



Severe malaria by *Plasmodium falciparum* in a patient with sickle cell disease (HbSS)

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has documented no financial relationships
to disclose or Conflicts of Interest (COIs) to
resolve.

OBJECTIVE

- Analyze salient features of severe malaria by *P. falciparum* in the rare setting of sickle cell disease

HISTORY OF PRESENTING ILLNESS

11 year old African American male with sickle cell disease (HbSS) presented with

- ⦿ 3 days of fever up to 39 C
- ⦿ Chills, rigors
- ⦿ Bi-frontal headache.

HISTORY CONT...

- ◉ Denied cough, rhinorrhea,
- ◉ Vomiting, diarrhea, photophobia,
- ◉ Neck pain, abdominal/chest pain/dyspnea.
- ◉ Denied joint swelling/pain.
- ◉ Denied sick contacts.

HISTORY CONT...

PMH: No hospitalizations for sickle cell crises/no surgeries

MEDICATIONS: none

EPIDEMIOLOGICAL HISTORY: Had been to Nigeria for 2 weeks and returned 10 days PTA.

EXAMINATION

- Temp: 38 °C/Pulse: 114/Resp: 20/BP127/57 mmHg
- Tachycardia+, able to answer questions
- Eyes: B/L scleral icterus
- Abdomen tender in RUQ, Liver edge 2cm below RCM
- Neurological: No meningeal signs/cerebellar/motor/sensory deficits/tremors

HOSPITAL COURSE

- ◉ Admitted in stable condition.
- ◉ Two hours later, C/o more abdominal pain and shortness of breath.
- ◉ Suddenly became more somnolent with desaturation (spo2 80%), hypotension and tachycardia.
- ◉ Transferred to PICU.

LABS	At admission
WBC	16.2
HB	6.2
Reticulocytes	20
Platelets	283
ALT	185
AST	296
Bilirubin/Direct bilirubin	12/2.6
LDH	985

LABS	At admission	2 hours later...
WBC	16.2	20
HB	6.2	4.5
Reticulocytes	20	21.4%
Platelets	283	144
ALT	185	255
AST	296	638
Bilirubin/Direct bilirubin	12/2.6	36.5/29.7
LDH	985	1580

DIFFERENTIAL DIAGNOSIS

- Infectious: Fever in a returned traveler:
 1. Typhoid
 2. Malaria
 3. Dengue
 4. Parasitic infections

- Non infectious: Sickle cell crisis

DIAGNOSTIC TESTING

Second peripheral blood smear for malarial parasites revealed:

