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SEVERE MALARIA – ANALYSIS OF PROGNOSTIC SYMPTOMS AND SIGNS IN 169 PATIENTS TREATED IN GDYNIA IN 1991 -2005

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ABSTRACT

In the period 1991-2005, 169 patients with the diagnosis of malaria were hospitalized in the Department of Tropical and Parasitic Diseases, Institute of Maritime and Tropical Medicine in Gdynia (from 2003 – the Academic Centre of Maritime and Tropical Medicine, Medical University of Gdańsk). All the cases were analysed for severity, occurrence of complications and permanent sequelae of the disease.

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According to the criteria set by the WHO (5), malaria was classified as severe in 36 cases. All of them were *Plasmodium falciparum* infections or mixed infections: *P.f.* and another species of the parasite. Patients in this group developed a number of complications, inter alia shock, acute respiratory distress syndrome (ARDS), acute renal failure, blackwater fever, severe anemia, disseminated intravascular coagulation, myocarditis, consciousness disorders of varied degree, acute transient psychoses, and exacerbation of ischemic heart disease. In one case of a pregnant woman, necrosis of the fetus occurred in the course of disease in the 4th month of pregnancy. Moreover, meningoencephalitis was diagnosed in two patients – in one of them concurrently with symptoms and signs of malaria, while in the other one - 3 weeks after the symptoms subsided.

In 6 patients, permanent sequelae of the disease developed and in 4 patients the disease was fatal. The cause of death was multi-organ failure, with the first sign of poor prognosis being rapidly progressing renal failure resistant to treatment in three men; in one case death resulted from cerebral malaria.

In cases of suspected malaria, relapsing malaria or in mixed infections, molecular testing was a valuable complementary tool of diagnosis, which helped in beginning the appropriate treatment.

INTRODUCTION

In spite of the progress in the diagnostic techniques and treatment of malaria, the incidence of the disease is not decreasing. In Africa, it is increasing in many areas, and new cases are reported even in some regions where from the disease had already been previously eradicated (1).

Malaria continues to be a major health hazard for people visiting tropical regions as tourists or staying there for long periods to work there.

For the indigenous population of endemic regions, and particularly for children up to 5 years of age, pregnant women, HIV-positive patients and people living in conditions of extreme poverty, malaria continues to be a serious health hazard.

In total, the malarious areas in 107 countries of the world are inhabited by 3.2 billion people, which accounts for nearly half of the entire population of the globe. Of this number, each year about 350-500 million people are infected and more than 1 million of them die. More than 90% of these deaths occur in Africa, where the disease is the most important cause of deaths among infants and young children (2). Malaria is endemic

Africa, Southeast Asia, Central Asia, Middle East, South and Central America, the Caribbean Islands and Oceania. Local transmission also occurs in North America.

In Western Europe about 12 000 new cases of malaria are recorded every year, all of them are imported infections (3).

The control of malaria in the world present many problems.

Rapidly progressing resistance of the vector – *Anopheles* mosquitoe to the most frequently used insecticides, as well as widespread resistance of the parasite to antimalarial drugs, particularly to the cheapest and safest agent – chloroquine, shortage of funds for malaria eradication or control programmes, and low level of financing the health services in the endemic countries are just some reasons why the struggle against malaria has not been successful (4).

According to data published by the WHO, severe forms of malaria with complications and multi-organ failure develop in about 1% of *P.falciparum* infected people, and very rarely - in patients with malaria caused by other species of the parasite.

In line with the definition formulated by experts, severe form of malaria is diagnosed in patients exhibiting one or more of the following signs and symptoms in combination with parasite presence in the blood (5):

- disorders of consciousness
- cerebral malaria (cerebral coma)
- severe normocytic anemia: hemoglobin (HGB) < 5 g/dL and HCT < 15 % – for residents of endemic regions or HGB < 7 g/dL and hematocrit (HCT) < 20% – for overseas travelers (non-immunized)
- renal failure (creatinine > 3 mg/dL) – without improvement after hydration
- pulmonary edema (acute respiratory distress syndrome – ARDS)
- disseminated intravascular coagulation (bleeding)
- collapse and shock
- hypoglycaemia (glycaemia < 40 mg/dL = 2.2 mmol/L)
- generalized seizures > 2 episodes/24 hrs
- lactic acidosis – arterial pH < 7.25 or plasma bicarbonate concentration < 15 μmol/L, lactate concentration in venous blood > 15 mol/L
- major weakness and prostration
- macroscopic hemoglobinuria
- hyperparasitemia (above 5% in non-immune subjects and above 10% in residents of endemic regions)
- jaundice (bilirubin level above 3 mg/dL)
- hyperpyrexia (rectal temperature above 40 °C with symptoms typical of heat stroke)

