Case records of Endemic and Tropical Medicine Department, Zagazig University Hospitals, Zagazig, Egypt

Case 1-2011: A 60 years Old Male with Coma and Fever with Recent Travel to South Sudan

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Presentation of the case:

A 60 years –old business man admitted to the intensive care unit of the Endemic and Tropical Medicine Department, Faculty of Medicine , Zagazig University , Egypt because of deep coma , fever and tachypnea.

The patient had history of recent travel to Juba, south of Sudan 2 weeks befor admission. 5 days after return from Sudan , he noticed fatigue and mild fever.He was given non-specific treatment. 5 days later jaundice appeared on his skin , he was admitted to private hospital in Zagazig .The investigation showed total bilirubin :10 mg/dl , direct 7 mg/dl , ALT:150 , AST :120,Hg :10 gm/dl ,platelets :110000 / dl .The patient was managed as having acute liver disease. Later on malaria parasite test (MP test) was done and revealed *P. falciparum* in thick and thin blood films.The patient was referred to Zagazig Fever Hospital with deterioration of conscious level , quinine was given intravenously without improvement . In the next day , the patient was referred to Tropical Medicine Intensive Care Unit. The patient was deeply comatose ,deeply jaundiced and pale, splenomegaly was found , bubbling chest crepitations were auscultated.The urine was black and the skin showed echymosis .The investigations showed total bilirubin :32 mg /dl, direct bilirubin 22 mg/dl, Hg :6 gm /dl ,platelets : 15000/dl , creatinin: 6 mg/dl , INR :7 ,PH: 7.31 , bicarbonate :12 mmol/l and glucose : 350 mg/dl. Hemoglobin was found in urine. Quinine was given by intravenous infusion in the dose of 20mg /kg loading dose then 10mg/ kg every 8 hours. Doxycyclin 100 mg /12 hours was given through the Ryle . Intravenous frusemide was given as well as oxygen inhalation as a measure against pulmonary edema , also chest consultation for the possibility of mechanical ventilation was requested.Transfusion of platelets, fresh frozen plasma ,and backed red blood cells were given . Intravenous fluids as glucose 10% with 15 unit regular insulin and Ringer lactate solution were given according to the CVP. Regular insulin according to blood glucose level was given every 6 hours subcutaneously. The patient showed no response after one day of extensive care and death was the the end due to multiple organ failure .

Differential diagnosis:

Febrile coma: Febrile coma occurs in cerebral malaria, meningitis , encephalitis , heat stroke, cerebral and pontine hemorrhage , hepatic coma, diabetic coma with infection and atropine poisoning[1].

Fever with jaundice: Fever accompanied by jaundice is caused by viral hepatitis, falciparum malaria , paratyphoid B, infectious mononucleosis , Weil 's disease , hemolytic crises, septic cholangitis, acute leukaemia, yellow fever and other viral hemorrhagic fevers as rift valley fever [1].

Discussion:

The above case is a case of severe malaria according to WHO definition of severe malaria[2] due to presence of coma , renal failure, pulmonary edema, high INR ,hemoglobinuria and acidemia .

Table 1 **-- 1990 WHO Definition of severe malaria**[2]

