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A 4-Year-Old Girl from Uganda in a Coma

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Clinical Presentation

History

It is the rainy season in rural eastern Uganda. A 4-year-old girl, previously healthy, is carried into the Accident and Emergency (A&E) Department. Her father reports that she was well until yesterday. She had a bad headache in the early afternoon but later in the evening developed shaking chills. Believing this was yet another episode of malaria, a common problem in their village, the family planned to take her to the health centre in the morning. The child slept restlessly. At 5 a.m. today the family woke to find the girl was in the midst of a seizure, which lasted about ten minutes. It has taken 4 hours for the family to reach A&E and the little girl has not awoken. The child has not had any recent head trauma and the family knows of no other reason that the child might be ill.

Clinical Findings

Her temperature is 38.7°C (101.7°F), pulse 150 bpm, respiratory rate 36 breath cycles per minute and blood pressure 98/40 mmHg. She has no neck stiffness or jaundice. Capillary refill is normal. There is nasal flaring with respirations. Blantyre Coma Scale is 1/5. Pupils are 2 mm and reactive, and extraocular movements are normal by oculocephalic manoeuvres. She has no papilloedema on direct ophthalmoscopy. With stimulation there is decerebrate posturing that resolves spontaneously. On cardiac examination she has a gallop rhythm. Her liver is palpable 2 cm below the right costal margin and her spleen is 4 cm below the left costal margin. A rapid test for glucose is normal.

Laboratory Results

Laboratory results are given in Table 4.1.

Questions

1. What is the differential diagnosis?
2. What additional work-up should be performed?

TABLE 4.1 **Laboratory Results on Admission**

Parameter	Patient	Reference Range
Haematocrit (%)	17.6	≥30
Platelet count $\times 10^9$/L)	28	150–450
Malaria RDT	Positive	Negative

Discussion

A 4-year-old Ugandan girl is brought to the hospital unconscious with no neurological localizing signs, a supple neck, hepatosplenomegaly and a positive malaria rapid diagnostic test. Early laboratory testing reveals anaemia and thrombocytopenia.

Answer to Question 1

What Is the Differential Diagnosis?

The most important underlying aetiologies of coma to consider are cerebral malaria, acute bacterial meningitis, viral encephalitis and intoxication (particularly organophosphates). Metabolic abnormalities (hypoglycaemia, or renal or hepatic failure) and non-convulsive *status epilepticus* may be primary causes of coma or complicate these infectious and toxic aetiologies. Although there is no neck stiffness, she is deeply comatose, making this clinical finding less reliable; the absence of neck stiffness should not lower the clinician's suspicion of meningitis. Rapid testing shows that hypoglycaemia is not the cause of the child's abnormal mental status and it has been 4 hours since her last clinical seizure, making a post-ictal state unlikely.

The World Health Organization (WHO) defines cerebral malaria as an 'otherwise unexplained coma in a patient with malaria parasitaemia'. This clinical diagnosis is, however, non-specific because of high rates of asymptomatic parasitaemia in those geographical areas where malaria is most common and the abundance of differential diagnoses.

People living in an area of high malaria transmission (such as rural Uganda in the rainy season) may be frequently bitten by malaria-infected female anopheline mosquitoes. Initially, this produces clinical illness (either uncomplicated or complicated malaria); but with repeated infectious challenges, a state of asymptomatic parasitaemia may be attained. Therefore in African children in a coma, a positive malaria rapid diagnostic test (RDT) does not rule out an underlying non-malarial aetiology of acute illness. In parasitaemic African children in a coma, direct or indirect ophthalmoscopy may be useful in differentiating malarial from non-malarial aetiologies of coma (see Summary Box).

Answer to Question 2

What Additional Work-Up Should Be Performed?