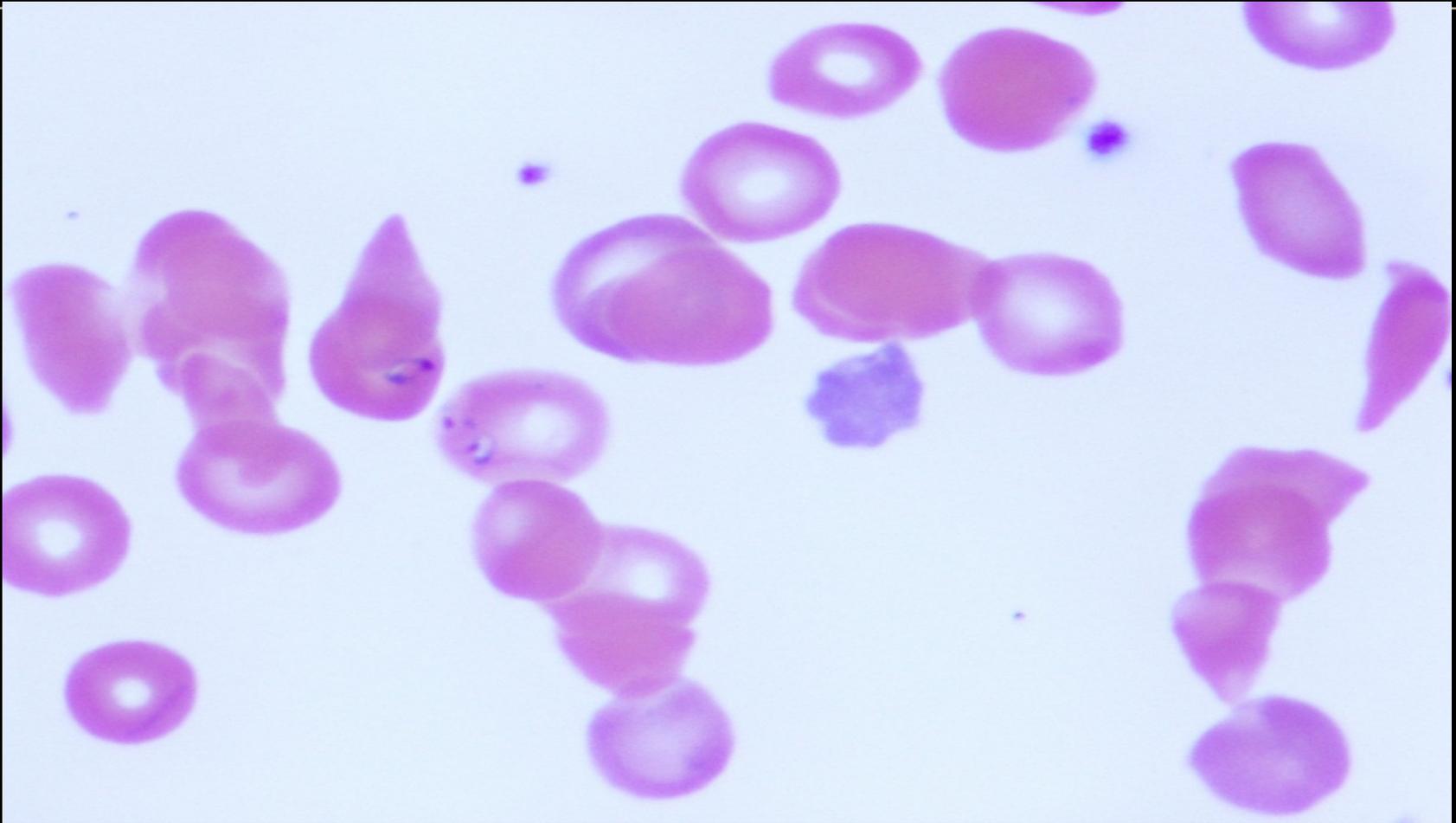


Figure 1: Peripheral blood smear, Giemsa stain, 100X (Courtesy of Christopher Doern, PhD)

DIAGNOSIS AND FOLLOW UP

- Second malarial smear was indicative of *Plasmodium falciparum* (ring forms):
Parasite index 2.2%
- Treatment: Intravenous Quinidine and Doxycycline for severe malaria. Course was complicated by pulmonary edema, DIC, shock, liver dysfunction, QT prolongation (on day 2 of quinidine). Quinidine discontinued and treatment completed with oral quinine and doxycycline for a total of 7 days.
- By day 6, parasite load was 0. Discharged home and doing well.

MALARIA

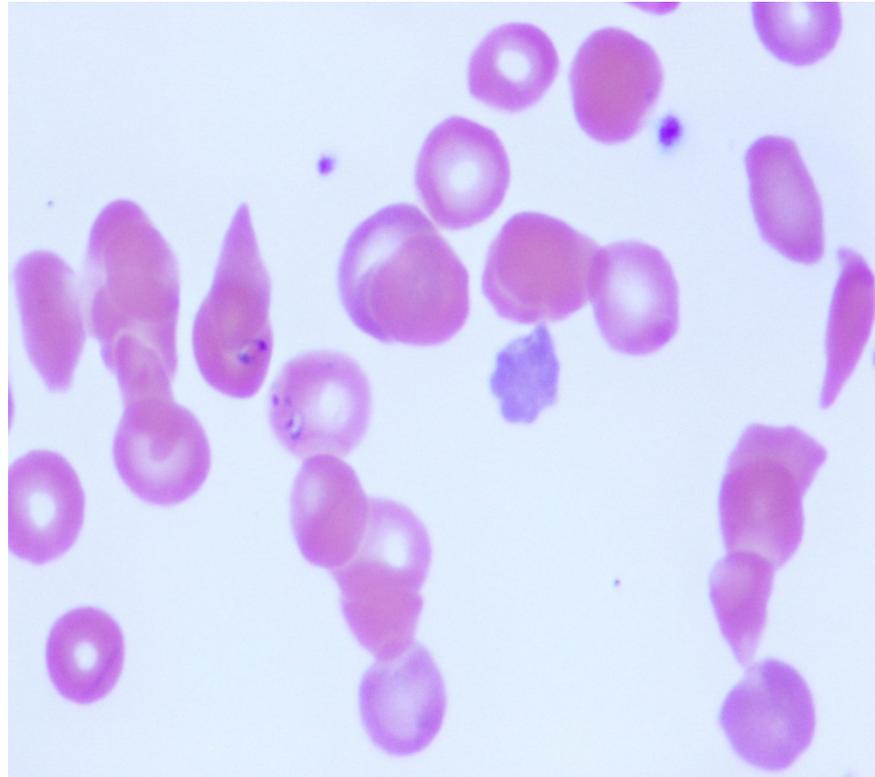
- In the *Susruta*, a Sanskrit medical treatise, the symptoms of malarial fever were described and attributed to the bites of certain insects.
- In 2700 BC, several characteristic symptoms of what would later be named malaria were described in the *Nei Ching*.
- Malaria became widely recognized in Greece by the 4th century BC. Hippocrates noted the principal symptoms

