Antioxidants may help prevent malaria complicaton that leads to learning impairment

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Using an experimental mouse model for malaria, an international group of scientists has discovered that adding antioxidant therapy to traditional antimalarial treatment may prevent long-lasting cognitive impairment in cerebral malaria. Their findings were published online June 24, 2010, in the journal *PLoS Pathogens*.

Malaria, an infection caused by parasites that invade liver and red blood cells, is transmitted to humans by the female Anopheles mosquito. Malaria is one of the leading infectious diseases worldwide, affecting more than 400 million people and causing more than 2 million deaths each year, mainly among African children. Recently, the U.S. Centers for Disease Control and Prevention (CDC) issued a report on 11 laboratory-confirmed cases of malaria among U.S. emergency responders and those traveling in the United States from Haiti.

Cerebral malaria is a severe, potentially fatal neurologic complication of infection by the most-feared malarial parasite, Plasmodium falciparum. Recent studies of children with cerebral malaria indicate that cognitive deficits, which may impair memory, learning, language, and mathematical abilities, persist in many survivors even after the infection itself is cured.

"Cerebral malaria and its molecular mechanisms are under intense study, but the cognitive dysfunction that can persist in survivors in the

aftermath of successful treatment has gone unrecognized until recently," says Guy A. Zimmerman M.D., professor and associate chair for research in the University of Utah School of Medicine's Department of Internal Medicine and a contributor to the study. "This complication may impose an enormous social and economic burden because of the number of people at risk for severe malaria worldwide. Our findings demonstrate that, by using experimental models of cerebral malaria in mice, we can explore mechanisms of cognitive damage and also examine potential treatments for reducing or preventing neurologic and cognitive impairment."

Zimmerman and colleagues in Brazil studied the persistence of cognitive damage in mice with documented cerebral malaria after cure of the acute parasitic disease with chloroquine, an antimalarial therapy. By administering a battery of behavioral tests to these mice, post-doctoral fellow Patricia Reis, Ph.D., determined that impairment in memory skills was still present 30 days after the initial malaria infection. Cognitive deficits that persist for years after the episode of cerebral malaria have also been reported in 11 percent to 28 percent of children who survive the infection.

"Although we believe that long-term cognitive dysfunction after cerebral malaria is initiated by injury to the brain during the initial period of untreated infection, it is possible that the mechanisms for persistent cognitive deficits are independent of those that cause neurological injury and death during acute cerebral malaria," says Zimmerman. "Future research is aimed at clarifying this point. However, we have been able to demonstrate that oxidative stress is present in the brains of mice infected with cerebral malaria."

Oxidative stress is a situation in which there is an imbalance between the production of reactive oxygen-containing molecules that can damage cell structures and the body's ability to detoxify these molecules or repair the

resulting damage.

Zimmerman and his colleagues found increased production of molecules indicative of high oxidative stress in the brains of mice with cerebral malaria. They also found that treating mice with a combination of chloroquine and two antioxidant agents, desferoxamine and N-acetylcysteine, at the first signs of cerebral malaria prevented both inflammatory and vascular changes in the tissues of the brain, as well as the development of persistent cognitive damage. The addition of antioxidants did not diminish the efficacy of chloroquine in eliminating Plasmodia from the blood. Combination therapy with antioxidants and a newer antimalarial called artesunate was similarly effective in treating cerebral malaria and preventing subsequent cognitive impairment in mice.

Both desferoxamine and N-acetylcysteine have been used to treat other medical conditions in humans and their side effects are already known. The study authors suggest that these antioxidant drugs should be studied as additive therapy for antimalarial drugs in clinical trials in order to investigate their potential to reduce or prevent cognitive damage after cerebral malaria.

"Our findings are exciting because the clinical implications may not be limited to cerebral malaria," says Zimmerman. "Oxidative stress is thought to be an important mechanism in brain injury in other types of severe infection and in chronic non-infectious conditions such as neurodegenerative diseases. Antioxidant treatment may be a successful therapeutic strategy for controlling long-lasting neurological consequences in these conditions, as well."

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