Severe Falciparum Malaria in Children at Somdejt Prachaotaksin Maharaj Hospital

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Objective: *Evaluate WHO guideline for the treatment of severe malaria.*
Material and Method: *A retrospective study in 41 pediatric patients who were admitted and diagnosed as severe malaria in Somdejtprachaotaksinmaharaj Hospital between July 2003 and June 2006 was performed.*
Results: *Most patients were older than 5 years (83%). The common clinical features and complications were cerebral malaria (12%), severe anemia (7.3%), metabolic acidosis (7.3%), acute renal failure (4.8%) and pulmonary edema (4.8%). These were not different from other reports. Hypoglycemia and hemoglobinuria were not found. 58.5% of the children were classified as having increased risk of dying. All of them received intravenous artesunate and oral mefloquine with improvement. None of them died. Paracitic clearance time was about 2.6 days, fever clearance time was about 3.4 days and resistant type1 was about 4%.*
Conclusion: *Intravenous administration of antimalarial drug is essential for the group of children at increased risk of dying and artesunate plus mefloquine is effective.*

Keywords: *Severe falciparum malaria, Clinical feature, Complications, Treatment*

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Malaria continues to be a major health problem in many parts of the world. More than two billion people, 40% of the world's population, in some 100 countries, are at risk[1]. In Thailand, this remains a serious health problem in ten provinces along the frontier[2]. Infection with *plasmodium falciparum*, which is responsible for the severe form of the disease, can be fatal in the absence of prompt diagnosis and urgent appropriate management. The situation is complicated by the increasing occurrence of falciparum parasites that are resistant to chloroquine and other antimalarial drugs[3-5]. Prompt management is especially important for high-risk groups such as young children. Delay in diagnosis and treatment can cause a severe form of the disease, may result in rapid deterioration in the patient's condition and development of life threatening complications[6,7]. Revised standard criteria of severe malaria have been proposed by the World Health Organization (WHO2000) to identify children at high risk[1].

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Somdejt Prachaotaksin Maharaj Hospital is in Tak Province, which is on the Thai-Myanmar border. This province had the highest incidence of malarial infection in Thailand[2]. During the past five years, (2001-2005), malaria has been one of the main causes of admission to the Pediatric Unit of the hospital.

The objective of the present study was to study the clinical features, complications, laboratory findings, and treatment in children with severe falciparum malaria.

Material and Method

A retrospective study was performed. The medical records of patients data aged less than fifteen years who were admitted to the Pediatric Unit, Somdejt Prachaotaksin Maharach Hospital, Tak Province, from July 2003 to June 2006 and who met the WHO (2000) criteria for severe malaria[1] were reviewed for demographic data, season on admission, clinical features, complications, treatment with antimalarial drugs, and outcomes. In the study hospital, complete blood count with peripheral blood film for malarial parasites was routinely done on the first day of admission and

repeated everyday until negative. Serum electrolytes, liver function tests, blood urea nitrogen, and creatinine tested on the first day of admission and repeated periodically if necessary. Chest x-rays were done in the patients with respiratory distress or abnormal lung signs. Lumbar puncture was performed when clinically indicated. When the patients improved clinically and malaria parasites disappeared from blood circulation, the patients were discharged and followed within 2-4 weeks thereafter for a complete blood count and blood film for malaria parasites.

The statistical analyses were performed with the use of the SPSS (Version10.0) and the data were analyzed by Chi-square test or Fisher's exact test. A p-value of less than 0.05 was considered as statistically significant.

Results

There were 41 severe malaria patients included in the present study. Twenty-five patients were males (61%) and 16 females (39%). Most of them were more than 5 years old (34 cases,83%). There was no patient whose age was less than 1 year. Most of the cases were in the rainy season (June to September), followed by winter (October to January) and summer (February to May) (Table 1).

All of the patients had fever on the first day of admission. Other clinical features,complications and laboratory findings are shown in Table 2.

