

Chapter-7

CLINICAL ASPECTS OF MALARIA.

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INTRODUCTION

Malaria has a variety of clinical pictures, from acute to chronic, and from simple fever to life-threatening multiple organ failure. The clinical picture differs with the species of parasite involved, but also with the immune status of the patient. *P. falciparum* is by far the most dangerous, with the most dramatic symptoms and signs.

Clinical syndromes like black water fever, cerebral malaria, hyperreactive malarial splenomegaly are recognised as distinct entities. In recent years minor, atypical malaria syndromes have been recognised. The impact of these syndromes on the general health in endemic countries is difficult to measure, but could be substantial. Therefore, studying malaria in expatriates returning from endemic countries is important in establishing the relationship between infection and clinical patterns. Translating these findings to malaria in endemic regions however should be done with caution.

Every patient can tell you “his” symptoms of malaria, and the proof of infection is given by the rapid decline in symptoms while taking treatment. This argument is weak: firstly because a lot of viral diseases heal spontaneously and secondly because some antimalarials are also antiphlogistics, although with delayed action.

There is no definitive, unique indicator of morbidity, hence no diagnosis is as controversial as malaria. The boundary between malaria “infection” and malaria “disease” is not clear. The finding of parasites in a blood smear does not necessarily mean that the patients’ symptoms are due to malaria, as the presence of parasites is required to build up and to maintain an immunity, which is never complete. Quite accurate techniques have been developed to determine the impact of malaria within populations, and the level of parasitaemia that is required to distinguish symptoms due to other diseases from symptoms due to malaria infection (see chapter ##, diagnosis of malaria disease). However, is the diarrhoea of an individual patient provoked by malaria infection, when one finds parasites in the blood, or is a different pathogen responsible? And what if no pathogen is found? This is an endless topic of debate and research, as scientists try to establish a pattern of symptoms and signs, or a marker that could unequivocally point to malaria as the cause of the patient’s complaints.

To our knowledge, no other disease requires such a long time and demands such a high price for an incomplete and transient immunity. In most endemic countries, children will suffer recurrent attacks from a few months after birth until the age of 5 to 10 before they acquire an immunity, and many of them will suffer from growth retardation, will be hospitalised several times, receive transfusions, or succumb.

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Symptoms and signs are highly dependent on the immune status of the patient. The transition from simple parasitaemia that sustains immunity, to symptoms unequivocally attributable to disease, is not step by step, but continuous. It is difficult to set a universal clinical threshold. It depends on the species and the strain of the parasite, the parasite load and the immunity of the patient.

The age of the patients who suffer from malaria will be influenced by the endemicity of malaria in a given region. In hyperendemic (“malaria stable”) countries, small children will be more affected. In hypo-endemic (“malaria unstable”) regions, among displaced people and migrants, adults will be affected in a similar way to children, depending on their exposure to mosquito bites. Immunity may fade temporarily in pregnancy, and temporarily or permanently in people leaving the endemic region.

Up until now, there is no definite proof of an enhancing or a protective effect of malnutrition on the clinical severity of malaria infection (Greenwood, 1991; Van den Broeck, 1993) Although iron chelation has a therapeutic effect in severe malaria, (Gordeuk, 1992) and iron supplementation to malnourished children can result in recrudescence of malaria infection, the protective effect of iron deficiency remains to be proved. (Greenwood, 1991) Recently, the long accepted excess risk of splenectomy for malaria infection and for severity of this infection was also challenged. (Looareesuwan, 1992)

In recent years increased travel, transmission, endemicity and resistance of the parasite to prophylactic regimens has caused a considerable increase in imported malaria in Western countries (Bruce Chwatt, 1980; Molineaux, 1989; Steffen, 1992; Gay, 1990; Ducoffre, 1991; Freedman, 1992). Since 1990 however, a decline has been reported for Caucasians, but not for Africans (Voyer, 1994; Anonymous, 1994). Delayed diagnosis is responsible for avoidable morbidity and mortality (Steffen, 1992). Together with an increase in the number of cases of imported malaria, a shift towards more subacute disease has been noted (Sansone, 1986; Charmot, 1988; Van Gompel, 1991; Wetsteyn, 1995).

Falciparum Malaria - Classical Presentation

Symptoms And Signs

Malaria is generally known as the disease that causes fever every two or three days. On a global scale, this description is totally false: only a small percentage of all malaria morbidity follows this pattern.

How can we explain this historical error ? Malaria was first described as the disease that afflicted some regions in Europe, and later as the disease imported by expatriates. In the first case, most of the disease was caused by P. vivax, where relapses in fact cause fever every two days. In the second case, because of the time taken to travel by boat, expatriates were seen two or three weeks after they left the endemic region, by which time P. falciparum infections could present as fever every two days, reflecting the normal pattern later in the course of the disease, if spontaneous evolution is not interrupted by treatment. Finally, the periodic pattern is only seen when the infection is caused by one strain, which is not always the case in endemic areas.

The physiopathological background of malaria infection has influenced the description of symptoms and signs: since we know that malaria causes haemolysis, we readily accept that malaria infection presents with pallor, jaundice and dark-coloured urine. In fact, these signs present rather late in the course of the infection, and are a sign of evolution towards severe malaria. In fact, they should not be mentioned in the classical presentation.

The classical presentation can be divided into two stages: the invasive and the late phase. During the first days of disease, fever will follow an irregular pattern, almost every day. In the second phase, fever can become periodic, every two days. (fig 1) During this phase, the disease can evolve towards a severe malaria, or produce a certain degree of immunity, and disappear (temporarily).

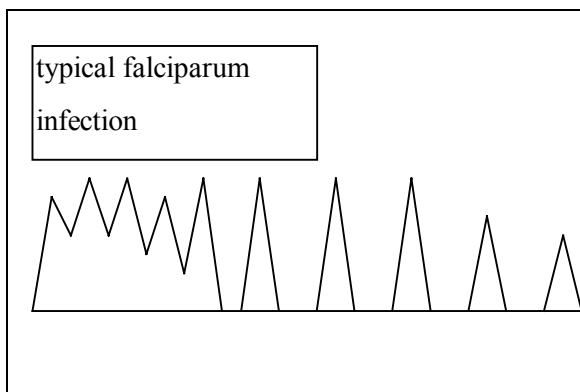


Figure 1.: falciparum infection: during the first phase the fever is present every day, in an irregular fashion. Afterwards, fever can become tertian, presenting every second day.

