Raising the curtain on cerebral malaria's deadly agents

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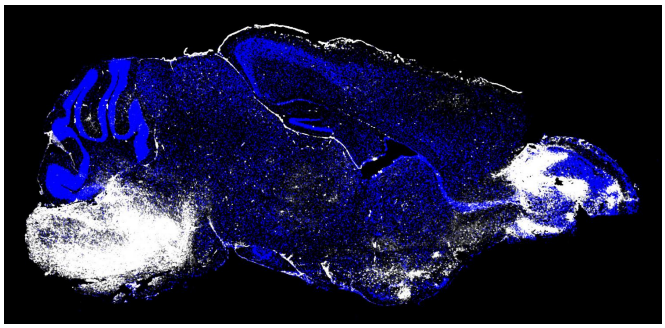

The brain of a mouse with cerebral malaria. White regions (left, brainstem and right, olfactory bulb) indicate areas of neuronal cell death and vascular leakage. Credit: Dorian McGavern, Ph.D., and Phillip Swanson II, Ph.D., NIH.

Using state-of-the-art brain imaging technology, scientists at the National Institutes of Health filmed what happens in the brains of mice that developed cerebral malaria (CM). The results, published in *PLOS Pathogens*, reveal the processes that lead to fatal outcomes of the disease and suggest an antibody therapy that may treat it.

"By looking into the living brain, we were able to watch the chain of events that cause cerebral malaria to kill thousands of people every year," said Dorian McGavern, Ph.D., scientist at the NIH's National Institute of Neurological Disorders and Stroke (NINDS). "Our study also suggests there may be a simple treatment available to stop this deadly disease."

Malaria is a parasitic infection that is spread by mosquitoes, primarily in the developing world. According to the Centers for Disease Control and Prevention, in 2015, there were more than 200 million cases of malaria worldwide and 400,000 deaths from the disease, mainly in children under five years old. Although many people experience mild symptoms, in some individuals the parasite affects the brain and causes cerebral malaria, which kills 15 to 30 percent of patients with that form of the disease. Individuals who survive cerebral malaria often experience long-term neurological symptoms including cognitive impairment and limb paralysis. The cause of death from cerebral malaria is often due to brain swelling and bleeding, but the mechanisms leading to these outcomes are not completely understood.

Previous studies in the rodent model of this disease indicated CD8+ T cells played a key role in the development of CM so Dr. McGavern's team focused its cameras on those cells.

Dr. McGavern and his colleagues peered inside the brains of mice infected with a parasite that causes CM, using an imaging technology known as intravital microscopy, which allowed them to watch cells in action.

The findings of this study showed that as red blood cells containing the parasite adhere to cerebral blood vessels (a hallmark of CM), the immune system attempts to clean them off. Despite these efforts, endothelial cells making up the walls of cerebral blood vessels shed bits of the parasite, which CD8+ T cells recognize, causing those immune cells to attach to and attack the vessels. Once the CD8+ T cells amassed on the surface of brain blood vessels, the vessels began to leak. The subsequent leaking led to swelling and increased pressure in the brain, which was fatal. Results also showed that the CD8+ T cells preferentially interacted with blood vessels in the brain and not in other parts of the body.

To determine which parts of the brain were affected by these events, the researchers injected mice with dyes that marked dead cells and blood vessel leakage. The results indicated that the brain regions with the most damaged vessels and cell death were the olfactory bulb (the area involved in

sensing smell) and crucially, the brainstem, an area that controls such vital functions as breathing and heart rate.

In another set of experiments, Dr. McGavern's group tested a potential therapy to see if it could be used to remove the CD8+ T cells from vessel walls. Initially, they watched as CD8+ T cells began to interact with the cerebral blood vessels in the CM mice. Then, they treated the mice with two FDA-approved, intravenous drugs that block the molecules that CD8+ T cells use to attach to blood vessels. Within 30 minutes of the treatment, the CD8+ T cells broke off from the blood vessels and could not stick to them, preventing the fatal brain swelling in all of the treated mice. These findings suggest that the interactions between CD8+ T cells and blood vessels lead to death from CM and preventing that binding may increase survival from the disease.

"These movies show us a terrible side effect sometimes associated with malaria—the parasite can fool the body's immune system into attacking the blood vessels within its own brain," said Dr. McGavern.

In future studies, Dr. McGavern and his colleagues will examine how the interaction between CD8+ T cells and cerebral vessels causes blood leakage and ways in which the brain recovers from CM infection. In addition, the live-action imaging technology from in this study may be used to watch ways in which other mosquito-borne illnesses, such as Zika and dengue, affect the brain.

More information: Phillip A. Swanson et al. CD8+ T Cells Induce Fatal Brainstem Pathology during Cerebral Malaria via Luminal Antigen-Specific Engagement of Brain Vasculature, *PLOS Pathogens* (2016). DOI: 10.1371/journal.ppat.1006022