Original Article

The Relationship between the Plasmodium Falciparum Clearance and the Clinical Effect of the Case with Cerebral Malaria Treated with Artemisinin

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Malaria is 1 mosquito-borne disease, which is most commonly caused by a parasite called *Plasmodium falciparum* (*P. falciparum*). Cerebral malaria is the most severe neurological complication presented in patients infected with *P. falciparum*. Impaired consciousness often lead to coma considers as one of the most significant manifestations of cerebral malaria. State of coma and existence of asexual forms of the parasite on peripheral red blood cells are the two most important factors for diagnosis. High mortality is associated with cerebral malaria and some surviving victims may sustain brain injury and lead to long term neuro-cognitive impairments.

The pathogenesis of neuro-cognitive sequelae in cerebral malaria is poorly understood; however, the clinical characteristics of cerebral malaria were believed to be caused by parasitized red blood cells sequestered in cerebral microcirculation, in addition to the involvement of possible metabolic factors, such as hypoglycemia and inflammatory mediators. Contrary to popular belief, some studies had suggested that the severity of clinical presentation in cerebral malaria was not in direct association with the number of infective agents existing in the system. In order to investigate the link between the number of infective agents and severity of clinical manifestation as well as the effect of medication therapy in a patient

with cerebral malaria, a 36-year-old Chinese man was chosen as the subject of the investigation.

PATIENT AND METHODS

Patient and treatment

The patient, male, 36 years old, who had traveled to Africa for work, came back to China after a four-month stay in Nigeria. Approximately ten days after his return to China, he presented with signs and symptoms such as chills, fever, headache, dark urine and jaundice. Two hours following his admission to the hospital, the patient developed high fever and neck rigidity along with neuro-cognitive impairments.

Proper investigation was conducted and appropriate detection were ordered. The causative pathogen was identified as *P. falciparum* and a diagnosis of cerebral malaria was confirmed based on clinical presentation and laboratory results.

Artesunate was selected as the primary line of treatment and the patient was treated with 100 mg in three consecutive occasions; however, the patient's situation did not make progress and Artesunate was considered as becoming slowly effective by oral treatment and Artemether 80 mg was administered accordingly.

Consequently, the patient responded positively to the treatment and his conditions took a turn toward stability. In addition to Artemether, other medications such as mannitol and methylprednisolone were administrated to reduce intracranial pressure.

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Table 1. The clinical presentation and treatment of the patient

		Day 1	Day 2	Day 3	Day 4	Day 7
Pathogenical treatment	Drugs and doses	Artesunate 100 mg (po)	Artesunate 150 mg (po); Artemether 160 mg (im)	Artemether 80 mg (im)	Artemether 80 mg (im)	Artesunate 50 mg Bid; Stop using Artemether
	Cumulant of drug	Artesunate 100 mg	Artesunate 250 mg; Artemether 160 mg	Artesunate 250 mg; Artemether 240 mg	Artesunate 250 mg; Artemether 320 mg	Artesunate 450 mg; Artemether 480 mg
Adjuvant therapy	Methylprednisolone	120 mg	120 mg	80 mg	40 mg	stop
	Dehydrating agent (20% mannitol)	125 ml, Q8H	125 ml, Q8H	125 ml, Q12H	125 ml, Q12H	stop
Effect	Number of plasmodium (/100 RBC)	16	4	2	0	0
	Body temperature	40.5°C	37.8°C	37.0°C	36.8°C	36.7°C
	Consciousness	Light coma	fidgety	Light fidgety	sanity	sanity
	Meningeal irritation sign	Chin-Sternum	Chin-Sternum	Chin-Sternum		
		Straight	Straight Distance	Straight	No	No
		Distance 5Fb	4Fb	Distance 2Fb		
	WBC (10 ⁹ /L)	19.06	16.88	17.74	12.05	7.83
	N%	72.1	53.8	47.8	44.3	46.8
	PLT (10 ⁹ /L)	33	51	79	65	218
	HGB (g/L)	69	62	79	75	96

Calculations of the plasmodium falciparum

Peripheral blood smears were prepared and Giemsa's staining method was applied to determine the numbers of *Plasmodium falciparum* per 100 red blood cells.

The number of pathogens per 100 red blood cells was calculated every day.

RESULTS

The patient with cerebral malaria caused by *P. falciparum* was treated with Artemisinin, the relationship between the clearance of *P. falciparum* of quantitative results and the effects of the treatment was shown in Table 1.

The patient was hospitalized for 10 days, and from the 7th day, Artemether intramuscular injection was suspended and changed to Artesunate orally. The patient was discharged on the 11th day, he walked out the hospital by foot and was told to keep taking Artesunate orally until back to hospital for the reexamination after 5 days. The condition of the patient in the 5th and 6th

days was almost the same with that of the 7th day. From the 4th day, his peripheral blood plasmodium was undetectable (Figure 1-Figure 3).

The quantity of the pathogen

The number of pathogens per 100 red blood cells was calculated for three consecutive days (16, 4, 2/100 RBC). On the 4th day the causative agent was no longer detectable Figure 4.

DISCUSSION

Malaria is a mosquito-borne infectious disease caused by human malaria parasites. Commonly, the disease is transmitted via a bite from an infected female Anopheles mosquito, which transmits the organisms from its saliva into a person's circulation system. In the blood, the protists travel to the liver to mature and reproduce, then get into the RBC and proliferated more merozoites, which were finally released from the broken RBC and caused the clinical manifestation.

Figure 1. *Plasmodium falciparum* detected before accepting artemisinin treatment (Giemsa's staining, peripheral blood smear)

Notes: 16/ 100matured RBC was detected, inside of the red cycles were the *Plasmodium falciparum*.