Symptoms include fever, chills, sweating, headache, arthralgia, myalgia, labial herpes, nightsweats, prostration, pain in the left subcostal region and gastrointestinal symptoms such as diarrhoea, vomiting and abdominal pain. Children may have convulsions. In the second phase, the so-called “typical malaria attack” can be seen: chills followed by high fever, resolving within a few hours with heavy perspiration, repeated every 48 hours. After the attack there may be a feeling of euphoria, but, once again, this is the exception rather than the rule.

The only reliable physical sign is splenomegaly. It develops after days or weeks. When clinically detectable pallor, jaundice and dark coloured urine develop, an evolution towards severe malaria should be suspected. Hepatomegaly is controversial: some authors give it emphasis, others do not. (Manson-Barr, 1987; Gentilini, 1985) Perhaps the way of confirming this sign can explain the difference in the literature: when percussion is added to the physical exam, more hepatomegaly might be found.

Of all these symptoms and signs, none is typical for malaria except the 48 hours periodicity, which is rare. Clusters of symptoms and signs are predictive in an hyperendemic region, mainly because the pretest probability is high, not because the clusters are specific (see chapter ##, diagnosis of malaria disease).

Laboratory

An uncomplicated malaria attack can be accompanied by a fall in the haemoglobin level, the thrombocyte count, the total serum cholesterol and HDL cholesterol levels. The leucocyte count can be affected in two ways, towards hyperleucocytosis and leucopenia.

Haemolysis parameters include a high reticulocyte count, a low haptoglobin level, a high indirect bilirubin and lactic dehydrogenase level.

Liver enzymes and direct bilirubin may be elevated; important elevations are indicative of severe malaria.

Transient albuminuria is possible in both complicated and uncomplicated P. falciparum malaria.

Severe and Very Severe Malaria

Introduction

In most people, there is a fine balance between malaria infection and immunity. When this balance is disturbed and the infection becomes dominant, it can cause an acute overwhelming infection by parasites leading towards multiple organ failure (MOF), or to a subacute downhill course with progressive destruction of red blood cells. Both acute and subacute evolutions are severe and can end in death.

The World Health Organisation has published criteria for severe and very severe malaria: they allow an early alarm, before a frequently irretrievable situation develops. (Warrel, 1990) Table 1 lists defining criteria along with manifestations that are common, but not necessarily indicative of severe malaria. A practical consequence of the diagnosis of severe malaria is the need for parenteral treatment and hence for referral. Severe vomiting is not a defining criterion of severe malaria, but has the same consequence, and is therefore often included in the defining list.

Severe malaria is life-threatening, but treatment is lifesaving: in a spectacular case of cerebral malaria with 70 % of RBC infected, the patient was resuscitated, he developed aspiration pneumonia, ARDS, renal failure, sepsis, peritonitis and splenic necrosis, but he survived with exchange transfusion. (Files JC, 1984) Another patient with 71% of RBC infected survived without exchange transfusion. (Marik, 1989)

TABLE 1 : CRITERIA FOR SEVERE PL. FALCIPARUM MALARIA

Defining criteria

unarousable coma

severe normocytic anaemia (haematocrit < 15 % or haemoglobin < 5 g/dl)

renal failure (creatinine > 3 mg/dl and urine output < 400 ml/24 h in adults, <12 ml/kg/24h for children)

pulmonary oedema

hypoglycaemia (whole blood glucose concentration < 40 mg/dl)

circulatory collapse, shock

spontaneous bleeding/disseminated intravascular coagulation

repeated generalised convulsions (> 2 convulsions/24 h despite cooling)

acidosis

malarial haemoglobinuria

Other manifestations

impaired consciousness, but rousable

prostration, extreme weakness

hyperparasitaemia (> 5 % infected RBC or > 250.000 parasites/ml)

jaundice (serum bilirubin concentration > 3g/dl)

hyperpyrexia

*Case Report*³

A.S., a 33-years-old seaman from Capo Verde, was hospitalised after a recent journey to West-Africa, with fever, diminished consciousness, jaundice and oliguria. No prophylactic drugs had been taken. Laboratory results included the presence of *Plasmodium falciparum* in both thick film and blood smear with 25% of RBC parasitized, haemoglobin of 5.12 g/dl, thrombocyte count of 28,000/mm, total serum bilirubin of 8.06 mg/dl, serum creatinine of 8.1 mg/dl and a plasma free haemoglobin level of 55,6 mg/dl. Plasma glucose and ions were normal.

Quinine, 500 mg IV t.i.d. was started immediately. Given the high parasitaemia and the clinical condition, an exchange-transfusion with 4 l of reconstituted blood was begun. At the end of the exchange transfusion the parasitaemia was 2% .

On the first and the fourth day, an additional transfusion of 2 respectively 3 units of packed-cells was given. Haemodialysis was performed on the first, third and fourth day. After the first 24 hours, administration of quinine was restricted to once a day, and an additional dose after each hemodialysis, until kidney function improved. Measurement of serum quinine level showed a concentration of 3 microgr/ml.

By the end of the exchange transfusion, consciousness returned to normal, and on the third day 2086 ml of urine was produced. The patient was discharged after complete recovery.

Clinical Picture

An evolution towards an acute MOF is possible after a first infection. If untreated, mortality in a nonimmune patient can be as high as 20% (Fairley, 1945). This evolution can also appear in the course of building up immunity, or superimpose on a subacute severe evolution. It is rare or non-existent in semi-immune older children and adults in endemic regions.

Often several organs are affected at the same time but exceptions are frequent, in which e.g. only cerebral malaria develops and where kidneys, liver and lungs are relatively unaffected. (Weber, 1991) Manifestations of lung involvement may be late, although early changes can be seen radiographically.

Cerebral

Cerebral malaria generally presents as an acute diffuse encephalopathy. Cerebral oedema and foramen magnum herniation are rare. (Looareesuwan, 1995) Convulsions are frequent in children with fever. An isolated convulsion does not establish the diagnosis of cerebral malaria, but it constitutes a serious warning. In adults, it unequivocally heralds a cerebral involvement. Repeated convulsions, or status epilepticus are defining criteria of cerebral malaria. Convulsions are mostly generalised, but Jacksonian convulsions or widespread myoclonias are possible. (Daroff 1967; Geerts 1995)

Altered consciousness is often the first sign of severe malaria, but can be provoked by high fever itself. Disorientation in time and space, amnesia, difficulty with speech can progress to drowsiness, ending in coma. This evolution can be very fast, a matter of a few hours.