The five patients who had cerebral malaria were 7-10 years old. It is worth noting that they usually had other complications concomitantly (Table 3). According to WHO 2000 criteria, 24 cases (58.5%) were classified into children at immediate increased risk of dying (group 1), one case (2.4%) was classified into children, who required supervised management because of the risk of clinical deterioration (group 2), and 16 cases (39%), were classified into children who required parenteral treatment because of persistent vomiting (group 3) (Table 4). All of the patients in group 1 were treated with a stat dose of intravenous artesunate 2.4 mg/kg, followed by 1.2 mg/kg at 12 hours and 24 hours and then 1.2 mg/kg once daily for 5 days and when the patients improved and could tolerate oral medication, oral mefloquine 15, 10 mg.base/kg at 6 hours interval were given. In this group, the paracitic clearance time was about 2.6 days, fever clearance time was about 3.4 days and resistant-type 1 was found in one case (4%). In group 2, the present study had only one case (9 years old) who received oral quinine sulfate 10 mg.base/kg every 8 hours combined with tetracycline 5 mg/kg four times per day for 7 days, the parasitic clearance time was 3 days, fever clearance times was 4 days and there was no resistance. In group 3, all of the patients received a stat dose intravenous quinine dihydrochloride 20 mg/kg in 4 hours (all of them had no history of previous quinine administration within 48 hours) followed by 10 mg/kg every 8 hours was given for the total treatment duration of 7 days. The paracitic clearance time was about 3.2 days, fever clearance time was about 4.2 days and resistant-type1 was found in two cases (12.5%). None of the patients died in the present study.

Discussion

In the present study, most of the patients were more than 5 years old and no patient who was in the first year of life. These may be due to the passive immunity offered by the maternal antibodies[8], retarded and poor growth of the parasites in the erythrocytes containing HbF[9,10], PABA (para-aminobenzoic acid) free breast milk feeding[11] and low risk of contact to anopheles mosquitoes. Most of the patients were found in the rainy season and males were found more than females. Clinical features and complications of severe malaria in children were different from adults[12,13]. The common clinical features were fever, anemia, hepatomegaly, splenomegaly, gastrointestinal symptoms es-

Table 1. Demographic data of the patients and seasonal distribution (n = 41)

	Male (25) n (%)	Female (16) n (%)	Weight Mean (kg), (range)	RS n (%)	W n (%)	S n (%)
Age-group (years)						
>1-5 yrs	3 (7.3%)	4 (9.8%)	13.10 (10-16)	4 (9.8%)	1 (2.4%)	2 (4.8%)
>5-10yrs	9 (22%)	8 (19.5%)	24.00 (17-29)	10 (24.4%)	5 (12.2%)	2 (4.8%)
>10-15yrs	13 (31.7%)	4 (9.8%)	33.50 (25-50)	12 (29.3%)	2 (4.8%)	3 (7.3%)

RS: Rainy season (June to September),W: Winter (October to January), S: Summer (February to May)

Table 2. Clinical features,complications and laboratory findings of the studied patients (n = 41)

	Finding (n)	%	Non-finding (n)	%	p-value
Fever	41	100	0	0	0.00
Prostration	24	58.5	17	41.4	0.27
Anemia	24	58.5	17	41.4	0.27
Vomiting	19	46.3	22	53.7	0.63
Chill	14	34.0	27	65.8	0.04
Abdominal pain/Diarrhea	8	19.5	33	80.5	0.00
Hepatomegaly	11	26.8	30	73.1	0.00
Splenomegaly	7	17.0	34	83.0	0.00
Cerebral malaria	5	12.0	36	87.8	0.00
Severe anemia (Hct < 15%)	3	7.3	38	92.7	0.00
Metabolic acidosis (HCO3 < 15 mmole/L)	3	7.3	38	92.7	0.00
Hypotension	2	4.8	39	95.1	0.00
Acute renal failure	2	4.8	39	95.1	0.00
Pulmonary edema	2	4.8	39	95.1	0.00
Febrile convulsion	1	2.4	40	97.6	0.00
WBC < 5,000/cumm	22	53.6	19	46.3	0.63
Platelet count < 150,000/cumm	33	80.5	8	19.5	0.00
Platelet count < 50,000/cumm	16	39.0	25	61.0	0.16
Malaria infection rate < 1%	13	31.7	28	68.3	0.02
Malaria infection rate 1-4%	23	56.0	18	44.0	0.43
Malaria infection rate > 4% (Hyperparasitemia)	5	12.0	36	88.0	0.00
Serum sodium < 130 mmole/L	10	24.4	31	75.6	0.00
Elevated AST/ALT	9	22.0	32	78.0	0.00
Elevated BUN/Cr	2	4.8	39	95.1	0.00

Table 3. Group of cerebral malaria (n = 5)