Although the child has a positive malaria RDT, a lumbar puncture should be performed to rule out bacterial meningitis. If available, an electroencephalogram (EEG) may be useful to rule out non-convulsive status epilepticus as either a primary coma aetiology or a contributor to illness. More sophisticated laboratory evaluations (creatinine, electrolytes, bilirubin) may be useful but are seldom available in the geographical contexts where malaria is most prevalent.

An ophthalmoscopic examination to evaluate for malarial retinopathy may be helpful. The presence of one or more retinal findings (retinal whitening, haemorrhages or orange-white vessels with or without papilloedema) would lend support to a malarial aetiology of acute illness (Fig. 4.1). Children with retinopathy-negative cerebral malaria may be more likely to have a non-malarial aetiology for their coma. As both retinopathy-negative and retinopathy-positive cerebral malaria may be complicated by bacteraemia, bacterial meningitis, seizures and/or metabolic abnormalities, a complete work-up for non-malarial coma aetiologies (including non-convulsive status epilepticus) is indicated in all patients presenting with WHO clinically defined cerebral malaria.

• **Fig. 4.1** White-centred haemorrhages and retinal whitening, both features of malaria retinopathy (Courtesy Dr Nicholas Beare).

The Case Continued. . .

A lumbar puncture was performed. The CSF was clear and acellular; opening pressure was normal. Blood cultures were taken, and mydriatic drops instilled to perform ophthalmoscopy. This revealed white-centred haemorrhages in both eyes. A diagnosis of retinopathy-positive cerebral malaria was made.

After administration of artesunate 2.4 mg/kg IV in A&E, the child was admitted to the high-dependency section of the hospital's paediatric unit for frequent monitoring of vital signs and serum glucose. Artesunate was repeated at 12 and 24 hours and then once daily. An EEG showed diffuse slowing but no epileptiform activity. Twelve hours after admission the child had one short (1 minute) generalized seizure that spontaneously resolved and did not recur. Forty hours after admission her Blantyre Coma Score was 4/5. The child was discharged home on hospital day five, with a follow-up appointment in the neurology clinic scheduled after 4 weeks.

• **Fig. 4.2** Infant with cerebral malaria hospitalized at Queen Elizabeth Central Hospital, Blantyre, Malawi (Courtesy Mr James Peck).

SUMMARY BOX

Cerebral Malaria and Malarial Retinopathy

Cerebral malaria is defined as an otherwise unexplained coma in a patient with *Plasmodium falciparum* parasitaemia. Malaria kills almost 450 000 people per year, the vast majority of them children younger than 6 years old living in sub-Saharan Africa. Many of these children have cerebral malaria (Fig. 4.2).

In African children with parasitaemia in a coma, direct or indirect ophthalmoscopy may be useful in differentiating malarial from non-malarial aetiologies of coma. In autopsy studies, identification of malarial retinopathy during life was 95% sensitive and

100% specific for the post-mortem identification of sequestered parasitized erythrocytes in cerebral vasculature. Sequestered parasitized erythrocytes in the CNS are a pathological hallmark of cerebral malaria and likely indicate that acute malarial infection was responsible for the patient's illness and death. In these autopsy studies, children who fulfilled WHO clinical criteria for cerebral malaria but lacked malarial retinopathy (i.e. they had retinopathy-negative cerebral malaria) had other non-malarial aetiologies of death on autopsy, including systemic infections (pneumonia) and Reye syndrome. In contrast, an epidemiological modelling study in children with retinopathy-negative cerebral malaria showed that the attributable fraction of disease as a result of malaria infection itself is at least 85%. The proportion of children with retinopathy-negative (cerebral) malaria who have non-malarial etiologies of coma remains unknown.

The mainstay of therapy is antimalarials, intensive supportive care and diagnosis and treatment of non-malarial infectious and non-infectious contributors to illness. Even in specialized centres, the case fatality rate for cerebral malaria is 15% to 25%. One-third of survivors are left with neurological sequelae, including epilepsy, cognitive impairment, attention problems and behavioural disorders.

Further Reading

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