Figure 2. *Plasmodium falciparum* detected the first day after accepting pathogenic treatment with artemisinin (Giemsa's staining, peripheral blood smear)

Notes: 4/ 100RBC, and shape of the ring bodies of the *Plasmodium falciparum* changed.

Figure 3. *Plasmodium falciparum* detected on the 3rd after admission (Giemsa's staining, peripheral blood smear)

Note: 2 /100RBC.

Figure 4. *Plasmodium falciparum* detected on the 4th day after admission (Giemsa's staining, peripheral blood smear)

Notes: no *Plasmodium* was detectable.

The main representation of malaria is recurrent attacks of remittent chill, high fever and body temperature down to normal after profuse sweating. There are four kinds of plasmodium that can affect human being, *Plasmodium vivax*, *Plasmodium ovale*, *malaria plasmodium* and *plasmodium falciparum*. The pattern of fever in *Falciparum malaria* is irregular high fever, most cases were persistent fever without intermission. Cerebral malaria is the most severe type.^{1,2}

Most cerebral malaria cases were caused by *Falciparum malaria*, occasionally caused by plasmodium ovale. The main clinical manifestations are headache, fever and varying degree of conscious disturbance. The mechanism of onset of cerebral

malaria was not very clear yet, present study believed that cerebral malaria onset was related to the cerebral capillary being blocked by infected RBC and the damage of the hemato encephalic barrier. The ligand produced by *Plasmodium falciparum*, for example PfEMP-1,³ would help to attach on the RBC and became red blood cells infected by *Plasmodium* (PRBC), which adhered to each other, and also adhered to the vascular endothelial cell, causing PRBC stasis in the cerebral capillary and brain tissue hypoxia-ischemia. *Plasmodium* was a kind of antigen to the human body, which would stimulate to produce some soluble factors leading to the damage of the hemato encephalic barrier (BBB),⁴ that would cause

local BBB leaking, and some chemical substances such as saliva haemagglutinin was detectable in brain tissue. And the chemical substances or factors would cause the brain tissue damage and dysfunction.^{5,6} And in some severe cases with acute liver failure (ALF) would lead to hepatic encephalopathy(HE), which would contribute to the brain dysfunction as well.⁷ Some other studies showed that in some severe cases with *falciparum malaria*s, not even the brain tissue would be damage, but also other organs such as liver, kidney, ect, could be found capillary leak and bleeding, which could be one of the causes of multiple organ dysfunction. Moreover, some researches reported that some soluble media such as tumor necrosis factor, interleukin-1 would cause temporary neurotoxicity and led to reversible conscious impairment.^{5,8,9} Numerous broken RBC would cause severe acute anemia, led to brain tissue hypoxia-ischemia, and worsen the conscious disturbance.⁹

Regarding this case, after receiving effective pathogenic therapy (artesunate and artemether), the plasmodium decreased quickly. On the 1st day of admission (before the pathogenic treatment), the amount of *P. falciparum* was 16/100 RBC, which were 4/100 RBC and 2/100 RBC on the 2nd and 3rd day after pathogenic therapy, respectively. And from the 4th day, the plasmodium couldn't be found any more, which meant that *P. falciparum* was sensitive to Artemisinin. Also, the clinical manifestation released, the body temperature dropped to normal gradually (dropping from the peak of 40.5°C at the 1st day gradually to 36.7°C, and then back to normal completely). The neurological symptom of the patient progressed on the 1st day, with light coma, and consciousness became clearer day by day, then back to normal completely on the 7th day; and the meningeal irritation sign, neck rigidity released slowly, then the neck became flexible and could

touch his sternum on the 7th day. The routine blood test showed the white blood cell (WBC), platelet and hemoglobin also improved as the clearance of *P. falciparum*. Our study showed that the severity to cerebral malaria was related to the amount of *P. falciparum* in peripheral blood. If the amount of *P. falciparum* was at a high level in the peripheral blood, the patient's manifestation was severe, and the manifestation released as the parasites decreased after treatment.

The manifestation of this case with cerebral falciparum malaria released quickly after treatment with Artemisinin, simultaneously with the *plasmodium falciparum* cleared in the blood stream, which implied that *plasmodium falciparum* might play a very important role directly in the mechanism of malaria.

REFERENCES

1. Yang SJ, Ren H. Epidemiology (7th edition), People's Health Publisher;267-275.
2. Li YL, Guan XH. Human Parasitology (6th edition), People's Health Publisher;61-75
3. Craig A, Scherf A. Molecules on the surface of the Plasmodium falciparum infected erythrocyte and their role in malaria pathogenesis and immune evasion. Mol Biochem Parasitol 2001;115:129-143.
4. Huang F, Xia MY. The damage of the blood-brain barrier is the sign of cerebral malaria? Intl J Med Paras Dis 2004;31:29-31.
5. Rubin LL, Staddon JM. The cell biology of the blood-brain barrier. Ann Rev Neurosci 1999;22:11-28.
6. Brown H, Turner G, Rogerson S, Tembo M, Mwenechanya J, Molyneux M, et al. Cytokine expression in the brain in human cerebral malaria. J Infect Dis, 1999;180:1742-1746.
7. Martins YC, Daniel-Ribeiro CT. A new hypothesis on the manifestation of cerebral malaria: The secret is in the liver. Med Hypotheses 2013;81:777-783.
8. Mayhan MG. Regulation of blood-brain barrier permeability. Microcirculation 2001;8: 89-104.
9. Glynn JR, Bradley DJ. Inoculum size, incubation period and severity of malaria. Analysis of data from malaria therapy records. Parasitology 1995;110:7-19.