Malaria

Malaria lecture

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2005
1. History and Distribution
2. Biology of Plasmodium Parasites and Anopheles Vectors
3. Pathogenesis
4. Clinical manifestations
5. Complications
6. Diagnosis
7. Prevention of Malaria Infection
8. Treatment and drug Resistant Malaria
Course Objectives

At the end of the course students should be able to:

1. Name the four species of human malarial parasites
2. Understand the basic histopathology of the malarial parasite.
3. Distinguish between the four species of human malarial parasites seen in thin blood smears; describe the findings and recognise the three main stages of the parasite (trophozoite, schizont and gametocyte), seen in the peripheral blood.
4. Describe the findings of thick blood smears for malaria and differentiate where possible between the four species of human malarial parasite.
5. Describe the life cycle of the four species of human malarial parasites.
6. Discuss the clinical differentiation of the four species of human malarial parasites.
7. Describe the general morphology and distribution of the mosquito vectors of malaria.
8. Discuss the worldwide epidemiology and situation of malaria.
9. Prepare and describe the preparation of a thin and thick smear for malaria.
10. Know the methods of malaria diagnosis
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9. Prepare and describe the preparation of a thin and thick smear for malaria.
10. Know the methods of malaria diagnosis
THE HISTORY

- originated in Africa
- known since antiquity
- fossils of mosquitoes up to 30 million years old
- 500 BC. Hippocrates: first to describe the manifestations of the disease.
  And early medical writings from India and China
- 1600 The first recorded treatment
- 1880 Laveran identified parasite (in Algeria)
- 1897 the Anopheles mosquito demonstrated to be the vector.
- Ross demonstrated mosquito transmission (1898)
- 1940’s Garnham described liver stage
- 1942 the discovery of the insecticide DDT
- Its first use in Italy in 1944
- Brought to the New World by early trans-Pacific voyagers
EPIDEMIOLOGY

- Found mainly in tropical and subtropical regions of the world, particularly in Africa, Asia and South America.
- Transmission occurs in > 100 countries.
- At present, at least 300,000,000 people are affected by malaria globally.
- About 1 million deaths annually, mostly amongst children of less than 5 years old.
- Malaria is one of the top infectious killers (1.5 - 2.7 million deaths, 90% Africa)
- The World Health Organization estimated that: “.. in the time taken to read this sentence out loud, one child will have died from *falciparum* malaria in sub-Saharan Africa.”
Transmission

- Bite of an infected female *Anopheline* mosquitoes.
- Direct inoculation of infected RBC:
  - Blood transfusions
  - Contaminated needles
  - Congenital
Four species of *Plasmodium* can cause human infection:

1. *P. vivax*
   - most widespread, found in most endemic areas including some temperate zones

2. *P. falciparum*
   - primarily tropics and subtropics

3. *P. malariae*
   - similar range as *P. falciparum*, but less common.

4. *P. ovale*
   - occurs primarily in tropical west Africa
Life cycle

- Complex.
- Certain aspects differ according to the species.
- Infective stage: sporozoites
- Two phase:
  - vector phase
  - Human phase
- In human:
  - Exoerythrocytic Phase
  - Erythrocytic Phase
**In man**

- **Liver stage**
- **Blood stage**

**In mosquitoes**

*Figure 4-15. Life cycle of human malaria parasites.*
Numerous fine ring forms.

Double chromatin dots.

Marginal forms.

Red cells are not enlarged
Plasmodium vivax and P. ovale may remain dormant (hypnozoites) in the liver cells for weeks, months, or years before developing and periodically releasing mature parasites into the bloodstream, causing attacks of malarial symptoms (relapses).

Plasmodium falciparum & P. malariae don't remain in the liver.
However, if the infection is untreated or inadequately treated, the mature form of Plasmodium falciparum may persist in the bloodstream for months, and the mature form of Plasmodium malariae may remain in the bloodstream for years, causing repeated attacks of malarial symptoms (recrudescence).
Only RBC trophozoites and schizonts cause disease.

