SIMPLIFIED MULTI-ORGAN DYSFUNCTION SCORE PREDICTS DISABILITY IN AFRICAN CHILDREN WITH PLASMODIUM FALCIPARUM MALARIA

RAIMUND HELBOK,* SAADOU ISSIFOU, PIERRE B. MATSIGUI, PETER LACKNER, MICHEL A. MISSINOU, DAVY KOMBILA, WOLFGANG DENT, ERICH SCHMUTZHARD, AND PETER G. KREMSNER

Department of Neurology, University of Innsbruck, Innsbruck, Austria; Medical Research Unit of the Albert Schweitzer Hospital, Lambaréné, Gabon; Department of Parasitology, Institute of Tropical Medicine, University of Tübingen, Tübingen, Germany

Abstract. In this prospective study, we assessed the simplified multi-organ dysfunction score (sMODS) in 485 consecutive African children, hospitalized with Plasmodium falciparum malaria. Children were grouped according to their ability to walk unaided (Group 1, N = 414), sit unaided (Group 2, N = 63), or inability of both (Group 3, N = 8) before contracting malaria. The SMODS on admission to hospital was highly correlated with prolonged disease duration in Groups 1 and 2 (Spearman r = 0.79 and r = 0.78, respectively). A sMODS of ≥ 16 was indicative for prolonged disease duration in Group 1 (> 48 hours of inability to walk, sensitivity of 87%, specificity of 82%) and Group 2 (> 24 hours of inability to sit, sensitivity of 100%, and specificity of 78%). The simplified MODS is a simple and sensitive measure of severity of illness in children with P. falciparum malaria and allows early prognostic evaluation.

INTRODUCTION

Plasmodium falciparum malaria accounts for over one million deaths annually and has a substantial social and economic impact in most tropical countries. Early diagnosis and prompt and effective treatment, in addition to careful evaluation of severity, are important to prevent high mortality. Indicators of severity based on sophisticated laboratory results cannot be used in most health institutions in high prevalence regions as resources are usually limited. Therefore, a clinical approach remains necessary, which is done by using clinical scores as the Glasgow Coma Score in adults and the Blantyre Coma Score in children, which both correlate with the outcome of disease. However, because malaria is a systemic disease, a proper marker for severity of illness should reflect the status of every organ system.

The multi-organ dysfunction score (MODS) is used in critically ill patients admitted to intensive care units to assess disease severity independently of diagnosis. It has recently been shown that both the MODS and simplified MODS (sMODS), which is based on clinical evaluation, are highly correlated with established clinical and laboratory indices of severity in adults with P. falciparum malaria, including tumor necrosis factor alpha in both uncomplicated and severe presentation. Even in uncomplicated P. falciparum malaria, different severity levels were expressed quantitatively, describing the clinical presentation of P. falciparum infection as a continuum from asymptomatic, mild malaria, severe malaria, to multi-organ manifestation and mortality. Single organ failure can be separated from multi-organ failure by the MODS. Moreover, a moderate clinical presentation reflected by mild dysfunction in several organ systems without fulfilling any criteria for severity as defined by the World Health Organization (WHO) can also be expressed more precisely by the MODS.

In hyper-endemic areas, malaria usually affects young children. Clinical assessment of severity of illness is difficult, and medical staff frequently relies on laboratory results. Therefore, a specified report is needed, as detailed information about disease-related symptoms can only be assumed. Detailed history given by parents or guardians is essential. We applied commonly used criteria for organ dysfunction within the ASA criteria of the MODS with hemoglobin concentration and parasitemia as the laboratory support and assessed disease severity using the simplified MODS in Gabonese children with P. falciparum malaria.

In this prospective study, our aim was to identify different levels of severity in indoor patients with P. falciparum malaria using the simplified MODS and to determine the correlation with morbidity and mortality.

MATERIALS AND METHODS

Study site. The study was conducted at the Albert Schweitzer Hospital in Lambaréné, Gabon. In this region, P. falciparum malaria is hyperendemic with perennial transmission and an estimated inoculation rate of ~50.9,10 There is very little variation in temperature and humidity throughout the year, but rainfall varies, with considerably less rainfall during the long dry season in July and August.

Patients’ consent and ethical approval. The protocol was approved by the ethics committee of the International Foundation of the Albert Schweitzer Hospital in Lambaréné, Gabon. Children were included in the study after informed consent was obtained from their parents or guardians. A total of 485 consecutive children between 4 months and 14 years of age admitted to the pediatric ward of the hospital with P. falciparum malaria were enrolled in this prospective study between August 2003 and May 2005.

