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Life cycle of *Plasmodium vivax:*

Introduction:

Malaria parasites belonging to genus Plasmodium, are classified in the Kingdom Protista, Phylum Apicomplexa. All members of the phylum Apicomplexa are obligate intracellular parasites of vertebrates (humans, birds, lizards, rodents, and primates) causing considerable damage and even leading to death of the host. The disease is widespread in tropical and subtropical regions around the equator, including much of Sub-Saharan Africa, Asia, and America.

Habit, Habitat and Distribution of *Plasmodium Vivax:*

Plasmodium vivax lives as an intracellular parasite in the red blood corpuscles (R.B.Cs) of man in the form of its mature adult condition, called trophozoite. The species of Plasmodium are reported from reptiles, birds and various mammals.

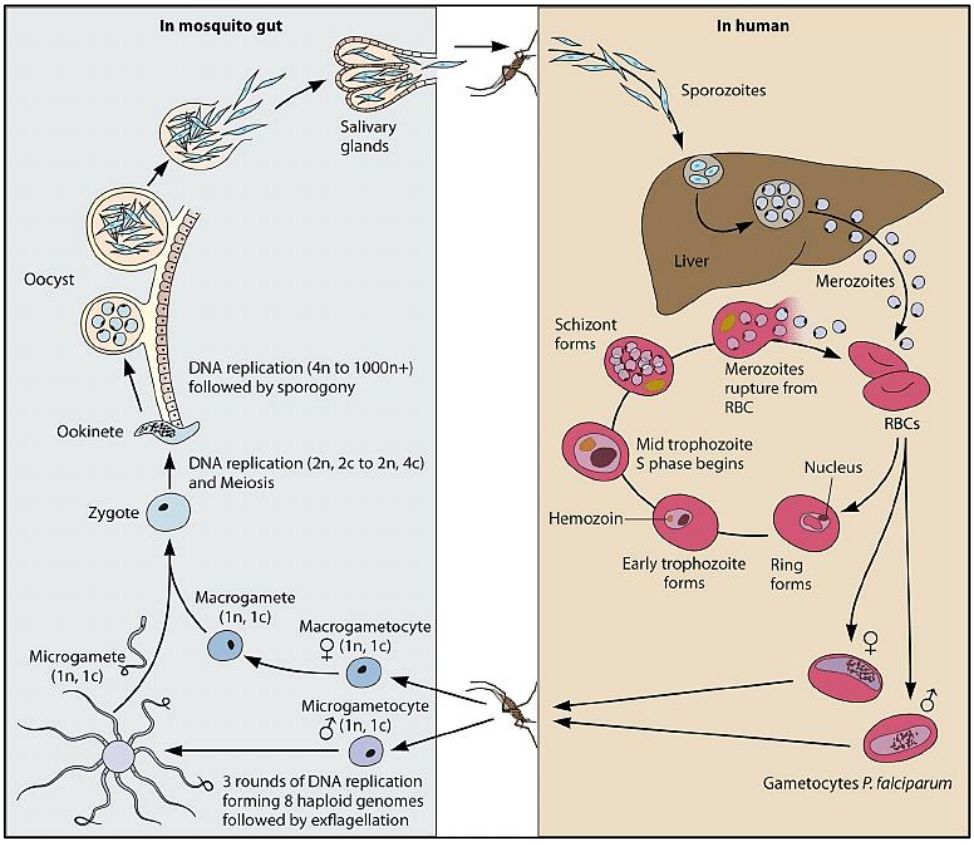
However, Plasmodium is widely distributed in tropical and temperate countries of the world but they are no longer a problem in the colder countries of the world. Countries like India, Sri Lanka, Bangladesh, Nepal, Pakistan, etc., are worst affected. In our country, states like Bihar and Uttar Pradesh suffer a greater setback by the infection of this parasite. In fact, the infection of Plasmodium is a global problem.

Over 100 species of Plasmodium parasitize a wide range of vertebrates, including birds, reptiles and mammals; however four are known to infect man causing different kinds of malaria. These are:-

P. malariae , P. vivax . P. falciparum , P ovale

Life cycle of *Plasmodium vivax:*

Life cycle of *Plasmodium vivax* is digenetic i.e. they complete their life cycle in two hosts:



1. Primary host or definitive host: Female Anopheles mosquito is the primary host. The organism which contains sexual phase of the parasite and is regarded as definitive host.

2. Secondary host or intermediate host: human is the secondary host. Human contains asexual phase of the parasite and develops symptoms of disease due to the presence of parasite and is termed as secondary host.**Life cycle of *Plasmodium vivax* is divided into:**

1. Asexual life cycle or schizogony in man
2. Sexual life cycle or sporogony in female Anopheles mosquito

1. Asexual cycle or Schizogony in man:

When an infected female *Anopheles* mosquito bites a healthy person, it injects thousands of sporozoites along with saliva into the bloodstream. Schizogony is the process of asexual reproduction by which *Plasmodium* undergoes asexual multiplication in liver cell (liver schizogony) and RBCs (erythrocytic schizogony) of man.