	Finding (n)	%	Non-finding (n)	%	p-value
Convulsion	3	60	2	40	0.65
Severe anemia (Hct < 15%)	2	40	3	60	0.65
Metabolic acidosis (HCO3 < 15 mmole/L)	3	60	2	40	0.65
Hypotension	2	40	3	60	0.65
Acute renal failure	2	40	3	60	0.65
Pulmonary edema	2	40	3	60	0.65
Serum sodium < 130mmole/L	4	80	1	20	0.18
Platelet count < 150,000/cumn	4	80	1	20	0.18
Malarial parasites > 4%	1	20	5	80	0.18

Table 4. Groups of patients according to WHO2000 criteria, treatment and results

	n (%)	Parasitic clearance time (days) Mean (days)	Fever clearance time (days) Mean (days)
Group 1	24 (58.5%)	2.6	3.4
Group 2	1 (2.4%)	3	4
Group 3	16 (39%)	3.2	4.2

pecially vomiting. These clinical features were not specific for malaria[11-13]. In the present study, the clinical features were not different from the previous report[14]. In the area of low endemicity (unstable area) such as Thailand, severe infection occurs in all age groups including adults and the morbidity and mortality tend to be very high[1,6,7,11-13]. These patients may present with confusion or drowsiness with extreme weakness (prostration). In addition, cerebral malaria, severe anemia, hypoglycemia, metabolic acidosis with respiratory distress, fluid and electrolyte disturbances, acute renal failure, acute pulmonary edema, circulatory collapse, abnormal bleeding, jaundice, hemoglobinuria, high fever and hyperparasitemia may develop[7,11-13].

The most serious symptoms of cerebral malaria include convulsion with coma and metabolic acidosis combined with hypoglycemia[7,11-13]. It has been reported that the malaria parasite was not found in the first blood film in some patients[6], therefore empirical therapy with appropriate antimalarial drug should be given in the malaria-suspicious patient and repeated blood film periodically. Coma scale should be used to monitor levels of consciousness and therapeutic response[15]. Convulsion was found in 50-80%[6,16,17]. It may be confirmed by EEG[18]. One report in Thailand revealed that convulsion was found in non cerebral malaria and was more common in small children under three years of age[19]. Increase intracranial pressure was found in 80%[20,21]. If CSF examination is indicated to exclude central nervous infection, it should be done carefully. In the present study, almost all patients with cerebral malaria were more than 7 years old and many of them had hyponatremia and thrombocytopenia but only a few had the other complications. CSF examination was done in only one case; normal CSF was found but the pressure was not measured. Metabolic acidosis, which was found in 60% of the cases, was no different from the previous report[22].

Severe anemia is the most common complication in children and the frequency of 55% was reported in a previous study[13]. Frequency and severity depend on the severity and duration of parasitemia. In hyperparasitemia, it may develop rapidly due to hemolysis of the parasitic red cells[9,10]. In the present study, this was found in only 7.3% and may be because hyperparasitemia occurred in only 12% and most of the patients were admitted early. Packed red cell transfusion 5-10 ml/kg may be used if Hct < 20% although WHO suggested that blood transfusion is indicated for Hct < 15% to avoid HIV-transmission[1].

Hypoglycemia (blood sugar < 40mg/dl) is common in children compared to adults and a frequency of 16-52% has been reported in previous studies[16,23]. It may be associated with lactic acidosis and may result from impaired gluconeogenesis, increased tissue demand for glucose, hyperparasitemia, and quinine induced hyperinsulinemia[24,25]. The patients may present with convulsions or impaired consciousness. Hypoglycemia was not found in the present study. It may be because almost all patients received early management with intravenous fluids and electrolytes in the emergency room and hyperparasitemia were found in only 12%.

Metabolic acidosis are complex. A number of interrelated measures have been used in different studies and respiratory distress has been associated with hyperlactatemia. These features probably resulted from increased anaerobic metabolism due to tissue hypoxia[22,24]. In the present study, it was found in only 7.3% and most of them had cerebral malaria.

Bleeding tendencies with prolonged clotting, thrombocytopenia and decreased coagulation factors, spontaneous bleeding from various sites including upper gastrointestinal tract may occur[1,6,7,10]. In the present study, thrombocytopenia was found in 80.5% of the cases but almost all of them had no clinical abnormal bleeding.

Jaundice is less common in children. This may be due to intravascular hemolysis and impaired liver function[6,7,12]. In this study, elevated AST/ALT was found in 22% of the cases but almost none of them had jaundice.

