AN ETIOLOGIC STUDY OF HEMOGLOBINURIA AND BLACKWATER FEVER IN THE KIVU MOUNTAINS, ZAIRE

by

C. DELACOLLETTE¹, H. TAELMAN² & M. WERY²

¹ Lutte contre les Maladies Transmissibles et Carentielles, BP. 337, Bujumbura, Burundi
² Institute of Tropical Medicine, Nationalestraat 155, B-2000 Antwerpen 1, Belgium

Summary – Between January 1985 and March 1986, in the high altitude area of Kivu, Eastern Zaïre, 38 patients presenting with hemoglobinuria as main manifestation were investigated. Profound glucose-6-phosphate dehydrogenase deficiency was detected in 4 patients, leptospirosis in 2 and Hantaan virus infection in 2. Hemolysis was doubtful (haemoglobin > 40 mg/dl, Hemoglobin > 12 g/dl) in 2 patients. Other potential causes of hemoglobinuria such as hemoglobinopathy, toxic agents, infectious diseases or blood transfusion incompatibility were carefully screened and excluded.

The syndrome observed in the remaining 28 cases was strongly suggestive of blackwater fever (BWF) as described in malaria patients by several authors under the French name "fièvre bilieuse hémoglobinurique". Quinine was used as curative treatment of malaria before admission in a significant greater proportion (p < 0.01) of patients with BWF compared to patients with uncomplicated malaria, suggesting that this drug might have played a triggering role in the genesis of BWF. However, quinine was usually administered at inadequate doses to malaria patients non responding to chloroquine and belonging to a population of whom 50% are non immune. It may thus also be hypothesized that BWF in our patients could result from a hyperparasiticemic state that remained undetected because of an unusual synchronous lysis of infected erythrocytes. In the latter case BWF would correspond to a major complication of falciparum malaria only coincidentally related to the use of quinine.

KEYWORDS: Hemoglobinuria; Blackwater Fever; Etiology; Quinine; Malaria; Zaïre

Introduction

Blackwater fever (BWF) also called malarial hemoglobinuria or "fièvre bilieuse hémoglobinurique" (FBH) by the French authors, is classically defined as a condition combining severe intravascular hemolysis, anemia, jaundice, hemoglobinuria and renal failure, and associated with Plasmodium falciparum (Pf) malaria but with scanty or often without parasitemia (4, 5, 12, 26, 31). It was rather frequently observed in the past in non-immune individuals, mostly caucasians, who had been residing for some time in malaria endemic areas and with a history of irregular intake of quinine as chemoprophylactic drug and inadequate treatment of attacks of Pf malaria. It has been hypothesized that the hyperhemolytic process characterizing BWF may be an immune-mediated response to erythrocytes altered by quinine or the parasite, or both, and accounting thus for the low or even the absence of parasitemia (26, 31).

For most of the authors before the forties, BWF was thus a well-defined condition, a disease related to Pf malaria and use of quinine. An indirect evidence for the involvement of quinine was the virtual disappearance of BWF since the use of synthetic antimalariais in the chemoprophylaxis and treatment of malaria (17, 34).
Malaria associated hemoglobinuria may also result from Pf hyperparasitemia and to the use of some antimalarial drugs in glucose-6-phosphate dehydrogenase (G-6-PD) deficient patients (22).

Other causes of acute hemolysis and hemoglobinuria in the tropics include incompatible blood transfusion, hemoglobinopathies, snake and spider-bite envenoming, septicemias, especially typhoid fever (30), the hemolytic-uremic syndrome (33) or the use of some traditional medicines (2).

Hemoglobinuria must also be differentiated from hematuria particularly when this is associated with liver and renal failure such as in leptospirosis, yellow fever, Hanta virus infection and other viral hemorrhagic fevers.

During the study period (1/1/85-31/3/86), an increasing number of autochthonous patients with hemoglobinuria have been diagnosed at the reference hospital of Katana, Kivu region, eastern Zaïre: 2 cases in 1982, 11 cases in 83, 13 cases in 84 and 65 cases during the study period (19). In spite of the fact that isolated cases were observed in the late fifties and early sixties, the present observations are surprising because BWF had no more been officially reported for the last five decades. Remarkable was the coincidence of this sudden upsurge of hemoglobinuria cases with the emergence of Pf chloroquine-resistance and the increased use of quinine (7, 8, 41, 42). The issue to be addressed was thus: "is there indeed a comeback of the genuine BWF as seen by the clinicians before the forties?" Consequently we decided to investigate closely each new patient with hemoglobinuria at the Katana hospital.

