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Mind-Boggling, Pyrexia Causing Protozoan And Helminth Parasites

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Abstract - *"Fever is the most common systemic manifestation of the inflammatory response and cardinal symptoms of infectious diseases and are subject to physical and chemical stimuli" Protozoan and helminth parasites cause different fevers. Malaria important parasitic disease of humans. Malaria kills millions of people. The presence of multi-organ dysfunction adversely affects prognosis. Plasmodium vivax causes "Benign tertian malaria fever." Plasmodium malaria causes "Quartan malaria fever" or "Quotidian malaria fever." Plasmodium falciparum causes "Malignant tertian malaria fever," Blackwater fever," Cerebral malaria fever," "Aestivo autumnal malaria fever," and Plasmodium ovale causes "Ovale tertian malaria fever. "Giardia intestinalis, produce a fever is called "Beaver fever." Leishmania donovani produces "Kala-azar" or "Black fever" or " Dumdum fever." Pyrexia is often an early symptom, and it may be continuous or remittent in type and become intermittent at a later stage. Toxoplasma gondii produces fever with generalized lymphadenitis (Slim's disease). Schistosoma japanicum has "Katayama fever" or "Snail fever" in Japan. It is a generalized anaphylactic reaction characterized by fever, urticarial rash, eosinophilicle ucocytosis. Paragonimus westermani produces "Serum sickness-like fever" with generalized lymphadenitis." Filarial fever" is caused by Wuchereria bancrofti or Filaria bancrofti. It is usually accompanied by a rise in temperature from 103 C to 104C, which may continue for several days.*

Keywords - *Benign tertian malaria fever," Quartan malaria fever," "Quotidian malaria fever." "Malignant tertian malaria fever," "Aestivo autumnal malaria fever, Blackwater fever, "Cerebral malaria fever," "Ovale tertian malaria fever," "Beaver fever." "Black fever," or'' Dumdum fever," "Katayama fever," or "Snail fever," "Sersickness-like fever," "Filarial fever."*

I. INTRODUCTION

Giardiasis, popularly known as beaver fever (1). It is generally assumed that approximately 25 to 30% of the world's human population is infected by Toxoplasma (2). According to WHO, Malaria is more prevalent in areas with species of Anopheles that have a longer lifespan or breeding habits leading to increased mosquito population (3). Haemoglobinuria (Blackwater fever) is a less common but dangerous complication seen almost exclusively with P.falciparum infection. It is characterized by acute intravascular hemolysis accompanied by hemoglobinuria (4,5). The presence of IgM Malarial antibodies in the serum of infants with congenital Malaria at the age of 12 weeks has been demonstrated, which disappeared after the 2nd course of antimalarial therapy (6). The emergence of conventional antimalarial drugs and insecticides means that new chemotherapeutic approaches with alternative targets are needed (7). Molecular diagnostic approaches to the diagnosis of Malaria include DNA probes and ribosomal RNA probes. Other rapid tests rely on the detection of plasmodial antigens or enzymes (8(—visceral leishmaniasis (VL), also known as kala-azar (9). Black fever is the second-largest parasitic killer globally (after Malaria), responsible for an estimated 20,000 to 30,000 deaths each year worldwide (10). Schistosomiasis, also known as snail fever and bilharzia, is a disease caused by parasitic flatworms called schistosomes (11). *Fasciola hepatica*, Common signs, and symptoms of the hepatic phase are abdominal pain, fever, eosinophilia, and abnormal liver function test (12). *Trichinellaspiralis* can cause symptoms varying from generalized fever, abdominal pain, diarrhea, nausea, vomiting, myalgia to more severe, like myocarditis and encephalitis (13). Chronic infection of *Paragonimuswestermani* presents with fever, anemia, weakness, and weight loss (14). Fever associated with elephantiasis is called “elephantoid fever." (15).

