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New twist in age-old war against malaria parasite

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Falciparum malaria parasite carried by mosquitoes might be cerebral but has it been outsmarted?
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Cerebral malaria, or malaria of the brain, means being deeply unconscious with perpetual cycles of seizures and spasms. It can cause death, or often disability. About 600,000 people suffer this terrible affliction each year and most of them are children.

Children who get cerebral malaria have a one-in-five chance of dying. If they survive, they have a high chance of being disabled - with hearing or vision loss, epilepsy or learning difficulties. But with little understanding of how to stop the brain becoming damaged, we've so far we've been fighting the battle blindfolded.

A tale of two halves - and six species

Malaria is caused by the Plasmodium parasite, which lives half its life in humans and the other half in the guts of female mosquitoes, who infect the next human victim when they feed on blood to make their eggs.

The deadliest of the Plasmodium parasites is found in Africa and accounts for 90% of all malaria deaths. It kills mostly children under five.

But only one of the six types of malaria parasites that is found in humans - *Falciparum malaria* - causes cerebral malaria. *Falciparum malaria* also occurs most commonly in Africa and also in Asia

and South America.

An evasive parasite

For malaria to survive in our bodies it must trick our immune system. It's a battle that has been waged between our immune systems and the malaria parasite for as long as recorded human history (malaria proteins have been found in ancient mummies).

Despite our defences, malaria has some tricks up its sleeve. Because the immune system is highly adapted to recognise anything foreign in the blood, the counter move is to hide and multiply inside our own red blood cells.

The body can also filter out abnormal red blood cells through the spleen but *Falciparum malaria* is especially tricky because it escapes the spleen by sticking to the walls of blood vessels - particularly the tiny blood vessels in the fat under your skin, the lungs, heart, gut and brain.

This ability to stick to the blood vessels in vital organs - called sequestration - is what makes the falciparum parasite more deadly than the other types of malaria. But given that sequestration occurs in many different places in our body, why is it so particularly damaging to the brain?

Sticking around, causing trouble

To study this vital question we examined the brains of children who had died of cerebral malaria. We found thousands of tiny clots that weren't found in other organs in the blood vessels of their brains. We noticed that these clots occurred in parts of the vessels where the parasites were stuck. We therefore wondered what was different about the lining of blood vessels in the brain than other organs and what the parasite was doing to cause clotting.

The lining of blood vessels - called the endothelium - is a highly specialised non-stick surface. Yet it must be able to rapidly adapt. When the body faces a bacterial or viral infection, the blood vessel lining traps the immune system's white blood cells by becoming more sticky - catching them and passing them through into the tissue where the infection is to kill it. In the case of damage from injury it must rapidly cause the blood to clot so we don't bleed to death.

The endothelium detects changes in the blood using receptors that jut out from its surface and it then feeds back messages to the blood cell. A particular set of receptors - the protein C receptors - act like a form of biological Teflon, keeping the blood cells from sticking and clotting.

However, we found that when the *Falciparum malaria* parasite sticks to the lining of the blood cells it removes these protein C receptors, allowing the parasite to hijack the endothelium's signalling system. So the blood vessel becomes stickier, helping other parasites to stick and, at the same time, causing the blood to clot. This happens particularly easily in the brain because there are fewer protein C receptors in the brain than in other organs.

Sometimes a 'cure' isn't good enough

There are medicines that are very good at killing the malaria parasite by clearing the infection from the blood. But if the process of developing cerebral malaria has already taken hold, the disease can carry on getting worse and even cause death before the drugs kill enough parasites to turn the situation around.

Because our understanding of how the cerebral malaria parasite caused damage in the brain was incomplete there have so far been no effective therapies for treating it.

Our research, which was published in Blood, the journal of The American Society of Hematology, suggests that treatments that stop clotting or that restore a normal signal to the endothelium might help prevent the terrible damage caused by cerebral malaria to the brain - and help prevent people who get it from dying or from becoming disabled before the anti-malarial drugs have a chance to kill all the parasites.

If so, it would give the immune system another weapon to fight the battle with *Falciparum malaria* and takes us one step closer to one day win the war.