No liver pathology caused by hepatic schizonts or sporozoites.
Parasite development in RBC

P. falciparum

Surface changes in RBC

Metabolism of Hemoglobin

Lysis of infected RBC

Cell debris

Hemoglobin

Ag

Fever

Hemoglobinemia

+ Ab

Hemoglobinuria

Nephritis

P. falciparum

ANEMIA

Adherence of parasitized RBC to endothelium

Malaria pigment formation

Fe store depletion

Splenomegalay

Increased Normal RBC destruction

Black water fever

Bone marrow depression
Erythrocyte production impaired

Adrenal shock

Cerebral
Hyperpyrexia, coma

Gastrointestinal
Dysentery

Hepatic
Jaundice

Pulmonary
Edema

Heart
Edema

Renal
Anuria

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Disease caused by:

1. RBC destruction:
   - by parasite
   - immune hemolysis
   - splenic pooling


3. Schizonts of \textit{P. falciparum} sticking to capillary (esp. cerebral) endothelial cells.

4. Lymphokines and other ill-defined shock and capillary leakage produced products.
<table>
<thead>
<tr>
<th>Severe Malaria: Common Clinical Manifestations</th>
<th>Pathogenesis</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral</td>
<td>Sluggish flow caused by sticky knobs on parasitized red cells leading to stagnant hypoxia and vascular damage.</td>
<td>Impaired level of consciousness. Hyperpyrexia. Convulsions. Generalized and localized neurological signs.</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Destruction of parasitized and nonparasitized red cells by immune complexes, bone marrow suppression and splenic pooling.</td>
<td>Pallor and jaundice. High output cardiac state.</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>Unknown</td>
<td>Diarrhoea.</td>
</tr>
</tbody>
</table>
## Malaria

### Pathogenesis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Hepatic</td>
<td>Unknown. ? Partially due to haemodynamic changes.</td>
<td>Jaundice (mainly attributable to haemolysis). Elevated serum enzyme levels, impaired elimination of drugs, prolonged prothrombin time, bleeding.</td>
</tr>
<tr>
<td>Fluid and electrolyte balance</td>
<td>Unknown. ? Partially due to inappropriate release of antidiuretic hormone.</td>
<td>Increased intravascular volume. Electrolyte changes, hypoglycemia, hyperkalemia and hemolysis.</td>
</tr>
<tr>
<td>Obstetric</td>
<td>Sluggish blood flow in placental vessels leading to vascular damage.</td>
<td>Fetal death. Premature labour.</td>
</tr>
</tbody>
</table>

DR. Abdulkader Tonkal
Symptoms usually begin 10 to 35 days after a mosquito injects the parasite into a person (incubation period).

Often, the first symptoms are a mild fever that comes and goes, headache, muscle aches, and chills, together with a general feeling of illness (malaise).

Sometimes symptoms begin with shaking chills followed by fever (malaria paroxysm).

These symptoms last 2 or 3 days and are frequently thought to be symptoms of the flu.

Subsequent symptoms and patterns of disease vary among the four types of malaria.
malaria paroxysm

cold stage

- feeling of intense cold
- vigorous shivering, rigor
- lasts 15-60 min
malaria paroxysm

hot stage

- intense heat
- dry burning skin
- throbbing headache
- lasts 2-6 hours
malaria paroxysm

**sweating stage**

- profuse sweating
- declining temperature
- exhausted, weak → sleep
- lasts 2-4 hours
Malaria Paroxysm

- Paroxysms associated with synchrony of merozoite release
- Temperature is normal and patient feels well between paroxysms
- Falciparum may not exhibit classic paroxysms
  - Continuous fever
  - 24 hr periodicity

Tertian Malaria
Quartan Malaria
Malaria Fever chart

Figure 4-13. Temperature curves in malaria showing relation to growth and schizogony of malarial parasites.
Species Infecting Humans

