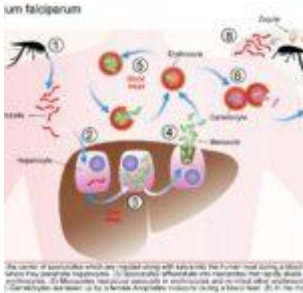


Two year old with spiking fevers and depressed level of consciousness



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Patient Presentation

A 2 year old boy presented to a district hospital with decreased oral intake, listlessness and fever. On arrival he was adequately resuscitated but continued to have spiking fevers and a depressed level of consciousness.

Acknowledgement

This case study was kindly provided by Barclay Stewart, Medical University of South Carolina, Fogarty International Clinical Research Scholar, Nairobi, Kenya

History

Six months ago the patient presented to the hospital with a two day history of irritability, decreased appetite, discomfort on lying down, recurrent fever, profuse sweating and diarrhea, no vomiting. On admission he was lethargic and dehydrated which worsened over a few hours and culminated in a seizure. He had no prior history of seizures. He was then diagnosed with severe malaria. He was treated appropriately and discharged 2 weeks later with no residual effects.

Past medical and surgical history

- There is no additional significant medical or surgical history.
- Road to health card shows all growth parameters to be within normal limits, with all vaccinations up to date.

Family and social history

- He lives with his mother, father, and two older siblings who are all healthy.
- His mother was recently tested and is HIV negative; his father has not been tested.
- Their home, which has electricity and water, is located in a low-lying area near Musina, a town in South Africa's Limpopo province. This is the country's most northerly located town, with a seasonal high rate of malaria transmission from October through May.

Travel History

No travel outside of Musina since birth.

Differential diagnosis

- Encephalitis
- Meningitis
- Gastroenteritis with severe dehydration

- Pneumonia
- Toxic Shock Syndrome
- Typhoid Fever
- Brucellosis
- Relapsing Fever
- Katayama Fever
- Urinary tract infection
- Bacteraemia

Examination

On appearance the child is miserable and toxic looking.

Vitals

- Pulse – 166
- Respiratory Rate – 34
- Temperature – 39.8
- Pulse-Oxygen – 95%

Height and weight were in the 65 percentile

General

- Eyes were sunken and jaundiced.
- No lymphadenopathy

ENT

- Erythematous, non bulging tympanic membranes.
- Non-inflamed nasal passage, no discharge.
- Pale oral mucosa

Eyes

- No papilloedema
- No retinal haemorrhages

Chest

- Midline trachea

- Chest shape normal in appearance, tachypnoea present
- Mild subcostal retractions.
- Clear on auscultation bilaterally.

Cardiovascular

- Tachycardia with a regular rhythm.
- Normal S1 and S2 with a 2/6 mid systolic murmur best auscultated over the upper left sternal border with minimal radiation.
- Bounding pulses felt radially, femorally and dorsalis pedis
- Capillary refill within 2 seconds.

Abdomen

- Normal on inspection.
- Bowel sounds diminished but present.
- No hepatomegaly.
- 4cm splenomegaly.

Neurological

- Child listless though attempts to follow commands.
- Not resisting or crying in response to aggravating stimuli.

Investigations

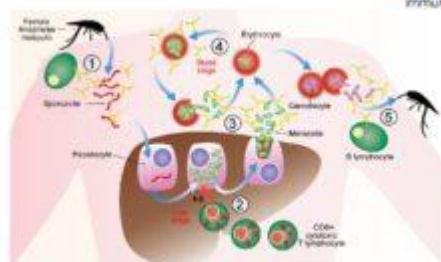
| Examination | Value | Normal Limits |
|-------------|-------|----------------------------------|
| WBC | 12 | (4 – 12 x 10 ⁹ /l) |
| HB | 7.2 | (12.1 – 15.2 g/l) |
| HCT | 0.22 | (.31 - .42 g/l) |
| Platelets | 222 | (140 – 450 x 10 ⁹ /l) |
| LDH | 294 | (70 – 250 U/l) |