**Background**

The general hospital of Katana (reference level) with a covered population of 210,000 inhabitants is situated on the shores of lake Kivu in Zaïre at an altitude of 1,500 meters. In Katana, the average annual temperature is 24° centigrade. The dry season extends from June to September and the rainy season from October to May. Malaria transmission occurs the whole year round resulting in a mesoenzootic prevalence. The peak incidence of clinical cases is observed at the end of the rainy season and the beginning of the dry season.

In the 0-9 years age group, the prevalence may vary from 15 to 55 percent in different villages of the same altitude range (± 1500 meters). As may be expected, the prevalence decreases at higher altitudes: at 1750 meters, a village showed a parasite index of only 7 percent. Seroepidemiological studies using a homologous Pf antigen in immunofluorescence, have shown that the geometrical mean titer increases slowly with age, and that in adults only about 50 percent of the individuals have detectable antibodies (9). This situation probably results from a state of unstable malaria transmission.

Furthermore, since 1982 we have observed in the Kivu region a marked decrease of Pf sensitivity to chloroquine (7, 8, 41, 42). As a result of chloroquine resistance, quinine produced locally and easily available was increasingly used, often inadequately, by the population. Self treatment with quinine is rarely sufficient in both daily dose and total duration e.g. because of side effects.
Patients and methods

From January 1, 1985 until March 31, 1986, each new patient admitted to Katana Hospital with black or red urine was screened for hemoglobinuria (Multistix Ames) and when found positive, in the absence of erythrocytes in the urine sediment, was enrolled in the study. Out of 8600 admissions, 65 cases (42 men, 16 women, 7 children < 14 years) could be considered for an etiologic work up and investigation of potential BWF. Due to the separate organization of the different units of the hospital, only men older than 14 years old could be completely investigated, representing 42 cases with hemoglobinuria. Each patient or his family, was interviewed on his origin and tribe, the experience of previous hemolytic crisis by himself or a member of his family, sickle cell trait (which normally does not exist in this area of the Kivu region), drug allergy, recent transfusion, recent infections, splenectomy, intake of drugs (drug regimen) during the past few hours or days. Each patient had an extended clinical examination with particular consideration of fever, jaundice, conjunctival pallor, lumbar myalgia, arthralgia, headache, clonus, delirium or coma, heart disturbances, digestive signs and urinary symptoms. Signs of bleeding, focal or generalized lymph node enlargement, splenomegaly and/or hepatomegaly, were also given special attention. All the patients were admitted to – and followed in the Intensive care Unit of Katana Hospital.

Laboratory investigations included microscopic examination of thick blood films, determination of hemoglobin level, red blood cell, leucocyte and thrombocyte counts, blood group, Emmel test, hemoglobin electrophoresis, indirect and direct Coombs tests, determination of conjugated and unconjugated bilirubin, ALAT, alkaline phosphatase, urea and creatinine levels in serum, screening for albumin, glucose, bilirubin and urobilinogen in urine, examination of urine sediment.

A qualitative test to detect G-6-PD deficiency (Sigma Diagnostics) was carried out systematically on days 1 and 10 after admission in the hospital on the patients who were found to be very anemic. Blood samples for aerobic cultures (Trypticase soy agar) and serum for VDRL test (Biomerieux, France) were taken on the first day. Haptoglobin level was determined by immunodiffusion, using Nor-Portigen Haptoglobin plates (Behringwerke code OSLL 03). Free hemoglobin level was determined using the peroxidase method (6). Serum was also sampled on days 1 and 10 for serological tests. Indirect immuno-fluorescence was used to titrate antibodies against Pf (antigen from cultivated african isolate) (11) and Hanta virus (antigen CG 13891 isolated in Belgium from a belgian patient) (24). ELISA test was used to titrate antibodies against Leptospira (heat resistant group antigen from Institut Pasteur Nr 79623) (27). Serological tests, determination of haptoglobin and free hemoglobin levels were performed at the Institute of Tropical Medicine in Antwerpen, Belgium.