- **Plasmodium falciparum**
  - Tropical Africa, Asia, Latin America
  - Relapses: No
  - Fevers: 24-48

- **Plasmodium vivax**
  - Worldwide
  - Relapses: Yes
  - Fevers: 48

- **Plasmodium ovale**
  - Tropical West Africa
  - Relapses: Yes
  - Fevers: 48

- **Plasmodium malariae**
  - Worldwide but very patchy
  - Relapses: No
  - Fevers: 72
Febrile Attack
In *falciparum malaria*, abnormal brain function may occur, a complication called cerebral malaria.

Symptoms include a fever of at least 104°F, severe headache, drowsiness, delirium, and confusion.

Cerebral malaria can be fatal.

It most commonly occurs in infants, pregnant women, and travelers to high-risk areas.
In *vivax malaria*, delirium may occur when the fever is high, but otherwise brain symptoms are uncommon.
Usually, mild jaundice develops if malaria is untreated,

The spleen and liver become enlarged.
Hepato-splenomegaly

10-15% die - survivors partially immune often with splenomegaly
In all types of malaria, the total white blood cell count is usually normal, but the numbers of lymphocytes and monocytes increase.

Low levels of blood sugar are common and may be severe in people who have high levels of parasites.

Sometimes malaria persists when low levels of parasites remain in the blood. The Symptoms including:

- apathy, periodic headaches, a feeling of illness, poor appetite, fatigue, and attacks of chills and fever.
- The symptoms are milder, and the attacks don't last as long as the first attack.
If the person is untreated, the symptoms of *vivax*, *ovale*, or *malariae* malaria subside spontaneously in 10 to 30 days but may recur at variable intervals.

Untreated *P. falciparum* malaria is fatal in up to 20% of people.
CLINICAL ASPECTS OF MALARIA IN THE ASIR REGION, SAUDI ARABIA


TABLE 1. Common symptoms of malaria in the Asir region.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Number of cases (334)</th>
<th>Percentage*</th>
</tr>
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<tbody>
<tr>
<td>Fever</td>
<td>333</td>
<td>99.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>162</td>
<td>48.5</td>
</tr>
<tr>
<td>Rigors</td>
<td>110</td>
<td>32.9</td>
</tr>
<tr>
<td>Headache</td>
<td>90</td>
<td>26.9</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>67</td>
<td>20.1</td>
</tr>
<tr>
<td>Cough</td>
<td>60</td>
<td>18</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>55</td>
<td>16.5</td>
</tr>
<tr>
<td>Backache</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>10.8</td>
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<td>Convulsions</td>
<td>16</td>
<td>4.8</td>
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TABLE 2. Common signs of malaria in the Asir region.

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<td>High temperature (&gt;38.0 °C)</td>
<td>296</td>
<td>89.7</td>
</tr>
<tr>
<td>Tachycardia (&gt;100 beats/min)</td>
<td>246</td>
<td>75.7</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>148</td>
<td>44.7</td>
</tr>
<tr>
<td>Hypotension (BP &lt;100/60)</td>
<td>95</td>
<td>40.9</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>117</td>
<td>35.3</td>
</tr>
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<td>Chest crepitations</td>
<td>20</td>
<td>6.1</td>
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<td>Jaundice</td>
<td>16</td>
<td>4.8</td>
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<td>CNS abnormality**</td>
<td>2</td>
<td>0.6</td>
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TABLE 3. Types of malaria parasites in Saudi and non-Saudi patients and the response of Falciparum malaria to chloroquine

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Cerebral malaria (P. falciparum).

Anemia

Hypoglycemia and acidosis

GI and liver syndromes

Pulmonary edema

Algid malaria

Tropical splenomegaly syndrome

Blackwater fever (severe hemolysis).

Nephrotic syndrome (P. malariae)

Acute renal failure.