Acute signs of focal affection of the brain (paralysis, cranial nerve dysfunctions, cortical blindness...) are relatively rare in adults, but not in children. These focal signs may persist as

³This case has been published before. (Van den Ende, 1994: trop geo medicine)

sequelae in up to 10% of survivors, especially when the cerebral malaria is complicated by hypoglycaemia. (Taylor TE, 1988; Schmutzhard E, 1984). Acute and delayed cerebellar dysfunction with hypotonia and nystagmus have also been described.

Neck stiffness has been described as one of the presentations of cerebral malaria. It may be part of an opisthotonus or of a decerebration rigidity. Lumbar puncture yields a normal fluid. Meningitis and other locally common causes of encephalitis should be excluded.

Retinal haemorrhages may occur, exudates and papilledema are rare. Pupils are normal, as are corneal and eyelash reflexes, but disorders of gaze are frequent.

Tendon reflexes are generally increased, but abdominal reflexes are absent, which may help in excluding a hysterical crisis in a feverish patient.

Liver

Some hepatocellular necrosis is common in all forms of malaria. In severe malaria, hepatic enzymes may rise severely (but never as high as in viral hepatitis), and direct bilirubin can contribute substantially to the total bilirubin elevation. Liver-related symptoms are rare; frank jaundice is possible, and reflects both haemolysis and liver dysfunction. Clinical signs and/or liver failure are never seen. The production of coagulation factors can be affected, with prolonged prothrombin time. Hepatic dysfunction may contribute to low serum albumin, hypoglycaemia and lactic acidosis. kidneys

The pattern of the kidney dysfunction is that of an ischaemic nephropathy or an acute tubular necrosis. Adults are much more subject to this complication than children; in African children it is uncommon (White 1988; Molyneux 1989). The symptoms include oliguria, anuria, and occasionally polyuria. Dark coloured urine is due to concentration and haemoglobinuria. Urea and creatinine rise, despite correct rehydration and hemodialysis or peritoneal dialysis is often necessary. During recovery, which can take several weeks, a polyuric phase is possible.

lungs

The exact pathogenetic mechanism of lung involvement in severe malaria is not known. It may be explained by increased pulmonary vascular resistance during severe falciparum malaria infection, hypoalbuminemia and volume overload caused by infusions. (Poonkasem Charoenpan, 1990; Feldman 1987; Tatke 1990; Pradeep Bambery, 1991)

Too often, pulmonary dysfunction is provoked or increased by the rapid administration of large amounts of fluid, with the aim of reversing oliguria or anuria, based on the idea that tubular haemoglobin might be responsible for renal function impairment. However, cases also occur with a normal or negative fluid-balance.

The classical clinical picture is one of pulmonary oedema or ARDS, with cough, dyspnea, polypnea and cyanosis. This complication has a high mortality, and often comes late in the course of the severe malaria, sometimes in patients recovering from other manifestations of the disease. (Brooks, 1968) Polypnoea can also be provoked by acidosis, but auscultation should allow the distinction between the two causes, with inspiratory crackles and rales, together with X-ray images, which can be quite impressive, ranging from an interstitial overload to white lungs. (figure 2.) Blood gas analysis shows low oxygen content and saturation.

Recently, development of ARDS as a direct consequence of the procedure of exchange transfusion has been challenged (Vachon, 1990). In the series of Miller et al., six out of twelve patients developed this complication (Miller, 1989).

gastro-intestinal

Nausea, vomiting and abdominal pain are common symptoms. Severe diarrhoea and even choleraform diarrhoea have been described with hyperparasitaemia, leading to dehydration and hypotension. The diarrhoea resolves with treatment of malaria alone.

cardiovascular

Hypotension is common with dehydration, pulmonary oedema, acidosis and septicaemia as contributory factors. In spite of a high parasite load in the capillaries of the heart, cardiac manifestations such as heart failure or arrhythmias are rare. Diffuse intravascular coagulation can lead to vascular occlusion, and cause necrosis of fingers and toes (figure 3.).

blood

High parasitaemia is common, and the number of parasitised red blood cells can exceed 50% of red blood cells parasitised. (Files JC, 1984; Marik 1989) Mortality is to some extent related to parasitemia (Warrel, 1987; Warrel 1989). Some authors describe cases of cerebral malaria with no parasitaemia, (Warrel 1990; Chia 1992; Commey, 1984) while others discuss this clinical entity, and emphasise its rarity. (White 1992)

Low haemoglobin levels and thrombocyte counts are common. Leucocyte counts can be normal, low or high. A high leucocyte count reflects clinical severity. (Warrell 1982; Molyneux 1989) Very low thrombocyte counts ($< 10.000 \times 10^9 / l$) can be observed without bleeding.

Acidosis is related to shock, liver dysfunction, renal failure and hypoglycaemia. It can be pronounced, and can lead to polypnea. Mild hyponatremia is common but profound hyponatremia which can cause coma, is rare. Diffuse intravascular coagulation is rare but it can cause low thrombocyte counts and the presence of fibrin dimers in serum and urine. Other findings are hypocalcemia, hypophosphatemia, hyperphospholipidemia, hypertriglyceridemia, hypocholesterolemia, and the sick euthyroid syndrome with low total serum thyroxine concentration and normal TSH. These findings are clinically not relevant.

hypoglycaemia

Hypoglycaemia is frequent in severe malaria in children in hyperendemic regions. (Warrell 1990; Phillips 1990; Marsh 1995; Mabeza 1995) It can contribute to clinical severity and to late sequelae. It is a predictor of mortality.

Hyperinsulinemia provoked by quinine treatment is one of the suggested causes of hypoglycaemia but in African children no correlation between hypoglycaemia and quinine therapy was found. (White 1987; Taylor, 1988) Hyperparasitaemia itself or the combination of malaria and pregnancy can also be a cause without quinine therapy. Hypoglycaemia is not restricted to severe malaria, but has also been described in other life-threatening conditions in children in poor countries. (Kawo 1990)

Often hypoglycaemia is not clinically recognisable: it contributes to coma, but may not produce the classical symptoms of sweating, dizziness, tachycardia etc. No one clinical sign is reliably indicative of hypoglycaemia.

Septicaemia

Gram negative septicaemia often occurs with very severe malaria, even in the absence of a focus such as an indwelling catheter or a decubitus ulcer. If hypotension is present, septicaemia should always be suspected, and treatment should begin without waiting for the results of hemocultures.