Asexual cycle or schizogony in human is completed in following phases:

a. Pre-erythrocytic cycle

When the sporozoites enters the blood it remains active for about half an hour. Then it enters into the liver through blood circulation by secreting lytic enzymes from the apical cap. Sporozoites in liver cell grow in size and become spherical in shape called schizonts. The nucleus of schizont multiply asexually (multiple fission) and forms thousands of merozoites. These gives pressure to the wall of liver cell and liberated out in the form of cryptozoites or cryptomerozoites through ruptured liver cell. **The process of formation of many cryptozoites from single sporozoites in liver cell is called pre-erythrocytic schizogony.**

b. Exo-erythrocytic schizogony

The cryptozoites are ready to infect the fresh liver cell where they grow and become schizont. The same process is repeated several times. The process of formation of many metacryptozoites from the cryptozoites in liver cell is called exo-erythrocytic schizogony. Some metacryptozoites are smaller in size called micro metacryptozoites and some are larger in size called macro metacryptozoites. **The micro metacryptozoites enter the red blood cells to start the erythrocytic phase while the macro metacryptozoites infects the fresh liver cells to continue exo-erythrocytic phase.**

NOTE: Exo-erythrocytic cycle is absent in Plasmodium falciparum.

c. Erythrocytic cycle

This cycle starts when the micro metacryptozoites enter into erythrocytes. When metacryptozoites invade the RBC it becomes rounded with large nucleus *and grows in size by ingesting hemoglobin of corpusles.* This stage of parasite is called trophozoite stage. Inside the trophozoite, a large non-contractile vacuole appears which pushes the nucleus towards periphery and forms a ring like structure known as signet ring stage.

The trophozoites after feeding, becomes rounded, grows in size and becomes erythrocytic schizont. Asexual multiplication takes place in schizont and forms merozoites which give pressure to the wall of weak RBC and liberated out in the form of erythrocytic merozoites.

The merozoites are arranged towards the periphery due to the presence of hemozoin at the center. The arrangement is just like the arrangement of petals in rose flowers. So this stage is called **rosette stage.**

Numerous yellowish eosinophilic granules appear in the cytoplasm of the host corpuscles which are called schuffner's granules. These dots are believed to be the antigen excreted by the parasites.

The process of formation of merozoites in the RBCs from the metacryptozoites is called erythrocytic schizogony. It completes about 48 hours. Many merozoites enter the fresh RBC and repeat the erythrocytic cycle.

d. Post-erythrocytic cycle

Sometimes, some merozoites produced after erythrocytic cycle invade the liver cell and undergo another schizogonic development in the liver cell. This is called post-erythrocytic cycle.

e. Formation of gametocytes

After some generation of erythrocytic cycle, some of the merozoites invade the new RBC. They grow in size and develop into gametocytes. The gametocytes are of two types: i. Macrogametocytes or female gametocytesii. Microgametocytes or male gametocytes:

Further development of gametocyte stop in man and only possible in mosquito due to its low temperature.

3. Life cycle in mosquito or Sexual Cycle in mosquito

When female *Anopheles* mosquito bites an infected persons, they suck the gametocytes and other stages of erythrocytic cycle (e.g. erythrocytic merozoite) along with blood. They reach the stomach where all the stages along with RBCs are digested except gametocytes. Now, the life cycle is continued towards the completion by following processes:

a. Gametogenesis/ Gametogony (Formation of gametes)

Process of formation of gametes from the gametocytes is called gametogenesis.

Formation of microgametes: Microgametocytes undergo ex-flagellation process in the mid-gut of mosquito. The nucleus of microgametocytes divides to form 6-8 daughter nuclei. These nuclei move to periphery along with cytoplasm, forming flagella like structure. Thus 6-8 flagella like male gametes are formed from each microgametocytes.

Formation of macrogametes: Macrogametocyte undergo some reorganization and become female gametes or macrogametes or megagametes. The female gamete is non-motile.

b. **Fertilization:**

One microgamete penetrates into macrogamete through the cone of reception and fertilization takes place known as syngamy. Zygote or synkaryon form in stomach of mosquito about 9 to 10 days after the blood meal.

c. Formation of ookinete:

After fertilization, the zygote remains rounded and non-motile for some time. Then it becomes elongated and vermiform known as ookinete. Ookinete is motile and has pointed ends. It penetrates the wall of stomach with the help of lytic secretion. It settles into the inner portion of stomach wall.

