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Case Report

Epidemiological, clinical and therapeutic aspects of cerebral malaria imported in Albania

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Abstract

This is a case-report of two patients with cerebral malaria (CM) imported from West-African countries. Notably, this form of malaria was developed as a second disease episode, while the first episode was experienced in West Africa. These findings suggest that the second episode of malaria was caused by a different strain of *Plasmodium falciparum* as compared to the first one. They are the first cerebral malaria cases imported in Albania after the eradication and absence of Plasmodium for five decades. Early treatment of cerebral malaria is decisive on the duration of coma and disease's outcome.

Key words: Cerebral malaria; *Plasmodium falciparum.*

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Introduction

Malaria by *Plasmodium falciparum* remains a major problem of public health in endemic areas, with more than one million deaths per year [1]. About 12,000 cases of imported malaria are reported each year in Europe, where France has the highest number of about 5,000 per year [2]. Twenty to 30 of these cases have been fatal. Severe imported malaria still carries a high mortality which is estimated to be 10-15%, although extensive studies are lacking. According to the WHO report in 2000 [2], severe imported malaria has been defined as the combination of: 1) the presence of *P. falciparum* asexual form in the blood; 2) one or more criteria of severe malaria in hospitalization or within two days prior to admission (Table 1).

One of the largest retrospective study of 400 cases with severe imported malaria, treated in 45 intensive care centers in France, has shown that mortality despite intensive treatment in these centers was 10%. The presence of 3 factors in the first 24 hours before admission that were independently associated with mortality were: old age, coma and high parasitemia level [1]. Severe malaria is a multisystemic disease and the cerebral affection is a key feature of its clinical spectrum. Cerebral malaria (CM) is a diffused encephalopathy but potentially reversible, caused by *P. falciparum*. This pathology is clinically presented with reduction of consciousness, convulsive attacks (15% of adults) and coma. Mortality rate is as high as 15%-30%, even under appropriate therapy in intensive care units [3]. Prolonged neurological damage may remain in 1% of adults. However, as in many survivors significant neurological deficits have not been found, this supports the idea that the mechanisms leading to coma can be quickly and completely reversible. The average time adult survivors needed to reestablish normal consciousness has been 48 hours (rarely more than a week), while children wake up from coma within 24 hours [3].

Pathogenesis of coma in CM is multi-factorial. The microvascular pathology of human CM is unique: it is caused by erythrocyte adherence infected with *P. falciparum* in vascular endothelium with other erythrocytes leading to microvascular obstruction,

endothelial activation, hemato-encephalic barrier alteration (and inclusion of a wide range of additional pathogenic and defense mechanisms). This process is called sequestration [4-6]. Coma causes are not yet fully explained. It is believed that the sequestration leads to reduction of blood flow. As a result of concentration of parasites with high metabolic activity in brain capillaries, the local cytokine cascades interfere with neurotransmitters [4-6]. There is a consensus that the coma is not caused by increased intracranial pressure (greater part of adults affected show a normal pressure during lumbar puncture), and edema is rare. Cerebral edema in these cases appears to be due to malaria infection. It does not seem to be the cause of coma in CM, since it is also found in non-comatose patients [6,7]. CM often begins with generalized convulsions followed by loss of consciousness lasting for at least 30 minutes. Other neurological signs may be divergence of eyes, bruxism, different postures (like neck hyperextension), decortication and decerebration [8]. Retinal hemorrhage has been noticed as well, while papilledema has been rare. Lumbar puncture should exclude bacterial meningitis. Nuchal rigidity and focal neurological signs are rare. Occurrence of the CM and its association with renal failure and/or metabolic acidosis lead to outcome deterioration [8]. Moreover, this pathology can be fatal within a few hours due to coma development, therefore being a medical emergency. The main objective of treatment of severe CM is the prevention of death and recrudescence. The management includes: clinical evaluation, specific anti-malarial treatment, and support therapy. The aim of this paper is to present the epidemiological, parasitological, clinical, biological, therapeutic features of two cerebral malaria cases imported from Equatorial Guinea that were managed at the ICU for infective diseases in UHC Tirana, Albania.