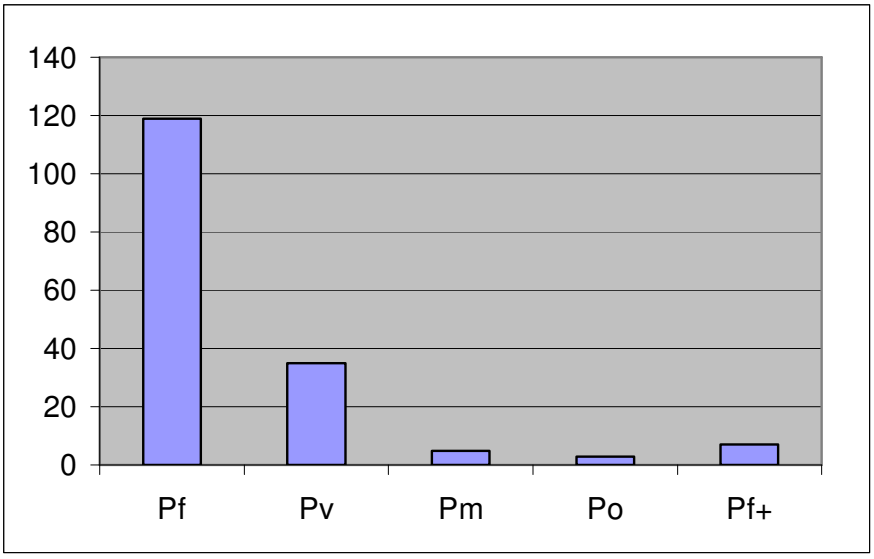
OBJECTIVE

The objective of this study was to analyse the course of malaria in patients treated in the Department of Tropical and Parasitic Diseases, and assess the incidence of severe malaria among them, its complications and permanent sequelae, according to the criteria set forth by WHO experts.

MATERIAL AND METHODS

In the period 1991-2005, there were 169 malaria patients hospitalized in our department. Among them, there were 144 men (85.2%) aged 23-70 years and 25 women (14.8%) aged 29-69 years. The majority of the patients were Poles, they visited or stayed in malaria endemic areas for business reasons. They were mainly seamen, missionaries and soldiers (Table 1). Among our patients were also 20 foreigners: 13 seamen, 3 tourists, 2 teachers, 1 missionary and 1 physician.

Figure 1. Patients with malaria hospitalized in the period 1991-2005.



Pf – *Plasmodium falciparum*

Pv – *Plasmodium vivax*

Pm – *Plasmodium malariae*

Po – *Plasmodium ovale*

Pf^{+} – two species of *Plasmodium sp.* (mixed malaria)

Table 1. Profession of patients in 169 malaria cases hospitalized in the Department of Tropical and Parasitic Diseases in Gdynia in the period 1991-2005.

Profession	**Number of patients**	**Percentage of patient cohort (%)**
Seaman	88	52.1
Missionary	39	23.1
Tourist	21	12.4
Soldier	7	4.1
Airline staff member	5	2.9
Traveller	4	2.4
Teacher	2	1.2
Physician	1	0.6
Forester	1	0.6
Botanist	1	0.6

Most of the patients were infected in Central and West Africa (129 cases); others - in Arabian Peninsula (11 cases), and Southeast Asia (10 cases); only few people were infected on other continents (Table 2).

The parasite was *Plasmodium falciparum* in 119 , *P. vivax* – in 35 , *P. malariae* – in 5, and *P. ovale* – in 3 patients; in 7 cases mixed infection was diagnosed: *P. falciparum* + *P. vivax* – in 5 cases, *P. falciparum* + *P. malariae* – in 1 and *P. falciparum* + *P. ovale* – also in 1 case. (Fig. 1).

Following the WHO criteria, in 36 patients (21.3%) severe malaria was diagnosed.

In this group, there were 31 men (86.1%) aged 23-70 years and 5 women (13.9%) aged 36-69 years, all of then Poles. All these cases were *P. falciparum* infections: in 30 cases only *P.f.* as a single parasite, in 4 cases mixed infection with *P. vivax*, in 1 case - with *P. malariae* and also in 1 case - with *P. ovale*.

