Hematology

Medical Committee
The University of Jorda

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- lecture number : 2
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Microbiology #2: Malaria

The Malaria parasite is a widespread disease in certain areas in the world (although it's not really found in Jordan), leading to high morbidity and mortality. There are almost 200 million cases a year, killing 0.5-1 million people (mostly children) yearly.

The malaria disease is caused by a parasite called **Plasmodium**, a member of the **apicomplexans**.

Properties of the apicomplexan parasites:

- They have a specialized organelle at their anterior end enabling them to penetrate cells, meaning they are INTRACELLULAR parasites.
- Two hosts: a primary host and an intermediate host.
- Two separate cycles of multiplication: Sexual (which occurs in the primary host) and asexual replication (which occurs in the intermediate host).

In the plasmodium, the female mosquito is considered the primary host (where sexual replication happens) and the human is the intermediate host (where asexual replication occurs).

Four main species of Plasmodium that cause disease in humans according to the frequency of encountering them:
Plasmodium falciparum (most common cause of malaria in Africa)
Plasmodium vivax (most common cause of malaria outside of Africa)
Plasmodium malariae
Plasmodium ovale
As far as the frequency, if you think of it, all over the world the most common cause of malaria is the *Plasmodium falciparum.*
Plasmodium knowlesi is mainly a parasite of primates like monkeys in Southeast Asia, but could occasionally be transmitted to humans, which means you could find cases of malaria caused by P. knowlesi in Southeast Asia.

Written by Layan Halboni

Life Cycle:

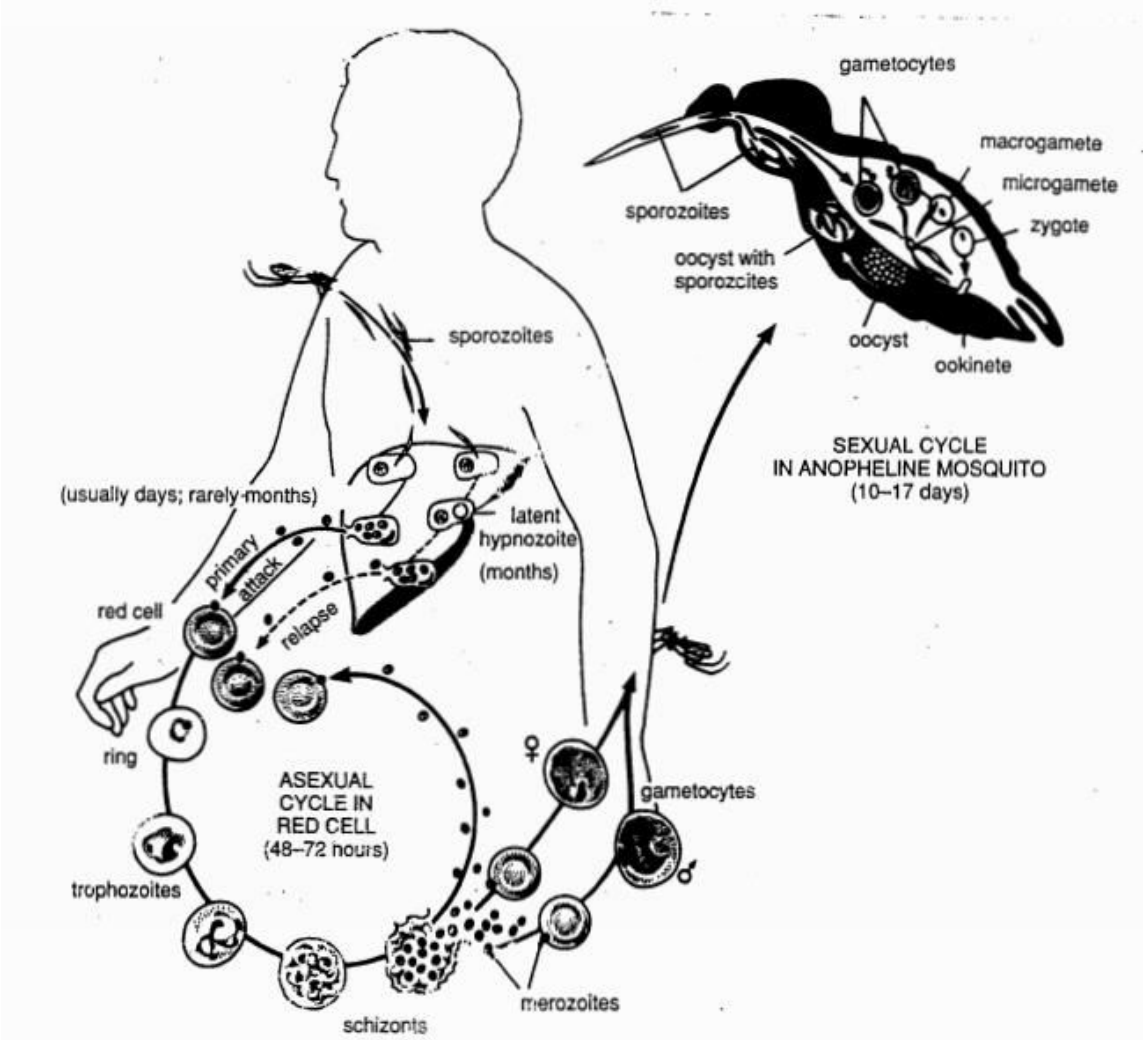

Figure 4–15. Life cycle of human malaria parasites.