Material and method

The material of the paper consists of cases of two Albanian patients (29 and 41 years of age), with severe malaria (*P. falciparum*) imported from Equatorial Guinea during years 2012-2013. The patients did not have a previous pathology. They were diagnosed with malaria on the basis of epidemiological and clinical-biological data, and confirmed through parasitological observation of the peripheral blood, with the thin and the thick blood film.

Both patients were analyzed by epidemiological standpoint: age, gender, occupation, interval of time between first presence in the endemic region and the occurrence of initial malaria symptoms, prophylaxis received; clinical data: febrile curve, hepatosplenomegalia and clinical-pathological syndromes of the affected biological systems and of various organs; therapeutic data: etiological and intensive care treatment. We observed the disease evolution and investigated for epidemiological, clinical or biological variables relevant to the disease's gravity and outcome.

Results

Epidemiological, clinical, laboratory, and therapeutic data from our patients are shown and summarized in Table 2. Notably, both patients had worked in a rural forest area, in construction (outside and inside the building). Physical and chemical protection against vector insect was not effective.

Table 1. Clinical and biological criteria of severe malaria according to WHO 2000 [2].

Clinical Criteria
Loss of consciousness, GCS < 11
Multiple seizures
Cardiovascular collapse, systolic pressure < 80 mmHg, despite appropriate volume replacement
Abnormal bleeding
Bilirubinemia, clinical jaundice or > 50 mmol/L (> 3 mg/dl)
Macroscopic Hemoglobinuria
Laboratory Criteria
Severe anemia, hemoglobin < 5g/dl
Hypoglycemia, blood glucose < 2.2 mmol/L (< 40mg/dl)
Acidemia, pH < 7.35
Hyperlactatemia, > 5mmol/L
Hyperparasitemia, ≥ 4%
Renal scarring, uremia > 265 mmolL, or creatinemia >17 mmol/L

Table 2. Epidemiological, clinical and laboratory data treatment of patients.

	Patient 1	**Patient 2**
Age (years)	29	41
Gender	M	M
Date of admission	16/12/13	22/11/12
Hospitalization diagnosis	Suspected Cerebral Malaria	Suspected Malaria
Epidemiology	Equatorial Guinea, worker for 6 months	Equatorial Guinea, worker for 4 months
Receiving prophylaxis	10 days (doxycycline)	None
State/Condition	Severe condition (comatose) 4-5 points GCS	Stupor condition, coma in the second day of admission in the hospital - 5-6 points
Time with fever prior to hospitalization (admission)	1 week	1 day
Number, place of previous malaria episodes and clinical form	First: in Guinea, not cerebral form. Second: 2 weeks after coming back or 104 days after the first episode	First: in Guinea, not cerebral form, 41 days after arriving in Guinea. Second episode: in Albania - one week after coming back / 86 days after the first episode.
Mechanical ventilation	Intubated with a tube with diameter 7mm, respirator linked with regimes: IPPV, VT 650ml, Fr 12/min, FiO_2 100%.	O_2 therapy with mask
Performance	Woke up from coma on the 7th day	Woke up from coma on the second day
Hemodynamic status (AP) under vasoactive therapy	80/60 mmHg,	90/60 mmHg
Convulsions	Generalized	No convulsions
Temperature (Fever)	39-40^{0}C	39-40^{0}C
Duration of the symptoms	6 days	4 days
Co-infection	Hemoculture: *Staphylococcus spp*.	None
Plasmodium type	*P. falciparum*	*P. falciparum*
Parasitemia		195 / 1000 eritrocites
Thin blood film	0.2%	0.2%
Thick blood film	9000/µl	
Leukocytes	16 900/mm³	4 700/mm³
Erythrocytes	2.93 x 10/mm³	1.87 x10^6/mm³
Hemoglobin	8.8 g/dl	5.7 g/dl
Trombocytes	80000/mm³	26000/mm³
Glucose	143 mg/dl	209 mg/dl
Azotemia	145 mg/dl	178,7 mg/dl
Creatininemia	3.6 mg/dl	3.2 mg/dl
Bilirubinemia	8,8 mg/dl	5.2 mg/dl
AST	124 U/L	192 U/L
ALT	137 U/L	55 U/L
LDH	426 U/L	1620 U/L
CK	2052 U/L	872 U/L
Prothrombine	77%	60%
O_2Saturation	90%	95%
Respiratory rate	26/min.	24/min.
Duration of treatment	7 days Artemeter	4 days Artemeter
Therapy	Artemisinin 160mg×2, Doxicyclin 100mg×2, Cefepime 2g×2, Dexamethasone 4mgx3, Manitol 20% 100ml x3, Dopamine 200mg/50ml.	Meflokine 250mg, Artemisinin 160 mg×2, Doxycycline 100mg×2, Dexamethasone 4mgx3, Manitol 20%, 100mlx3, Hemotransfusion.