Methods employed in the diagnosis of the disease and the responsible parasite species included:

1. Microscopic blood examination (thick drop and thin smear), with Giemsa staining
2. Detection of *Plasmodium sp.* antigens in venous blood with the use of Optimal Malaria Rapid Test (producer DiaMed AG)
3. Molecular assays (PCR)
4. ELISA serological test

RESULTS

Seamen were the largest professional sub-group among our patients who were treated for in the 1990ties, accounting for over 65% of them. In the group of 40 patients treated in 2000-2005, there were 10 seamen, 11 missionaries and 8 tourists; among remaining 11 patients were people of other professions.

36 cases of severe malaria were analysed, they accounted for 21.3 % of all patients hospitalized. All of them were infected in Africa. In this group, various complications were recorded: severe anemia requiring blood transfusion – in 13 patients, shock – in 7 patients, acute renal failure – in 7 patients, including blackwater fever in 2 cases, disseminated intravascular coagulation – in 4 patients and acute respiratory distress syndrome (ARDS) in 3 patients, myocarditis in 2 cases, and meningoencephalitis also in 2 cases (Table 3). In one pregnant woman, who was infected in the 4th month of pregnancy, death of the fetus occurred and disseminated intravascular coagulation developed. In three patients we observed exacerbation of ischemic heart disease, and in two others – acute transient psychoses.

Duration of hospitalization was generally long; it was shorter than 10 days in 8 patients only, including three fatal cases when hospital stay lasted 11 hours, 4 days and 5 days, respectively. In other cases, the duration of stay in hospital varied from 11 to 66 days, with mean period of 18.7 days.

Table 2. The origin of imported malaria infections in 169 patients treated in Gdynia.

Continent	**Number of patients**	**Percentage of patient cohort (%)**
Africa	129	76.3
Arabian Peninsula	11	6.5
Southeast Asia	10	5.9
Central Asia	7	4.1
South America	6	3.6
Central America	3	1.8
Oceania	3	1.8

In a number of patients, permanent sequelae of the disease were observed, most frequently in the form of lesions to the central nervous system, myocardial damage manifested as conduction disorders, and drug-induced thrombocytopenia (Table 4.). Eight of the patients of that group required repeated (second or third) hospitalization, due to some of the complications of malaria requiring longer hospital treatment or

appearing with a several weeks delay, as it was the case with drug-induced thrombocytopenia, meningoencephalitis or psychoorganic dementive syndrome.

In 4 cases the disease was fatal; the mortality in the studied group of patients was 2.4%. Three of the patients were seamen and one was a traveler. In three patients death was caused by multi-organ failure in the course of tropical malaria, with the direct cause defined as treatment-resistant renal failure. In one case death resulted from cerebral malaria (Table 5).

Prognostic indicators of severe malaria in our cases are listed in Table 6. The analysis included such parameters as patient's age, level of parasitemia, presence of schizonts in peripheral blood, elevated white blood cell count, and appearance of malaria pigment in granulocytes. None of the patients demonstrated a full set of factors regarded as signs of poor prognosis.

Table 3. Signs and symptoms of severe malaria in 36 patients hospitalized in Gdynia, and the number of fatal cases

Sign/symptom	No. of patients	No. of deaths
Hyperparasitemia	19	
Disorders of consciousness	18	
Severe anemia	13	
Marked jaundice	7	
Shock (hypovolemic, septic)	7	
Renal failure	7	3
Hyperpyrexia	3	
Disseminated intravascular coagulation	4	
Cerebral malaria	3	1
ARDS (pulmonary edema)	3	
Blackwater fever (dark-coloured urine)	2	
Prostration	2	
Acidosis	1	
Generalized seizure	1	
Hypoglycemia	0	

Table 4. Complications and permanent sequelae of severe malaria among 169 patients treated in Gdynia

Fatal outcome, complications and sequelae	**No. of patients**
Deaths	4
Myocardial ischemia, arrhythmia and conduction disorders (due to myocardial hypoxia)	3
Myocarditis	2
Blackwater fever	2
Encephalitis	2
Psychoorganic dementive syndrome	2
Psychosis	2
Drug-induced thrombocytopenia (halofantrine)	1

Table 5. Life-threatening signs and symptoms of severe malaria – data on 4 fatal cases

Signs and symptoms	Patients			
	L.L.	W.J.	C.S.	R.M.
Neurological				
Deep coma	Disorders of consciousness	Coma	Disorders of consciousness	Disorders of consciousness
Generalized seizures		+		
Signs of decortication (opisthotonos)				
Increased intracranial pressure (retinal edema)				
Cardiovascular				
Shock				
Pulmonary edema	+			+
Cardiac arrhythmia				
Myocardial ischemia (ECG)			+	
Renal				
Rapidly progressing renal failure	+		+	+
Hemorrhagic				
DIC		+		
Liver damage				
Marked jaundice	+		+	+