Results

Of 42 patients with hemoglobinuria, 38 were thoroughly investigated. Profound G-6-PD deficiency was found in 4 patients (10,5%), serological evidence for leptospirosis was detected in 2 (5%), and to Hanta virus infection in 2 (5%). Acute hemolysis could not be demonstrated in 2 cases (5%) in whom haptoglobin level was higher than 40 mg/dl and free hemoglobin level was
lower than 10 mg/dL. None of these 10 patients died. Among the 28 remaining
cases belonging for 90% to the Shi tribe, 5 (18%) had a parasitemia between
2000 and 12000/μL and the other 23 patients (82%) had less than 2000 Para-
rasites/μL or no patent parasitemia.

### TABLE 1
Observations and laboratory data in 4 patients with G-6-PD deficiency and hemoglobinuria

<table>
<thead>
<tr>
<th>DRUG TAKEN</th>
<th>PATIENT 1</th>
<th>PATIENT 2</th>
<th>PATIENT 3</th>
<th>PATIENT 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSOCIATED INFECTION</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HEMOGLOBINURIA</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>ALBUMINURIA</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>UROBILIRUBINURIA</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HB (G/DL)</td>
<td>3,0</td>
<td>4,0</td>
<td>5,5</td>
<td>9,5</td>
</tr>
<tr>
<td>HAPTOGLOBIN</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PARASITEMIA /μL</td>
<td>600</td>
<td>neg</td>
<td>5200</td>
<td>9200</td>
</tr>
<tr>
<td>IFAT TITER</td>
<td>1/80</td>
<td>N.D.</td>
<td>N.D.</td>
<td>1/640</td>
</tr>
<tr>
<td>DIR. COOMBS TEST</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>IND. COOMBS TEST</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>RENAL FAILURE</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

N.D.: not determined

Of the four patients showing G-6-PD deficiency (table 1) one had a history
of a previous episode of black urine and another mentioned a similar episode
in one member of the family. Three of these four patients had taken quinine
before hemolysis occurred. G-6-PD deficiency is well known to be associated
with hemolysis in patients who have taken oxydant drugs or with an infectious
disease (22, 43). Oxidant drug intake (phenacetine) was recorded in only one
case. Since no other infection was diagnosed in the three other patients, it is
not certain whether G-6-PD played any role in the onset of hemolysis and
hemoglobinuria in these patients. Pf was found in the peripheral blood of
3 patients and anti-Pf antibodies were detected in the 2 screened.

Two of the patients with hemoglobinuria had antibody titers of respectively
1/640 and 1/20 to Leptospira mitis, indicating a previous exposure to this micro-
organism. The latter showed a fourfold increase of antibody titer detected on the
second sample collected 10 days later. Two other patients had an antibody titer
of 1/640 to Hanta virus, showing a recent infection with this virus.

All four patients had received quinine and had a thick blood film negative for
Pf. One patient had hepatomegaly. Anemia was found in one case, jaundice in
two and renal failure in three. The Coombs test was negative in the four patients.

Among the remaining 28 patients, quinine alone was taken by 17 (61%) be-
fore the onset of the hemolytic process, chloroquine alone was taken by 5 (18%),
chloroquine and quinine combined were taken by 4 (14%) and the remaining
2 (7%) mentioned no drugs or various drugs either taken alone or in combina-
tion: acetyl salicylic acid, phenacetin, paracetamol, nalidixic acid (fig. 1).
Figure 1 also gives the distribution of antimalarial drugs taken by 980 adults (> 14 years) to treat uncomplicated malaria attack in the area of Katana during the study period. These data were obtained during a malaria morbidity/mortality survey from 1985 to 1987 in the area (10). Quinine is more often used by adults than by children, although the difference is not significative. There is no difference between men and women in that respect.

![Figure 1: Drugs taken by malaria patients](chart)

Considering that chloroquine and quinine were used to treat respectively 50 and 10-20% of the non complicated cases of malaria in Katana (10) it is remarkable that more than 60 percent for whom no specific etiological factor for hemoglobinuria had been found had taken quinine.

![Figure 2: Clinical history of 28 patients with presumptive BWF](chart)

Statistical analysis shows that quinine was significantly more used by patients with BWF (p < 0.01) compared with those without BWF and suggests that quinine may act as a triggering factor of BWF. Details of the medical history are given in fig. 2. Of notice are the occurrence of a recent febrile illness in 35% of the patients, a history of reddish urine in the family in 10% and the absence of sicklelania.
Details on the clinical presentation and laboratory findings are given in fig. 3, 4 and in table 2.