The mosquito is the primary host. Only the female gender of Anopheles
mosquitos are able to transmit the disease to humans because they are the ones that suck blood. Male mosquitos do not suck blood, so they can't transmit the disease.

- A female mosquito bites the human, and it salivates into the puncture wound while doing so, since the saliva contains an anticoagulant that helps it draw blood at its own leisure. An infected mosquito has the parasite in its saliva, in a form (morphology) called **sporozoite**.
- The sporozoites enters the blood stream through the puncture wound, where they go towards the liver and invade the hepatocytes. This is because there's a protein on the sporozoite surface called circumsporozoite protein (CSP) that has receptors only on the liver cells.

- Inside the liver cells of the human (the intermediate host), the parasites change their morphology and start dividing by schizogony. They are known in this stage as **schizonts** (schizogony -if you remember- is a form of **asexual multiplication** where the whole schizont gets bigger and accumulates about 16-20 nuclei, then it ruptures releasing 16-20 separate organisms. (This is NOT binary fission). The daughter cells produced by schizogony are called **merozoites.** This is called the extra-eryrthrocytic (or liver) stage of multiplication; it takes a couple of weeks, so within two weeks after the bite the person does not get the symptoms of the disease and this can be considered as an incubation period.
- These merozoites leave the liver and enter the circulation. They invade the RBCs through special receptors on the RBC surface. For example *P. vivax* uses the Duffy blood antigen on RBCs. If you don't have the Duffy blood antigen, you can never be infected by *Plasmodium vivax* (but you are still susceptible to infection by other Plasmodium species that use other receptors to gain access into RBCs). *P. Falciparum* uses sialoglycoproteins present on RBCs.
- Inside the RBC, the merozoite changes its morphology into a **trophozoite.** It's sometimes known as a ring trophozoite, because it looks like a signet ring. The signet represents the chromatin of the parasite, while the rest of the ring is the cytoplasm.
- The trophozoite gets bigger and bigger, eating up and metabolizing the hemoglobin, leaving bits and pieces and some pigment inside the RBC called Haemozoin that could be seen under the microscope. So haemozoin is left-over hemoglobin pigments inside the RBCs that appear brownish in color.
- The trophozoite becomes bigger and bigger and turns into a schizont again, multiplying once more by schizogony giving rise to 16-20 daughter cells (merozoites). The merozoites rupture the RBC, re-entering the circulation and once more infect other red blood cells.

Erythrocytic stage: The duration from the entry of the merozoite into the RBC till the exit of the merozoites from the ruptured cell. It takes usually 48-72 hours, depending on the species. *P. falciparum*, *P. vivax and P. ovale* need 48 hours, so the symptoms (like fever) of the disease appear on the third day, since they occur with the rupture of the RBC. This is why we call it **tertian malaria.**
P. malariae on the other hand needs 72 hours, so the symptoms appear on the fourth day when the RBC ruptures. This is why we call it **quartan malaria**.

P. Knowlesi needs only 24 hours, so symptoms appear on the second day. (Could be called secondary malaria but it doesn't actually have a name).

Some of the trophozoites inside the RBCs do not undergo schizogony, but they develop into gametocytes. Bigger ones are called macro-gametocytes (the female equivalent of gametocytes), and the smaller ones are called micro-gametocytes (the male gametocytes). These remain in the RBCs without rupturing, and when a new female mosquito sucks blood from this person, it sucks in the male and female gametocytes. They enter the GI tract of the mosquito, where the microgametocytes divide asexually into many equivalents of sperms that then fertilize the female gametocyte (Sexual reproduction), giving rise to the zygote that divides and develops into sporozoites (sporogony). The sporozoites move up to the salivary glands of the mosquito, and will be released again with the saliva when this infected mosquito bites another victim.

In cases of *P. vivax* and *P. ovale*only, not all sporozoites reaching the liver become schizonts and divide. Some of them 'go to sleep' or become dormant in the liver, and they're called **hypnozoites**(latent)**.** These hypnozoites can become reactivated after a period of time and give rise to the disease again.