Diagnosis was defined by the presence of asexual forms of P. falciparum on Giemsa-stained thick blood smears. Parents or guardians were asked whether the child was able to walk before contracting malaria (Group 1, N = 414, 85%). Group 2 included children with the inability to walk because of young age or undernourished status but being able to sit before infection (N = 63, 13%). Children unable to walk and sit were enrolled in Group 3 (N = 8).

Clinical and laboratory evaluation. Physicians completed a structured questionnaire that included information about previous illnesses, current symptoms, and recent medications. They performed a physical examination including evaluation
of body temperature, blood pressure, respiratory rate, pulse rate, chest recession, abnormal deep breathing, chest crepitation, nasal flaring, cough, degree of dehydration, cyanosis, pallor, jaundice, hepatomegaly, splenomegaly, vomiting, diarrhea, mental status, observed convulsion, neck stiffness, prostration, oral thrush, otorrhea, and urinary tract infection. Blood for measurement of hemoglobin concentration and parasitemia was examined. Hemoglobin concentration was measured photometrically.

Simplified MODS. The degree of severity was assessed by using the sMODS as reported previously. In this study, it was adapted for children, evaluating 10 organ systems within the first 24 hours (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system).

Each organ system was evaluated according to its functionality and necessary therapeutic intervention: a score of 1 reflects normal organ function, whereas organ dysfunction and necessary treatment were scored by 2–5 points according to the grade of severity, leading to a total score of minimum 10 and maximum 50 points.

A score of 5 was given to organ failure despite maximum specific therapy. A score of 4 was given to organ dysfunction despite maximal specific therapy. Any specific treatment given scored 3 points. The scores of 2 and 3 are described separately corresponding to each organ system.

Cardiac evaluation: auscultation, pulse rate and signs for heart failure (range for normal values of pulse rate: children aged 1–11 months (120 bpm), 1–4 years (110 bpm), 4–6 years (100 bpm), and > 8 years (90 bpm) body temperature adjusted (per degree > 37.5°C plus 10 beats).

Vascular system: blood pressure (systolic blood pressure < 80 mm of Hg was scored with 2, < 60 mm of Hg with 3), necessary treatment (fluid challenge, specific vasoactive treatment equivalent to 2 and 3 points, respectively).

Blood: hemoglobin: < 90 g/L (score = 2), < 50 g/L (score = 3), parasitemia > 100,000/µL (score = 2), hyper-parasitemia > 250,000/µL (score = 3), bleeding without specific treatment (score = 2), specific treatment such as blood transfusion (score = 3).

Respiratory system: abnormalities in auscultation, percussion or chest X-ray, if done, (score = 2) tachypnea (score = 2); normal values: < 1 year 30–40/min, 1–2 years: 25–35/min, 2–5 years: 25–30/min, 5–12 years: 20–25/min, > 12 years: 15–20/min), mild respiratory distress syndrome (score = 2), severe respiratory distress syndrome (score = 3), any specific respiratory therapy (score = 3).

Metabolism: undernourished (score = 2), marasmus (score = 3), severe vomiting/diarrhea (score = 2), severe dehydration (score = 2), severe respiratory distress syndrome (score = 3), generalized or localized edema (suspected hypoalbuminemia; score = 2).

Gastrointestinal system: nausea, vomiting, anorexia, diarrhea, abdominal pain (score = 2), nasogastric feeding (score = 3), severe repetitive vomiting with the need for specific treatment (score = 3).

Liver: jaundice (score = 2), hepatomegaly with right upper quadrant pain (score = 2), severe jaundice (score = 3).

Kidney and urinary tract: mild to moderate dehydration (score = 2), severe dehydration (score = 3), oliguria (score = 2), anuria (score = 3), hemoglobinuria (score = 2), symptoms of urinary tract infection (score = 2).

Immunology: HIV-positive, if known (score = 2), AIDS or immunodeficiency as known (score = 3), malnutrition (score = 2).

