated bed nets and where appropriate indoor residual insecticide spraying, supplemented in some areas by intermittent preventive treatments and mass chemoprevention given to all target population. The main threats to malaria control are increasing anti-malarial drug resistance and increasing insecticide resistance.

Keywords: Hemoglobinuria, Tumor Necrosis Factor, Tachycardia, Hyperventilation, Septicemia, Interleukins, ELISA, Polymerase Chain Reaction

Introduction

More than 90% of deaths occurred in Africa, mostly among children where according to the WHO, A child dies every minute from Malaria [1]. When Malaria is transmitted by transfusion of parasitized blood, the incubation period varies 10 hrs to 60 days [2]. The parasite grows rapidly within hepatocytes, producing merozoites that can infect RBCs through unknown mechanisms the parasite render hepatocytes resistant to apoptotic signals [3]. Hepatic dysfunction and jaundice may be multi-factorial in etiology, including hemolysis, sequestration of infected RBC, in sinusoids or co-existent viral hepatitis [4]. Liver exhibits sinusoidal dilation, infiltration with lymphocytes and hyperplasia, of the Kupffer's cells with phagocytosis of cellular debris and red cells [5]. According to WHO, Malaria is more prevalent in areas with species of Anopheles that have longer life span or that have breeding habits leading to increased mosquito population [6]. To successfully find a human host, anthropophilic mosquitoes are thought to detect and integrate a variety of sensory cues emanating from humans including body odor, CO_2 moisture, heat and visual contrast [7]. The dormant stages of Plasmodium have now been demonstrated in the hepatic parenchyma cells of Chimpanzees infected by sporozoites of two widely disparate strains of Plasmodium Vivax [8].

Congenital transmission is very rare. However, pregnant women are more attractive to Anopheles mosquitoes than non-pregnant women, making them more vulnerable to Malaria [9]. In India, DDT resistance in malaria vectors was first reported in 1955 in Tamil Nadu, The major malaria vector, Anopheles culicifacies was found resistant to DDT in 1959 in Gujarat, to BHC in 1958 and malathion in 1973 [10]. In cerebral malaria, patient is febrile and unarousable. There may be some resistance head flexion but board-like rigidity of meningitis is not found. Anemia is common in children. Jaundice is uncommon in children but common in adults. Signs of bleeding, Low blood pressure, sinus tachycardia and hyperventilation may be seen [11]. Haemoglobinuria (Blackwater fever) is one of the less common but dangerous complications seen almost exclusively with P. falciparum infection. It is characterized by acute intravascular hemolysis accompanied by hemoglobinuria [12,13]. Molecular diagnostic approaches to the diagnosis of malaria include the use of recombinant DNA probes and ribosomal RNA probes. Other rapid tests rely on the detection of plasmodial antigens or enzymes [14]. The presence of

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IgM Malarial antibodies in the serum of infants with congenital malaria,at the age of 12 weeks has been demonstrated which disappeared after 2nd course of antimalarial therapy [15]. The emergence of conventional antimalarial drugs and insecticides means that new chemotherapeutic approaches with alternative targets are needed [16]. Treatment of malaria in pregnancy is more or less same as in non - pregnant women, but malaria in pregnancy is an enormous public health problem, with substantial risk for mother, her fetus and the neonates as the disease can result in maternal anaemia and placental parasitaemia [17]. Treatment failure can also be the result of incorrect dosing, problems of treatment adherence, poor drug quality, interaction with other drugs, compromised drug absorption or misdiagnosis of the patient [18,19]. A cost effective vaccine must be capable of being incorporated in to appropriate health delivery programs and of providing sufficient duration of immunity [20].

History

Fever was a symptom of disease rather than a disease in and of itself [21]. Galen, considered fever as a systemic disease in itself and it was only between 17th and 18th century that Hermann provided a more careful evaluation of the clinical phenomena related to fever [22]. Some evidence suggests that the P. Falciparum malaria may have originated in gorillas [23,24]. Hippocrates described periodic fevers, labeling them tertian, quartan, subtertian and quotidian [25].