The clinical symptoms and signs were similar to those observed in other febrile illnesses. Parasites (< 12000/µl) were found in the blood of 10 patients (37%). Hemoglobin was found to be less than 10 g/dl in all patients. White blood cells counts higher than 8000/µl were found in 15 (53%). Platelet counts higher than 100000/µl were found in all patients. S hemoglobinopathy was not found. Direct and indirect Coombs tests were positive in 29% and 33% of the patients respectively. Blood cultures were all negative.
TABLE 2
Laboratory findings inpatients with presumptive BWF

<table>
<thead>
<tr>
<th></th>
<th>MEAN</th>
<th>S</th>
<th>EXTREME VALUES</th>
<th>NORMAL VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAEMOGLOBIN</td>
<td>8.14</td>
<td>2.77</td>
<td>3.5-10</td>
<td>13-15 g/dl</td>
</tr>
<tr>
<td>HAEMATOCRIT</td>
<td>24.07</td>
<td>7.95</td>
<td>10-37</td>
<td>40-45%</td>
</tr>
<tr>
<td>RED BLOOD CELLS*</td>
<td>2.53</td>
<td>1.04</td>
<td>1.05-4.50</td>
<td>4.5-5/µl</td>
</tr>
<tr>
<td>RETICULOCYTOSES</td>
<td>14.6</td>
<td>19.3</td>
<td>10-83</td>
<td>10-30%</td>
</tr>
<tr>
<td>HAPTOGLOBIN</td>
<td>10</td>
<td>11.1</td>
<td>0-75</td>
<td>40-200 mg/dl</td>
</tr>
<tr>
<td>WHITE BLOOD CELLS</td>
<td>9340</td>
<td>3644</td>
<td>4000-15000</td>
<td>4000-8000/µl</td>
</tr>
<tr>
<td>% EOSINOPHILS</td>
<td>2</td>
<td></td>
<td></td>
<td>0-5</td>
</tr>
<tr>
<td>% NEUTROPHILIA</td>
<td>61</td>
<td>12</td>
<td>37-81</td>
<td>40-70</td>
</tr>
<tr>
<td>% LYMPHOCYTES</td>
<td>37</td>
<td>7</td>
<td>16-56</td>
<td>20-45</td>
</tr>
<tr>
<td>PLATELET NRS**</td>
<td>234</td>
<td>72.7</td>
<td>100-370</td>
<td>200 -400/µl</td>
</tr>
<tr>
<td>DIRECT BILIRUBIN</td>
<td>1.86</td>
<td>2.84</td>
<td>0.2-13.6</td>
<td>&lt;0.6 mg/dl</td>
</tr>
<tr>
<td>INDIRECT BILIRUBIN</td>
<td>1.88</td>
<td>1.72</td>
<td>0.2-7.4</td>
<td>&lt;0.4 mg/dl</td>
</tr>
<tr>
<td>ALAT</td>
<td>61</td>
<td>47.5</td>
<td>20-172</td>
<td>&lt;45 U/ml</td>
</tr>
<tr>
<td>ALKALINE PHOSPH.</td>
<td>43.8</td>
<td>12.06</td>
<td>24-60</td>
<td>&lt;40 U/ml</td>
</tr>
<tr>
<td>UREA</td>
<td>65</td>
<td>40</td>
<td>18-150</td>
<td>&lt;60 mg/dl</td>
</tr>
<tr>
<td>CREATININ</td>
<td>2.19</td>
<td>0.99</td>
<td>1.05-3.90</td>
<td>&lt;1.50 mg/dl</td>
</tr>
<tr>
<td>P. FALCIPARUM IFAT</td>
<td>1/264**</td>
<td>1/260</td>
<td>1/20-1/1260</td>
<td>≤ 1/20 = neg</td>
</tr>
</tbody>
</table>

* n.10^6/µl
** n.10^9/µl
*** Geometric mean titer

Discussion

From January 1, 1985 until March 31, 1986, 38 African patients, mostly of the Shi-tribe, were admitted to the rural hospital of Katana because of hemoglobinuria and thoroughly investigated, particularly for potential BWF. Acute intra-vascular hemolysis was documented in 36 of them. These findings were surprising but confirmed the previous observations of an increasing incidence of cases of hemoglobinuria made between 1982 and 1984 (19).

Four of our patients with hemoglobinuria were G-6-PD deficients. In Africa, the variant commonly associated with hemolysis is GdA- which mostly involves the old erythrocytes and may not be detected when the affected cells have been destroyed by the hemolytic process (22). Therefore the determination was repeated after 10 days.

