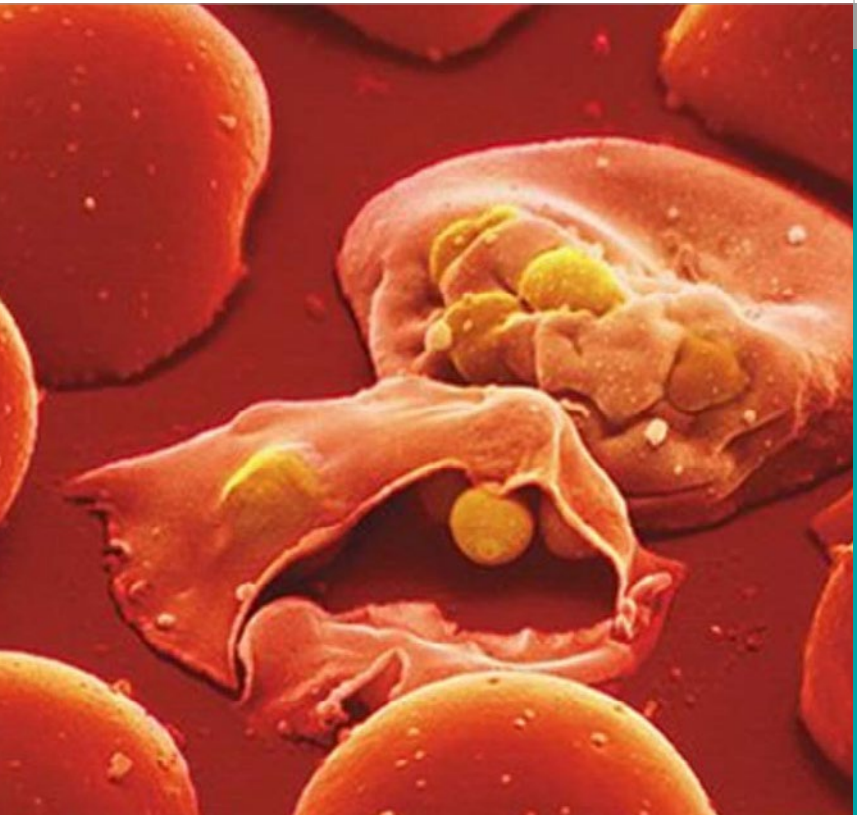
SWISS SOCIETY OF NEONATOLOGY

Don’t forget the history – a sleeping disease can be awakened



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Title figure:
Malaria parasites infect two blood cells
(source: www.smithsonianmag.com)

Congenital malaria is a rare disease, even in endemic countries. Compared to Plasmodium falciparum, Plasmodium vivax is more frequent in non-endemic regions because of its dormant asymptomatic hepatic stage in infected women (Fig. 1). When traveling from an endemic to a non-endemic region, infected women can lose their immunity due to a lack of recurrent exposure. Pregnancy-induced immune depression may facilitate malaria relapse in women and increase the risk for intrauterine transmission to the fetus. Clinical findings of congenitally infected newborns are variable and range from asymptomatic newborns to presentations mimicking neonatal late-onset sepsis. Although rare, malaria is an important differential diagnosis when evaluating febrile, thrombocytopenic or septic newborns of migrant mothers or mothers with a travel history to a country where malaria is endemic.