Table 6. Prognostic factors in 4 cases of severe malaria with fatal outcome

Patients	**L.L**	**W.J.**	**C.S..**	**C.S.**
Age < 3 years and > 70 years	35	44	36	32
Hyperparasitemia (> 5 %)	22	10	33	2.5
Peripheral schizontemia	+	+	+	-
Polymorphonuclear leukocytosis	9.8	9.4	3.6	5.2
Leukocytes with malaric pigment (> 5%)	-	-	-	+

Table 7. Laboratory examination results in 4 fatal cases of falciparum malaria

Parameters		**Patients**			
		L.L.	**W.J.**	**C.S.**	**R.M.**
Abnormal blood count	RBC (10^9/L) Hemoglobin (g/dL) Platelets (10^6/L)	2.67 8.3 26000	4.81 14.4 35000	2.35 8.0 15000	5.07 16.1 30000
Elevated renal parameters	Urea (mg/dL) Creatinine (mg/dL)	288 6.2	131 2.2	174 5.8	114 6.9
Metabolic acidosis		+	–	+	+
Marked jaundice	Bilirubin (mg/dL) AlAT (IU/ L) AspAT (IU/L)	11.8 118 248	2.7 92 112	22.1 112 194	9.5 102 305
Blood coagulation disorders	AT III (%) D-Dimer, FDP (µg/dL)	60 FDP>40	58 >1000	 >10000	52.9 >10000
Hypoglycemia	Glucose in whole blood below 40 mg/dL	–	–	–	–
High serum concentration of TNF-α					+

Considering the cases concluded with patient's death, A list of "alarming" results of laboratory tests in fatal cases is presented in Table 7. Two patients developed severe anemia, which resulted of the high-level parasitemia (22 and 33% in red cells), three

patients had metabolic acidosis, and also three patients developed hyperbilirubinemia, which reached the level of 22.1 mg/dL in one of them.

The application of PCR testing allowed us to diagnose mixed infections in 6 of the patients.

DISCUSSION

Polish seafarers have been medically examined and treated in our Institute for decades, therefore those of them who were infected with malaria were a large group of our patients.

Also patients of other professions were treated in our department, from both Poland and other countries. Among them, there were also missionaries who spent many year in the tropics.

During the recent 10-15 years, increasing numbers of citizens of this country have traveled as tourists to many areas of the world, also to malaria endemic regions. Unfortunately, most of them are unaware of the health risks connected with traveling to the tropics, and they do not care for malaria prevention and chemoprophylaxis. Some of them take drugs irregularly or in inadequate doses.This problem is known also in other European countries and in the USA (6).

Among patients treated for malaria during the last 15 years, there has been a change observed in both relative numbers of representatives of different professions and their motives for visits and stays in the tropics.

In the period 2001-2005, we had in our Department less patients treated for malaria each year and among them also less seafarers. This may be due to the increasing possibility of treatment of tropical diseases not only in our Center but also in several other medical centers in Poland; and to gradually wider use of antimalarials by travelers.

American data indicate that the percentage of tourists traveling in groups and missionaries among all patients treated for malaria, 8.5% and 10.6%, respectively, decreased in the years 1989-2001 as compared to 1969-89, while the percentages of individual tourists and business travelers increased – 21.3 and 19.2% (7). This may indicate which groups of travelers are exposed to malaria infection, and which of them shall be regularly informed about methods of malaria prevention.

In the USA, in the period 1963-2001, mortality due to malaria was determined as 0-4.4%, with mean of 0.9%, which is less than in our study; however, mortality rates similar to that in our study were reported in studies carried out in other European countries. In Greece, in the period 1989-1995 there were 109 cases of malaria recorded,

with no resulting deaths at all. On the other hand, in Germany there were 3747 patients treated for malaria, with mortality rate equal to 3.6% (3).

In severe malaria, typical are signs indicating for multi-organ failure. A number of parasitic toxins released in the course of infection lead to activation of several factors of the immune system, especially cytokines, like TNF and pro-inflammatory interleukins (IL), as well as free radicals and nitric oxide. As a result of the destructive actions of these substances, damage of endothelial cells and tissues of the host ensues. Research conducted in African children with severe malaria proved that elevated levels of pro-inflammatory cytokines: TNF-α, interleukin-1β and interleukin-6 are associated with cerebral malaria (8), while relatively low levels of anti-inflammatory cytokine IL-10 are found in patients with severe anemia in the course of malaria. Another research, carried out in adult patients in Vietnam also revealed correlation of elevated cytokine serum levels with severe course of the disease and multi-organ failure. However, Day et al. (9) have not detected such relationship in adult subjects with cerebral malaria.