Central nervous system: headache, Blantyre Coma Score (BCS) 4 (score = 2), one convulsion in history and/or on admission or prostration (score = 2), BCS = 3 or 2 or more convulsions within the last 24 hours, BCS = 2 or 1 (score = 4), BCS = 0 (score = 5).

sMODS and WHO criteria for discriminating patients. Outcome was defined by an immobility of > 48 hours versus ≤ 48 hours. Severe P. falciparum malaria was defined by a sMODS ≥ 16 and by using WHO criteria for severe malaria in the same patient independently. Analysis included 410 patients of Group 1 (4 patients who died were excluded).

Definitions. Hyper-parasitemia was defined by > 250,000 parasites/µL (corresponding to > 10% infected erythrocytes) and severe anemia by hemoglobin of < 50 g/L.

Hypotension was defined as systolic blood pressure < 80 mm of Hg. Undernourished children were defined as having too low weight for their age. Severe jaundice was defined by evidence yellow lines on the patients palms beside yellow conjunctiveae. Severe dehydration was defined by 1) very dry mucosa/tongue, 2) a capillary refill of > 3 seconds, and 3) examination of the skin elasticity: pinch retracting very slowly. Cerebral malaria was defined with a BCS ≤ 2 or impaired consciousness with at least two convulsions within 24 hours before being hospitalized. The severity index was defined as the proportion of children admitted with severe and non severe P. falciparum malaria (MODS ≥ 16 and ≤ 15).

Treatment and outcome. Children diagnosed with malaria received standard quinine treatment initially as a loading dose: 20 mg/kg followed by 10 mg/kg every 8 hours intravenously or orally over 5 days. Seizures were treated with diazepam (0.3 mg/kg intravenously or 0.5 mg/kg per rectum). Severe anemia was corrected by transfusion of packed red cells (15 mL/kg over 4 hours). Adjunct treatment was given as required.

Our outcomes were 1) the ability to sit, 2) to walk unaided, 3) the ability to eat and/or drink, and 4) neurologic sequelae assessed on discharge by using the Glasgow Outcome Score.

Statistical methods. Data were analyzed by SPSS version 12.0 software (SPSS Institute, Chicago, IL). The distribution of continuous variables was assessed for normality by using the Kolmogorov-Smirnov test. Non-normally distributed parameters were analyzed by Wilcoxon rank-sum test or signed Wilcoxon rank-sum test, respectively (when paired samples were analyzed). Correlations were assessed by Spearman rank method. Analyzing the symptom duration, Kaplan-Meier curves were plotted to compare patients with low and high sMODS on admission, and a log-rank test was used to check for significance. To determine the discriminatory power of sMODS in identifying patients with prolonged disease duration, receiver-operating characteristic analysis was applied. Subsequently, the performance of a sMODS ≤ 16 in detecting patients with a prolonged disease duration (> 48 hours unable to walk) with respect to the WHO criteria for severe malaria was analyzed by comparing the correctly classified patients in the two scoring systems. Non-inferiority hypothesis was tested by a one-sided McNemar test.
RESULTS

General characteristic and laboratory results. Demographic data are given in Table 1.

In Group 1 (414 patients), 186 children were not able to walk on admission (45%), 105 children were unable to sit (25%), and 75 children were unable to drink or eat (18%). Of the 63 children in Group 2, 33 were unable to sit on admission (52%) and 13 were unable to drink or eat (21%). Of the eight patients enrolled in Group 3, two were unable to drink or eat (25%).

Most of the patients (76%) had received antipyretic treatment before admission; 159 patients (33%) got specific antimalaria treatment. Splenomegaly was observed in 51%. One child was known to be HBs-antigen positive. He had an uncomplicated course of disease. Two patients were known to be HIV-positive, but no other patients were tested for HIV. Oral thrush was observed in 13 children (3%).

sMODS in all children. The mean sMOD score on admission was 15 ± 3 (SD; range = 10–34), with significant improvement after 24 hours (12 ± 2, range = 10–35; P < 0.001). The mean sMODS did not differ between Groups 1 and 2 (means = 15 ± 3 and 15 ± 4).