Gilles and Ikeme were the first to report, in 1960, hemoglobinuria among G-6-PD deficient Nigerians using oxidant drugs, eating fava beans or affected by an infectious disease (22,43). G-6-PD has been found in 4 to 23.5% of healthy Africans (25) and in 13.8% of the individuals of the Shi-tribe (29) predominantly represented in our patients. The 10% G-6-PD deficiency prevalence

57
found in this series is thus consistent with the findings of the previous prevalence studies. The finding of G-6-PD deficiency together with hemolysis does not necessarily imply a causal relationship between the two conditions if a triggering factor is not found. In our G-6-PD deficient patients only one had a history of oxidant drug intake. Quinine was the sole drug taken by the other three patients, but quinine is not known to be hemolytic in G-6-PD deficient (3, 21). In addition, none of the patients had another associated infectious disease except malaria found in 3 of them. It is thus uncertain whether G-6-PD deficiency did account for hemoglobinuria in those patients.

Ten patients (26%) had a positive direct Coomb's test. It has been suggested that the hemolysis of Pf malaria may partly result from the immune destruction of red blood cells (44). Although studies carried out in the Gambia have shown positive direct Coomb's tests in up to 50% of children infected with Pf (14, 15), no correlation was found between a positive direct Coomb's test and anemia by Abdallah and Weatherall (1). Similar studies conducted in Thailand have also concluded to the lack of evidence for an immune hemolysis as the cause of anemia of Pf malaria (28).

Two patients had titers of antibodies to *Leptospira mitis* consistent with an exposure to this microorganism. A fourfold increase of antibody titer in one of them was strongly suggestive of an acute leptospiral infection. A focus of leptospirosis in Eastern Zaire has previously been described by Van Riel (39). This disease must be considered in the presence of hepato-nephritis but dark or red urines leptospirosis are usually related to hematuria rather than hemoglobinuria. However, Van Riel *et al* (38) having observed 5 cases of BWF associated with leptospirosis have suggested that this infection may act as a triggering factor of BWF in patients already infected with Pf. But these observations have not been confirmed subsequently.

Serological evidence for a recent Hantavirus infection was found in two of the patients. Actually this disease had been looked for because of its clinical similarity to leptospirosis. However in Hantavirus infection as in leptospirosis, dark urines invariably result from hematuria. Hemoglobinuria is not expected, and in the present cases may have been coincidental.

Although we cannot exclude leptospirosis and Hantavirus infection to have acted as triggering factors in the onset of hemoglobinuria we have no clear evidence in favor of it. Moreover, high titers of anti-Pf antibodies suggesting an acute infection with Pf were found in 3 of the 4 patients.

Acute hemolysis and hemoglobinuria may also result from an overwhelming Pf infection. Patent parasitemias in our patients never exceeded 12000/μL.

Blood cultures on aerobic media remained negative in all the patients. Although blood cultures on anaerobic media were not performed, clostridial sepsis was highly unlikely in our patients considering that most of the cases of *Clostridium perfringens* hemolysis are related to septic abortions and that the patients were men.

Hemolytic-uremic syndrome as a cause of hemoglobinuria could be eliminated on the basis of lack of signs of consumption coagulopathy. However, coagulation was not investigated in the laboratory.

Hemoglobin electrophoresis was normal in all the screened patients. This finding is consistent with the absence of a sickle cell anemia in Eastern Zaire (23). Hemoglobinopathy as a cause of hemolysis was thus excluded.

No history of spider or snake bite or intake of traditional medicine was recorded in this series.
So, having excluded all the possible causes of hemoglobinuria, the sole
diagnosis that was left for the remaining 28 cases was classical BWF as described by the ancient authors.

Up to the forties, BWF was a well known and a rather frequent syndrome in Africa occurring mostly among Europeans and nearly always associated with malaria and the use of quinine as prophylactic drug. However, although rare, cases of BWF among Africans have been reported previously. In 1933, Van Nitsen (36) in Southern Zaire diagnosed 54 cases of BWF in African adults of whom all, except one, were migrants originating from the highlands of Rwanda or Burundi that had been submitted to quinine prophylaxis because they were considered as non-immune. Similar observations were reported by Van Riel (37) in Eastern Zaire. In addition, Duren (13) in 1937, gathered 105 cases of BWF among the 5 million cases of diseases in Africans reported to the Colonial Medical Services between 1918 and 1934.

