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Handling cerebral malaria patient with limited resources: a case report

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Cerebral malaria is an emergency condition. All patients with *Plasmodium falciparum* infection followed by neurological symptoms should be treated as cerebral malaria. The pathogenesis of cerebral malaria is caused by the damage of blood vessels endothelium due to parasites sequestration, production of pro-inflammatory cytokines and leakage of blood vessels which can cause brain hypoxia. The proper management is needed, however this become quiet challenging issue in the setting of limited resouces. We report a case of a 35 year old patient presenting with a loss of consciousness accompanied by shivering fever for 5 days. On examination of the peripheral blood smear, the *Plasmodium falciparum* was found. The patient was later diagnosed as cerebral malaria and treated with anti-malarial drugs. The fifth day of treatment the patient has fully alert. In the next day, the patient was allowed to go home. The management of cerebral malaria is challenging, particularly in the area with limited resources.
Keywords: *cerebral malaria, emergency, Plasmodium falciparum, artesunate, limited resources.*

Malaria serebral merupakan suatu kondisi gawat darurat. Semua pasien dengan infeksi *Plasmodium falciparum* yang diikuti dengan gejala neurologis harus diperlakukan sebagai malaria otak. Patogenesis malaria serebral disebabkan oleh rusaknya pembuluh darah endotel akibat sekuestrasi parasit, produksi sitokin pro-inflamasi, dan kebocoran pembuluh darah yang dapat menyebabkan hipoksia otak. Kebutuhan penatalaksanaan yang tepat diperlukan, namun hal ini menjadi suatu tantangan pada situasi dengan sumber daya terbatas. Kami melaporkan kasus pasien berusia 35 tahun yang mengalami kehilangan kesadaran disertai demam menggigil selama 5 hari. Pada pemeriksaan apusan darah tepi ditemukan *Plasmodium falciparum*. Pasien kemudian didiagnosis sebagai malaria otak dan dirawat dengan obat antimalaria. Hari kelima pengobatan pasien sadar baik. Keesokan harinya, pasien diperbolehkan pulang. Penanganan malaria otak merupakan tantangan, terutama di daerah dengan sumber daya yang terbatas.
Kata kunci: *malaria serebral, gawat darurat, Plasmodium falciparum, artesunate, sumber daya terbatas*.

BACKGROUND

Malaria is a disease caused by protozoa, genus plasmodium and living intracellularly, which can be categorized as acute or chronic infection. The World Health Organization (WHO) defines severe malaria if there is *P. falciparum* parasitemia in the asexual phase accompanied by one or more of the following clinical or laboratory features: 1) clinical manifestations include: weakness, impaired consciousness, respiratory distress (respiratory acidosis), recurrent seizures, shock, pulmonary edema, abnormal bleeding, jaundice, hemoglobinuria, 2) laboratory tests, such as, severe anemia, hypoglycemia, acidosis, impaired kidney function, hyperlactatemia, and hyperparasitemia.[1]

Cerebral malaria is a serious infection caused by the parasite named *Plasmodium falciparum* with a high mortality rate.[2,3] The infection is transmitted through the bite of anopheles mosquito.[2] In 2015, around 214 million cases of malaria were found worldwide.[3] WHO reports that this case most widely found in Africa (90%) then followed by Asia (7%).[3] In 2018, there were 228 million cases of malaria worldwide with 405,000 deaths.[4] Several species of plasmodium were found but *Plasmodium falciparum* and *Plasmodium vivax* were most oftenly caused complications in humans. Cerebral malaria is one of the 'scariest' complications of *Plasmodium falciparum* infection and the most frequent cause of death, which is around 13%.[4]

Symptoms of cerebral malaria resemble encephalitis syndrome in the form of decreased consciousness, seizures, ataxia, hemiparesis, hemiplegia, psychiatric disorders, coma to death.[6,7] Symptoms of severe malaria can be worsen within hours.[7] Other symptoms include upper motor neuron symptoms, there are no focal neurological symptoms, cranial nerve palsy, neck stiffness, deserebration, conjugate deviation while retinal bleeding was sometimes found. The decrease of consciousness is not only due to neurological disorders but can also be exacerbated by metabolic disorders such as acidosis, hypoglycemia, which means that this disorder can occur due to

