

Headache and Malaria: A Brief Review

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Abstract- Malaria is an important tropical mosquito-borne infectious disease. In this article, the author briefly reviewed headache profile in patients with malaria focusing on its mechanism. Headache is an important presentation in malaria, either cerebral type or not. The cytokine is believed to be an important factor leading to headache in acute malaria. Some antimalarial drugs can cause headaches. In addition, headache is one of the symptoms of postmalaria neurologic syndrome.

Key Words: Headache, Malaria

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INTRODUCTION

Malaria is an important tropical mosquito-borne infectious disease especially in the tropical regions. Millions of people suffer from this infection annually. At present, the endemic areas are the tropical countries in Africa and Asia. World Health Organization classified malaria as a severe global public health threat⁽¹⁾. Similar to other blood-borne infections, alterations in basic laboratory results occur in patients infected with malaria. Concerning the laboratory abnormalities in patients with malaria, aberration of hematological laboratory parameters is very common. The diagnosis usually depends on the examination of blood smear. Presentation of inclusions as malarial parasite or malarial pigment is the key to definite diagnosis. Four main kinds of malaria can be seen including vivax, falciparum, ovale and malariae. All three types of blood cells can be affected by malarial infection. Considering red blood cell, anemia, as a result of malarial infection, is

widely mentioned. Severe and refractory anemia can lead to hypoxia and cardiac decompensation in malarial patients⁽²⁾. Fatality is common for falciparum malaria. Several mechanisms have been proposed in the pathogenesis of malarial anemia, such as erythrocyte lysis and phagocytosis, and sequestration of parasitized red blood cells⁽²⁾. Erythrocyte lysis is related to several kinds of cytokine productions especially tumor necrotic factor⁽³⁾. This is the main pathophysiology of high fever in malaria. Currently, antimalarial drugs are quite effective. However, the most effective prevention is to control mosquito and mosquito bite. In this article, the author reviews the headache profile in patients with malaria, focusing on the underlying mechanism.

MAGNITUDE OF HEADACHE IN MALARIA

As previously mentioned, the major manifestation of malaria is an acute febrile illness. Fever and headache

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are classical presentations of malaria. Suyaphan et al noted that up to 80 % of malarial infected cases presented headache⁽⁴⁾. The onset of headache is usually acute and there is no specific location⁽⁴⁾. Patients had accompanied symptoms such as nausea and vomiting⁽⁴⁾. The headache usually lasts for the whole duration of illness⁽⁴⁾. Benson and Davis noted that there should be a high index of suspicion for anyone from an endemic area presenting with fever, vomiting, diarrhea, headache and/or muscle pain, even if he or she has been tested or treated for malaria⁽⁵⁾. Faiz et al reported that intermittent fever, vomiting, headache, convulsion and history of travel or residence in malaria endemic area were important features noted in patients with cerebral malaria⁽⁶⁾. Faiz et al reported that 75.5 % patients with malaria had headache⁽⁶⁾. However, only 30.8 % of cerebral malarial cases reported having headache in India⁽⁷⁾. According to these quoted studies, it can be accepted that the headache is an important presentation in malaria, either cerebral type or not.

MECHANISTIC PATHOGENESIS OF MALARIA-RELATED HEADACHE

The mechanism of headache in acute malaria is not well described. The cytokine is believed to be an important factor that might lead to headache in acute malaria. Indeed, malarial pathogenesis is now generally associated with excessive production of pro-inflammatory cytokines, such as tumor necrosis factor, which is known to induce headache⁽⁸⁾. Not only tumor necrosis factor, interleukin 1, another cytokine that can be detected in a high level in acute malaria⁽⁹⁻¹⁰⁾ is believed to lead to headache. In addition, it should be noted that cytokine levels are usually high in cerebral malaria⁽¹¹⁻¹²⁾ but this does not relate to severity⁽¹⁰⁾. There is no difference in the frequency or intensity of headache between cerebral and non-cerebral malaria⁽¹³⁻¹⁴⁾. In fact, studies showed no evidence on the difference among different types of malaria⁽¹³⁻¹⁴⁾. The exact mechanistic pathogenesis of malaria-related headache requires further studies.

ANTIMALARIAL DRUGS-RELATED HEADACHE

Antimalarial drugs can induce headache. Quinine, the drug of choice for severe malaria, is widely mentioned for possible headache induction. High concentrations of quinine or cinchonism are toxic to the cardiovascular system, producing hypotension and abnormal myocardial conduction⁽¹⁵⁻¹⁶⁾. Auditory symptoms, gastrointestinal disturbances, vasodilatation, sweating, and headache can occur with moderately elevated plasma quinine concentration⁽¹⁷⁾. The headache in cinchonism is believed to be due to extreme vasodilation⁽¹⁷⁾.

Concerning mefloquine for prophylaxis, headache is documented as an adverse reaction. Kitchener et al reported that the most commonly reported adverse effects of mefloquine were sleep disturbance, headache, tiredness and nausea⁽¹⁸⁾. However, these adverse events are tolerable⁽¹⁸⁾. The condition namely "mefloquine syndrome" should be mentioned⁽¹⁹⁾. This syndrome may present with severe headache, gastrointestinal disturbances, nervousness, fatigue, disorders of sleep, mood, memory and concentration, and occasionally frank psychosis⁽¹⁹⁾. This makes intolerance to mefloquine prophylaxis⁽¹⁹⁾. This adverse reaction is significantly more frequent in women than in men⁽²⁰⁾. The frequency of headache in patients who took the mefloquine for malarial prevention was reported as 4.8 %⁽²¹⁾. Rendi-Wagner et al suggested that the unexpectedly severity of adverse reactions after therapeutic dosage of mefloquine in healthy subjects might influence future recommendations regarding the use of mefloquine for stand-by treatment of suspected malaria cases⁽²²⁾.

POSTMALARIA NEUROLOGIC SYNDROME

Neurologic signs and symptoms are common in acute malarial infection⁽²³⁾.

However, after the parasites have been cleared from the blood and the patients had recovery, transient neurologic or psychiatric symptoms may occur or recur within two months after the sickness⁽²³⁾. This is known as post-

malaria neurologic syndrome⁽²³⁾. The exact pathogenesis for this discrete transient neurological syndrome after

recovery from severe infection is not well described. Headache is one of the features of postmalaria neurologic syndrome that can be seen in about 10 % of all cases^(23,24). Headache features of this syndrome include a severe headache associated with nausea and possible profound confusion and impaired memory⁽²⁴⁾. The latency from infection to neurological dysfunction is described and complete spontaneous resolution is mentioned^(24,25). Steroid might be useful in some severe cases^(24,25). Nguyen et al. suggested that although mefloquine was not the only risk factor for postmalaria neurologic syndrome but it was a strong one⁽²⁶⁾. They indicated that if there was an effective alternative drug available, mefloquine should not be used after treatment of severe malaria⁽²⁶⁾.

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