

## Malaria

- ❖ The name itself is derived from Mal-Air. Mal: Latin word means bad, so malaria means the bad air around swamps and dirty ponds, Malaria is caused by a *mosquito* living around those ponds.
- ❖ It transmitted by a **female anopheles mosquito**.
- ❖ Malaria is a widespread disease around the world causes many millions of infection every year (causes 1-3 million deaths a year MAINLY CHILDREN – at least 1 million children die every year), and it hasn't been eradicated especially in tropical and subtropical areas. But here in Jordan we had eradicated malaria since about 1950 in effort of swamp elimination and spraying, but we may still have the disease from imported cases (from outside).
- ❖ Malaria is caused by a parasite known as *Plasmodium*, a coccidian which belongs to the group of *Apicomplexa* (a group of parasites that have specialized structure on its anterior end allows them to enter cells to cause intracellular infection, so it is an intracellular parasite) and one of them is Malaria Plasmodium.
- ❖ The multiplication of Coccidia has two varieties:  
**Sexual** and **Asexual**, depending on the host they are in,
  - ✓ as in malaria; human is the intermediate host where asexual multiplication takes place and is referred to as **schizogony** (the form of malaria is called **schizont**)
  - ✓ while in mosquito which is the primary host, sexual multiplication takes place and is referred to as **sporogony** ( results into sporozoites, which are transmitted to human and cause the infection).  
 (there is some asexual reproduction take place in mosquito but mainly it is sexual)
  - ✓ The division does not occur by binary fission (where each parasite divides into two); instead in schizogony the trophozoite enlarges → while repeatedly replicating its nucleus (the number of nuclei depends on the species) → these eventually will rupture and give rise to organisms to be released in the blood.
- ❖ There are many different species of plasmodium but only 4 are relevant and the others are very rare, here the doctor just mentioned the 4 majors which are:
  - 1- *Plasmodium Vivax*. (most common)
  - 2- *Plasmodium Falciparum*.

3- *Plasmodium Malaria*.

4- *Plasmodium Ovale*.

\*They are ordered by frequency from most to least.

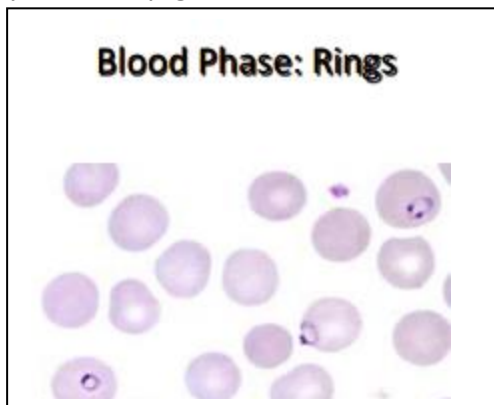
- There is other specie which is very rare and affects both humans and monkeys known as *plasmodium knowlesi* (disease of apes or ape malaria) which is found mainly in South East Asia.
- \* So, *Plasmodium knowlesi* is restricted to South East Asia, while the other types mainly affect tropical and subtropical areas.

### ❖ Life Cycle

- ✓ We will start by biting of ***female anopheles mosquito*** to human (Only female bite and suck blood to get food to nourish its eggs while male don't).
- ✓ Here the infective form of plasmodium is called **sporozoite**, and found specifically in mosquito saliva, where there is anticoagulant agents that are injected to let it suck the blood easily.
- ✓ Once sporozoite enter blood stream it spreads to the whole body but it will **only** infect the **liver** because of special protein on the surface of sporozoite **CSP (circumsporozoite protein)** and its receptor is on hepatocytes of the human liver.
- ✓ Once sporozoite enter hepatocyte (hepatic stage of multiplication or extraerythrocytic (outside the erythrocyte)) it will start reproduce **asexually intracellularly** by process known **schizogony** and its morphology changes from **sporozoits** to **trophozoit** then **schizonts** (derived from schizogony).
- ✓ It will continue dividing for 14 days at least (2-6 weeks or even months) and at this time no symptoms appear (Asymptomatic) hence it would be the **incubation period**.
- ✓ After the incubation period the schizonts are released from liver and enter blood circulation to infect RBCs, by this time its morphology change to **merozoite**.
  - In case of *P.Falciparum* and *P.Malaria* once it is released from liver and become **merozoites**, its role in the liver stops. but in *P.Vivax* and *P.Ovale* once you administer a drug and killed them in the blood, some of them will stay alive in liver and continue as **hypnozoites**; it is a sleeping (dormant) plasmodium that will be reactivated later in life causing what is known as **relapse of disease**, (it is as same as the original disease but comes from the

latent plasmodium). Here we prescribe **different** drug for killing hypnozoites. **(Double treatment, one for merozoites and another for hypnozoites)**. We should administrate primaquine – against hypnozoites- in conjunction with chloroquine or doxycycline for example. Usually, the liver is not afflicted.