Falciparum Malaria

- increased morbidity and mortality
- higher parasitemias
- sequestration
Cerebral Malaria

- ‘most important’ complication of severe *falciparum malaria*
- a diffuse encephalopathy with loss of consciousness
  - consciousness ranges from stupor to coma
  - unresponsive to pain, visual, and verbal stimuli
  - onset can be gradual or sudden
- Associated with sequestration in micro-vasculature of brain
  - avoidance of spleen
  - low oxygen tensions
  - better invasion

### Neurological Sequelae Among Survivors of Cerebral Malaria

<table>
<thead>
<tr>
<th>Time</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>at discharge</td>
<td>23.3%</td>
</tr>
<tr>
<td>at 1 month</td>
<td>8.6%</td>
</tr>
<tr>
<td>at 6 months</td>
<td>4.4%</td>
</tr>
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</table>

*P. falciparum* expresses ‘knobs’ on the surface of infected erythrocytes. Knobs mediate cytoadherence to endothelial cells.
Sequestration Hypothesis

cytoadherence
→
cerebral ischemia
→
hypoxia, metabolic effects
→
coma
→
death
Cytokine Theory Problem

minimal lymphocyte infiltration or inflammation
Blackwater fever is a rare complication of malaria caused by the rupture of large numbers of red blood cells, which results in the release of hemoglobin into the bloodstream.

The hemoglobin, which is then excreted in the urine, turns the urine dark.

Blackwater fever occurs almost in people with chronic *falciparum* malaria, especially those who have taken quinine for treatment.
Immunity
• slow to develop
• short lived ‘premunition’
• non-sterilizing
  • lower parasitemia
  • less symptoms

Anti-Parasite Immunity
• immune response prevents merozoite invasion, eliminates infected erythrocytes, etc.

Anti-Disease Immunity
• eg., neutralization of exo-antigens or toxic effects
Malaria Diagnosis

a) Clinical picture:
   - fever, chills
   - travel history

b) Examination of blood:
   - thin film.
   - thick film.
   - antigen capture (EIA)
a) Clinical picture:

- \textit{P. falciparum}: daily fever, rarely every 2 day fever.
- \textit{other species}: regularly intermittent fevers every 2 or 3 days.

b) Examination of thin smear for characteristics of species.

- Shape and size of: trophozoite, schizont and gametocyte
- \% of RBCs with parasites
- Metabolic debris in RBC around parasite (Schuffner's dots in \textit{P. vivax} infection)
- Size of infected RBCs (\textit{P. vivax} and \textit{P. ovale} infect younger (larger) RBCs)
different drugs required for different stages of life cycle:

- Quinine
- 4-aminoquinalines - eg. chloroquine, etc.
- 8-aminoquinalines - eg. Primaquine
- antifolates - eg pyrimethamine, proquanol, sulfas, sulfones
- antibiotics - tetracycline, clindamycin
- combinations - Fansidar, Malarone
- miscellaneous - mefloquine, halofantrine, artemisinine, atovoquone
Anti-Malaria Chemotherapy

- **Causal Prophylaxis**
  - prevent infection (ie, liver stage)

- **Suppressive Prophylaxis**
  - prevent clinical disease
  - blood schizontocides

- **Treatment Therapy (or clinical cure)**
  - relieve symptoms
  - eliminate blood stage parasites

- **Curative Therapy (or radical cure)**
  - eliminate parasites w/o regard to symptoms