| Examination | Value | Normal Limits |
|--------------------------|--------------------|----------------------|
| Haptoglobin (free serum) | 23 | (27-139 mg/dl) |
| Reticulocyte Count | 6 | (0.8 – 4% RBC) |
| Metabolic Panel | | |
| AST | 52 | (5 – 35 U/l) |
| ALT | 101 | (25 – 120 U/l) |
| Total Bilirubin | 2.1 | (0.1 – 1.3 mg/dl) |
| Direct Bilirubin | 0.1 | (0.0 – 0.3 mg/dl) |
| Sodium | 143 | (135 – 147 mmol/l) |
| Potassium | 4.0999999999999996 | (3.5 – 5.1 mmol/l) |
| Bicarbonate | 25 | (22 – 33 mmol/l) |
| Chloride | 93 | (95 – 107 mmol/l) |
| Anion Gap | 25 | (8 – 16 meg/l) |
| Creatinine (serum) | 1.8 | (0.7 – 1.3 mg/l) |
| BUN (serum) | 21 | (7 – 20 mg/dl) |
| Glucose (serum) | 50 | (65 -110 mg/dl) |
| Urine Analysis | | |
| Spec. Gravity | 1.0289999999999999 | (1.010 – 1.030) |
| pH | 6.3 | (4.8 – 7.5) |
| Ketones | Trace | Absent |
| Protein | Trace | Absent |
| Bilirubin | Trace | Absent |
| Glucose | Absent | Absent |
| RBC | Trace | Absent |

| Examination | Value | Normal Limits |
|------------------------------|----------------------------|---------------|
| WBC | Trace | Absent |
| Blood Culture | Negative | |
| Urine Culture | Negative | |
| Malaria Thick and Thin Smear | Positive for P. falciparum | |
| CSF Chemistries | Normal | |
| CSF Culture | Negative | |

Discussion

Immune response to Plasmodium falciparum



Humoral and cell-mediated immune responses help to control Plasmodium falciparum infection. (1) Anticardiolipin antibodies and complement are involved in the clearance of infected erythrocytes. (2) CD4⁺ T cells produce interferon- γ (IFN- γ) and interleukin-2 (IL-2), which activate macrophages and T cells. (3) CD4⁺ T cells produce interferon- γ (IFN- γ) and interleukin-2 (IL-2), which activate macrophages and T cells. (4) Anticardiolipin antibodies and complement are involved in the clearance of infected erythrocytes. (5) Anticardiolipin antibodies and complement are involved in the clearance of infected erythrocytes.

Epidemiology

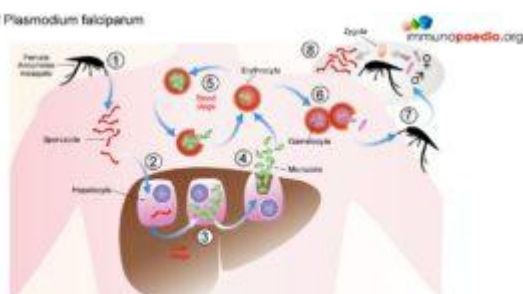
Malaria causes between 300 and 500 million clinical episodes worldwide and 0.5 to 3 million deaths annually, disproportionately affecting immune naïve children under the

age of 5 years living in sub-Saharan Africa.

Human malaria infection is caused by four protozoa species of the genus Plasmodium. These are *P. falciparum*, *P. malariae*, *P. vivax*, and *P. ovalae*, of which the preponderance of severe malaria and mortality is due to *P. falciparum*. Children living in endemic areas typically have a primary malaria episode during their first few years of life and most toddlers and juveniles develop some degree of acquired immunity against severe disease but still experience periodic clinical episodes. Those who survive to adulthood are often clinically immune, however, low grade parasitaemia is often present but causes few symptoms. Adults in endemic areas maintain low-grade infections throughout the transmission season. Endemicity is typically defined as parasitaemia rates or palpable spleens in children aged 2-9 years. The categories

include holoendemic where the rate is >75% (transmission of infection is year round and the bulk of mortality is seen in infants), hyperendemic where the rate is 51-75% (mortality is also mostly seen in infants), mesoendemic where the rate is 11-50% (regular seasonal transmission affecting infants, toddlers and adults who develop chronic ill health) and hypoendemic which is <10% (occasional epidemics, whole population is susceptible to severe and fatal disease). Clinical immunity also fails if a person moves away from an endemic area and during pregnancy.