Discussion

This report resulted interesting in different aspects. In the epidemiological aspect, it was noted that both patients neither were virtually under drug prophylaxis nor they adopted physical/chemical measures of prevention that would have avoided the infection. They were young males, immune-competent who had never had contacts with malarial regions. It was evident that both had gone through a malarial episode, although not in the cerebral form, during their stay in Guinea (between 41 to 80 days after their arrival in Africa). While the second episode, the cerebral form, occurred between 86 days to 104 days after the first infection. A question arises: since the patients were exposed to malaria for the first time in their life, why the first episode was not a cerebral form? In both cases, the identification of *P. falciparum* alone in our facility and the lack of primakin-treatment in Guinea clearly demonstrated that the first episode of malaria had not been caused by additional Plasmodium types. These data suggest that these patients either were not adequately treated in Guinea, or they were re-infected from a different strain of *P. falciparum*. Accepting that treatment worldwide (including Guinea) is based on official guidelines, the second hypothesis is more plausible. Similarly, to other reports, our findings demonstrate that the cerebral form of malaria may also appear during the second disease episode caused by an additional strain of *P. falciparum* [9-11]. Meanwhile, a disease' reactivation without a reinfection is nearly excluded because of adequate treatment (according to international guidelines) [2,4,12].

Regarding the clinical aspect, our patients were hospitalized and treatment was commenced respectively 7 and 1 day following the occurrence of fever. Meanwhile, the cerebral affection included cerebral convulsions (only in one of the two cases), progressive encephalopathy without focal signs or nuchal rigidity, leading to coma from 4-5 to 5-6 Glasgow scale. Both patients experienced multiple organ dysfunctions, due to induction of thrombocyto-penia, severe anemia as well as hyperbilirubinemia, and the development of cerebral injury was part of the multi-organ damage. Therefore, a genuine form of CM as described in literature [6,13], is less unlikely.

The treatment of patients was complex. The etiological treatment was based on parenteral administration of artemisinin [3,14]. While the adjuvant treatment included respiratory assistance, which in one of the cases was applied through mechanical ventilation [14,15]. The waking up from coma on different days suggests that administration of medication with appropriate timing may be decisive on the disease outcome. Thus, the etiological treatment was applied only 7 days after the onset of malarial seizure in the patient who waked up from coma on the seventh day of treatment. In contrast, the patient who initiated the treatment on the day of the disease occurrence, remained in coma only for two days. The importance of early treatment during severe malaria especially in the case of the cerebral form is a major hallmark in the management of this infectious disease [2,3,12]. Our report suggests that subjects who have resided in endemic countries and have shown signs of febrile symptoms with encephalopathy should be considered for imported malaria.

In conclusion, these cases demonstrate that cerebral malaria can occur even in a second episode of infection by *P. falciparum*, associated by multi-organ dysfunction. Early treatment of cerebral malaria with artemisinin is decisive on the duration of the coma and for the disease outcome.

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