1.	Cerebral malaria – unrousable coma not attributable to any other cause in a patient with falciparum malaria. The coma should persist for at least 30 min (1 h in the 2000 definition) after a generalized convulsion to make the distinction from transient postictal coma. Coma should be assessed using the Blantyre coma scale in children or the Glasgow coma scale in adults.
2.	Severe anaemia – normocytic anaemia with haematocrit <15% or haemoglobin <5 g/dL in the presence of parasitaemia more than 10 000/μL. Note that finger prick samples may underestimate the haemoglobin concentration by up to 1 g if the finger is squeezed. If anaemia is hypochromic and/or microcytic, iron deficiency and thalassaemia/haemoglobinopathy must be excluded. (These criteria are rather generous; and would include many children in high transmission areas. A parasitaemia of >100 000/μL might be a more appropriate threshold.)
3.	Renal failure – defined as a urine output of <400 mL in 24 h in adults, or 12 mL/kg in 24 h in children, failing to improve after rehydration, and a serum creatinine of more than 265 μmol/L (>3.0 mg/dL). (In practice for initial assessment, the serum creatinine alone is used.)
4.	Pulmonary oedema or adult respiratory distress syndrome.
5.	Hypoglycaemia – defined as a whole blood glucose concentration of less than 2.2 mmol/L (40 mg/dL).
6.	Circulatory collapse or shock – hypotension (systolic blood pressure <50 mmHg in children aged 1–5 years or <70 mmHg in adults), with cold clammy skin or core-skin temperature difference >10°C. (The more recent review declined to give precise definitions, but noted the lack of sensitivity or specificity of core-peripheral measurements.) Capillary refill time is not mentioned but recent studies indicate this simple test provides a good assessment of severity.
7.	Spontaneous bleeding from gums, nose, gastrointestinal tract, etc. and/or substantial laboratory evidence of DIC. (This is relatively unusual.)
8.	Repeated generalized convulsions – more than two observed within 24 h despite cooling. (In young children, these may be febrile convulsions, and the other clinical and parasitological features need to be taken into account.) Clinical evidence of seizure activity may be subtle (e.g. tonic clonic eye movements, profuse salivation, delayed coma recovery).
9.	Acidaemia – defined as an arterial or capillary pH <7.35 (note temperature corrections are needed as most patients are hotter than 37°C; add 0.0147 pH unit per degree Celsius (°C) over 37°C), or acidosis defined as a plasma bicarbonate concentration <15 mmol/L or a base excess >10. (Operationally, the clinical presentation of 'respiratory distress' or 'acidotic breathing' is focused upon in the 2000 recommendations. Abnormal breathing patterns are a sign of severity indicating severe acidosis, pulmonary oedema or pneumonia.)
10.	Macroscopic hemoglobinuria – if definitely associated with acute malaria infection and not merely the result of oxidant antimalarial drugs in patients with erythrocyte enzyme defects such as G6PD deficiency. (This is difficult to ascertain in practice: if the G6PD status is checked following massive haemolysis, the value in the remaining red cells may be normal even in mild G6PD deficiency. This part of the definition is not very useful.)
11.	Postmortem confirmation of diagnosis. In fatal cases a diagnosis of severe falciparum malaria can be confirmed by histological examination of a postmortem needle necroscopy of the brain. The characteristic features, found especially in cerebral grey matter, are venules/capillaries packed with erythrocytes containing mature trophozoites and schizonts of *P. falciparum*. (These features may not be present in patients who die several days after the start of treatment, although there is usually some residual pigment in the cerebral vessels.)
	The 2000 recommendations also include the following:
12.	Impairment of consciousness less marked than unrousable coma. (Any impairment of consciousness must be treated seriously). (Assessment using the Glasgow Coma Scale is straightforward, but the Blantyre Scale needs careful local standardization particularly in younger children.)
13.	Prostration: Inability to sit unassisted in a child who is normally able to do so. In a child not old enough to sit, this is defined as an inability to feed. This definition is based on examination not history.
14.	Hyperparasitaemia – the relation of parasitaemia to severity of illness is different in different populations and age groups, but in general very high parasite densities are associated with increased risk of severe disease, e.g. >4% parasitaemia is dangerous in non-immunes, but may be well tolerated in semi-immune children. In non-immune children studied in Thailand a parasitaemia ≥4% carried a 3% mortality (30 times higher than in all uncomplicated malaria) but in areas of high transmission values much higher may be tolerated well. Many use a threshold definition of 10% parasitaemia in higher transmission settings.
	The followings were not considered criteria of severe malaria:
	Jaundice – detected clinically or defined by a serum bilirubin concentration >50 μmol/L (3.0 mg/dL). This is only a marker of severe malaria when combined with evidence of other vital organ dysfunction such as coma or renal failure.
	Hyperpyrexia – a rectal temperature above 40°C in adults and children is no longer considered a sign of severity.