II. CHRONOLOGICAL RECORD OF SIGNIFICANT EVENTS

The first likely description of Giardia was in 1681 by Antonie van Leeuwenhoek, who described "animalcules" resembling Giardia trophozoites in a letter to Robert Hooke stool (16,17). In 1915, Charles Stiles renamed the organism *Giardia lamblia* in honor of Lambl and Professor Alfred Mathieu Giard of Paris (18). The first evidence of malaria parasites was found in mosquitoes preserved in amber from the Palaeogene period, approximately 30 million years old (19). Humans may have originally caught Plasmodium falciparum from gorillas (20). In 1908, while working at the Pasteur Institute in Tunis, Charles Nicolle and Louis Manceaux discovered a protozoan organism in the tissues of a hamster-like rodent known as the gundi, Ctenodactylusgondii (21). Leishmaniasis is a vector-borne disease caused by flagellated protozoans of the genus Leishmania (22). However, over 90% of new cases occur in just 13 countries (23). Filariasis has been known from antiquity. Elephantiasis had been described in India by Sushrutha (600) BC and in Persia Rhazes and Avicenna. Clarke, in 1709 in Cochin, described elephantiasis as "Malabar leg." Ancient Greek scholars differentiated lymphatic filariasis from leprosy, describing leprosy as elephantiasis graecorum and lymphatic filariasis as elephantiasis arabum(24). *W. bancrofti* was named after physician Otto Wucherer and parasitologist Joseph Bancroft. (25). The adult worm was found in lymphatic abscess by Bancroft in 1882. Sir Patric Manson experimentally proved that one arthropod vector is responsible for transmitting the disease (26). Research on the role of interleukins in pyrexia Parasitic worms appears to have applied a more powerful selective pressure on certain interleukin genes than did viruses, bacteria, or fungi (assuming that pathogen diversity has remained relatively stable over time (27).

III. INTERLEUKINS

Interleukins or Lymphokines are regulatory proteins secreted by monocytes or macrophages, or T-lymphocytes. They are involved in signaling between cells of the immune system. Interleukins are a group of biologically active factors released by primed lymphocytes. Lymphokines can be secreted by both T and B lymphocytes, though T cells are assumed to be the main source. These are non-antibody proteins and polypeptides secreted by lymphocytes in contact with an antigen. They act as inter-cell mediators in immune responses. There are many lymphokines that have a wide range of biological activities. Many lymphokines show multiple biological activities, and so the descriptive names can be misleading. A nomenclature interleukin is introduced, followed by a number. Interleukin-1(IL-1). This was originally called a lymphocyte activating factor (LAF). Initially, it was observed to be secreted by monocytes and macrophages (hence known as monokine), but now it is known to be produced by all nucleated cells. The production of interleukin-1 is introduced by the antigens, lectins, and lymphokines from T- cells such as macrophage activating factor.IL-1 stimulates B-cell proliferation, differentiation, and synthesis of immunoglobulins. It activates T-cells and promotes the synthesis of lymphokines. It is endogenous pyrogen, hence induces and stimulates an increase in acute phase serum proteins. (28). IL-1 consists of two proteins.IL-1 alpha, and IL-beta, both have exactly the same functions.IL-1 is produced by all antigen-presenting cells, but activated macrophages and monocytes produce the same in relatively large amounts.IL-1, thus liberated from activated macrophages, binds to its high-affinity receptors on the enlarged T-cells leading to rapid internalization of IL-1. The IL-1 readily induces RNA and protein synthesis of the responsive T-cells.

The cell enlarges to a blast-like appearance. Most febrile illnesses are due to infection, and often the diagnosis can be made by clinical examination alone. In other instances, a diagnosis may require confirmation by hematological examination, radiography, scanning, bacteriological or serological investigation of blood or other body fluids, discharges, or excreta. Often, the detection of specific antibodies in the serum may have to be undertaken before the diagnostic problems may be solved. Occasionally the cause of a febrile illness remains uncertain in spite of investigation, and such a case is categorized PUO (Pyrexia of unknown origin). To establish the diagram, enquire again, the patient has lived or traveled overseas. Repeat the examination of the patient for new signs, if any. Examine urine repeatedly for protein, white and red blood cells, and microorganisms. Inspect the temperature charts for evidence of some characteristic appearance, such as the undulations seen in some cases of lymphoma or the periodicity of Malaria. Review the results of laboratory investigations, thoroughly recrutinise any radiographs and repeat such examinations as may seem necessary (29)

IV. PYREXIA OF UNKNOWN ORIGIN (PUO)

Sometimes the cause of febrile illness (Greater than 38 degrees C) remains uncertain in spite of investigations, and such a case is known as PUO(Pyrexia of unknown origin).In this classic study of PUO, only patients with persistent fever for 3 weeks or longer were included. It is to be remembered that most cases of PUO are often relatively common disorders with atypical presentation. The most frequent causes of prolonged PUO include chronic infections, tumors, connective tissue disorders, granulomatous disease, and drug hypersensitivity reactions.