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several pathological processes. Predisposing factors for severe malaria are children under five, pregnant women, patients with low immunity, for example patients with malignant diseases, HIV, patients on corticosteroid treatment, residents from malaria endemic areas who have long left and returned to the endemic area.[1]

The diagnosis was made based on clinical neurological symptoms accompanied by the discovery of an asexual form of the parasite on a peripheral blood smear. It is important to rule out other causes of encephalopathy (such as hypoglycemia, bacterial meningitis and viral encephalitis).[8] The difference between cerebral malaria and persistent post-ictal coma is that the impaired consciousness in cerebral malaria can last about 30 minutes after the patient has had a seizure. All patients with plasmodium falciparum infection with neurological symptoms of varying degrees should be treated as cerebral malaria. The pathogenesis of cerebral malaria is the destruction of blood vessel endothelium due to parasite sequestration, the production of cytokines that cause inflammation and leakage of blood vessels.[7,8] As for the management, proper management with adequate monitoring is mandatory. However, it possess several challenges in the setting of limited resources.

The following article reported a patient who came with complaints of decreased consciousness accompanied by shivering fever. Further investigation then carried out by examining the peripheral blood smear; that was later found the *Plasmodium falciparum*. The management in the setting of limited resources were applied for the patient.

CASE ILLUSTRATION

A 35-year-old man was brought by his family to the emergency room with complaint of fever since five days before being admitted to the hospital. According to family, the patient admitted that the fever improved by taking anti-fever drugs but then the fever returned. Fever more likely to increase at night accompanied by shivering and sweating profusely thereafter. The patient also complained of headache for five days. He came to the emergency room, with a decreased consciousness state. The family said that the patient began to fall unconscious one day before being admitted to the hospital. The patient also experienced nausea and had no appetite for five days. He also complained of tea-colored urination. The patient admitted that he had suffered from malaria three years ago. Other medical history was denied. Family history of having the same complaint is refuted. The patient lived in remote area.

Physical examination found a somnolence state with a glasgow coma scale (GCS) E3V4M3, the patient has had seizures for two times at home. The vital sign found blood pressure is 80/60 mmHg, pulse 120 times/minute, respiration rate (RR) 20 times/minute, axilla temperature 39°C, SpO2 94%. The visual analog scale (VAS) pain score 4/10, height 165 cm and body weight 60 kg. Eye examination revealed scleral icterus. Abdominal examination revealed right upper quadrant tenderness and the liver was palpable three fingers below the rib arch and ½ toward the xyphoideus process. Spleen palpable on Schuffner III. The extremities felt cold.

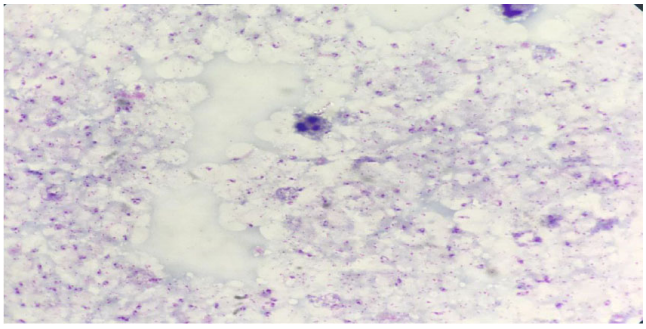

Figure 1. Microscopic appearance of plasmodium falciparum on examination of the peripheral blood smear.

On neurological examination, there were no symptoms of upper motor neuron disorders, there were no focal neurological symptoms, cranial nerve palsy, neck stiffness, deserebration and conjugate deviation. On routine blood laboratory examination when the patient first arrived was found: Hb 19.9 g/dl, hematocrit 60.9%, leukocytes 14,500/dl, and platelets 120,000/l. Complete liver and urine function tests are not available. Ultrasound and radiological examinations such as x-rays are not available. On the examination of the peripheral blood smear, a trophozoite plasmodium falciparum (+++) was obtained and a banana shaped stage of gametocytes (figure 1) so that it could be confirmed that the patient was suffering from cerebral malaria.

