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Medications that Reduce Endothelial Activation Prevents the Spread of Experimental Cerebral Malaria

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Introduction

The most severe neurological effect of Plasmodium falciparum infection-related malaria is cerebral malaria (CM). The parasite is successfully removed by the existing antimalarial medications, but the death rate in CM patients is still as high as 20%. CM exhibits endothelial activation and dysfunction at the vascular level. The brain vascular endothelium is a possible target for adjuvant therapy since a number of endothelial activation indicators have been linked to CM severity and death. Drugs used to treat hypercholesterolemia and hypertension, namely statins and angiotensin II receptor blockers (ARBs), have also been found to have endothelium protective action in other disorders [1].

Description

In a mouse experimental model of CM, we combined an ARB (irbesartan) and a statin (atorvastatin) as an adjuvant treatment to traditional antimalarial medications. When atorvastatin and irbesartan were administered, we saw a reduction in the levels of endothelial activation indicators such von Willebrand factor and angiopoietin-1. Treatment of mice with the combination of traditional antimalarial medications enhanced survival rates of animals 3–4 times compared to treatment with antimalarial medications alone, with animals exhibiting fewer and smaller haemorrhages in the brain. Our findings collectively provide credence to the idea that preventing endothelial activation would significantly lessen the pathology and mortality connected to CM [2,3].

Over the past 20 years, the prevalence of malaria has decreased by more than 40% because to concerted efforts by international organisations, regional governments and private foundations. While malaria continues to kill more than 600,000 people annually, with two-thirds of those deaths occurring in children under the age of five, these advancements have stalled in recent years. The most severe neurological consequence of malaria produced by Plasmodium falciparum infection, cerebral malaria (CM), is particularly dangerous for children in sub-Saharan Africa. The mortality rate associated with CM is between 15 and 20 percent and up to 25% of survivors experience long-term neurological consequences [4].

Antimalarial medications are efficient in removing parasites from the blood, but they have no particular impact against CM. Clinicians concur that patients need CM-specific adjunct therapy to prevent malaria-related mortality and/or cognitive deficits while antiplasmodial medication eliminates circulating parasites. Clinical studies for CM treatment have not yet shown any encouraging findings. Brains from patients with fatal CM are distinguished at the vascular level by the sequestration of parasitized red blood cells in the microvasculature, which is connected to the breach of the blood-brain barrier.

A substantial amount of data also shows endothelial activation and dysfunction during CM. Importantly, a number of endothelial activation indicators have been linked to malaria mortality and severity, making endothelial cells a viable target for CM adjuvant therapy. Angiopoietin-1, Angiopoietin-2 osteoprotegerin (OPG), thrombomodulin-2 and soluble cell-surface adhesion molecules are some of these indicators. Among them, Angpt-1 and 2 have received the greatest attention in the context of infectious illness research and there is a wealth of data supporting their involvement in endothelial dysfunction. The antagonistic ligands of the Tie2 tyrosine kinase receptor are known as Angpt-1 and Angpt-2.

In non-pathogenic conditions, Angpt-1 concentrations are higher than Angpt-2 concentrations, promoting the survival of endothelial cells. However, in cerebral malaria, Angpt-2 is released by endothelial cells and its concentration rises to surpass that of Angpt-1, increasing the blood-brain barrier's permeability. In this situation, CM may be used to "buy time" until conventional anti-Plasmodium medications remove the parasite by using vasoprotective therapies that stop blood-brain barrier disruption. Angiotensin II receptor blockers (ARBs) and statins, two medication families that have been shown to ameliorate endothelial dysfunction and partially protect against CM in animal models.

In our earlier research, we showed that ARBs, a family of medications used to treat hypertension, dramatically improved survival in a mouse model of CM and protected human endothelium monolayer integrity against P. falciparum-induced disruption. Similar to this, others have discovered partially protective effects of atorvastatin, a medication commonly used to treat hypercholesterolemia that also lessens mortality, lessens neuro inflammation and prevents cognitive impairment in mice with CM. It also prevents *P. falciparum* cytoadherence and endothelial damage *in vitro* [5].

Conclusion

For a number of disorders where endothelium integrity is impaired, such as Ebola infection, sepsis, pneumonia and influenza, therapies employing statins and/or ARBs have shown positive results in trials including both human populations and animals. According to certain theories, the positive effects of these medications are caused by the suppression of endothelial activation, which strengthens blood vessels and reduces edoema and haemorrhage. Since the levels of endothelium activation in patients or experimental animals were not assessed in these trials, this hypothesis could not be proved.

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