Hyperreactive Malarial Splenomegaly (HMS)

Introduction

The tropical splenomegaly syndrome (TSS) originally referred to cases of splenomegaly in the tropics for which no cause was found despite thorough investigation (De Cock, 1983). Many early investigators applied the term "tropical splenomegaly" to syndromes representing probably non-cirrhotic portal fibrosis (Williams, 1966; Hewlet, 1987), or visceral leishmaniasis (Hewlet 1987). Since 1976 TSS refers specifically to "a condition resulting from an aberrant immunological response to malaria" (Marsden, 1976). In 1981 Fakunle set major and minor diagnostic criteria (Fakunle, 1981) (Table 2). Splenomegaly, elevated antimalarial antibodies, elevated IgM and response to long term treatment or prophylaxis are major criteria. Hepatic sinusoidal lymphocytosis, occurring in over 80 % of cases (Marsh 1986), and hypersplenism are minor criteria. In 1983 an international group of workers interested in the problem of splenomegaly in the tropics proposed replacing the name "tropical splenomegaly syndrome" by "hyperreactive malarial splenomegaly" (HMS) in order to distinguish between splenomegaly of obscure origin and splenomegaly related to malaria (Bryceson 1983).

It is not uncommon to find cold agglutinins amongst the non-specific, "wild", IgM antibodies. These cold agglutinins can further exacerbate haemolysis. The splenomegaly by itself can cause hypersplenism, in which not only erythrocytes, but also leucocytes and thrombocytes will be destroyed or removed from the circulation. However, this hypersplenism is not a pre-requisite for the syndrome.

HMS has only rarely been reported in Caucasians. HMS can develop years after a stay in an endemic region: in one case, it developed 8 years after the last stay in a tropical country (Torres-Rojas, 1981).

Long term exposure to malaria over a period of five years or more is necessary for the development of this syndrome which only affects adults and older children.

TABLE 2 DIAGNOSTIC CRITERIA of HYPERREACTIVE MALARIAL SPLENOMEGALY

Major diagnostic criteria : always present

gross splenomegaly in older children and adults

high antibody levels for *P. falciparum*

elevated serum (polyclonal) IgM of at least 2 standard deviations above the mean of the population from which the patient comes.

clinical and immunological response to long term appropriate antimalarial therapy, but no reduction in spleen size may be apparent for the first three months.

Minor diagnostic criteria: frequently or nearly always present

hepatic sinusoidal lymphocytosis is a diagnostic histologic finding, occurring in over 80% of cases (only seen in Felty's syndrome, non-tropical idiopathic splenomegaly or Dacie's syndrome, and some rare cases of chronic lymphocytic leukaemia)

normal cellular and humoral immune responses to antigenic challenge, (except to malarial antigens, where enhanced lymphocyte proliferation has been shown)

normal response to PHA

hypersplenism

lymphocyte proliferation (in some populations)

occurrence within families, tribes

Case Report⁴

VH, a Dutch boy, was born in north-eastern Zaire where he lived until the age of 6. He had been taking chloroquine, 5 mg/kg twice a week as malaria prophylaxis. He had a normal development and never experienced any serious health problem in Zaire. Eighteen months after return, he became ill (December 1987). The parents noticed pallor, weight loss, asthenia and diminished performance in sports. The boy had two short episodes of fever with headache. He was treated empirically by the parents with chloroquine (25 mg/kg, in three days). They reported slight improvement. A paediatrician found an impressive splenomegaly. A sonographer reported a maximum spleen diameter of 17 Cm. A thick film did not reveal plasmodium parasites, but serum antibodies to P. fieldi (a laboratory plasmodium strain that shares antigenic properties with P. falciparum) were 1/320 in immunofluorescence.

The boy was referred to the outpatient department of the Institute of Tropical Medicine, Antwerp, where he was seen on April 15, 1988. Asthenia and weight loss were still present. Clinical examination revealed a pale face, with normally coloured conjunctivae, and a spleen that descended 4 fingers under the costal margin. Haemoglobin was 11,2 g/dl, leucocyte count $7.5 \cdot 10^9$ /l with normal formula, thrombocyte count $188 \cdot 10^9$ /l, reticulocyte count 6.4 %, sedimentation rate 39 mm/h, and haptoglobin 0 mg/dl. A thick film was negative for parasites. A Knott concentration technique revealed microfilaria of Dipetalonema (Mansonella) perstans. Schistosoma infection was excluded by negative stool examination (direct and after concentration), and by negative serology (ELISA, enzyme linked immunosorbent assay). P. falciparum antibodies were 1/5120 in indirect immunofluorescence (IFAT, Ig-class aspecific). Antibodies for P. vivax, P. ovale and P. malariae were 1/320, 1/640 and 1/320. Gammaglobulin fraction was 25,9 % or 2,04 g/dl; IgM content was 1090 mg/dl (normal values for age 6-8 y: 27-118 mg/dl (Stiem 1966). Osmotic resistance of erythrocytes gave a normal curve, except for complete haemolysis which required 0,100 g/dl.

Ultrasonography of the upper abdomen showed a normal appearance of the liver, gallbladder, kidneys and pancreas. The maximal spleen diameter was 13,5 Cm.

The patient was treated with mefloquine, 30 mg/kg in divided doses over 24 hours. His complaints disappeared, and he regained weight.

The evolution of spleen size and laboratory parameters is shown in table 3. All laboratory parameters responded to the first treatment. For the haptoglobin, IgM and P. falciparum antibodies it took several months to regain normal values.

Given the persistence of the splenomegaly and the extremely low haptoglobin, a second identical treatment with mefloquine, followed by weekly mefloquine, 6 mg/kg/week for 8 weeks was prescribed, 8 months after the first treatment. No effect on splenomegaly was noticed.

⁴ This case has been published elsewhere (Van den Ende, 1994: annales)

During the next 4 years all laboratory parameters normalised, and a normal development was noticed. The spleen did not decrease in size, but became normal for age as height increased.

TABLE 3 Evolution of clinical parameters of the HMS case.

DATE	15/04/	13/05/	16/06/	4/08/	13/01/	20/10/	11/04/	01/06/
	88	88	88	88	89	89	90	92
Hb	11,2	12,2	12,4	12,5				
Ret	64	25	16	13				
Sed. rate	39	21	12					
Hapto	0	0	0	0	77	62	37	85
IFAT	5120	1280	1280	1280	640	1280	320	20
Gamma	2,04	1,76	1,59	1,39				
IgM	1090	717	520	341			177	177
Spleen size	13.5	14	14	14	14	14	14	13
Height	118							156

Hb : haemoglobin in g/dl.

Ret : reticulocyte count per 1000 erythrocytes.