In cerebral malaria severe intravascular changes develop in the vessels of the central nervous system due to sequestration of parasitized red blood cells (pRBCs) as well as functional and morphological changes within the endothelial cells of cerebral vessels as a result of their interaction with platelets, monocytes, lymphocytes and dendrocytes accumulating within cerebral microcirculation (10). Generalized activation of vascular endothelial system is confirmed by the presence of activation markers, with significantly increased concentrations of ICAM-1 and E-selectin and their deposition within cerebral blood vessels (11). In humans ICAM-1 was identified as a vascular endothelial ligand for erythrocytes infected with *P. falciparum*. Assessment of these indicators is now possible for research purposes only and has no practical application in clinical management of patients with malaria.

It is important to mention that the diagnosis of cerebral malaria should not be established in just every case of consciousness disorders or neurological symptoms indicating affection of the central nervous system. In our study cohort, there were two cases (both of them seamen) of meningoencephalitis of undetermined etiology. Diagnostic tests were performed and infections with Polio, Coxackie B, Echo, Herpes, CMV, rubella, HIV, and arboviruses as well as toxoplasmosis were ruled out. In one of the two patients, disorders of consciousness and acute psychosis with subsequent presence of meningeal signs and typical inflammatory changes in cerebrospinal fluid and CT-scan of the head developed within the first days of treatment of malaria. The outcome in this case was psychoorganic dementive syndrome and permanent impairment of health. The illness was classified as a case of occupational disease and the patient was granted health pension due to his disability preventing him to continue his employment (12). In the other patient cerebral and meningeal symptoms with

accompanying fever and inflammatory changes in the cerebrospinal fluid appeared 3 weeks after completion of the treatment. Also in this case the etiological factor could not be determined. After several months full recovery was observed in this patient. It is possible that both the patients developed reactive immunological meningoencephalitis in response to *Plasmodium falciparum* infection. Case reports exist describing this type of inflammatory changes within the CNS in the course of malaria, which are sometimes referred to as acute disseminated encephalomyelitis, ADEM (13).

Results of some laboratory tests may be of prognostic value. Marked anemia, most frequently related to high-level parasitemia, thrombocytopenia which may be inter alia the effect of disseminated intravascular coagulation (DIC), polymorphonuclear leukocytosis, disorders within the plasma coagulation system, elevated and rapidly increasing levels of renal function parameters, high level of plasma bilirubin indicating severe lesion of the liver, metabolic acidosis and hypoglycemia (observed much more frequently in residents of endemic regions, particularly in children, than in non-immune individuals), are important indicators of unfavourable course of the disease – progressing up to the point of multi-organ failure (14).

Four of our cases of malaria were fatal. In one case the cause of death were cerebral complications, while in three others death resulted from multi-organ failure with renal failure being the dominant clinical manifestation. Malaria of severe, lethal course is related to the activation of diverse substances of endothelial origin. Parasitic endotoxins cause damage of the endothelium, which results in: increased vascular permeability, escape of protein to the extravascular space, abnormal vasodilation, a decrease in arterial blood pressure and depression of the myocardium. These changes lead to hypovolemia and deterioration of organ perfusion, which is particularly dangerous for such organs as kidneys or brain. Some phenomena also occur which are specific for *P. falciparum* malaria e.g. constriction of microcirculation vessels as a result of the action of an adhesive protein found on the surface of parasitized erythrocytes. What is more, plasticity of parasitized erythrocytes is less than normal, which impairs their ability to adjust their size to the diameter of fine blood vessels of microcirculation (15). As a result of these processes is local intravascular coagulation ensues, which in the case of kidneys may lead to irreversible organ damage.

The assessment of cytokine or TNF-α levels are not widely available; therefore, they have neither become an element of standard evaluation and monitoring of the course of malaria nor an accepted prognostic factor. A few attempts to use TNF-α inhibitors in treatment of patients with severe forms of malaria have been made within experimental studies only (16). In one of the fatal cases of malaria observed in our study, high serum concentration of TNF-α was detected. Further research is in progress to explore the significance of such findings.

CONCLUSIONS

- Tropical malaria may be the cause of severe complications. In our patients, clinical manifestation of this type of the disease were mostly symptoms of multi-organ failure.
- Cerebral dysfunction and rapidly progressing renal failure are the highest risk of death of the patient.
- In some of our patients, malaria left behind persistent sequelae. Such complications may lead to permanent disability.

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