Several cases were also reported among young children who had received quinine treatment (16,32,25). But from a critical analysis of these reports it appears that a substantial number of cases reported as BWF were actually cases of hemoglobinuria resulting from a hyperparasitemic Pf malaria.

Hemoglobinopathies and G-6-PD deficiency-induced hemolysis, both conditions yet unknown at that time, might well have played a causal role in the hemolytic process in some of those cases.

Malignant tertian BWF, originally absent in West-Africans, was also observed in 1945 among soldiers of the British West-African troops returning from Asia, suggesting that a loss of immunity against local strains may contribute to the genesis of BWF (17).

It is clear that, in our study, the significantly higher number of patients with BWF treated with quinine when compared to the number of malarial patients without BWF treated with quinine, is in favor of an association between BWF and the use of quinine and seems to incriminate this drug as a risk or causal factor. However, the result of this statistical analysis requires some comments on the intervention of potential misleading factors. Indeed, the decision of malarial patients to use quinine, an expensive drug, instead of chloroquine, a cheap drug, is often the non-therapeutic response to this drug due to the frequent occurrence of RII or RIII type of chloroquine resistance of Pf in the area. Moreover, most of the patients admitted to Katana hospital with BWF had been treated with an inadequate dose of quinine and for too short periods of time. The circumstances which have led to the use of quinine might thus have favoured the progression of Pf infection and consequently selected a proportional greater number of patients with malignant malaria i.e. a selection bias of complicated cases.

There are other more general arguments that plead against quinine as a triggering factor of BWF:

1. antibodies directed against quinine have never been detected in patients with BWF (quoted in 40);

2. among our 28 cases of BWF 25% had not taken quinine.

Another issue to be addressed is the restricted geographical location of BWF. The fact that a substantial proportion of the adult population (±50%) in the area of Katana is non immune against malaria, may explain that people originating from this area are MORE prone to develop complications particularly when there is delay in effective treatment.
An argument commonly used in favor of quinine as a causal factor of BWF is its dramatic decrease and even disappearance when chemoprophylaxis with quinine was abandoned and replaced by mepacrine and proguanil (18, 20).

It is true that in the British Army in Africa, the incidence of BWF fell from 13% in 1942 to 0 in 1945, but, as noted by Bruce-Chwatt (5), at the same time there was also a successful control of malaria through vector control methods. The disappearance of BWF from the statistics may also have resulted from the reporting of BWF as a complication of malaria and not under the specific entity BWF. However, in the Ethiopian campaign of 1935-1936, involving 500,000 Italian troops who all took 600 mg of quinine daily under strict supervision, there were only 23 deaths attributed to malaria including only a few cases of BWF.

From these data, it may thus be concluded that BWF might result from the relative inefficiency of quinine as a suppressor drug when taken irregularly.

From all the available data of our study we conclude that:

- BWF started appearing with the increased use of quinine which itself coincided with and resulted from the emergence of strains of Pf resistant to chloroquine.
- Quinine was taken as a curative drug often inadequately, in a meso-endemic area for malaria where 50% at least of the adult population is non immune to this disease.
- The clinical picture of our patients with hemoglobinuria was similar to the description of BWF of the first half of this century.
- Other causes of hemoglobinuria could be excluded in most of the patients.
- Despite the absence of Pf parasites, the majority of the patients had high levels of Pf antibodies suggestive of a recent Pf attack.

To explain the occurrence of BWF in Katana we suggest the following sequence of events: patients with a malaria attack, of whom at least 50% are non immunized against this disease, take chloroquine as initial treatment because it is available and cheap. A substantial number of patients do not improve because of chloroquine resistance and are compelled to use quinine, another currently available drug more efficient than chloroquine against the local strains of Pf. However, the price and duration of quinine treatment are often reasons for poor compliance leading to incomplete schemes and inadequate dosages. The relative inefficiency of such inadequate treatment favors the progression of Pf infections resulting in hyperparasitemic states which, at the time of admission are often undetectable because of massive hemolysis of most of the parasitized erythrocytes (35).

The acute intra-vascular hemolysis and hemoglobinuria of BWF may thus be no more than a major complication of malaria: a hyperparasitemic malaria with, as suggested by Warrell (40), an unusual synchronous lysis of infected erythrocytes accounting for the frequent absence of parasites in the peripheral blood.