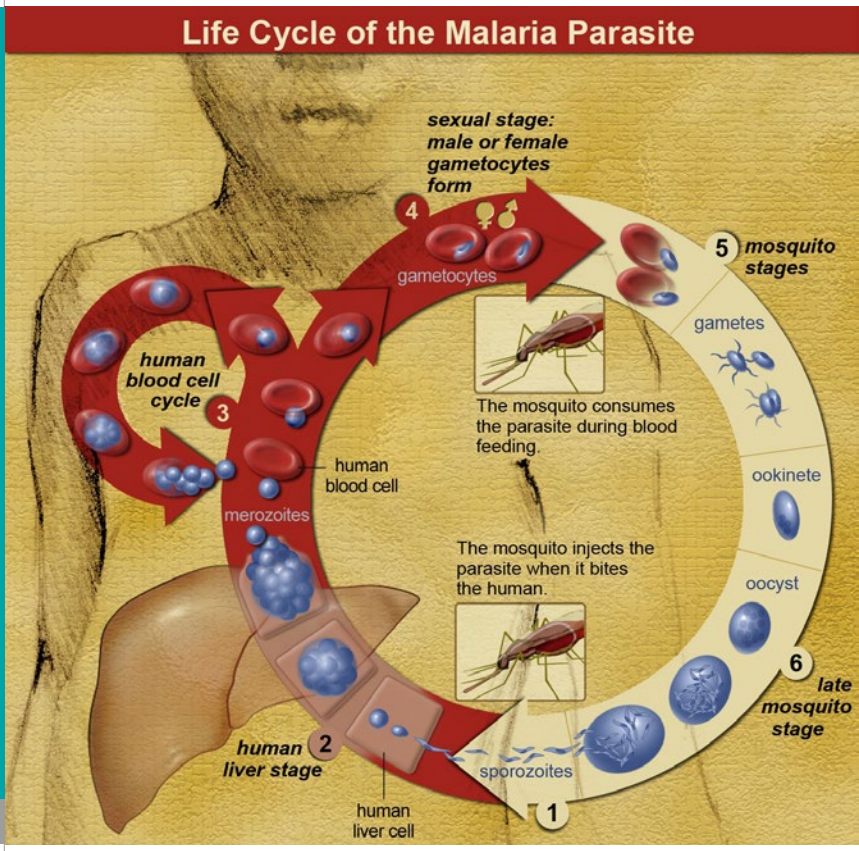

Fig. 1

The life cycle of malaria parasites. A mosquito causes an infection by a bite. First, sporozoites enter the bloodstream, and migrate to the liver. They infect liver cells, where they multiply into merozoites, rupture the liver cells, and return to the bloodstream. The merozoites infect red blood cells, where they develop into ring forms, trophozoites and schizonts that in turn produce further merozoites. Sexual forms are also produced, which, if taken up by a mosquito, will infect the insect and continue the life cycle (source: www.wikipedia.org).

This 24-day-old newborn female infant presented to our pediatric emergency department with a short history of fever, reduced feeding and irritability. Sepsis work-up was performed, and C-reactive protein (CRP; 33 mg/l) and procalcitonin (PCT; 1.17ug/l) were elevated, platelets were low (61 × 109/l), whereas white cell count (WCC), automated differential WCC and hemoglobin were normal. Except for mild indirect hyperbilirubinemia in the breastfed infant, further laboratory work-up including urinary and stool analysis was unremarkable. Blood and urine cultures were obtained. Chest X-ray and abdominal ultrasound showed no abnormalities. Lumbar puncture was postponed due to thrombocytopenia. A working diagnosis of late-onset sepsis was made, and intravenous amikacin and amoxicillin were started.

The infant's mother had immigrated to Switzerland 2.5 years ago from Eritrea. Since then, there had been no return visits to Eritrea or other countries. She had received adequate prenatal care, and screening examinations for group B streptococcus, hepatitis B, HIV and syphilis had been negative. The apparently healthy mother denied any chronic medical conditions, episodes of fever or chronic cough, neither during pregnancy nor in the past years while living in Switzerland.

In the following days, the child's fever persisted, and thrombocytopenia worsened (min. 14×10^9/l).

Additional work-up for HSV, respiratory viruses and CMV was done and acyclovir was started empirically. Furthermore, a manual differential WCC was performed, which, surprisingly, revealed malaria parasites (Fig. 2) with a calculated parasite load of 8.4 %. Intravenous artesunate was started empirically (3 mg/kg at 0 h, 12 h, 24 h and 48 h) as the precise plasmodium species could not be confirmed initially. The infant's condition improved rapidly and she defervesced within 24 hours. Forty-eight hours after initiating treatment, plasmodia were no longer detectable in the blood smear.

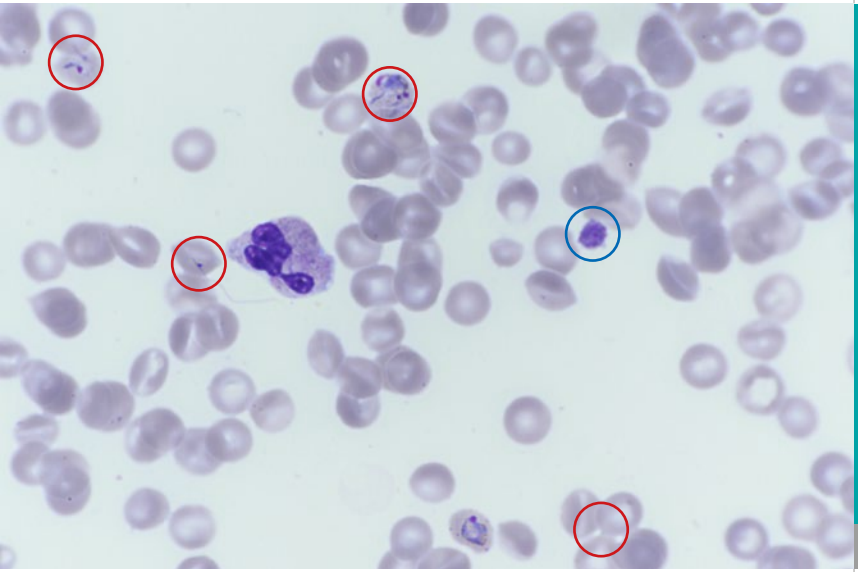

Fig. 2

Peripheral blood smear with Plasmodium vivax: red circles: different stages of trophozoites (comment A); blue circle: schizont (comment B).