Sed. rate : sedimentation rate (mm/h).

Hapto : haptoglobin in mg/dl.

IFAT : anti P. falciparum antibodies in immunofluorescence (dilutions)

Gamma : gammaglobulin fraction in g/dl.

IgM content in mg/dl.

Spleen size in cm maximal diameter.

Body height in cm.

Clinical Picture

This syndrome may be relatively asymptomatic (Hewlet, 1987), but pallor, weight loss, asthenia, diminished performance in sports, dyspnoea on exertion, pain and heaviness in the left subcostal region can occur, as can short episodes of fever.

Pale conjunctivae and tachycardia signal anaemia. Splenomegaly is always found on physical examination and can be confirmed by ultrasound but no typical changes in the spleen or in the liver will be seen.

A thick film will generally not reveal plasmodium parasites. Serum antibodies to P. falciparum (indirect immunofluorescence, IFAT, where available) will be extremely high. Cross immunity to P. vivax, P. ovale and P. malariae is also common.

A low haemoglobin level, leucocyte count (with normal formula) and thrombocyte count reflect hypersplenism. A low serum haptoglobin level, a high reticulocyte count and serum lactic dehydrogenase level are signs of haemolysis. The sedimentation rate, the serum gammaglobulin fraction and the serum IgM content reflect a wild antibody response (Stiem 1966). The osmotic resistance of erythrocytes gives a normal curve.

Cold agglutinins can cause quick agglutination when taking a blood slide (this phenomenon has nothing to do with coagulation). In some cases, a rapid “sedimentation”, within a few minutes, can be observed in blood collecting tubes. Again, this is agglutination, not sedimentation.

One of the criteria for diagnosis is the evolution of spleen size and laboratory parameters with treatment. Reduction in spleen size can be very slow (Fakunle 1981, Hewlett 1987).

Liver biopsy can show hepatic sinusoidal lymphocytosis. Given its intrinsic morbidity, it should not be performed routinely. In most cases, one can obtain enough clinical evidence for HMS by ruling out other causes of splenomegaly and observing the improvement of the clinical condition during antimalaria treatment. Moreover, although hepatic sinusoidal lymphocytosis is often referred to as a pathognomonic sign, it is also seen in Felty's syndrome, non-tropical idiopathic splenomegaly or Dacie's syndrome, and some rare cases of chronic lymphocytic leukaemia (Crane 86).

Subacute Malaria

Introduction

Between acute malaria and HMS we find an array of ill-defined syndromes of subacute malaria. When a first infection is not adequately treated, partial immunity may develop, and a certain morbidity may follow. An overwhelming infection in a semi-immune patient, where the delicate balance between immunity and parasite is ruptured, can have the same consequences. This is certainly the case in a lot of children in endemic countries, who will develop an increasing anaemia, even without bouts of fever. (Greenwood, 1987) The same is the case in pregnant women, who are particularly vulnerable to subacute disease, with repercussions for the foetus.

In adults in endemic countries, the balance clearly favours immunity, they will develop malaria attacks from time to time but subacute morbidity is rare. For migrants and expatriates, the situation is different, and can be compared with the situation of children in endemic countries. For the clinical picture in children and pregnant women we refer to chapter ## (malaria in children and pregnant women).

In recent years subacute malaria has become also more frequent in travellers and residents after return from malarious countries. The emergence of chloroquine-resistant P.falciparum strains, and the partial suppression of the infection by ineffective prophylaxis or treatment have been blamed for this increase (Charmot, 1988; Sansonetti, 1986; Van Gompel 1991; Wetsteyn, 1995). However, prophylaxis use or inadequate treatment are not absolute prerequisites (Van den Ende, unpublished data).

There are no strict criteria which can delineate subacute malaria from HMS, except for spleen size. Patients with subacute malaria develop high plasmodium antibody titres and high serum IgM levels; some will develop frank HMS, but some other patients fulfil all major criteria for HMS, except for the splenomegaly.

The overall impact of subacute malaria on general health in endemic regions is not well known, and will be discussed in chapter ## (diagnosis of malaria disease).

Case Report

A 62-year-old Belgian missionary, living in Zaire since 1957, had a medical check-up in 1984, without complaints. An anti-P.falciparum IFAT titer of $> 1/640$ was detected. Malaria prophylaxis was proposed, but not taken. In 1986 he presented with diarrhoea, vomiting and weight loss of 8 kg. A thorough work-up could not elicit an aetiology for the diarrhoea. Sedimentation rate was 81 mm after 1h, in the thick film rare trophozoites of P. falciparum were reported, malaria antibodies again

were higher than 1/640 and serum IgM content was 1295 mg/dl. Malaria was treated. The patient spent six months in Belgium, and the sedimentation rate dropped to 21 mm/1h.

In Zaire he again neglected to take malaria prophylaxis. He returned to Belgium in 1989 with diarrhoea, fatigue and weight loss. Physical examination was negative. The thick film was negative, the sedimentation rate was 63 mm after 1h, the malaria antibodies 1/5120, and the serum IgM 1720 mg/dl. Antinuclear antibodies were 1/80. Circulating immune complexes were detected. Maximum sonographically measured diameter of the spleen was 15 Cm. Again, no cause for the diarrhoea was detected. After an initial treatment with quinine and doxycycline, mefloquine (1500 mg in one day) was added because laboratory parameters did not improve. After two months, all symptoms had disappeared, including the diarrhoea. The sedimentation rate had dropped to 35 mm/1h and the IgM to 910 mg/dl. Prophylaxis with chloroquine 300 mg once a week, and proguanil, 200 mg/day was prescribed.

This time, prophylaxis was taken regularly, but in 1992 diarrhoea and weight-loss occurred again. Physical examination was negative. Haemoglobin was 11.8 mg/dl and the sedimentation rate 102 mm/1h; a thick film showed 4 trophozoites of P. falciparum per 100 microscopic fields (10x100), malarial antibodies ranked as high as 1/10240, IgM was 2680 mg/dl. Anticytoplasmatic antibodies were 1/5000 in a speckled pattern. The spleen was not enlarged sonographically. A one day treatment of halofantrine (1500 mg) was prescribed. The patient remained in Belgium. After six months he was symptom free, the sedimentation rate was 38 mm/1h, the haptoglobin 112 mg/dl, the anticytoplasmatic antibodies 1/640, the malarial antibodies 1/10240 and the IgM 925 mg/dl.
clinical picture

In expatriates and migrants, episodes of fever, nightsweats, pallor, weight loss, asthenia, dyspnea on exertion, pain and heaviness in the left subcostal region have been reported. On physical examination pale conjunctivae and splenomegaly can be found. In a minority of cases repeated thick films can confirm the diagnosis, even in the absence of fever. Serum antibodies to P. falciparum are high.