MALARIA EPIDEMIOLOGY

- ◉ 3.3 billion people (half the world's population) are at risk according to WHO.
- ◉ In 2010, WHO estimated 655,000 deaths.
- ◉ Highest mortality in Africa: a child dies every minute from malaria.
- ◉ 5th most frequent cause of death from infectious diseases worldwide
- ◉ United States: 1500 cases annually

PLASMODIUM FALCIPARUM

- Etiologic agent of Blackwater fever, cerebral malaria
- Multiple ring forms in 1 red blood cell
- RBC size remains same



MALARIA: CLINICAL FEATURES

- Acute febrile illness.
- **Seven days or more** (usually 10–15 days) after the infective mosquito bite.
- If not treated promptly, *P. falciparum* malaria can progress to severe illness and death.

HIGH RISK GROUPS

- ◉ Young children
- ◉ Non-immune pregnant women
- ◉ HIV-infected
- ◉ International travelers
- ◉ Immigrants from endemic areas living in non-endemic areas

CDC CRITERIA FOR SEVERE MALARIA

- Positive smear OR History of recent possible exposure and no other recognized pathology who have one or more of the following clinical criteria:

Impaired consciousness/coma, Severe normocytic **anemia**, Renal failure, **Pulmonary edema**, ARDS, **Circulatory shock**, **DIC**, acidosis, hemoglobinuria, **jaundice**, Repeated generalized convulsions, and/or parasitemia of > 5%

MALARIA: DIAGNOSIS

WHO recommends Parasite-based diagnostic testing by :

- ◉ Microscopy
- ◉ Rapid diagnostic tests: required to have 75% positivity at parasite levels of 200 parasites/ul (threshold for low level of parasitemia, particularly important in areas with low transmission)

RAPID DIAGNOSTIC TESTS FOR DIAGNOSIS OF MALARIA (WHO)

Table 5. Antigen targets of rapid diagnostic tests for malaria

<i>Plasmodium</i> species	HRP2	pLDH				Aldolase
		pLDH-Pf	pLDH-pan	pLDH-Pvom	pLDH-Pv	
<i>P. falciparum</i>	X	X	X			X
<i>P. vivax</i>			X	X	X	X
<i>P. malariae</i>			X	X		X
<i>P. ovale</i>			X	X		X

HRP2 – histidine-rich protein 2; pLDH – *Plasmodium* lactate dehydrogenase; Pf – *P. falciparum*
 pan – all *Plasmodium* species; Pvom – *P. vivax*, *ovale* and *malariae*; Pv – *P. vivax*

P.FALCIPARUM TREATMENT

- ◉ Uncomplicated: CQ sensitive (Central America, Haiti and Middle east: Chloroquine
- ◉ Uncomplicated CQ resistant:
 - ❖ Atovaquone-proguanil (Malarone)
 - ❖ Artemether-lumefantrine (Coartem)
 - ❖ Quinine sulfate plus one of the following: Doxycycline, Tetracycline, or Clindamycin
 - ❖ Mefloquine (Lariam)

SEVERE MALARIA: TREATMENT

- ◉ Quinidine gluconate plus one of the following: Doxycycline, Tetracycline, or Clindamycin
- ◉ Artesunate followed by one of the following: Atovaquone-proguanil (Malarone), Doxycycline (Clindamycin in pregnant women), or Mefloquine
- ◉ Exchange transfusion if parasite density $>10\%$