Scientific studies on malaria made their first significant advance in 1880, when Charles Louis Alphonse Laveran - A French Army doctor working in the Military Hospital observed parasites inside the red blood cells of infected people for the first time [26]. For this and later discoveries, he was awarded the 1907 Nobel Prize for Physiology or Medicine [27]. This work followed earlier suggestions by Josiah C. Nott, and work by Sir Patrick Manson, the "**Father of Tropical Medicine**", on the transmission of filariasis [28]. He isolated malaria parasites from the salivary glands of mosquitoes that had fed on infected birds [29]. For this work, Ross received the 1902 Nobel Prize in Medicine [30]. The recommendations were implemented by William C. Gorgas in the health measures undertaken during construction of the Panama Canal [31]. The first effective treatment for malaria came from the bark of the cinchona tree, which contains quinine. It was included in the London Pharmacopoeia as an anti malarial treatment [32]. In 1820, the active ingredient, quinine, was extracted from the bark, isolated and named by the French Chemists, Pierre Joseph [33, 34]. Quinine was the predominant malarial medication until the 1920s when other medications began to appear. In the 1940s, chloroquine replaced quinine as the treatment of both uncomplicated and severe [35].

The medicinal value of Artemisia annua has been used by Chinese herbalists in traditional Chinese medicines for 2,000 years [36]. For her work on malaria, Tu Youyou received the 2015 Nobel Prize in Physiology or Medicine [37].

Where the Research Go Next?

Major Advances in and Discoveries

Recent evidence suggests that the symptoms and pathologic changes seen in malaria may be less directly the 4 result of the effect of the parasite on RBC than of proteins (Cytokines) secreted by the host cells in response to the presence of the parasite. Tumor necrosis factor and functionally related proteins such as the interlukins are produced as a normal part of the host response to infection. A direct relationship between elevated TNF levels and death from cerebral malaria has been found. Sera from patients with a variety of infections and neoplastic diseases contain elevated levels of TNF in two thirds of those with malaria and Kala Azar but in fewer than 8 of healthy subjects or persons with neoplastic disease [38]. Glucose-6-phosphate dehydrogenase deficient cells are from 2-80 times more resistant to invasion by PF than normal erythrocytes.G-6-P-D deficiency involves 3 allells. GdA,GdB and GDA. Clinically one sees no increased resistance in homozygous (GdA) boys (the gene involved is on the X - Chromosome) or homozygous (GdA-/GdA) girls, but resistance of heterozygous (GdA-/GdB) girls is greater. West African Blacks and their descendants in the Americans and elsewhere posses a relatively immunity to P. vivax.

Significant Gap in Research

Now a days, far from being out dated, research on avian malaria is essential to fence new health and environmental challenges in this time of unprecedented global challenge [39].

Mice model may be used to obtain malarial parasites that present a high level of resistant to different anti-malarial drugs such as artemisinin in vivo and in vitro [40]. There is a need to take advantage in studying immunity to malaria, sequencing the DNA and protein microarray technology for the development transgenic animal and parasite models.

Current Debate

Most of the characteristic hypergammaglobulinemia observed during acute malaria may be attributed to polyclonal activation. The role of antibodies in protection

has best been demonstrated by the passive transfer of serum from immune donors to infected recipients where antibodies have been completely cleared within 48 hours of transfer of immune serum. Similarly, in the newborn child of an immune mother, the passive transfer of IgG across the placenta protects the child during early months of life. Individuals living in an area endemic for malaria have high levels of antibodies against many malarial antigens as demonstrated by ELISA or IFAT. In malaria, there is an increased number of macrophages in the spleen, liver and bone marrow. The increased number of macrophages in the spleen has been related to the release of T-cell cytokines, which seems to trigger a major cellular influx leading to spleenomegaly. In addition to their phagocytic activity, macrophages aqnd monocytes can produce a variety of toxic substances, which damage or destroy malarial parasites. These are reactive oxygen intermediates (H_2O_2 and hydroxyl radicals) and tumor necrosis factor-alfa. In addition to damaging parastes with in erythrocytes, the activated macrophages derived toxic products may also damage the paraste in its exo-erythrocytic cycle,either directly or by means of production of nitric oxide (NO)The infectivity of gametocytes may also be reduced as a result of the presence of macrophage products [41].