Life-cycle of Plasmodium falciparum



(1) The female Anopheles mosquito is the carrier of sporozoites which are injected along with saliva into the human host during a blood meal. (2) The sporozoites gain access to blood vessels and travel to the liver where they parasitize hepatocytes. (3) Sporozoites differentiate into merozoites that rapidly divide asexually. (4) Merozoites are released from ruptured hepatocytes and enter erythrocytes. (5) Merozoites reproduce asexually in erythrocytes and, in the case of P. falciparum, also invade other erythrocytes. (6) Some merozoites differentiate into male and female gametocytes. (7) Gametocytes are taken up by a female Anopheles mosquito during a blood meal. (8) In the mosquito, sexual reproduction produces new sporozoites.

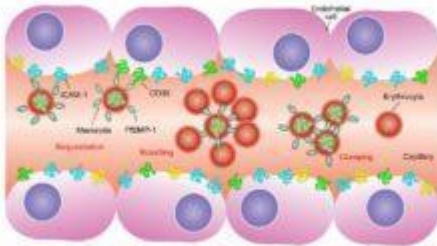
Parasitology – Malaria Life-Cycle

The female Anopheles mosquito inoculates the host with 10 to 100 malaria sporozoites from her salivary glands during a blood meal. These microscopic motile forms of the malaria parasite are carried via the bloodstream to the liver. Within 30 minutes, those sporozoites not bound by previously formed antibodies, invade and begin replicating in hepatocytes. Parasites not destroyed by cytotoxic T lymphocytes in the liver replicate for 2-10 days creating merozoites. Tens of thousands of merozoites are released into the bloodstream as the hepatocyte bursts. Each merozoite is then able to bind, invade, and infect erythrocytes. After red blood cell (RBC) infection, each merozoite matures to form a highly metabolically active trophozoite, which replicates asexually to become multinucleate schizonts. As the schizonts enlarge they rupture erythrocytes 48 hours after their formation which results in 20-30 new merozoites which continue the cycle. Some sexual forms of the parasite develop during this erythrocytic stage; these gametocytes are responsible for infecting the

salivary glands of female *Anopheles* mosquitoes. The gametes mature into ookinetes then into an oocyst. The oocyst ruptures and releases sporozoites which can then infect another host during a blood meal.

Adhesion of infected erythrocytes to vascular endothelial cells

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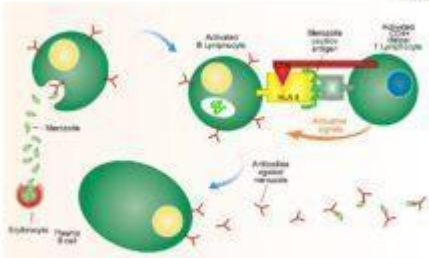


Infected erythrocytes express parasite-derived (PfPRK8) proteins on the cell surface. These proteins have high affinity for endothelial receptors such as CD36 and ICAM-1 expressed on vascular endothelial cells. Binding of infected erythrocytes to these receptors is required for sequestration of the parasite-infected cells in the spleen where infected cells are removed. In addition, binding of parasites to endothelial receptors is thought to be involved in the pathogenesis of cerebral malaria. Infected erythrocytes can adhere to endothelial cells in blood capillaries that can lead to cerebral malaria. Infected erythrocytes can adhere to endothelial cells in blood capillaries that can lead to cerebral malaria. Infected erythrocytes can adhere to endothelial cells in blood capillaries that can lead to cerebral malaria.