Acute renal failure and pulmonary edema are rare complications in children[6,7,11-13]. A slight increase in urea and creatinine may sometimes occur due to dehydration and it becomes normal after rehydration. Pulmonary edema may be due to plasma leakage or fluid overload. In the present study, both complications were found 4.8% each, most of them were associated with cerebral malaria and the cause of pulmonary edema was fluid overload. Hemoglobinemia and shock are also not common in children[6,7,10-13]. Hemoglobinemia was not found in the present study but hypotension and hyponatremia on admission were found in 4.8% and 24.4% of the patients, respectively.

Management of severe falciparum malaria is a medical emergency, the patients should receive intensive monitoring, good nursing care, prompt treatment of complications and antimalarial therapy. The mortality rate of cerebral malaria has been reported to be about 13.5-22%[16,17,23], the risks of mortality were

patients under 3 years old and had multiple complications[26]. In the present study, the group at immediate increased risk of dying (group 1 of the WHO 2000 criteria) was treated with intravenous artesunate combined with oral mefloquine. The parasitic clearance time was about 2.6 days, fever clearance time was about 3.4 days and resistant type 1 was about 4%. This supports the previous report[27] that atesunate made patients rapidly gain consciousness, become afebrile, and malarial parasites disappeared faster than with quinine. None of the patients died in the present study. It may be because 83% of the patients were more than 5 years old and received prompt diagnosis and treatment with appropriate antimalarial drugs.

Conclusion

Severe falciparum malaria in children is always a serious infection and requires emergency diagnosis and management. Classification of patients according to the WHO 2000 criteria should be used in general hospitals. Intravenous administration of antimalarial drug is essential for the group of children at increased risk of dying and artesunate plus mefloquine is effective.

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โรคมาลาเรียฟัลซิพารัมชนิดรุนแรงในเด็ก ที่โรงพยาบาลสมเด็จพระเจ้าตากสินมหาราช

เบญจศิลป์ นิภาเกษม

การศึกษาครั้งนี้มีวัตถุประสงค์ เพื่อศึกษาโรคมาลาเรียฟัลซิพารัมชนิดรุนแรงในเด็กตามเกณฑ์ของ WHO 2000 โดยทำการศึกษาเกี่ยวกับ ลักษณะทางคลินิกที่สำคัญ โรคแทรกซ้อน ผลการตรวจทางห้องปฏิบัติการที่สำคัญ และการรักษา ได้ทำการศึกษาข้อมูลย้อนหลังของผู้ป่วยเด็กที่เป็นโรคมาลาเรียฟัลซิพารัมชนิดรุนแรงที่เข้ารับการรักษาในกลุ่มงานกุมารเวชกรรม โรงพยาบาลสมเด็จพระเจ้าตากสินมหาราช จังหวัดตากระหว่างวันที่ 1 กรกฎาคม พ.ศ 2546 ถึงวันที่ 30 มิถุนายน พ.ศ 2549 รวมระยะเวลา 3 ปี พบมีผู้ป่วยรวมทั้งสิ้น 41 ราย ผู้ป่วยส่วนใหญ่มีอายุมากกว่า 5 ปีโดยพบร้อยละ 83 ลักษณะทางคลินิกทั่วไปและภาวะแทรกซ้อนไม่แตกต่างจากการศึกษาอื่น ๆ โดยพบมาลาเรียขึ้นสมองร้อยละ 12 ภาวะซีดมากร้อยละ 7.3 ภาวะเลือดเป็นกรดร้อยละ 7.3 ภาวะไตวายและภาวะปอดบวมน้ำพบเท่ากันคือร้อยละ 4.8 แต่ไม่พบภาวะน้ำตาลในเลือดต่ำและภาวะปัสสาวะดำ ผู้ป่วยกลุ่มที่มีโอกาสเสียชีวิตสูงพบร้อยละ 58.5 ซึ่งผู้ป่วยกลุ่มนี้ได้รับยา artesunateชนิดฉีดร่วมกับ mefloquine ชนิดรับประทาน ไม่พบมีผู้ป่วยเสียชีวิตในผู้ป่วยกลุ่มนี้ ระยะเวลาเฉลี่ยที่ตรวจไม่พบเชื้อ 2.6 วัน ระยะเวลาเฉลี่ยที่ไข้ลด 3.4 วัน พบการดื้อยาแบบที่ 1 ร้อยละ 4 ดังนั้นการใช้ยาต้านเชื้อมาลาเรียชนิดฉีดเข้าเส้นเลือดยังมีความจำเป็นในผู้ป่วยเด็ก กลุ่มที่มีความเสี่ยงต่อการเสียชีวิตและการใช้ยา artesunateชนิดฉีดร่วมกับยา mefloquineชนิดรับประทานยังมีประสิทธิภาพอยู่