- ✓ Once schizonts are released from hepatocytes they only infect RBCs, finding their way by specific protein receptors known as Sialoglycoprotein Receptor. while in *P.Vivax*, they have another special protein receptor the **Duffy receptor** for Duffy +ve blood group (A protein on RBC surface when present called Duffy +ve).
- ✓ So cells that lack Duffy (Duffy -ve) receptor are resistant to *P.Vivax*.
- ✓ Once **merozoites** infect RBC, it will become **trophozoite** (its shape looks like a singlet ring and has one dot (or rarely two) which represent the nuclear chromatin). Now it will start growing and occupies most of the RBC and assumes different shapes and sizes depending on the species, and start degrading the Hemoglobin of the RBC. By the end of this, the remnants of degraded haemoglobin will be known as Haemozoin and appear as brownish yellowish pigment in the middle of the cytoplasm.



- ✓ Now **trophozoite** will develop to become **schizont** in the RBC then it will become **merozoites** again. After that they will start dividing asexually increasing in number and the RBC will rupture releasing the **merozoites** with the remnants of haemoglobin and several things, the merozoite now infect another fresh RBC, and this repeated again and again, so the malaria symptoms start to appear (fever).
- The period of intraerythrocytic stage (from entering RBCs until they exit), differ from one specie to another as in *P.Ovale* , *P.Vivax* and *P.falciparum* it is around 48 hours while in malaria it is 72 hours.

- So *P.Ovale* , *P.Vivax* and *P.falciparum* **symptoms** will appear on the third day (TERTIAN malaria). In contrast **P.Malaria** **symptoms** appear on the fourth day (after 3 days of incubation period) and we call it QUARTAN malaria.
- Usually 2-3% of the RBCs are infected. But the *P.falciparum* is the worst as the RBCs infected could reach 40% at one time (high degree of parasitimia), they cause severe disease and death so we call it **Malignant Tertian Malaria**.
- Others are called Benign (**Benign Tertian Malaria** for *P.Ovale* and *P.Vivax* and **Benign Quartan Malaria** for *P.Malaria*).
- During the **intraerythrocytic stage**, some proteins are transported from trophozoite to RBC surface by Actin which acts as Actin Bridge. In case of *P.falciparum* one of the parasitic molecule (which is transported by Actin bridge) act as **adhesion factor** which let the **RBCs** cluster around each other (as rose shape) known as **rosette** which might close some tiny **capillaries** in the body leading to **thrombus** formation. While another protein act as adhesion factor for **endothelial cells** which let RBCs adhere to vascular endothelial cells and is referred as **sequestration**.
- As a result from sequestration and rosette, the measured **Parasitaemia** (number of infected cells) of *P.falciparum* from blood smear would be lower than expected (which is 40%) because a lot of infected cells are adherent to endothelial cells.
- The RBCs infected by *P.falciparum* lack synchronization (life cycles are overlapping, the temperature of the patient's body goes up and down haphazardly ..etc) .
- In PUO (pyrexia of unknown origin) you should suspect malaria as it can cause it. (other possible causes of PUO: typhoid fever, influenza).

#### ❖ Symptoms of the malaria:

- 1- Starts with chills, stuttering and shivering for 1-3 hours.
- 2- Fever (the hallmark), temperature is high but the patient shivers and feels cold.
- 3- After few hours the temperature will go up 40-41°, by that time the patient feels ill Malaise, headache, nausea, muscle aches, abdominal pain and vomiting, this lasts for few hours.

- 4- Followed by **diaphoresis** (excessive sweating), temperature back to normal, the breakdown products of RBCs have been removed and the patient feels better.

❖ **Other clinical manifestation :**

1. Hemolytic anaemia
2. Jaundice because of bilirubin (indirect) and haemoglobinuria( blackwater fever).  
In haemoglobinuria :Hb will be excreted in the urine, if you take a fresh sample and leave it for a while, it will be Oxidized and its color becomes black → it is called Blackwater fever.  
(the previous manifestations are more pronounced in *P.falciparum*)
3. Hypoglycemia, because there are lots of parasites consuming a lot of glucose and glycogen, also the patient probably is not taking any food, usually associated with *P.falciparum*.
4. Splenomegaly and hepatomegaly because the body has to phagocytize the broken RBCs.
5. Acute tubular necrosis.
6. Immune complex glomerulonephritis.
7. Cerebral malaria.

❖ **Recurrence :**

- **Relapse:** Due to the reactivation of hypnozoites in the liver as mentioned earlier.  
Occurs in *Ovale* and *Vivix*.
- **Recrudescence:** *plasmodium malaria* tends to become chronic, so with treatment -or without sometimes- the number of infected cells becomes very low and patient will feel well. After a long time the cells will be recruited and cause Recrudescence. So, because of the chronicity of *P.malaria* It will give continuous supply of antigens and the body will give continuous supply of antibodies → immune complexes → tend to deposit in the tissues producing type 3 hypersensitivity "***immune complex glomerulonephritis***" which could lead to renal failure.
  - In the case of *P.falciparum*, the parasite exports its antigenic molecules on the surface of RBC and produce knobs on its membrane, RBCs will become sticky so they stick to each other and to endothelial cells of blood vessels, the RBCs cluster around each other (known as **rosette formation**) → sequestration → block the blood vessels, if these blood vessels were in vital area like the kidney it will cause **acute nephritis** [**acute tubular necrosis**] and this may lead to renal failure and death.

- It may lead also to **cerebral malaria** (not meningitis) when it goes to brain and block the blood vessels there and you may observe seizures, deficit of motor or sensory functions, loss of consciousness and may lead eventually to death.

That's why *P.falciparum* is more serious.

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