Scientists advance understanding of deadly form of malaria

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Scientists are making strides against cerebral malaria, a fatal form of malaria in children that can ravage the brain and is extremely difficult to treat. New research points to platelets - known for their role in blood clotting - as playing an important role in the disease, stimulating the immune system and turning on molecules that increase inflammation. The inflammation leads to the obstruction of blood vessels in the brain, causing brain damage similar to that seen with a stroke.

The latest research, conducted by scientists at the University of Rochester Medical Center and published in the online journal PLoS ONE, is part of an ongoing effort to better understand the origin and development of cerebral malaria, which predominantly affects children under the age of 10 living in malaria-endemic areas, such as sub-Saharan Africa.

"Malaria is a complex disease and we need to look at it from every possible angle, focusing on both vaccine research and basic research, as we've done in this study," said Craig Morrell, D.V.M., Ph.D., assistant professor within the Aab Cardiovascular Research Institute at the Medical Center and lead author of the study. "Our findings increase our knowledge of cerebral malaria and suggest that targeting platelets may prove to be a viable intervention strategy."

Malaria is one of the world's biggest killers, accounting for approximately 1 million deaths each year. Research continues to expand, due in large part to the new emphasis organizations such as the Bill &

Melinda Gates Foundation have brought to the area. While research efforts are mainly focused on vaccine development, new therapies to treat malaria are needed, as the parasite that causes malaria - Plasmodium falciparum - is becoming resistant to current treatments. Morrell's team is one of the few groups studying the development and progression of cerebral malaria, with the goal finding new ways to intervene and treat the disease.

Malaria occurs when Plasmodium falciparum infects red blood cells. Once infected, red blood cells activate platelets, which secrete a key protein - platelet factor 4 or PF4/CXCL4. Morrell's lab found that PF4 jumpstarts the activity of the immune system, whose job it is to protect against foreign intruders - in this case, the malaria parasite - by turning on pro-inflammatory cells, known as monocytes. Monocytes contribute to the inflammation in the blood vessels that leads to obstructions in the brain.

Morrell's prior research demonstrated that mice without PF4 protein are protected from cerebral malaria compared to mice with PF4 intact. When PF4 is removed monocytes are not activated, and mice experience less inflammation and consequently less cerebral malaria. Morrell hopes that future experimental therapies targeting PF4 will prove to be viable treatment options for cerebral malaria.

Researchers also identified a key transcription factor - KLF4 - that is important for the development and overall function of monocytes in cerebral malaria. Targeting KLF4 may also hold promise for treating other vascular inflammatory diseases, such as atherosclerosis.

"Dr. Morrell's research is highly significant. He has discovered that platelets play a big role in malaria. His research may lead to novel treatments for malaria that target platelets instead of the parasite," said Charles Lowenstein, M.D., chief of Cardiology and director of the Aab

Cardiovascular Research Institute at the University of Rochester.

Morrell and team are currently building on this research, and have found that the role of platelets is more complex than they initially thought. Ongoing research will focus on when to intervene and influence the activity of platelets, as timing has been found to make a marked difference in the outcome. Additionally, scientists at Rochester are collaborating with researchers from Johns Hopkins University to look at drugs that are approved for the treatment of other conditions to see if they might be effective in treating cerebral malaria.

Cerebral malaria is the most serious and life-threatening form of malaria, and results from problems with the vascular and immune systems. In a recent study of children admitted to a hospital in Kenya who had malaria, 47 percent had neurologic symptoms indicative of cerebral malaria. Children are more vulnerable to cerebral malaria than adults, and if not treated within 24 to 72 hours the condition can be fatal.

Provided by University of Rochester Medical Center