4. Formation of Oocysts:

The ookinete changes into spherical shape, take nutrition from the wall of stomach and get enclosed in a thin, elastic and permeable cyst wall, such stage is called oocyst stage or sporont.

5. Sporogony:

It is the process of formation of sporozoites from the zygote nucleus by asexual multiple fission. Oocysts matures and develops and form slender or sickle shaped sporozoites. The sporozoites are very active and motile, they reach to the salivary glands of the mosquito. Then the sporozoites are ready to infect the healthy person after each bite. So when the infected mosquito bites a healthy man, thousands of sporozoites are injected into his blood along with saliva.

Inoculation:
When an infected female Anopheles mosquito bites a healthy person it suck his/her blood for meal, she injects saliva containing sporozoites into the wound through its needle like mouth parts. This is called inoculation.

Pre patent period:
The interval between inoculation and initiation of erythrocytic cyce is called pre-patent period.

Incubation period:
The period between the entry of parasite and appearance of first symptoms is called incubation period. It is about 14 days in *P. vivax* and *P. ovale*, 12 days in *P. falciparum* and 28 days in *P. malariae*.

Relapse: In P. vivax and Povale malaria has the capacity to relapse, that is, there can be a reappearance of parasites in the blood after the patient has been treated and seemingly recovered. This type of relapse, called recurrence, is due to the delayed liberation of merozoites from exo-erythrocytic schizonts in the liver, called hypnozoites. It accounts for about 45% of all malaria cases. Parasites are often difficult to demonstrate in the peripheral blood film during relapses.

Signs and Symptoms:

The signs and symptoms of malaria typically begin 8-25 days following infection. The symptoms do not appear immediately after humans get infected with Plasmodium sporozoites. The time interval between the infective bite of mosquito and onset of clinical symptoms is called the incubation period.

Initial clinical symptoms: The initial signs and symptoms of include: headache, fever, shivering, joint pain, vomiting, hemolytic anemia, low blood pressure, jaundice, anorexia, hemoglobin in the urine, retinal damage and convulsions . Other symptoms include headache, bone and muscle pains, malaise, anxiety, mental confusion, massive weight loss and ever delirium. Severe anaemia and leukopenia are common.

Hepatomegaly: Liver becomes enlarged as kupffer cells increases in number and their cytoplasm is filled with parasites, malarial pigment and cellular debris.

Splenomegaly: Enlargement of spleen is one of the important physical signs of malaria. In chronic cases, spleen becomes enlarged and fibrosed so much that it ruptures under the influence of trauma. The spleen continues to enlarge, becoming hard and blackened in color due to the accumulation of malaria pigment, hemozoin.

Malarial paroxysm / Febrile paroxysm: It is the classical manifestation of acute malaria. Each paroxysm shows a succession of three stages:

1. COLD STAGE: This is characterized by sudden onset of fever with rigor and sensation of extreme cold. Patient desires to be covered with blankets. This lasts between 15 minute and one hour.

2. HOT STAGE: Temperature may rise to 41°C (106°F). Patient feels burning hot and casts off his clothes. There is intense headache. This stage lasts from 2 to hours.

3. SWEATING STAGE: Fever comes down with profuse sweating. This stage lasts from 2 to 4 hours. Temperature drops rapidly to normal and skin is cool and moist.

Mode of Transmission:

Source of infection: Sporozoites are introduced into the vertebrate host during the blood meal by infected female Anopheles mosquito.

Transmission ways: The bite of a female Anopheles sp. mosquito, which occurs mainly between dusk and dawn introduces the parasite in human leading to malaria.

Congenital malaria caused by transmission of erythrocytic asexual forms of parasite to foetus via placenta.

Transfusion malaria occurs by blood transfusion, sharing of contaminated needles, and organ transplant.

Prophylaxis:

There is no vaccine for malaria. Methods used to prevent malaria include medications, mosquito elimination and the prevention of bites. This can be achieved by: Treatment of infected individuals

Individuals infected with malarial parasite should be treated with appropriate anti- malarial drugs.

Vector control:

Adult mosquitoes can be most effectively combated in dwellings. The following methods can be employed to kill them:

Fumigation: The adult mosquito could be killed by fumigation.

Spraying: Mosquitoes can be killed inside human dwellings by spraying DDT, the pyrethrum and other insecticides.

Source Reduction: Destruction of Anopheles' larvae can be achieved by eradicating the breeding places of mosquito. If possible, the breeding grounds may be filled up with earth or stones, etc. Bushes and shrubs should be cleared off. Open drains should be closed or made underground. Removing or covering standing water around houses. Removing or changing water from air coolers.

Chemical larviciding: A thin film of oil can be sprayed on the water surface, suffocating the larvae and pupae. Oil solutions or emulsions of DDT, DDD and benzene hexachloride are effective larvicides.