Patients received 0.9% 20 dpm NaCl therapy, 1000 mg paracetamol flash, 4 lpm nasal cannula oxygen and antimalarial drugs (a combination of artesunate and DHP/dihydroartemicinin piperaquin), and to treat seizures the patient received 10 mg diazepam intravenously. On the first day of treatment, the patient still had shivering fever accompanied by yellow eyes with decreased consciousness (GCS E3V4M3). The patient had no seizures after receiving 10 mg diazepam intravenously when he first arrived at the hospital. Vital sign examination obtained blood pressure 100/60 mmHg and pulse rate 120 times/minute, respiratory rate 20 times/minute, axillary temperature 39°C and SpO2 94%. The patient received 150 mg intravenous artesunate therapy at 24 hours of admission. Examination of the peripheral blood smear found plasmodium falciparum (+++), which means that 1-10 parasites were found in 1 HPF (high power field).

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On the second day of treatment the patient's condition had started to improve, the fever gradually dropped and the complaint of shivering was denied. Vital sign examination showed blood pressure 110/80 mmHg and pulse 80 times/minute, respiratory rate 20 times/minute, axillary temperature 37.9°C, and SpO2 94%. The patient received 150 mg of intravenous artesunate therapy. Examination of the peripheral blood smear found plasmodium falciparum (++), which means that 11-100 parasites were found in 100 HPF.

On the third day of treatment the patient's condition had improved, fever and shivering were denied. Awareness of patients was improved with GCS of E4M6V5. Vital sign examination showed blood pressure 110/80 mHg and pulse 80 times/minute, respiratory rate 20 times/minute, axillary temperature 37°C, and SpO2 94%. The patient received 150 mg of intravenous artesunate therapy. Examination of the peripheral blood smear found no plasmodium falciparum (-).

On the fourth day of treatment, the patient's condition was good, the fever was gone. Vital sign examination showed blood pressure 110/80 mmHg and pulse 82 times/minute, respiratory rate 20 times/minute, axillary temperature 37°C, and SpO2 94%. The patient received 150 mg intravenous artesunate therapy and 4 tablets of DHP every 24 hours. Examination of the peripheral blood smear found no plasmodium falciparum (-).

On the fifth day of treatment the patient was fully conscious, fever and shivering were gone. Vital sign examination showed blood pressure 110/80 mmHg and pulse 82 times/minute, breath 20 times/minute, axillary temperature 36.7°C, and SpO2 96%. The patient received 4 tablet of DHP every 24 hours while intravenous artesunate therapy was discontinued. Examination of the peripheral blood smear found no plasmodium falciparum (-). On the sixth day of treatment, the patient was allowed to go home. Table 1 provided patient's monitoring while being treated at the hospital.

DISCUSSION

Malaria is a parasitic infections caused by *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* which attacks erythrocytes and is characterized by the presence of the asexual forms in the blood. The characteristic of the plasmodium falciparum parasite compared to other plasmodiums is the presence of sequestrating infected red blood cells in the blood vessels of various organs, especially in the brain. After the sporozoites enter the bloodstream through the bite of anopheles mosquito, these parasites then enter the liver cells (hepatocytes) and then the stage called 'extra erythrocyte schizogony' occurs. The mature schizones will then break (rupture) and then the merozoites will invade erythrocyte cells, inducing intraeritrocyte schizogony, that makes the erythrocytes containing parasites to undergo changes in cell structure and biomolecular (to maintain the parasite cycle). These changes include cell membrane transport mechanisms, decreased deformability, rheological changes, knob formation, expression of neoantigen variants on the cell surface, citoadheren, rosseting and sequestration. The ripe schizont will then break.[1]

In this case the patient was diagnosed as cerebral malaria caused by falciparum malaria. The base for the diagnosis is the presence of fever attacks at certain intervals (paroxism), interspersed with a fever-free period (latent period) and on the peripheral blood examination found plasmodium falciparum, so that it can be confirmed that the patient is suffering from cerebral malaria.

Table 1. Patient daily monitoring at the hospital.