Acknowledgments – We are most grateful to Dr M. Kivits who supported this study and who provided us with relevant bibliography. We thank the laboratory staff personnel of Katana hospital, particularly chief technician Habyamere, as well as the intensive care unit staff of Katana hospital. We also acknowledge the contributive collaboration of the laboratories of hematology (Prof. G. Van Ros) and of microbiology (Prof. P. Piot and Dr G. Van der Groen) of the Institute of Tropical Medicine in Antwerp for performing some laboratory analyses. We also thank Drs R. Colebunders and J. Van den Ende for their careful reading of the article and constructive criticism.
Une étude étiologique de l'hémoglobinurie et de la fièvre bilieux hémoglobinurique dans le Kivu montagneux, Zaire.

Résumé — Entre le 1er janvier 1985 et le 31 mars 1986, 38 patients ont été hospitalisés à Kata na dans le Kivu montagneux (Zaire) avec comme symptôme principal la présence d'urines rouge foncées ou franchement noires. Parmi ces patients, 4 présentaient une déficience grave en glucose-6-phosphate déshydrogénase, 2 une leptospirose et 2 une infection par le virus Hantaan. L'hémolyse n'était pas prononcée chez 2 malades (haptoglobine ≥ 40 mg/dl et hémoglobinine 12 g/dl). D'autres étiologies possibles d'hémoglobinurie ont été soigneusement recherchées comme l'absorption d'agents toxiques, certaines maladies infectieuses ou une transfusion de sang incompatible. L'ensemble des signes cliniques observés chez ces 28 patients restants étaient très suggestifs de fièvre bilieux hémoglobinurique (FBI) également décrite par les angiosaxons sous le terme de « Blackwater fever ». Parmi les patients suspects de FBI, une proportion significative (p < 0,01) avait utilisé la quinine dans les heures ou les jours qui précédaient contrairement aux malades s'étant présenté avec un paludisme simple, suggérant que la quinine pourrait jouer un rôle décisif dans la genèse de la FBI. Il faut cependant savoir que la quinine dans cette région était utilisée spontanément et à des doses inadéquates par des patients dont 50% ne présentaient aucune immunité contre P. falciparum et chez qui la chloroquine ne semblait avoir aucun effet. Il pourrait donc être aussi suggéré que la FBI parmi ces patients pourrait résulter d'une hyperparasitisme non détectée à cause d'une brutale lyse synchrone des érythrocytes. Dans ce dernier cas, la FBI pourrait être une complication majeure de l'infection à P. falciparum au décours de laquelle la quinine ne jouerait qu'un rôle marginal.

Etiologische studie van hemoglobinurie en zwartwaterkoorts in de bergstreek van Kivu, Zaire.


Hemolyse was twijfelachtig (haptoglobine > 40 mg/dl, hemoglobinine > 12 g/dl) bij 2 patiënten. Andere mogelijke oorzaken van hemoglobinurie zoals hemoglobinopathie, vergiftigingen, infectieziekten of bloedtransfusie incompatibiliteit werden zorgvuldig onderzocht en uitgesloten. Het geheel van klinische symptomen bij de overige 28 patiënten gaf een sterk vermoeden van zwartwaterkoorts, een complicatie bij malaria, zoals beschreven door verschillende auteurs onder de naam van febris haemoglobinurica. Aangezien quinine werd gebruikt door een significat groter aantal (p < 0,01) van de patiënten die de symptomen van zwartwaterkoorts vertoonden vergeleken met de patiënten die een minder vorm van malaria doormaakten, werd verondersteld dat dit geneesmiddel een bestissende rol speelt in de ontwikkeling van zwartwaterkoorts.

Men moet echter weten dat de quinine spontaan ingenomen werd in onaangepaste dosering door patiënten waarvan 50% niet de minste immuniteit vertoonden tegen P. falciparum en bij wie chloroquine geen invloed bleek te hebben. Men zou kunnen denken dat de zwartwaterkoorts bij deze patiënten veroorzaakt is door een niet opgespoorde hyperparasitemie wegens een plotse en synchrone lysis van de erytrocyten. In dit laatste geval zou de zwartwaterkoorts een zware verwikkeling kunnen zijn van de besmetting met P. falciparum tijdens dwelke quinine slechts een bijrol zou spelen.

Received for publication on September 30, 1994.

REFERENCES