A. Hypothalamus

Temperature is regulated in the hypothalamus. The trigger of a fever, called a pyrogen, results in the release of prostaglandin E2 (PGE2) (30). Norepinephrine increases thermogenesis in brown adipose tissue, and muscle contraction through shivering raises the metabolic rate (31).

V. RECENT ADVANCES IN DIAGNOSTIC TECHNOLOGY

Film Array Global Fever Panel Diagnostic tests The Bio Fire System is the new standard for syndromic infectious disease diagnostic. Simple, fast, and comprehensive,

the Bio Fare system delivers accurate results in about one hour. Bio Fare is one of the leading institutions in molecular diagnostics. Their research work is highlighted in publications in academic journals. The Bio Fire Film Array Torch is the latest advancement in molecular infectious disease diagnostics. It is fully integrated, designed to meet the laboratory's syndromic infectious disease testing needs. It provides quick, comprehensive, and accurate results. Laboratory bench space is limited. It provides a higher probability of identification of pathogens associated with infectious diseases with a single KIT. Easy to read and to report Advantages. Fully automated Sample preparation, Amplification, Identification, and reporting Single instrument integration-Minimal consumables. Freeze Dried Reagents--Room temperature stable. Disadvantages-- These Kits are not available outside the US. A comprehensive set of 20 Global fever panels, It includes viral and bacterial, and Protozoan pathogens in about one hour. The BioFire RP identifies the most common viral and bacterial and Protozoan pathogens that cause fevers.

VI. BIOTECHNOLOGY OF MOLECULAR DIAGNOSIS OF FEVERS

A. Plasmodium falciparum

Aestio autumn malaria Quantification of parasitemia should be done: parasites are counted against 200 leucocytes in a thick film or as a percentage of 500-red blood cells in a thin.

Leishmania donovani-- Kala Azar Specimens--Blood, spleen, liver, and bone marrow puncture are important in Kala-azar Microscopic examination--Giemsa stained smears and sections may show amastigotes, especially in material from Kala-azar.

Culture-NNN medium, biphasic blood agar culture, Tobiesmedium, is especially suitable Serology--Formaldehyde test for Napier is a non-specific test that detects an elevated serum globulin level in Kala Azar The IHA (Indirect hemagglutination antibody) test orIFA (Indirect Flo fluorescent antibody) test may be useful Serological testing is much more frequently used in areas where leishmaniasis is endemic. A 2014 Cochrane review evaluated different rapid diagnostic tests. One of them (the rK39 immunochromatographic test). A second rapid test (called latex agglutination test). (32) The DAT anti-leishmania antigen test, standard within MSF, is much more cumbersome to use and appears not to have many advantages over the K39 test (33).

Giardia lamblia--Beaver fever finding the cysts in the stool. or trophozoites in stool

Examination of duodenal aspiration. *Schistosoma japanicum* /Katayama fever/Snail fever

1. Identification of eggs in stools

2. Antibody detection-

Antibody detection can be useful to indicate schistosome infection in people who have traveled to areas where schistosomiasis is common and in whom eggs cannot be demonstrated in fecal or urine specimens.

3. Molecular diagnostics---Polymerase chain reaction (PCR) based testing is accurate and rapid (34). Loop-mediated isothermal amplification is being studied as they are lower cost. LAMP testing is not commercially available as of 2019 (35)

Wuchereria bancrofti--Filarial fever Diagnosis of filariasis depends on the clinical features, history of exposure in an endemic area, and laboratory findings.

Demonstration of microfilaria in peripheral blood. Microfilaria may also be detected in other specimens such as chylous urine or hydrocele fluid. Sometimes it can be seen in biopsy specimens. Demonstration of the adult worm in biopsy specimens. Diethylcarbamazine(DEC) provocation test can be employed. The patient is given 100mg of DEC orally, and peripheral blood is examined for microfilariae in 35-45 minutes.DEC provokes the microfilariae to come in peripheral blood even during the daytime.