Biological control: The insect larvae could also be destroyed by biological methods using larvicide fishes. Larvicidal fishes, like stickle-backs, minnows (Gambusia) and trouts, etc., ducks and aquatic nymphs and adult insects like dragon-flies, which are natural enemies of mosquito, may be introduced in ornamental fountains, ditches, ponds, lakes, canals, tanks, etc. They feed upon mosquito larvae and pupae.

Prevention from mosquito bite: Prevention of infection can be achieved by putting screens on all the doors, windows and entilators of the houses. One can use mosquito-nets to prevent mosquito biting during night.

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Diagnosis of infection of Plasmodium:

1. Malaria is diagnosed by demonstration of malarial parasite in peripheral blood smear. Two types of blood smear are useful - a thick smear and a thin smear. Blood smear are best stained with Giemsa stain and very much helpful for the detection of the parasite.

2. ELISA is used to assist in the diagnosis of malaria.

3. The parasite can be detected by using radioactive chemicals.

4. Magnetic Resonance Imaging (MRI) is most recently used to diagnose cerebral malaria

Treatment: Untreated malaria may cause death of victim. So, treatment is very essential. Many antimalarial drugs are as follows:

1. Chloroquine, Amodiaquine, Quinine, Mepacrine are potent drugs having action on early erythrocytic phases of the parasite. Administration of Primaquine prevents relapses of malaria.
2. Some protective drugs like Proguanil, Pyrimethamine, etc. can destroy pre-erythrocytic phases of the parasite in liver and inactibve gametocytes. Cycloguanil is used as a long acting injectable preventing drugs.

Table 1. **Comparative Account of Four Species of Human Infecting *Plasmodium*.**

Characters	*P. vivax*	*P. malariae*	*P. ovale*	*P. falciparum*
1. Geographical distribution	Worldwide, in tropical, sub-tropical and warmer temperate regions.	Worldwide, in tropical and sub-tropical regions.	Tropical Africa.	Worldwide, in tropical, tropical, subtropical and warmer temperate regions.
2. Duration of pre-erythrocytic cycle (pre-patent period)	8 days	7-12 days	9 days	5-6 days
3. No. of metacrypto-zoites formed per schizont.	10,000	2,000	15,000	40,000
4. Duration of erythrocytic cycle	48 hours	72 hours	48 hours	36-48 hours
5. No. of mero-zoites formed per schizont.	12-24	6-10	6-12	18-24
6. Incubation period (average)	14 days	18-24 days	14 days	12 days
7. Signet ring form in R.B.C.	About 1/3 diameter of R. B. C. Large ring with vacuole and usually one chromatin dot.	About 1/3 diameter of R.B.C. Usually one ring and one chromatin dot.	About 1/3 diameter of R.B.C. Usually one ring and one chromatin dot.	Small ring situated at edge of R. B. C. Sometimes 2 chromatin dots.
8. Late trophozoite in R.B.C.	Amoeboid and large.	Compact and often band-shaped, small.	Compact and small slightly amoeboid.	Compact and medium-sized. Rarely seen in peripheral blood.
9. Schizont in R.B.C.	Large, 10μ diameter, With 2-24 mero-zoites.	Medium sized, 7μ diameter. With 6-12 merozoites.	Medium sized, 7μ diameter. With 6-12 merozoites.	Small, 5μ diameter. Not seen in peripheral blood.
10. Gametocytes in R.B.C.	Round. Fill R.B.C. Male 9μ, Female 10-11μ. Pigment granules evenly distributed.	Round or ovoid, Fills R.B.C., 7μ. Pigment granules at centre and periphery.	Round or ovoid. Fill 3/4 of R. B. C., 9μ. Pigment granules, evenly distributed.	Crescentic. Male 9-11μ. Female 12-14μ. Pigment granules around nucleus.
11. Host R.B.C.	Enlarged, Red Schuffner's dots usually seen.	Not enlarged. Ziemann's dots seen.	Slightly enlarged, Schuffner's dots seen.	Not enlarged. Greenish Maurer's dots or clefts seen.
12. Pigment (haemozoin)	Yellowish-brown. Fine granules and rodlets.	Dark brown to black. Abundant as coarse granules.	Dark brown. Less abundant coarse granules	Dark brown or black. Coarse granules in a compact mass.
13. Microgametes formed	4 to 8	2 to 5	---	4 to 8
14. Duration of sexual cycle at 25°C.	10 days	25-28 days	16 days	10-12 days
15. Type and effects of Malaria fever	Benign tertian. Death rate low	Quartan. Severe.	Ovale or mild tertian Severe	Malignant tertian. Death rate high.

* *A sporoblast* stage, as found in *Monocystis*, is absent in *Plasmodium* in which the sporozoites are formed directly from the oocysts.