Some anti-parasitic drugs used only target parasites present in the blood. In this case, the dormant parasites in the liver would be forgotten, and after a few months of feeling well, they would be reactivated and the disease would reoccur, without being bitten by an infected mosquito again. This is known as a RELAPSE. That is why patients should be treated with drugs that target both parasites in the blood and the liver (the erythrocytic stage and hypnozoites lurking in the liver).

Symptoms:

Usually, about 2-3% of the RBCs in the blood are infected in *P. vivax*, *P. malariae, and P. ovale*. However in *P. falciparum* up to 40% of all RBCs are infected, which is why this species is associated with more symptoms and the highest degree of parasitaemia. This is why we call *P. falciparum* **malignant tertian malaria**.
Benign tertian malaria refers to *P. ovale* and *P. vivax*.

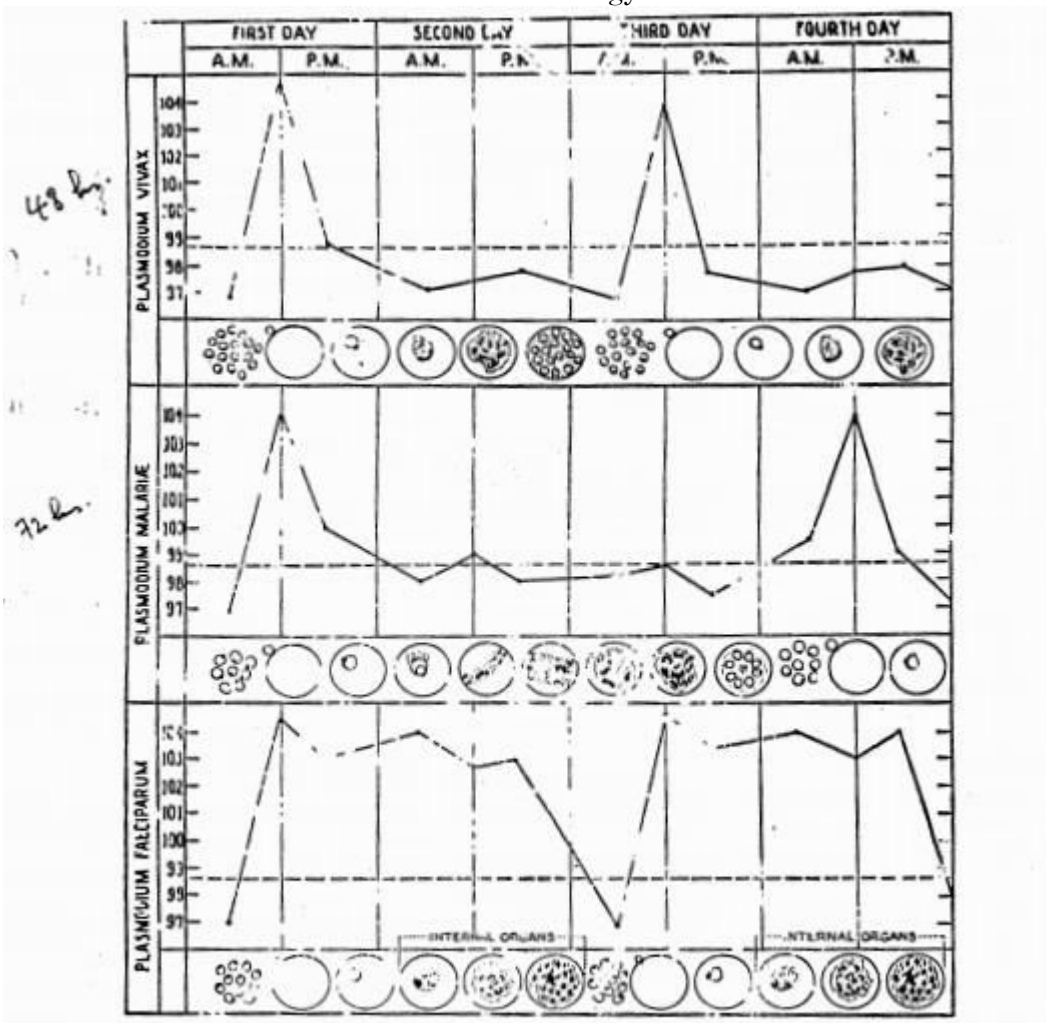

Figure 4–15. Temperature curves in malaria showing relation to growth and schizogony of malarial parasites.

With the rupture of the RBCs and the release of merozoites and all the muck that has accumulated and foreign antigens, clinical signs of the disease arise. In malaria we have **synchronization**, which means that the majority of the merozoites will enter the RBCs in the same time, staying inside for 2-3 days depending on the species, and leave it after it ruptures at the same time.