MALARIA, SICKLE CELL TRAIT AND SICKLE CELL DISEASE

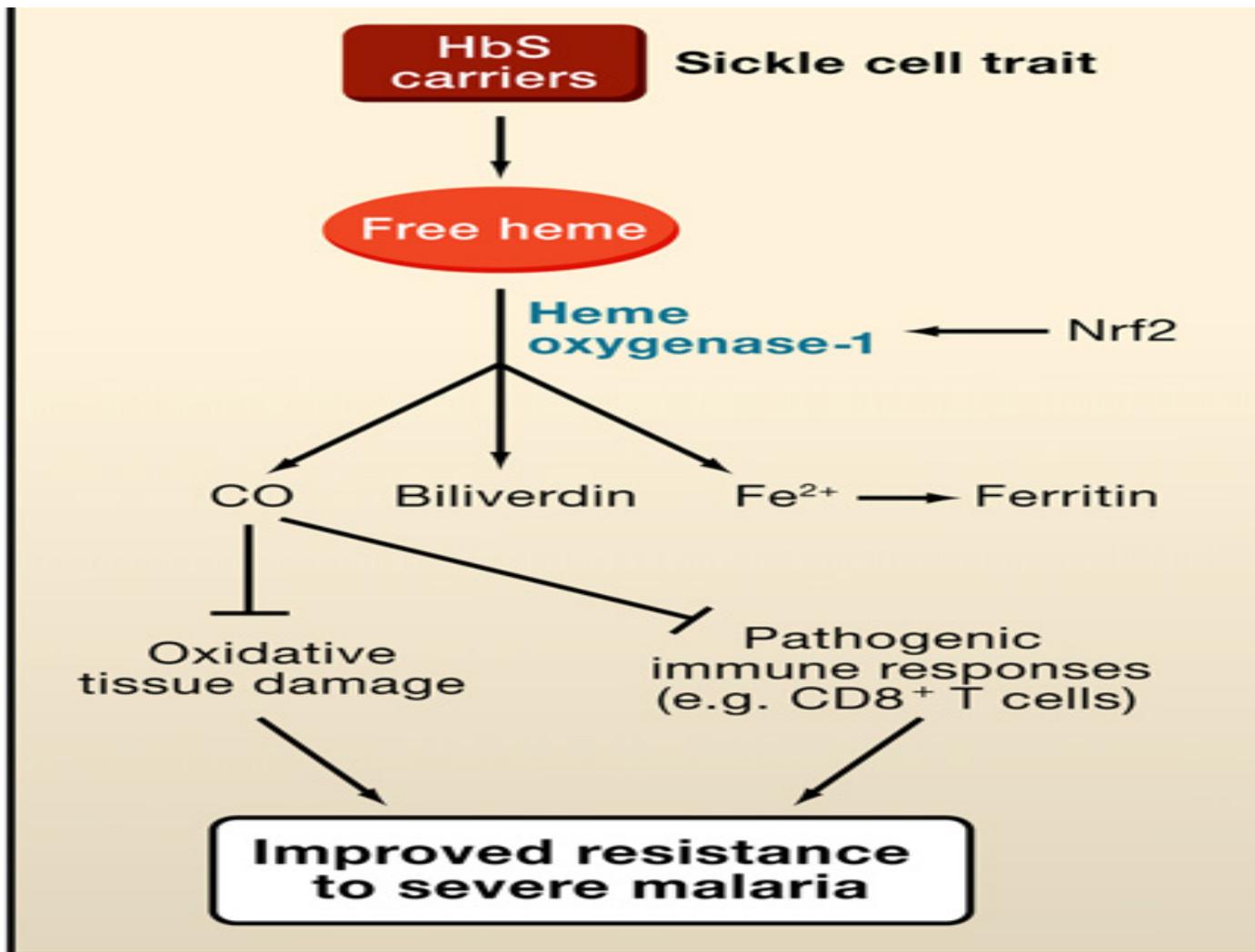
- Usually low parasite loads seen in sickle cell disease
- Unclear why sickle cell trait has protective effect while sickle cell disease predisposes to severe malaria?

MALARIA, SICKLE CELL TRAIT AND SICKLE CELL DISEASE

- According to one theory, Homozygous and heterozygous patients for the HbS allele have higher levels of free heme in blood
- Heterozygotes (sickle trait) show resistance to severe malaria and cerebral malaria and have survival benefit because HO-1 (Heme oxygenase) and carbon monoxide are upregulated in sickle cell trait.

An Antioxidant Link between Sickle Cell Disease and Severe Malaria Cell 2011 29;145(3):335-6.

HEMEOXYGENASE UPREGULATION IN HBS LEADS TO IMPROVED MALARIA RESISTANCE



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MALARIA, SICKLE CELL TRAIT AND SICKLE CELL DISEASE

- ◉ Whereas modest increases in free heme is protective, higher concentrations of free heme scavenges nitric oxide.
- ◉ Low levels of nitric oxide linked to endothelial dysfunction in human and mouse severe malaria and could explain severe disease in sickle cell disease patients.

An Antioxidant Link between Sickle Cell Disease and Severe Malaria Cell 2011 29;145(3):335-6.

THANK YOU !

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