The above case was treated by quinine infusion with doxycyclin by the Ryle as well as by supportive measures for severe malaria.

Treatment of Severe *P. falciparum* Malaria[3]:

Specific antimalarial treatment:

Regimen 1:

1st drug

Artesunate 2.4 mg/kg iv or im on admission; then at 12 h and 24 h, then once a day for at least

24 hours, followed by full course of ACT(artimisinin combined therapy) , and

2nd drug

Doxycycline 100mgs BID (2.2mg/kg BID for <45kgs) for 7 days OR Clindamycin 20mg base/kg/day divided in three doses for 7 days in pregnancy OR Malaron 4 tab daily for 3 days OR Mefloquine 4 tab in 1st day , 2 tab in 2nd day.

Regimen2:

1st drug

Artemether 3.2 mg/kg i.m. given on admission then 1.6 mg/kg per day for at least 24 hours, followed by full course of ACT , and

2nd drug

As above.

Regimen3:

1st drug

Quinine 20 mg salt/kg on admission (iv infusion or divided im injection), then 10 mg/kg every 8 h; infusion rate should not exceed 5 mg salt/kg per hour; course for 3 days for malaria acquired in Africa and South America, 7 days for malaria acquired in south east (SE) Asia , and

2nd drug

Doxycyclin and clindamycine as above.Do not use mefloquine in combination with quinine.

Regimen 4:

1st drug

Quinidine gluconate 10 mg salt/kg (equivalent to 6.2 mg base/kg) iv infused over 12 hours, followed immediately by 0.02 mg/kg/min salt (equivalent to 0.0125 mg/kg/min base) continuous iv infusion; course for 3 days for malaria acquired in Africa and South America, 7 days for malaria acquired in SE Asia , and

2nd drug

Doxycycline or clindamycin, do not use mefloquine.

ALWAYS AVOID THE FOLLOWING COMBINATIONS:QUININE, MEFLOQUINE, PRIMAQUINE,CHLOROQUINE WITH EACH OTHER.

Adjunctant Treatment in Severe P.falciparum:

Table -2 Adjunctant treatment [3]:

Manifestation/complication	Immediate management (in addition to antimalarial treatment)
Hyperpyrexia	Administer tepid sponging, fanning, cooling blanket and antipyretic drugs
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatment such as corticosteroids, heparin and adrenaline; intubate if necessary
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde
Hypoglycaemia (blood glucose concentration of<2.2 mmol/l; <40 mg/100ml)	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion
Severe anaemia (haemoglobin <5 g/100ml or packed cell volume <15%)	Transfuse with screened fresh whole blood
Acute pulmonary oedema	Over-enthusiastic rehydration should be avoided so as to prevent pulmonary oedema. Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxaemia
Acute renal failure	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure add haemofiltration or haemodialysis, or if unavailable, peritoneal dialysis. The benefits of diuretics/dopamine in acute renal failure are not proven
Spontaneous bleeding and coagulopathy	Fresh frozen plasma, platelets transfusions, vit K.
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe add haemofiltration or haemodialysis
Shock	Suspect septicaemia, take blood for cultures; give parenteral antimicrobials, correct haemodynamic disturbances

The above case is an imported malaria because malaria is eradicated from Egypt except small focus in Elfayoum Governorate .In 2007, Zaher et al ,reported a case of imported malaria died by cerebral malaria due to delayed diagnosis before admission to Almaza Military Fever Hospital , Cairo.[4].Also Birnbaumer concluded that death of imported malaria cases was due to miss or delay diagnosis[5].

Conclusion:

Malaria in travelers typically manifests days or weeks after patients left the endemic area. Malaria symptoms are non specific and rapid diagnosis and treatment are needed .Specific chemoprophylaxis for travelers to chloroquine resistant areas should be given.

References:

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5. Birnbaumer D. Malaria diagnosis missed in nearly half of patients at risk ; Imported malaria prospective analysis of problems in diagnosis and management . *Clin Infect Dis* 1998 ;27;142-149