A low haemoglobin level, leucocyte count (with normal formula) and thrombocyte count are generally present. A low serum haptoglobin level, a high reticulocyte count and a high serum lactic dehydrogenase and bilirubin level show haemolysis. The sedimentation rate, the serum gammaglobulin fraction and the serum IgM content are elevated. Cholesterol and HDL-cholesterol are low. (Cuisinier-Raynal, 1990) As in HMS, cold agglutinins may be present.

Black Water Fever (BWF)

Introduction

Numerous definitions or descriptions of BWF and its cause have been proposed and discussed by various authors. (James, 1922; Findlay, 1949; Ross, 1962; Bruce-Chwatt, 1980; Knochel, 1993) There are widespread descriptions of cases with fever, jaundice and haemoglobinuria or passing black urine throughout history of medicine, dating as far back as Hippocrates. Case reporting started mainly around 1820; by 1850 cases were reported from almost all continents. BWF has been related to P. falciparum infections since 1920. (Plehn, 1920) BWF has even been recorded in induced plasmodium infections for the treatment of syphilitics. (James, 1922) It is likely that many cases of BWF in the past were caused by other diseases or conditions, such as glucose-6-phosphate dehydrogenase deficiency (G-6-PD) or leptospirosis.

BWF is apparently triggered by antimalarials. The possible etiologic role of quinine was recognised in 1937. (Stephens 1937) It is not clear if the haemolysis is purely drug-induced, or if there is another physiopathological link with antimalarials. Until now, the exact pathogenic role of the parasite and the antimalarial drugs has not been clarified. In BWF the direct Coombs test is negative, whereas in a classical drug-induced haemolysis the Coombs test is unequivocally positive. (Dacie, 1991)

Recently mefloquine and halofantrine have been added as possible triggers, although a classical drug-induced haemolysis was not excluded in these cases. (Danis, 1993; Vachon, 1992; Mojon, 1994) The triggering by mefloquine and halofantrine may not be so surprising since the three amino-alcohols have rather similar structures (see figure ##, chapter ## by Wensdorfer, pp ##), and cross-resistance has been shown in vitro between amino-alcohols. (Peel, 1994) Recently two cases of successive BWF syndromes have been described, where the first attack was triggered by quinine, the second by halofantrine. (Van den Ende, unpublished data)

The absence of BWF from the literature for decades is interesting. There are two possible explanations :

after the world war II the campaign for the global eradication of malaria resulted in a temporary and relative control of malaria endemicity. The decreased efforts for malaria control in many areas of the world, the resistance of mosquitoes to DDT, and of the parasite to chloroquine, provoked a world-wide revival of malaria. Perhaps we see more BWF because we see more malaria.

I

in that period quinine was restricted to seriously ill patients. The widespread advent of chloroquine resistance made treatment with quinine or newer antimalarials such as mefloquine and halofantrine more popular, also as presumptive treatment for minor symptoms.

Case Report

A 64-year-old Belgian catholic sister, working in Mali, did not take any prophylactic medication for malaria, but for two years she treated bouts of fever or fatigue with small doses of quinine, aware of parasite resistance to chloroquine.

On the second of October 1990 she complained of vomiting, fatigue and anorexia. Quinine was started at a rate of 2 x 500 mg/day. The third of October she reported red urine, fever up to 38.5°C and an incipient jaundice. The following day there was frank jaundice, fever, nausea and dark urine. A thick film showed very rare trophozoites of P. malariae (diagnosis in Mali, blood smear not available for confirmation). Laboratory abnormalities included : haemoglobin 6.2 g/dl, sedimentation rate 145 mm after one hour, urea 83.4 mg/dl, serum creatinine 0.64 mg/dl, alkaline phosphatase 95 U/l (nl 21-92), conjugated bilirubine 3.19 mg/dl, non-conjugated bilirubin 5.6 mg/dl, ALT (alanine amino transferase) 125 U/ml (nl < 40), AST (aspartate amino transferase) 145 U/l (nl < 45). Intravenous liquids, 4 x 500 mg quinine IM and 3 x 300 mg chloroquine orally were administered before repatriation.

On the 6th of October, the patient arrived at the Antwerp University Hospital. She was very pale, and dyspneic with the slightest exertion. The temperature was 38° C, auscultation revealed a few faint crackles, the liver extended 2 cm under the costal margin, the spleen was not felt.

Key laboratory tests: Haemoglobin 4.9 g/dl, lactate dehydrogenase 2040, total bilirubin 3.5, AST and ALT normal, haemoglobinuria (27 mg/l), elevated urea (113 mg/dl) and creatinine (1.8 mg/dl). A thick film for malaria was negative, cultures of blood and urine remained sterile.

Further work-up for haemolysis : cold agglutinins anti-I : 1/32 at 4°C, osmotic resistance slightly lowered; HAM test, polyvalent RAGT test, sucroselyse and Donath-Landsteiner negative. Vitamin B 12, folic acid and glucose-6-phosphate dehydrogenase were within normal range.

Serology: hepatitis B surface antigen negative, hepatitis A IgM antibodies negative, Mycoplasma pneumoniae antibodies 1/100, HIV antibodies negative, antibodies for P. falciparum 1/10240 in indirect immunofluorescence (IFAT). A chest X-ray was normal. An abdominal ultrasound showed hepatosplenomegaly, thickening of the gallbladder wall, and a few small lymph nodes in the porta hepatis. An echocardiographic examination showed some thickening of the aortic valve without vegetations.

Four units of packed cells, halofantrine (3x500 mg/12 h, once) and subcutaneous heparin as thrombosis prevention were administered. One month later, she was symptom free. Haemoglobin was 12 mg/dl, and the sedimentation rate was 110 mm/h. Two months later the sedimentation rate had dropped to 68 mm/1h, and the IFAT to 1/5120. She returned to Africa with 300 mg of chloroquine a week and 200 mg of proguanil a day as malaria prophylaxis.

Clinical Picture (Table 4)

A diagnosis of BWF should be considered in a person living in a malarious area if there is haemoglobinuria, a dramatic fall in haemoglobin, and a thick film showing no or very few parasites.