Laboratory Diagnosis of Malaria

The symptomatology of malaria vary and resembles many other diseases, laboratory diagnosis will be helpful in support for clinical care. Besides the routine methods the following newer techniques like Fluorescent microscopy, direct acridine orange staining, and immunological methods like ELISA mostly used. RDTs (Rapid diagnostic tests are based on the detection of antigens derived from malaria patients in lysed blood, using immunochromatographic methods. Most frequently, they employ a dip stick or test strip bearing monoclonal antibodies against the target parasite antigens. The test can be performed in about 15 mnts Histidine-rich protein 11(HRP11) is water soluble protein produced by trophozoites and young gametocytes of P. falciparum. Parasitic Lactate dehydrogenase (PLDH) is produced by asexual and sexual stages (Gametocytes) of Malarial parasites. The polymerase chain reaction (PCR) is a technique widely used in molecular biology. DNA polymerase is used to amplify a piece of DNA by in vitro enzymatic replication. As PCR progress, the DA thus generated is itself used as template for replication. RT-PCR is one step procedure and hence quick. Besides this Flow cytometry Mass spectrometry are also currently used in research laboratories.

Treatment

For many years, quinine was the only effective drug for chemo prophylaxis or treatment of malaria. The drug is a potent blood schizonticide against all four species of human malarial parasites. Quinine may produce maternal and fetal hyperinsulinemia and hypoglycemia and it is important to monitor blood glucose levels during its administration. Quinine dihydrochloride has been used for intravenous administration in patients who are unable to take the oral drug, but it is now being supplemented by intravenous quinidine, which is both more readily available and somewhat more effective. Chloroquine-resistant P.falciparum (CRPF) may be seen in all Middle East, Central America, West of Panama, Mexico. 4 Aminoquinolines to bind to and alter the properties of DNA or through the effects of chloroquine in raising the Ph of the parasite vesicle. Amodiaquine (Camoquin) is generally similar to chloroquine in clinical efficacy and toxicity and in development of resistance by P.falciparum though in some areas.

It may be effective against strains that are resistant to chloroquine. Pyrimethamine (Daraprim) was used extensively, mainly and safety in pregnancy. Mefloquine (Lariam) was early found effective against both chloroquine-and-resistant strains of P.falciparum and P. vivax. Owing to its lengthy half life and in case of therapeutic failure of mefloquine, it must be born in mind that the substitution of quinine may expose the patient to increased risk of cardiac conduction problems or convulsions. Proguanil (Paludrine) is a blood schizonticide that initially was effective against all four species of malaria. Halofantrine (Halfan), a lipophilic phenanthrene methanol, was released for the treatment of multiple drug resistant P.falciparum in USA in 1996. Extract of Artemisia annuva, known in China as Qinghao, has been used for centuries to treat malaria. Conjugation of Quinine or Mefloquine and doxycycline drugs are antimalarial drugs. Various combinations of pyrimethamine with sulfonamides or sulfones have proved to be effective antimalarials. Primaquine is effective against the hypnozoites of P. vivax and is gametocidal for all four species of malaria. This drug should be given with caution where glucose-6-phosphate dehydrogenase deficiency is common and is contraindicated in presence of severe varient of the deficiency [42].

Vaccines

Pre-erythrocytic vaccines are designed to target the the pre-erythrocytic stages of the parasite life cycle and therefore inhibit infection. Blood stage vaccines are designed to control parasitaemia by preventing invasion of uninfected erythrocytes (Merozoite targets) which leads to

pathogenesis) 49%. Similarly, malaria vaccine targeting the merozoite surface protein-2 (MSP-2) Experimental studies have demonstrated the possibility of a safe and effective, genetically attenuated whole organism malaria vaccine UIS-3 (Up regulated in infective sporozoites gene-3) gene is essential for early liver stage development. The prospect of having an effective vaccine against malaria is still a dream. It will be long time before a malaria vaccine becomes a reality. Parasite's antigenic diversity and low immune response are some of the obstacles.

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