Abnormalities were recorded most frequently in the gastrointestinal system (403 of 485, 83%), with the need for nasogastric feeding in 22 patients (5%). In the blood system, the grade of abnormalities was 372 of 485 (77%). Ninety-two patients received at least one blood transfusion (19%). Hypopotension was rare (51 of 485, 11%); however, 2 patients developed cardiovascular collapse. Respiratory dysfunctions were recorded in 361 patients (84%). Three patients developed respiratory failure. Liver involvement occurred in 142 cases (29%), and abnormalities in metabolism in 167 children (34%), including 14 with clinical evidence of severe undernourishment (3%). Abnormalities in the heart and immunology were observed in 223 and 126 children (46% and 26%), respectively, and abnormalities in the urinary system were noted in 98 children (20%). For the central nervous system, detailed information is given in Table 1.

sMODS and surveillance of severe P. falciparum malaria. Little seasonal variation was observed in our study period (data not shown). Comparing seasonal differences in clinical presentation, we found a severity index, expressed by the sMODS (± 16 and ± 15), of 1.9:1 and 1.4:1 in April and December, respectively, compared with 0.4–0.9:1 during the other months.

sMODS and outcome in group 1. The sMODS showed a strong correlation with the time to unaided walking (Spearman $r = 0.79$, P < 0.001; Figure 1), to sit unaided (Spearman $r = 0.68$, P < 0.001), and eat or drink (Spearman $r = 0.63$, P < 0.001). These differences were still significant after adjustment of parasite density (P < 0.001; Figure 2).

To determine the ideal MODS cut-off to foresee prolonged disease duration (> 48 hours unable to walk), a receiver-operating curve (ROC) was drawn. An area under the curve (AUC) of 0.92 (95% CI, 0.89–0.95) was found, and a sMODS of ≥ 16 showed the best accuracy with a sensitivity of 87% and a specificity of 82%. Abnormalities recorded in more than four organ systems (sMODS > 1) were associated with an inability to walk for > 48 hours with a sensitivity of 97% and a specificity of 74% (AUC, 0.90; 95% CI, 0.87–0.93).

sMODS and outcome in group 2. A positive correlation was found between the sMODS and the duration of illness until the patients regained the ability to sit unaided and drink/eat (Spearman $r = 0.81$, P < 0.001 and $r = 0.45$, P < 0.001, respectively; Figure 3). A cut-off level of ≥ 16 sMODS to predict prolonged disease duration (> 24 hours unable to sit) showed an AUC of 0.90 (95% CI, 0.87–0.93) with a sensitivity of 100% and specificity of 78%.

TABLE 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in months, mean (± SD)</td>
<td>43 ± 37</td>
</tr>
<tr>
<td>Range</td>
<td>4–169</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>245 (51)</td>
</tr>
<tr>
<td>Sleeping under mosquito net (%)</td>
<td>273 (56)</td>
</tr>
<tr>
<td>Duration of signs and symptoms before admission [days], mean (± SD)</td>
<td>3.6 ± 2.5</td>
</tr>
<tr>
<td>Range</td>
<td>1–17</td>
</tr>
<tr>
<td>Parasitemia [ul-1], geometric mean (range)</td>
<td>29,855 (20–1,016,400)</td>
</tr>
<tr>
<td>Hemoglobin [g/L], mean (± SD)</td>
<td>7.8 ± 2.5</td>
</tr>
<tr>
<td>Body temperature [°Celsius], mean (± SD)</td>
<td>38.5 ± 1.2</td>
</tr>
<tr>
<td>Systolic blood pressure [mm Hg], mean (± SD)</td>
<td>88 ± 11</td>
</tr>
<tr>
<td>Pulse rate [beats/min], mean (± SD)</td>
<td>120 ± 21</td>
</tr>
<tr>
<td>Respiratory rate [per min] mean (± SD)</td>
<td>39 ± 10</td>
</tr>
<tr>
<td>Range</td>
<td>10–75</td>
</tr>
<tr>
<td>Hyperparasitemia* (%)</td>
<td>78 (16)</td>
</tr>
<tr>
<td>Vomiting (%)</td>
<td>281 (58)</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>121 (25)</td>
</tr>
<tr>
<td>Hepatomegaly (%)</td>
<td>102 (21)</td>
</tr>
<tr>
<td>Prostration (%)</td>
<td>102 (21)</td>
</tr>
<tr>
<td>Severe anemia† (%)</td>
<td>92 (19)</td>
</tr>
<tr>
<td>Nasal flaring (%)</td>
<td>66 (14)</td>
</tr>
<tr>
<td>Chest crepitation (%)</td>
<td>56 (12)</td>
</tr>
<tr>
<td>Jaundice (%)</td>
<td>56 (12)</td>
</tr>
<tr>
<td>Blantyre coma score ≤ 3 (%)</td>
<td>42 (9)</td>
</tr>
<tr>
<td>Severe respiratory distress syndrome† (%)</td>
<td>25 (5)</td>
</tr>
<tr>
<td>Severe vomiting‡ (%)§</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Severe dehydration¶ (%)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Case fatality rate (%)</td>
<td>5 (1)</td>
</tr>
</tbody>
</table>

* Parasite count > 250,000 μL.
† Hemoglobin < 5 g/dL.
‡ Presence of either marked indrawing (recession) of the bony structure of the lower chest wall or deep (acidotic) breathing (WHO 2000).
§ Repeated vomiting with inability of eating and drinking.
¶ Very dry mucosa, and capillary refill > 3 seconds and pinch retracting very slowly.