Comment A: *The initial (freshly infected) erythrocyte stage of the parasite is called trophozoite; this is a growing stage, and the parasite may appear in different sizes with full or incomplete ring structure.*

Comment B: *At the schizont stage, the malaria parasite starts to reproduce. This reproduction is referred to as asexual because the parasite is neither male nor female but reproduces itself by simple division. There are several obvious phases in this stage, ranging from parasites with two chromatin pieces to parasites with a number of chromatin dots and definite cytoplasm (in the presented blood smear many chromatin dots can be detected). At the end of reproduction, daughter parasites are released. The process of forming schizonts, which takes place in the liver and in red blood cells, is referred to as schizogony.*

Microscopic evaluation and PCR testing at the Swiss reference center in Basel (Swiss Tropical and Public Health Institute) confirmed the presence of P. vivax. Treatment was adjusted to a 3-day-course of oral chloroquine base (initial dose 10 mg/kg followed by 5 mg/kg after 12 h, 24 h and 36 h) via nasogastric tube. Inflammatory markers normalized, and thrombocytopenia resolved within 5 days. Malaria PCR was negative at the end of the treatment with chloroquine.

The mother's work-up revealed a negative malaria rapid diagnostic test, a normal blood count and a negative blood smear. Malaria PCR however was positive for P. vivax. On further questioning, she disclosed that she had suffered from malaria in Eritrea 3 years ago. At the time, she had received some form of treatment. After the discharge of her child, she was also treated with chloroquine.

Congenital malaria is very rare in developed countries. Precise data on incidence or prevalence of congenital malaria in non-endemic countries, particularly P. vivax, are not available. In Switzerland, reporting of malaria cases to the national surveillance system is mandatory, however, summary reports do not allow to identify congenital malaria cases in the affected pediatric age group. In the most recent United States malaria surveillance summary from 2014, only one case (P. falciparum) was reported; the Nigerian mother was symptomatic when visiting the United States (1) .

Congenital malaria is an important differential diagnosis when evaluating febrile newborns of migrant mothers or mothers with a travel history to endemic areas (2). P. falciparum is more frequent in endemic areas whereas P. vivax seems to be more frequent in non-endemic countries because of the asymptomatic persistence of hypnozoites in the maternal liver (3, 4). In Switzerland, P. vivax was detected in 3.7 % of healthy asymptomatic refugees newly arriving from Eritrea (5).

Congenital malaria can mimic neonatal sepsis (3, 4, 6). Clinical findings include fever, anemia, poor feeding, lethargy, irritability, and jaundice (7). Thrombocytopenia, frequently seen in malaria cases in older individuals, may be a clue to include malaria in the work-up of such neonates. Diagnosis is confirmed by thick and thin blood smears and malaria-specific PCR testing.

Maternal infection may lie months or even several years in the past (3). In our case, the mother had probably only been treated for P. falciparum and not for possible P. vivax or P. ovale.

During pregnancy, malaria may relapse, likely due to pregnancy-induced immunodepression (8). Of note, reactivation is more frequent in non-endemic areas due to lack of recurrent exposure with subsequent loss of immunity to malaria in formerly infected women (9). Postulated mechanisms of mother-to-child transmission during pregnancy or delivery include induction of an immune-mediated inflammatory response in the placenta, materno-fetal transfusion during pregnancy or delivery, direct parasite penetration through the chorionic villi or premature separation of the placenta (8, 10). Different mechanisms protect the fetus from plasmodia invasion, including the physical barrier of the placenta, transfer of maternal antibodies, fetal hemoglobin and fetal immunity (11, 12).

Vertical transmission of malaria can have adverse effects on fetal development. Intrauterine growth restriction, low placental weight, stillbirth and preterm delivery have been reported (13). Symptoms of congenital malaria usually appear between 10 – 30 days after birth but can also be delayed for weeks or even months (14). This delay is thought to be caused by several factors, including the presence of fetal hemoglobin with reduced multiplication of mala-

ria parasites, failure of the parasites to grow in cord blood, and passive immunity (13, 15).

For congenital P. vivax malaria, treatment with oral chloroquine is recommended (15, 16). Congenital P. vivax malaria does not relapse once parasite-infected red blood cells have been eradicated. Apparently, sporozoites are unable to enter the fetal circulation from the maternal blood stream and fetal hepatic infestation does not occur, rendering additional treatment with primaquine obsolete (3, 15).

See also: COTM January 2013: Neonatal care in a resource-limited country in sub-Saharan Africa (PDF)

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