In the absence of microfilaraemia, definitive diagnosis of wuchereria is difficult. In such situations, serological diagnostic methods are useful. The tests commonly employed are the haemagglutination test(Antigen derived from Dirofilariaimmitis), Fluorescent antibody test(Antigen derived from Brugia and other microfilaria and ELISA(Antigen derived from Brugiapahangi). These tests are non-specific antigens; further, there is extensive cross-reactivity between filarial antigens and antigens of other helminths like a roundworm. This makes the interpretation of serological tests difficult(36) Strongyloides stercoralis--Fever It causes fever of unknown origin (37)

B. Researchers struggle to develop a new treatment for parasitic fevers

The goals of treatment for infection of schistosomiasis are: The main antiparasitic drug recommended is praziquantel, and some antimalarial drugs were found to have some antischistosomal properties, such as artemisinin, synthetic trioxolanes, and mefloquine. In the systematic review and meta-analysis, the combination of artemisinin derivatives plus praziquantel showed a higher cure rate than praziquantel monotherapy (38). There are three main goals in the treatment of Strongyloidesstercoralis infection: The drug of choice to treat uncomplicated infections is oral ivermectin (100µk Kg -1 for 2 days). In cases of hyper infection, the minimum time is for 2 weeks (39,40). Liver flukes Praziquantel is a drug of choice for the treatment of fluke infection, including opisthorchiasis and clonorchiasis. The standard dose of praziquantel is 75 mg/kg in three divided doses for 1 day, which results in an egg reduction rate of 98% to 99% for both O. viverrini and C. Sinensis infection (41,42,43).

Plasmodium For many years, quinine was the only effective drug for chemoprophylaxis or treatment of Malaria. Quinine may produce maternal and fetal hyperinsulinemia and hypoglycemia, and it is important to monitor blood glucose levels during its administration. Quininedihydrochloride 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. Aminoquinolines 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 the development of resistance by P. falciparum in some areas. It may be effective against strains that are resistant to chloroquine. Pyrimethamine(Daraprim) was used extensively, maily and safe in pregnancy. Mefloquine (Lariam) was early found effective against both chloroquine-and-resistant strains of P.falciparum and P. vivax. Owing to its long half-life and in case of therapeutic failure of mefloquine, it must be borne in mind that the substitution of quinine may expose the patient to an 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 phenanthrenemethanol, was released for the treatment of multiple drug-resistant P. falciparum in the USA in 1996.

Extract of Artemisia annual, known in China as qinghao, has been used for centuries to treat Malaria. Conjugation of Quinine or Mefloquine and doxycycline drugs is 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 the presence of a severe variant of the deficiency (44). There are several deworming drugs that are used to combat microfilariae infections. In sub-Saharan Africa, albendazole is being used with ivermectin to treat the disease. Albendazole is used with diethylcarbamazine-targeting treatments, is part of a larger strategy to eventually eliminate lymphatic filariasis by 2020. The antibiotic doxycycline is also effective in treating lymphatic filariasis. The parasites responsible for elephantiasis have a population of endosymbiotic bacteria, Wolbachia, that live inside the worm. (45) DEC kills mainly the microfilariae and, to a lesser extent, the adult worms. It is not effective against the third and fourth stage larvae. Ivermectin is another drug that appears to be promising in the treatment of lymphatic filariasis; other drugs recently evaluated for the condition include levamisole, mebendazole, and centprazine. Future directions and challenges CDC = It is important the timing of treatment for schistosomiasis with praziquantel. The dose and duration of praziquantel depend on the species and immune response of the patient (46).

WHO = Aims to prevent morbidity with Praziquarentel is the commended treatment for schistosomiasis (47). Strongyloidstercoralis CDC = The recommended first line of therapy is ivermectin. The dosage and duration depend on the stage; acute and chronic strongyloidiasis versus hyper infection syndrome/disseminated (48). WHO = WHO recommends periodic treatment with anthelminthic (deworming) medicines. (49). Flukes CDC: Praziquantel or albendazole are the drugs of choice to treat Clonorchis infection (50). WHO = Praziquantel is the only medicine recommended by WHO for the treatment of clonorchiasis (51).