FIGURE 1. Correlation of the MODS on admission with the time until patients regained the ability to walk unaided in 414 children with P. falciparum malaria (Group 1; Spearman $r = 0.79$, P < 0.001).
The involvement of more than four organ systems in a patient (sMODS > 1) was associated with the inability to sit unaided for > 24 hours with a sensitivity of 100% and a specificity of 60% (AUC, 0.85; 95% CI, 0.81–0.89).

Of all 485 children admitted to the study, 5 patients (1%) died after 1, 2, 3, 15, and 28 hours of admission with a sMODS on admission of 27 (3 patients), 29 (1 patient), and 36 (1 patient). One patient remained in a vegetative state after having an initial score of 25. All patients with a score of ≤ 22 had recovered fully until discharged from hospital.

**sMODS and the WHO criteria for severe malaria.** The performance of a sMODS ≥ 16 in detecting patients with prolonged disease duration (> 48 hours unable to walk) with respect to the WHO criteria for severe malaria was analyzed by comparing the correctly classified patients by the two scoring systems. Of the 410 patients, 74% were correctly classified by the WHO criteria and 80% by the sMODS. Interestingly, 45 patients were correctly classified by the sMODS and misclassified by the WHO criteria whereas only 21 patients misclassified by the sMODS were correctly identified by the WHO criteria. According to this data, the sMODS proved non-inferior to the WHO criteria at a significance level of P < 0.01.

**Convulsions, cerebral malaria, and the simplified MODS.** Thirty-five patients had cerebral malaria (7%) with a sMODS on admission of ≥ 22. Four of these children died (11%), one patient remained in a vegetative state, and one patient moderately disabled because of visual field impairment. In Group 1, children with cerebral malaria had a significantly higher sMODS on admission (21 ± 3 compared with 14 ± 2, P < 0.001) and a prolonged disease duration (able to walk unaided: mean 85 versus 17 hours, P < 0.001; able to sit unaided: mean 52 versus 6 hours, P < 0.001). Only four patients with cerebral malaria were enrolled in Group 2.

The MODS on admission was significantly higher in patients with reported convulsions before admission (N = 106, 22%; mean 17 versus 14; Student t test, P < 0.001) and observed seizures during hospitalization (N = 66, 14%; mean ± 18 versus 14; Student t test, P < 0.001).

**Severe respiratory distress syndrome and sMODS and outcome.** The sMODS in severe respiratory distress syndrome (sRDS) was significantly higher compared with the non-sRDS group (19 ± 2 and 14 ± 3, P < 0.001) with prolonged disease duration in Group 1 (able to walk and sit unaided, P < 0.001). Only four patients with sRDS were enrolled in Group 2.

**Severe anemia, sMODS, and outcome.** The MODS in severe anemia was significantly higher compared with the group without severe anemia (17 ± 3 and 14 ± 2, P < 0.001) with prolonged disease duration in Group 1 (able to walk unaided: mean 44 versus 17 hours, P < 0.001; able to sit unaided: mean 20 versus 67 hours, P < 0.001).

**DISCUSSION**

The sMODS has previously been proven effective to assess the severity of *P. falciparum* malaria in a low transmission area. We now have extended this work to a setting in sub-Saharan Africa where transmission is high and asymptomatic infection is common.

The sMODS on admission allowed the identification of different levels of severity of illness in children based on clinical evaluation. All organ systems except “the blood” were evaluated by clinical means. The score was strongly correlated with the outcome results such as regaining the ability to walk, sit, drink, or eat: a sMODS of ≥ 16 was indicative for prolonged disease duration in all groups. Moreover, abnormalities recorded in more than four organ systems could also accurately detect patients unable to walk for > 48 hours (Group 1) or unable to sit for > 24 hours (Group 2). Both these parameters can easily be used to identify children at risk already when admitted to the hospital.