In most cases it is possible to trace a history of successive malarial attacks, often inadequately treated. (Maegraith, 1948) In most cases, BWF follows the intake of quinine, mefloquine or halofantrine. Massive haemolysis in one or several waves is common: several million RBC /mm³ can be destroyed in 24 hrs. The urine is often red at first and afterwards dark-brown. Blood urea nitrogen is elevated, overt renal failure can be present. Sometimes a polyuric phase follows recovery from anuria. Acute epigastric discomfort, nausea and vomiting can be present. Jaundice was present in 33 of 46 (71%) fatal cases of BWF in the British West African Colonies in the period 1941-43. (Findlay, 1949) Liver function abnormalities appear early in many cases. Vascular collapse is possible, followed by death in 20 to 30 % of patients. (Bruce-Chwatt, 1980) Methaemalbuminemia is frequent and representative of the severity of the haemolysis. (Dacie, 1991; Tietz, 1990)

Blackwater fever should be distinguished from very severe malaria with hyperparasitaemia, where massive haemolysis, liver and renal failure contribute to jaundice. Other causes of intravascular haemolysis must be excluded.

TABLE 4 : SYMPTOMS AND SIGNS OF BWF

Key features

exposure to malaria
massive haemolysis
haemoglobinuria
no or scanty parasites on thick film

Additional characteristics

history of successive malarial attacks, often inadequately treated.

intake of quinine, mefloquine or halofantrine
epigastric discomfort, nausea and vomiting
jaundice
elevated blood urea nitrogen, renal failure
polyuric phase during recovery
liver function disturbances
vascular collapse
glomerulonephritis

Transient albuminuria is possible in both complicated and uncomplicated P. falciparum malaria. In rare cases a frank glomerulonephritis may develop. Plasmodial antigen and antiplasmodial antibodies in glomerular deposits can be demonstrated. (Sinniah, 1988; van Velthuysen, 1996)

Albuminuria, the presence of casts in urine, and a nephrotic syndrome with oedema of the face and ankles and ascites are the main clinical features. Hypertension is absent. In contrast with P. malariae renal involvement, this picture never evolves towards chronic glomerulonephritis and renal failure. Treatment with antimalarials alone is 100% effective.

Spontaneous Splenic Rupture

Introduction

This complication is not confined to P. falciparum alone: it has also been reported in infections with other types of malaria. Rupture can happen during the early or late phase. The enlarged spleen is very vulnerable, and the slightest abdominal trauma or shock can be sufficient for rupture. It is a real pitfall for clinicians, as it can happen outside fever attacks, and without trauma.

Case Report

On one of my (JVdE) supervision tours in Zaire in 1984, I was called to a 24-year-old woman, who was 7 months pregnant. Pregnancy was well supervised, and no abnormal finding had been reported. A weekly malaria prophylaxis with 300 mg of chloroquine had been administered. She presented with diaphoresis and abdominal pain. There was no vaginal bleeding or discharge. There was no history of trauma. Physical examination revealed a blood pressure of 70/40, a heart rate of 110/min, a negative abdominal palpation, a uterus height corresponding to 7 months, and a negative vaginal exploration. Ultrasound was not available and emergency evacuation was impossible given the distance and the extremely bad roads. Facing a dramatic clinical situation, we decided to operate at the health centre. On opening we discovered a large amount of free blood in the abdominal cavity, and with further exploration we found a transversely ruptured spleen. A splenectomy was unavoidable. Foetal heart sounds were normal at the end of the operation, so no cesarean section was carried out. At dawn however, the patient had a still-birth. Pneumococcal vaccine was not available, but the patient was put on life-long malaria prophylaxis.

Clinical Picture

Abdominal pain, hypotension and transpiration may be the only symptoms. Abdominal guarding is not always present, and the ruptured spleen can be missed on palpation. In the first hours, laboratory tests are useless, since haemoglobin levels are not yet adjusted by haemodilution. Abdominal ultrasound or abdominal puncture can confirm the diagnosis of this complication, but in field conditions only an exploratory laparotomy can reveal the true diagnosis.

Vivax Malaria

Introduction

Vivax malaria clinical presentation is different from *P. falciparum* infections in several respects. Its incubation time is longer, relapses from hepatic hypnozoites are frequent, tertian fever pattern is frequent, strain type influences clinical findings, and it never leads to very severe malaria.

The WHO defined three strain types: type I has a short incubation, and frequent relapses; type II has the same short incubation and few relapses; type III has a long incubation time and few relapses.

*Case Report*⁵

In October 1992, a 24 year-old Belgian woman travelled to Calcutta, India. She meticulously took chloroquine 300 mg once a week as malaria prophylaxis. Two weeks after arrival in India she developed fever. Without parasitological diagnosis, chloroquine was given, and the fever disappeared. After she returned to Belgium in December 1992, she experienced several minor episodes of fever which remained untreated. In June 1993 she developed high fever and chills every second day. A thick smear showed *P. vivax* (1 parasite/high power field 10x100). Blood cell counts and biochemical parameters were normal. Chloroquine was given for 3 days (900-300-300 mg), followed by primaquine 15 mg/d for 14 days. The glucose-6-phosphate dehydrogenase level was 2.1 U/ml (normal 1-2.1).

In August 1993 she again developed high fever. Smears were again positive for *P. vivax* (5 parasites/microscopic field 10x100 : 72% trophozoites , 28% gametocytes). With chloroquine (900-300-300 mg) the fever disappeared on the fourth day. General malaise and night sweats persisted. Eight days after initiating treatment, the fever returned and a thick smear showed the same parasitemia for *P. vivax* (5 parasites/high power field, 93% trophozoites). Oral quinesulphate (3x500 mg/d) was given initially, but was substituted by intravenous quininehydrochloride (3x500 mg/d for 5 days), since the fever did not drop after 48 hours. The quinine was combined with oral doxycycline 200 mg the first day and 100 mg/d for one week. The fever disappeared and the thick smear became negative. She returned home with primaquine, 22,5 mg/d for 15 days.

On the 12th day of primaquine treatment, the fever reappeared. Again smears were positive for *P. vivax* (4 parasites/high power field). Treatment with oral quinine sulphate and doxycycline was repeated. Since higher doses of primaquine often provoke serious side-effects (5), the patient favoured a prophylactic regimen of mefloquine 250 mg/week. No further relapses occurred.