Monitoring	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Symptoms	Fever day-5, shivering, decreased consciousnesssscleral icterus And seizure	Fever day-6, shivering, decreased consciousnesssscleral icterus	Fever day-7, fever decreased, improved consciousness	Fever (-), improved consciousness	Fever (-), vomitus (-)	Fever (-), fully awake, vomitus (-)
Blood smear	*Plasmodium falciparum* (+++)	*Plasmodium falciparum* (+++)	*Plasmodium falciparum* (++)	*Plasmodium falciparum* (-)	*Plasmodium falciparum* (-)	*Plasmodium falciparum* (-)
Lab						
White Blood Cell (WBC)	14.500	9.9	8.8	8.0	7.3	7.1
Hemoglobin	19.9	19.2	17.4	16.9	16.0	15.5
Hematocrite	60.9	50.9	46.6	45.1	43.5	44.0
Platelets	120.000	87.000	131.000	169.000	178.000	180.000
Therapy	Started artesunate 170 mg (at 12 AM, and 12 PM) and IV diazepam 10 mg	Artesunate 150 mg (at 12 AM)	Artesunate 150 mg	Artesunate 150 mg	DHP 1x4 (Orally) Artesunate 150 mg	DHP 1x4 (Orally)

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In this patient, a 5-day history of fever was found with three consecutive stages (typical of malaria), namely the cold stage where the patient was shivering, the fever stage where the patient's body temperature increased and the sweating stage where it appeared while the body temperature decreased. Symptoms of cerebral malaria in adults are usually preceded by fever.[9] Initial symptoms usually appear 10 to 15 days after the bite, these symptoms include high fever (40°C-40.5°C), muscle aches, headache, sweating and other symptoms resembling flu syndrome.[10,11,12] Fever begins at the same time as the rupture of the blood schizonts secreting various antigens. This antigen will stimulate macrophage, monocyte or lymphocyte cells that secretes various cytokines, including TNF (Tumor Necrosis Factor) and IL-6 (Interleukin-6). TNF and IL-6 will be carried by the bloodstream to the hypothalamus, which is the center for controlling body temperature and a fever occurs.[13]

Plasmodium falciparum is the most common species in Indonesia. The second most common is *Plasmodium vivax*. The highest prevalence of *Plasmodium falciparum* is in eastern Indonesia, namely Papua (33%) followed by Nusa Tenggara (29%) and Sumatra (21%).[14] In 2010, it was estimated that 132.8 million people is at risk of malaria infection mainly by P. falciparum. Its distribution is in the western region of Indonesia covering Java with a population of 80.4 million, Sumatra with 23.3 million and Kalimantan with a population of 8.5 million. The population at risk in the eastern region of Indonesia is 20.7 million and spread across Sulawesi, Maluku and Papua.[14]

The physical examination included scleral icterus accompanied by hepatomegaly and splenomegaly. Hepatomegaly and splenomegaly occur due to increased production and destruction of erythrocytes and other blood cells involved in the immune response to plasmodium in the liver and spleen, which are reticuloendothelial organs.[13,15] Cerebral malaria can be diagnosed based on the following criteria: impaired consciousness or coma, absence encephalopathy or other conditions resembling cerebral malaria and the discovery of the parasite *Plasmodium falciparum* on peripheral blood tests.[16]

Examination of the patient's peripheral blood smear revealed a high parasite density. There was a relationship between parasite density and mortality from falciparum malaria. Mortality increased at the parasite density of 100,000 / µl and when the parasite density was 500,000 / µl the mortality rate reached 50%. The parasite density rate can be used to assess the severity of the disease. In malaria endemic areas, high parasite densities are often found in asymptomatic individuals, on the other hand, there are cases of death due to malaria with low parasite density. The severity of the disease is determined more by the number of parasites sequestered into the tissue than by the number of parasites in the circulation.

The patient also had seizures on arrival at the hospital. Seizures occurred throughout the body with a duration of 10 minutes and did not recur. After the seizure, the patient was then being unconscious for 30 minutes. Seizure (both focal or general type) in cerebral malaria occur about 20% in adults while in children is around 70%.[10,11,16]

Seizures in cerebral malaria are often associated with increased intracranial pressure. The clinical manifestations of seizures and decreased consciousness are caused by microvascular abnormalities that cause increased cytokines and metabolite products that damage neurons. Sequestrated parasites produce local toxins and ischemia or affect inflammatory products such as cytokines and produce multiple seizures and neuronal damage.[8] The role of TNF-α and other interleukins mediates the release of nitric oxide in tissues. Several interleukins are involved in febrile seizures and epileptogenesis.[18] Status epilepticus is rare in cerebral malaria.[10,16] After seizures stop the patient is then unconscious. Coma in cerebral malaria is caused by a decrease in blood flow to the brain, which causes an increase in the production of lactic acid in cerebrospinal fluid.[19]