- **Anti-Relapse Treatment**
  - eliminate hypnozoites
# Selected Anti-Malarials

<table>
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<th>Drug Action</th>
<th>Drugs</th>
</tr>
</thead>
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<tr>
<td>Fast-acting blood schizontocide</td>
<td>chloroquine (+ other 4-aminoquinolines), quinine, quinidine, mefloquine, halofantrine, antifolates (pyrimethamine, proquanil, sulfadoxine, dapsone), artemisinin derivatives (quinhaosu)</td>
</tr>
<tr>
<td>Slow-acting blood schizontocide</td>
<td>doxycycline (other tetracycline antibiotics)</td>
</tr>
<tr>
<td>Blood + mild tissue schizontocide</td>
<td>proquanil, pyrimethamine, tetracyclines</td>
</tr>
<tr>
<td>Anti-relapsing</td>
<td>primaquine</td>
</tr>
<tr>
<td>Gametocidal</td>
<td>primaquine, 4-aminoquinolines (limited?)</td>
</tr>
<tr>
<td>Combinations</td>
<td>Fansidar (pyrimethamine + sulfadoxine), Maloprim (pyrimethamine + dapsone), Malarone (atovaquone + proquanil)</td>
</tr>
</tbody>
</table>
Treatment Strategies

• chloroquine sensitive (all species)
  • CQ + primaquine (vivax/ovale)

• chloroquine resistance (or unknown)
  • Fansidar, mefloquine, quinine, artemesin derivatives

• severe malaria
  • i.v. infusion of quinine or quinidine (or CQ, if sensitive)
  • i.v. artemisinin derivatives (if available)
Chemoprophylaxis

- Recommended for transient visits to endemic areas
- Choice of drug depends on risk of malaria and degree of resistance in that area
- Many non-toxic drugs of limited use because of resistance
  - eg., chloroquine, pyrimethamine, proguanil
- Presumptive (or ‘standby’) treatment
  - carry Fansidar, mefloquine, quinine
Drug Resistance

- defined by treatment failures (28 days)
- degree of resistance (RI, RII, RIII)
MALARIA DISTRIBUTION AND REPORTED DRUG RESISTANCE

- Malaria transmission areas
- Reported drug resistance to:
  - chloroquine
  - sulfadoxine - pyrimethamine (Fansidar)
  - multi-drug resistance

Source: WHO/CTD Health Map, 1995

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Malaria Control

1. Reduce Human-Mosquito Contact.
2. Reduce Vector Capacity.
3. Reduce Parasite Reservoir.
Malaria Control

Reduce Human-Mosquito Contact:

• impregnated bed nets.
• Repellants.
• Protective clothing.
• Screens.
• House spraying.
• Fogging and residual wall spray with variety of insecticides (eg. DDT).
Malaria Control

Reduce Vector Capacity

- environmental modification
- Larvacides / insecticides
- biological control
- Breeding site control
• The genus *Anopheles* includes more than 400 species of mosquitoes.
• Many may act as vectors of human diseases such as malaria, filariasis and some arbovirus.
• Eggs present a pair of lateral floats and are laid singly on the water surface.
• Larvae lay in a horizontal position under the water surface.
Breeding site control:

- Fill in or cover water breeding sites
- Larviciding of breeding water sites
- Biological control
Malaria Control

Reduce Parasite Reservoir

- diagnosis and treatment
- chemoprophylaxis
Mosquito Transmission

- susceptibility of *anopheline* species
- longevity
- feeding habits
- density
- climatic factors:
  - temperature, humidity, rainfall, wind, etc...
- seasonal or continuous transmission

*Anopheles*
العوامل البيئية التي تساعد على إنتشار البعوض

- درجة الحرارة المناسبة (20 - 30):
- لا يحدث التبرغ في أقل من 16 ولا أكثر من 33.
- الرطوبة (60%): الرطوبة العالية تزيد من عمر البعوضة.
- درجة حرارة الماء.
- الأمطار.
- زيادة الرطوبة: تساهم في زيادة عمر البعوضة وبالتالي زيادة مناطق التكاثر.
- مواسم الجفاف: تقلل من حركة الأنهار وبالتالي زيادة مناطق التكاثر.
- برامج الري: مثل (السدو - المجاري المائية) مما يؤدي إلى زيادة الاملاك.

DR. Abdulkader Tonkal
Thank You