Pathogenesis and Clinical Features

A person's first infection usually creates no symptoms for 7-10 days, which is followed first by nonspecific symptoms such as headache, fatigue, abdominal discomfort and muscle aches. This is then followed by fever. During this latent period, parasite maturation occurs in the liver and parasites undergo a cycle of blood stage replication. Symptoms begin when the parasites undergoing an asexual blood cycle, reach threshold density sufficient to initiate the host's pathogenic immune response process. Fever, malaria's hallmark, is due to parasite-derived molecules released from ruptured host cells. These molecules activate host inflammatory cells, such as macrophages, which secrete pro-inflammatory pyrogenic cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)- α . As parasites synchronise their replication cycles the fever becomes periodic. Although childhood febrile convulsions can occur, generalised seizures are typically associated with *P. falciparum* infections and may herald cerebral malaria. Splenomegaly results from massive reticuloendothelial system activation to clear parasitised erythrocytes. Mild hepatomegaly is common in young children, while mild jaundice is more common in adults. Anaemia is also common and is partly due to the phasic rupture of RBCs by mature schizonts, splenic sequestration of red blood cells and ineffective erythropoiesis.

Antigenic variation of merozoite surface proteins

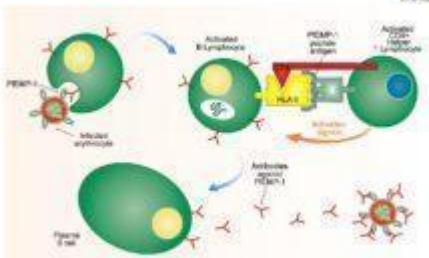


Antibody responses to cell surface proteins on merozoites are targeted to the antigenic variation of these proteins such as merozoite surface protein 1 (MSP-1). Mutations alter forms of MSP-1 as encoded in the genome of the parasite and expression of these proteins varies after each generation. New antibody responses are therefore needed when a different MSP-1 protein is produced by another CD4+ helper T lymphocyte response which gives activation signals to B lymphocytes and subsequent MHC class II antigen presentation. Variation of the MHC class II epitope when a different protein is expressed also affects the CD4+ helper T lymphocyte response.

Parasitised erythrocytes circulate to the microvasculature where they bind to the scavenger receptor CD36 or the intercellular adhesion 1 (ICAM-1) and occlude microvessels. Binding of

infected erythrocytes to these receptors (sequestration) allows the cells to escape from circulation to the spleen where infected cells are detected and destroyed. In addition, infected erythrocytes can also stick to uninfected erythrocytes (rosetting) or infected erythrocytes can stick together (clumping). In particular, parasitized RBCs adhere to the endothelial lining of capillaries in the brain, kidneys, gut and liver. Inflammation caused by these parasite-receptor interactions and release of immune stimulatory molecules from infected RBCs upon rupture are thought to be responsible for organ specific pathology such as cerebral malaria, renal disease, Blackwater Fever (due to widespread intravascular haemolysis giving rise to dark urine) and respiratory distress

Antigenic variation of erythrocyte surface proteins



Infected erythrocytes express parasite derived cell surface proteins such as PfPRIM-2. Antibody responses to the protein occur and allows infected erythrocytes to be sequestered and destroyed. However, the genome of the parasite encodes multiple variants of the PfPRIM-2 protein and encodes a different protein after each generation. New antibody responses are therefore needed to respond to the PfPRIM-2 protein. In addition CD4+ helper T lymphocytes respond which give activation signals to B lymphocytes and subsequent MHC class II antigen presentation. Variation of the MHC class II epitope when a different protein is expressed also affects the CD4+ helper T lymphocyte response.