Another symptom of a *Plasmodium falciparum* infection is anemia. Anemia or decreased blood hemoglobin levels is caused by the destruction of excessive red blood cells by the parasite. Anemia also occurs due to impaired formation of red blood cells in the bone marrow and a shorter lifespan of red blood cells.[20] *Plasmodium falciparum* usually infects all red blood cells so that falciparum malaria results in greater form of anemia.

In this case the patient had elevated hemoglobin and hematocrite levels. This is probably due to the hemoconcentration. Hemoconcentration in patients is caused by fever. Hemoconcentration, among others, is caused by plasma leakage, lack of fluid intake and loss of fluids due to fever.[21] Complete blood count examination when the patient first arrived, found thrombocytopenia. The mechanism of thrombocytopenia in malaria is not fully understood, many studies have estimated the pathoimmunological mechanism of thrombocytopenia in malaria. Oxidative stress, Macrophage Colony Stimulating Factor (M-CSF), platelet-related immunoglobulin, namely platelet associated immunoglobulin G (PAIgG), an increase in free plasma cells circulating levels of nucleic acid in plasmodium falciparum and platelet phagocytosis are mechanisms that may result in excessive platelet damage.[7] In this patient the thrombocytopenia and hemoconcentration improved as the patient's clinical condition improved.

Cerebral malaria has a fairly high mortality rate, which is around 15-50%.[10,16,20] The prognosis of cerebral malaria depends on how we handle the complications that occur such as renal failure, severe jaundice and metabolic acidosis

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conditions. In this case the patient suffered from mild jaundice, but due to limited facilities, liver function tests such as AST or ALT and bilirubin tests were not possible to undergo.

Improper malaria treatment can lead to resistance, leading to widespread of malaria cases and increased morbidity. WHO has recommended the treatment of malaria globally using the ACT drug regimen and has been approved by the Indonesian Ministry of Health since 2004 as the first line drug in Indonesia. The goal of radical therapy in malaria is to eliminate all stages of parasites including the asexual stage and the sexual stage (gametocyte) from the blood to achieve clinical and parasitological state of 'plasmodium-free' and break the chain of transmission. It is known that gametocytes play an important role in the transmission of malaria infection. Gametocytes are an infective stage that will continue the next stage of development in the mosquito's body.[21]

The findings of gametocytes in the patient's blood indicated that the source of infection was still there. Treatment with ACT must be accompanied by confirmation of microscopic detection of malaria parasites or at least by means of an RDT (Rapid Diagnostic Test) examination. Currently, the national program is using artemisinin derivatives with the aminokuinolin class, namely a combination of dehydroartemisinin and piperaquine (DHP) and artesunate-amodiakuin.[21]

Treatment of cerebral malaria are using intravenous artemisin derivatives, such as artesunate and quinine. In this case the patient received intravenous artesunate at a starting dose of 170 mg. During 5 days of hospitalization, it was found that the patient's condition had improved and on the examination of the peripheral blood smear there was no plasmodium falciparum. Artesunate use is known to reduce mortality by about 34.7% compared to quinine, besides that artesunate also reduces episodes of seizures, coma, and hypoglycemia. Artesunate has low toxicity, is easy to obtain and is effective in all parasite cycles. Therefore artesunate is the drug of choice.[10,11]

SUMMARY

A case of a patient with cerebral malaria had been reported. The diagnosis of cerebral malaria should be considered in patients who live in a place with a high prevalence of malaria with symptoms of shivering fever accompanied by seizures and decreased consciousness. Cerebral malaria treatment is mainly medical, namely by intravenous artesunate. During five days of treatment the clinical improvement was seen. In the sixth day of hospitalization, the patient was allowed to go home.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

ETHICS CONSIDERATION

This case report has obtained informed consent from the patient as well as the following COPE for publication ethics guidelines.

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None.

AUTHOR CONTRIBUTIONS

All authors contribute to the study from selecting a case, evaluating the laboratory results until interpreting the case study through publication.

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