The prognostic value of a new scoring system in *P. falciparum* malaria is evaluated by its usefulness in the early prediction of mortality. In our group of patients, only five children died, and mortality could therefore not be tested by statistical methods; however, all of these patients had an excessively high score of ≥ 27 on admission. Second, a score should predict morbidity such as disease duration, prolonged disability, or permanent neurologic sequelae. The sMODS is not inferior to the WHO criteria for predicting prolonged disability in *P. falciparum* malaria. Using this simple tool, we
can now provide additional information to the patients’ relatives early on admission.

Criteria for severe *P. falciparum* malaria still rely on partially sophisticated laboratory based data such as NO, arginine, or lactate levels, which, however, have been strongly predictive for poor outcome. Using the sMODS, we now have a simple and effective measure of severity where all organ systems except “the blood” are evaluated by clinical means. This score is strongly correlated with the MODS based on laboratory analysis.6

Within the MODS, every organ system is equally weighted. This may underestimate certain strong predictors for poor recovery such as severe anaemia, hyper-lactatemia, and coma.4 However, severe manifestation in a single organ system is usually accompanied by dysfunction in other systems. Children with severe anaemia differ in their clinical presentation when mild dysfunction of other organ systems is manifest (e.g., tachycardia, hyperventilation). The sMODS accurately reflects severity by its quantitative approach and should detect a high risk of deterioration in patients.

This score can be useful in various conditions: 1) clinical field workers can evaluate the patients’ severity and identify children at risk to refer them for hospitalization; 2) physicians can allocate more resources to patients with a high score on admission before their condition deteriorates; 3) the MODS and sMODS may also be useful for researchers, who often struggle to select appropriate patients for their research.

Moreover, the sMODS can be used for surveillance of severity. Our observation of predominance of severe manifestation in certain months—as described already two decades ago—should be interpreted with caution because we did not include outpatients in our analysis. However, if properly applied, the sMODS could be used as marker for seasonal variability of malaria severity to allocate economic and hospital-based resources. Furthermore, surveillance of severity could be performed more precisely over years.

In our group of patients, a high sMODS on admission was associated with a history of convulsions and observed seizures during hospitalization. Neurologic sequelae were rarely observed. *P. falciparum* malaria complicated by seizures and cerebral malaria is associated with long-term neurologic sequelae of seizures and focal neurologic deficiencies mainly consisting of speech and language problems. The predictive value of the sMODS for developed impairment and cognitive deficiencies in children was not addressed.

This study has stressed the usefulness of the simplified MODS in discriminatory analysis of the severity of *P. falciparum* malaria in African children. This simple and effective score is based on physical examination with only a thermometer a stethoscope and a sphygmomanometer. Hemoglobin concentration and parasite count are the only laboratory parameters. This score is easy to apply and can therefore be used in health institutions with limited resources in tropical countries.

Received December 9, 2005. Accepted for publication April 1, 2006.

Acknowledgments: We are indebted to all the patients who took part in the study and to their parents or guardians whose dedication to collaborate made this study possible.

Financial support: This project was supported by Medical University Innsbruck Project P5190-013-011-Intensiv.

Authors’ addresses: Raimund Helbok, Clinical Department of Neurology, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria, E-mail: Raimund.Helbok@ukibk.ac.at. Saadou Issifou, Albert Schweitzer Hospital Research Unit, Lambaréné, Gabun. E-mail: issifou@lambarene.mimcon.com. Pierre Blaise Matsiegui, Albert Schweitzer Hospital Research Unit Lambaréné, Gabun. Peter Lackner, Clinical Department of Neurology, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria, E-mail: Peter.Lackner@uibk.ac.at. Michel Missinou and Davy Kombila, Albert Schweitzer Hospital Research Unit, Lambaréné, Gabun. Wolfgang Dent, Clinical Department of Neurology, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria, E-mail: Wolfgang.Dent@macnews.de. Erich Schmutzhard, Department of Intensive Care Unit and the Department of Neurology Clinical Department of Neurology, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria, E-mail: Erich.Schmutzhard@uibk.ac.at. Peter G. Kremsner, Institute for Tropical Medicine, University Hospital Tübingen, Wilhelmstrasse 27, 72074 Tübingen, Germany, E-mail: Peter.Kremsner@uni-tuebingen.de.

REFERENCES