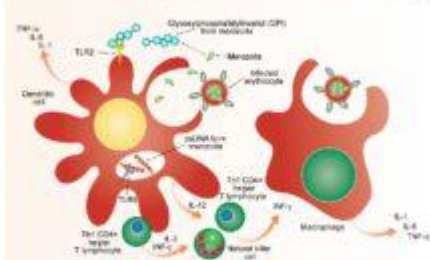
Clinical Features of Severe Falciparum Malaria

Correctly treated uncomplicated *P.falciparum* carries a mortality rate of 0.1%. When organ dysfunction or parasitaemia of >3% occurs mortality also

increases dramatically. These manifestations, which were also seen in this clinical case, include:

Cerebral Malaria

Onset may be gradual or sudden following a convulsion. Features include obtundation, delirium, abnormal behaviour and coma. Focal neurologic signs and meningism do not typically occur. Fifteen percent of children who survive cerebral malaria, especially when associated with hypoglycaemia, coma



Control of merozoite growth is dependent on a strong and immediate immune response leading due to the pro-inflammatory responses IL-12 and INF- γ . Innate immune responses to blood stage merozoites occur via stimulation of pattern recognition receptors such as TLR2 that binds GPI as well as TLR9 that binds parasite DNA. Stimulation of these receptors induces secretion of pro-inflammatory cytokines such as IL-1, IL-6, INF- γ and others from IL-12 producing T cells and NK cells. Macrophage CD40 receptor cells stimulate conventional responses by secretion of IL-2 and INF- γ . This enhances phagocytosis of infected erythrocytes and merozoites and is needed for CD40-CD28 responses against the infected erythrocytes.

The innate immune responses have already been discussed above. Regarding acquired immune responses many studies show that antibodies and T cells are vital to the development of a protective immune

response against malaria infection. Specific immune responses are required to defuse the infection at multiple points in the parasite life cycle.

- Antibody responses are induced during the sporozoite stage. Antibody bound sporozoites are prevented from invading hepatocytes.
- CD8+ T cells have been shown to be cytotoxic against maturing sporozoite infected liver cells.
- Both of these responses are potentially able to terminate the infection before the onset of clinical disease caused by the release of merozoites from hepatocytes and subsequent RBC invasion and rupture.
- CD4+ T cells are a requisite for the production of merozoite neutralising antibodies by B cells and the activation of macrophages which secrete interferon (INF) γ to enhance parasitized RBC.
- The host is also able to develop transmission-blocking antibodies directed to gametocyte specific antigens. These antibodies hinder the development of the parasite within the mosquito vector, thereby preventing further infections. Though this immune response is not particularly valuable to the infected host, it does assist in reducing population level transmission.

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Final outcome

The patient was treated with IV artesunate and anti-pyretics for 3 days. IV antibiotics were started on admission as there was no confirmatory diagnosis at the time and culture results were not yet available. On the third day the child was markedly improved. He was started on a full course of mefloquine on receiving laboratory results which confirmed infection with *P.falciparum*. Upon discharge there were no neurologic sequelae. He and his family were counseled on the use of insecticide-treated bed nets and indoor residual spraying.

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Evaluation – Questions & answers

What is the diagnosis?

Severe P.falciparum malaria, which has progressed to cerebral malaria.

With regards to parasitized erythrocytes which endothelial receptors do they bind to resulting in occlusion of microvessels?

CD36 and intercellular adhesion molecules-1 (ICAM-1).

What are the three ways that infected erythrocytes can bind to occlude microvessels?

Sequestration- binding of infected erythrocytes to receptors.

Rosetting- infected erythrocytes stick to uninfected erythrocytes

Clumping- infected erythrocytes stick together

What is the benefit of occlusion of microvessels?

It is an evasion strategy which allows the cells to escape circulating to the spleen where infected cells would be detected and destroyed.

Which organs are most affected by occlusion of microvessels?

In particular the endothelial lining of capillaries in the brain, kidneys, gut and liver are affected by occlusion of microvessels.

Describe the immune response required to neutralize malaria parasites at each stage during their development.

Sporozoites – Antibody

Maturing hepatic shizonts – CD8+ T cell

Merozoite – Antibody

Gametocyte – Antibody

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