As you can see in *P. vivax* of the figure above, once a merozoite enters the RBC it takes about two days for the cycle to finish and on the third day the cell ruptures, accompanied with the symptoms. That's why it's called tertian malaria. We have synchronization between all the different merozoites in the blood, i.e. the symptoms appear every third day.

- The hallmark of malaria is fever, or rigors, which is when the patient feels cold and is shivering or his teeth are stuttering, but he has a high rising temperature.
- After 5-7 hours, the temperature shoots up to 39-41 degrees. The patient stops shivering but he feels very ill and suffers from malaise, nausea, headache, muscle ache, abdominal pain etc. This can last for a few hours.
- Diaphoresis follows: the temperature drops back to normal. This is accompanied withprofuse sweating.

The stages above happen in 24hours. In tertian malaria this happens on the third day. And if it's synchronized this goes on and on in a pattern (being well for two days then getting sick in the third day).

Fever on the third day occurs in *P. vivax* and *P. ovale* (tertian).
Fever on the fourth day occurs in *P. malariae* (quartan).
In *P. falciparum*, because there are so many infected RBCs, synchronization between the parasites is not possible, and so there are overlapping cycles and the patient feels unwell most of the time, the fever is present almost non-stop.

As we mentioned in *P. falciparum* 40% of RBCs are supposed to be infected, yet only 5% infected RBCs can be seen in a blood smear of an infected person. This is because most of the infected cells are sequestrated into the capillaries of the viscera (for a reason we will mention later).

Other than fever, symptoms of malaria include hemolytic anemia (when the cells lyse), which is associated with jaundice, splenomegaly, and hemoglobinuria.

Malaria caused by *P. falciparum* is also called black water fever. This is because this species is associated with the most hemoglobinuria since almost 40% RBCs are infected. The urine has a lot of hemoglobin that would become oxidized in air and turns black, hence the name black water fever.

P. falciparum, or malignant malaria, found inside the RBCs can sometimes export some of its antigens onto the RBC surface, creating knobs on the membrane. These antigens make the RBCs sticky, sticking to one another and to the endothelium, and that's why the cells are sequestered into small capillaries of the viscera because they stick to the endothelium. Aggregated RBCs that are stuck together could lead to thrombosis, especially in small blood vessels, and this can be of serious consequences. For example, if blood vessels of the kidneys were blocked, the tubular cells will die, leading to renal failure due to acute tubular necrosis. If blood vessels in the brain are affected, depriving it of blood, you get what's known as cerebral malaria which is only associated with *P. falciparum*: Comatose, loss of consciousness, death, and various sensory or motor neurological deficits.

Hypoglycemia also occurs in falciparum infections because you have a large number of parasites so use a lot of energy and you consume sugar, which is really a bad indicator of the disease.

Usually, if a malaria patient gets treated hopefully he recovers and become healthy. If the patient is not treated (in cases of falciparum or vivax or ovale), the disease lasts from weeks to a few months, ending either in death (especially in falciparum) or recovery (in Vivax and Ovale). Many people actually recover without treatment (especially with vivax or ovale).

*P. malariae*is a chronic disease that can go on for years (7-8 years or more). The degree of parasitemia becomes very verysmall (1 in 1,000 or 10,000 RBC's), i.e. there is very little ongoing damage to RBCs, not much antigens in the circulation and no symptoms, the patient generally feels well. Nevertheless, there are still some RBCs in the body that are infected with the parasites. After a period of time, these become more active and they will invade more and more RBCs, leading to reactivation of the disease. This is called **recrudescence**. (The disease was not gone, it stayed in the blood and flamed up again). You must differentiate:

Relapse: fresh infection by the hypnozoites that were lurking in the liver.

Recrudescence: parasites are in the blood, but at times they are very very small in number and they don't cause symptoms, then after a while they do… Can go on for years. (internet: it is the recurrence of symptoms in a patient whose blood stream infection has previously been at such a low level as not to be clinically demonstrable or cause symptoms, or the reappearance of a disease after it has been quiescent.)

* You should differentiate betweem Relpase and Recrudescence,

Because of this chronicity of *P. malariae*, you find there is a persistentsupply of antigens, and thus a continuous supply of antibodies, forming together immune complexes which settle in narrow blood vessels or capillaries. These immune complexes can also settle in the glomeruli of kidneys and will produce an **immunological** inflammatory reaction called glomerulonephritis (the glomeruli is inflamed and not the parenchyma).

*In the kidneys there are two types of inflammatory reactions: bacterial (pyelonephritis like from E. coli) and immunological (glomerulonephritis).

- *P. malariae* tends to infect old RBCs, that's why they're usually smaller.
- *P. vivax and ovale* tend to infect younger cells especially reticulocytes.
- *P. Falciparum*infect all kinds of RBCs whether old or young, which explains the large degree of parasitemia.

Dedicated to "."