Clinical Picture

The incubation time is longer than for *P. falciparum* infection, and depends on the strains: currently 12 to 20 days, for some strains it may be 6 to 9 months. During the first days of disease, as in *P. falciparum* infection, fever will follow an irregular pattern, almost every day. There is nothing to differentiate a *P. falciparum* early infection from a *P. vivax* infection: fever, chills, perspiration, headache, arthralgia, myalgia, nightsweats, prostration, pain in the left subcostal region, dark coloured urine, labial herpes, can all be present. Gastrointestinal symptoms complete the picture. In children there may be febrile convulsions. Without treatment, fever disappears after some to several irregular attacks. This does not mean that the infection has disappeared, since hypnozoites may survive in the liver, and cause relapses.

⁵Already published elsewhere. (Van den Abbeele, 1995)

Splenomegaly is the only physical sign. Clinically detectable pallor and jaundice are rare, and are seen in the evolution towards the more subacute form, which is seen in immunocompromised people or during pregnancy.

In *P. vivax* infection, relapses cause fever every two days (“benign tertian fever”) (fig 4). The periodic pattern is seen only when the patient is infected by one strain; when infected by two strains, a “double tertian fever” may result, with a fever spike every day. In relapses “typical malaria attacks” are the rule: chills followed by high fever, resolving within a few hours with heavy sweating and a feeling of relative euphoria. Intervals between relapses depend on the strain. Chloroquin treatment has a rapid effect on the symptoms, but has no effect on future relapses.

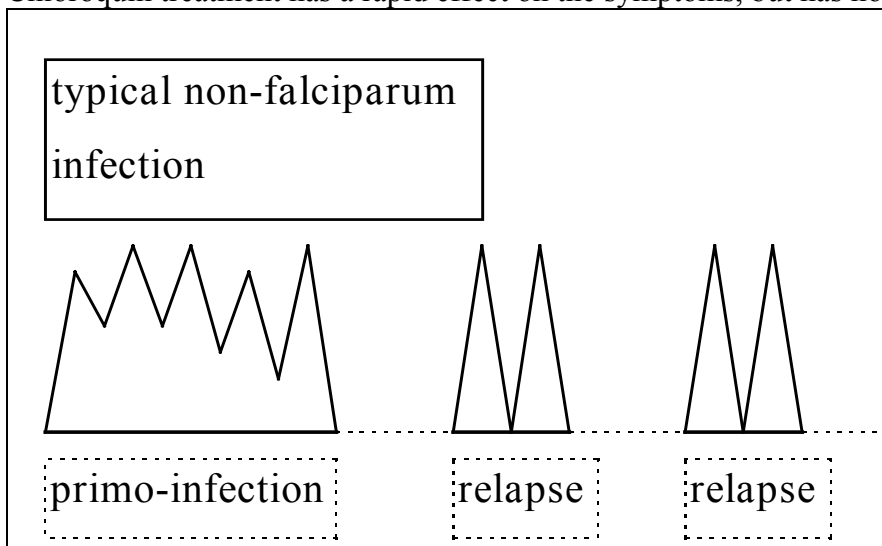


Figure 4.: in non falciparum infection, fever is irregular during the primo-infection. During relapses, which emerge from the liver for vivax and ovale infection, and from the blood in malariae infection, the fever will follow a certain periodicity: tertian with vivax and ovale, quartan with malariae.

In heavily infected patients, or where there is immunodepression as during pregnancy or malnutrition, a severe subacute form can follow the early phase.⁶ Slight fever with irregular bouts of high fever, prostration, weight loss, hepatosplenomegaly and anaemia may develop. As in subacute *P. falciparum* infections, leucopenia, thrombopenia, and high serum IgM levels can be found. Diagnosis can be difficult, as parasites are not continuously present.

P. Ovale Malaria

Clinical Picture

P. ovale takes the place of *P. vivax* in regions in Africa where the Duffy blood group is absent. Clinically, *P. ovale* infections are very similar to *P. vivax* infection. The incubation can be relatively long, the early phase is frequently absent or unrecognised. Diagnosis may be difficult, since parasitaemia may be very low for an impressive clinical picture, with shaking chills, high fever and prostration. Relapses present almost invariably as tertian fever and this may be an aid to diagnosis, together with haemolysis, thrombocytopenia and splenomegaly, in the absence of a positive thick film.

⁶The French literature calls this subacute form “paludisme viscéral évolutif”.

Case Report

I (JVdE) happen to know P. ovale infection rather well, since I have had the disease myself. One year after leaving Zaire in 1985, I started having chills on a Monday night. Fever rose to 40°C. I made a few thick films, took some aspirin and went to bed where I started sweating heavily a few hours later. The next day, our specialised laboratory could not find any parasites in the thick films. On Wednesday night I had again shaking chills, which were a lot more severe. Fever rose to 40.5 °C. Again I made thick films, quite sure that this was malaria. I took some aspirin, and sweating occurred a few hours later. The next morning, the same result came from the laboratory. I looked at the thick films myself, but was not able to find the slightest suspicion of a parasite. On Friday night, during a meeting at our institute, I started shaking again. Certain that it was malaria, given the undeniable periodicity, I took chloroquin after having taken several thick films. I had a terrible night with high fever, headache, myalgia and a kind of delirium. In the morning, the laboratory at first reported the thick films as negative but a concerted effort by two technicians and the chief parasitologist resulted in just one trophozoite after one hour of searching !

P. Malariae Malaria

Classical Presentation

If we do not take the renal complications into account, this is the least aggressive of all malaria species. However, the discussion about the anatomical origin of relapses, and the extreme life expectancy of this parasite make it the most enigmatic of all species.

Incubation is usually three weeks, and the early phase is generally very mild, without chills. Only fever and general malaise are reported. Anaemia is very uncommon.

The relapses are distinguishable from P. vivax or P. ovale in just one respect: in typical cases fever spikes are separated by two days, giving the quartan fever. Without treatment relapses die out after a few attacks, but can come back after years (up to 52 years after exposure!).

Renal Involvement

Mostly in children, a glomerulonephritis can develop. Proof of a relationship between P. malariae and this membranoproliferative state comes from a geographic congruence, and from the demonstration of plasmodial antigen and antiplasmodial antibodies in glomerular deposits.

Albuminuria, the presence of casts in urine, and sometimes an overt nephrotic syndrome with oedema of face and ankles and ascites are clinical symptoms of the acute phase. This acute picture often evolves towards chronic glomerulonephritis and renal failure. Treatment with antimalarials is not effective in the affected individual, but malaria eradication campaigns were able to make this disease disappear in the past.

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Legend of figures (photographs):

figure 2 : ARDS as a feature of severe malaria in a patient presenting with pulmonary oedema, cough, dyspnea, polypnea and cyanosis.

figure 3: diffuse intravascular coagulation leading to vascular occlusion and necrosis of toes.