VII. RESEARCH PROGRAM TO THE NEXT GENERATION WORLD

Malaria Research to produce a fully protective malaria vaccine is ongoing. pre-erythrocytic vaccines are designed to target the pre-erythrocytic stages of the parasite life cycle and therefore inhibit infection. Blood stage vaccines are designed to control parasitemia 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 a long time before a malaria vaccine becomes a reality. Parasite's antigenic diversity and low immune response are some of the obstacles.

VIII. PREVENTION & CONTROL

Prevention, we know, is always better than cure. Protocols for prevention focus on the routes of spread to break the chain of transmission. The droplets may be directly inhaled if you are in close proximity with somebody who has the infection through coughing, sneezing, or even talking loudly. Hand hygiene is the simplest, effective, and least expensive intervention to prevent infections. Hand hygiene includes either handwashing with soap and water or the use of alcohol-based hand rubs (sanitizers), which contain at least 70% alcohol or antiseptic hand wash. Avoid touching one’s mouth, nose and eyes with dirty hands. Wash hands frequently and thoroughly, for at least 40-60 seconds); include fingers and all surfaces of the hands. Alcohol-based sanitizers should be used for at least 20 seconds. Respiratory droplets spread the virus. Hence, the WHO recommends covering the nose and mouth with tissue when coughing or sneezing. Cough into sleeves, not hands, if tissue is not available. Dispose of the used tissue promptly in the dustbin. All frequently touched surfaces such as tables, doorknobs, light switches, handles, desks, phones, keyboards, toilets, taps, etc., should be regularly cleaned and disinfected.

Always cover your nose and mouth with a non-medical (cloth) mask when outside your home or in public places. Oral hygiene forms an integral part of personal hygiene. Schistosomiasis infection is controlled by 1) improvement of sanitation conditions; 2) environmental control to reduce exposure to the snail; 3) education to reduce unsafe water contact; and 4) Mass Drug Administration. *Strongyloides stercoralis* is controlled by 1) to eliminate the possible autoinfection, the organism must be cleared from the patients completely; 2) treat symptomatic infection; 3) prevent complications associated with asymptomatic infection From protecting themselves against filarial infection, individuals must avoid contact with infected mosquitoes by using personal protective measures, including bed nets, particularly those impregnated with insecticides such as permethrin. Adult *W. bancrofti* does not multiply in humans. Hence, to develop wuchereriasis, repeated mosquito bites are essential and so avoiding mosquito bites is important. Wucheraria has no animal reservoir. The recommended treatment is Diethylcarbamazine(DEC). Treatment may have to be repeated in endemic areas every two years or so. Mass chemotherapy has been tried, but it may pose difficulties in large endemic areas such as India. As DEC is non-toxic, it can be safely administered in combination with food items such as common salt.

IX. AN OPINION IS ARRIVED AT THROUGH A PROCESS OF REASONING

Malaria reduction and elimination can be achieved in the Americas, but this will require better coordination of patient diagnosis and treatment, including asymptomatic patients, with information on the behavior and ecology of the local malaria vectors. Elimination of breeding places by filling and drainage. When oil is applied to water, it lowers the surface tension of water and kills mosquito larvae. Paris green or copper auto arsenate is a greenish crystalline powder. It contains arsenious oxide. It kills anopheline mosquitoes. DDT, BHC, abate malathion, etc., insecticides control mosquitoes and are not favored because of developing resistance. Gambusia and Barbados fish are employed for the control of mosquito larva. The emergence of both parasite resistance to drugs and mosquito resistance to insecticides has rendered the task more difficult. However, Malaria is once again a priority for the WHO, which announced a new “ROLL BACK MALARIA” campaign in 1998. It has had good success in some countries. Acute filariasis is characterized by filarial fever, lymphedema, lymphadenitis (inflammation of lymph nodes).In chronic wuchereriasis, lymph varices, hydrocele, elephantiasis, chyluria occurs.

Control of parasitic infections depends on a number of different factors, including geographic location, public health, infrastructure, political stability, available funding, social and behavioral customs, and benefits, trained laboratory personnel, health care proper teams, environmental constraints, poor understanding of organism life cycles, and opportunities for control and overall commitment. Vectors and other carriers of infectious agents do not recognize political or control boundaries, both of which become meaningless. When newer infectious agents and or diseases are recognized, there is often little information available regarding the organism life cycle, potent reservoir hosts, and environmental requirements for survival (52)

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