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# Murine cerebral malaria: how far from human cerebral malaria?

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White and colleagues recently maintained that the murine model of cerebral malaria (CM) is not relevant for the human pathology [1]. This conclusion was based on two principal arguments: (i) there is a major pathological difference between the two syndromes – namely, in humans, parasitized red blood cells (pRBC) are sequestered in the brain, whereas, in mice, it is leukocytes, not pRBC, that are sequestered, and (ii) interventions against CM in mice are highly effective, whereas in humans they have been ineffective thus far.

Figure 1 by White and colleagues showing the decrease in the number of publications in human CM should indeed be cause for major concern. More research on human CM is surely needed to find better ways to treat this devastating disease. I believe, however, that the murine model can be valuable in this quest. No experimental model can perfectly reproduce any human disease, and researchers working on the murine CM model should acknowledge its limitations, as often they do. Significant limitations are also present in human CM studies [2], particularly with post-mortem findings, upon which White and colleagues based most of their conclusions.

In relation to the first argument, White and colleagues stated that there is often little or no cytopathological evidence of inflammation in fatal human CM, although their own studies showed the common presence of activated leukocytes as well as moderate to strong ICAM-1 expression in brain vessels [3,4]. It can be argued that patients who died of non-cerebral complications of malaria also showed these changes, but this is also true for pRBC sequestration. On the other hand, *Plasmodium berghei* ANKA (PbA) pRBC sequestration in the brain is a matter of debate, with studies showing it to occur and to correlate with CM development [5], whereas others failed to demonstrate it [6]. These issues have been critically reviewed recently [2]. Using brain intravital microscopy and histology, we found pRBC and RBC accumulation in brain vessels, mostly trapped by adherent leukocytes and eventually contributing to vascular obstruction [7,8]. Direct pRBC interaction with the endothelium was not evidenced but cannot be ruled out as PbA sequestration is relatively short-lived [6].

Although the predominant blood cell type sequestered in human or murine CM may differ, the causes and consequences of sequestration seem to be very similar in both syndromes. *P. falciparum* and PbA share the ability of driving endothelial activation [3,9] and dysfunction [10,11] with increased expression of endothelial cell adhesion molecules (eCAMs) in the brain and in other vascular beds, making them receptive to leukocyte, platelet and pRBC binding. The more transient nature of PbA pRBC sequestration may help explain the quantitative differences in the sequestered cell type, with eCAMs being available for leukocyte binding during longer periods of time. White and colleagues maintain that pRBC sequestration is the



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primary cause of human CM by causing microvascular obstruction and reduced blood flow. If mechanical obstruction of blood flow is the cause of CM, the pathology is therefore rather similar in murine CM, even if leukocytes replace pRBC as the major – not the only – obstructive agent. Indeed, cerebral microcirculatory hemodynamic disturbances in murine CM have been shown to be similar to the *in vivo* retinal changes in human CM, with narrowing of the vascular lumen by adherent leukocytes (similar to the filling defects supposedly caused by pRBC sequestration in the retinal vessels), reduced blood flow, and occluded vessels with areas of poor or no perfusion (similar to the 'ghost' vessels of retinal whitening) [7,12]. Other consequences of sequestration and microvascular dysfunction or damage are alike in human and murine CM, such as micro-hemorrhages, vascular leakage, edema and other indicators of severe vasculopathy [2,11]. There are certainly specifics related to predominant leukocyte versus pRBC sequestration such as cytokine release, cell flexibility, rheological and coagulation properties, etc., that can affect the proximal microenvironment, yet many of the effects seem very similar. Endothelial cells, for instance, in both cases assume a pro-inflammatory and pro-coagulant phenotype, may loosen tight junctions and may undergo apoptosis, among other changes [9]. All the similarities indicate that the model is suitable for studying several aspects of CM physiopathogenesis and for testing therapeutic interventions, for instance, to improve perfusion or reduce ischemic damage. Obviously, specifics also mean that not every intervention will make sense or may be expected to have the same effect in the model as compared to human CM.

White and colleagues also presented a list of 48 'adjunctive' interventions with 92% success in preventing or ameliorating murine CM. Criteria to compile this list are unclear, as there were many studies missing and many unsuccessful interventions were not accounted for (Supplemental Table 1). For instance, anti-LFA-1 treatment is cited as effective, yet it is not acknowledged that in the LFA-1 studies a total of 7 interventions were tested, out of which only the anti-LFA-1 treatments were effective. My concern, however, is with the misuse of the term 'adjunctive treatments' to define these interventions. White and colleagues recognize that in none of the listed studies the treatment was given together with a 'primary' (antimalarial) drug, therefore these interventions by definition cannot be labeled 'adjunctive therapies' and obviously cannot be compared to human trials. Most of these studies were actually designed to investigate murine CM pathophysiology to define the role of a given cell, molecule or pathway in the development of the disease. This approach is appropriate, necessary and valid to identify mechanisms of pathogenesis and prospective targets for intervention. Nevertheless, improper claims for adjunctive therapy may have occurred in some studies, and White and colleagues are correct that such potential can only be ascertained with experiments using antimalarial drugs. This approach should indeed be encouraged.

Cerebral malaria is a scourge that demands a fight on several grounds, and the murine model stands as a precious resource. However, breakthroughs in physiopathogenesis and therapeutics in this model will be meaningless without a prospect for translational research. Reversing the trend in the number of studies in human CM is at the best interest of all involved in fighting this disease.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References


1. White NJ, et al. The murine cerebral malaria phenomenon. Trends Parasitol 2010;26(1):11–15. [PubMed: 19932638]
2. de Souza JB, et al. Cerebral malaria: why experimental murine models are required to understand the pathogenesis of disease. Parasitology 2009;23:1–18.
3. Pongponratn E, et al. An ultrastructural study of the brain in fatal *Plasmodium falciparum* malaria. Am. J. Trop. Med. Hyg 2003;69:345–359. [PubMed: 14640492]
4. Silamut K, et al. A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain. Am. J. Pathol 1999;155:395–410. [PubMed: 10433933]
5. Nie CQ, et al. IP-10-mediated T cell homing promotes cerebral inflammation over splenic immunity to malaria infection. PLoS Pathog 2009;5:e1000369. [PubMed: 19343215]
6. Franke-Fayard B, et al. Murine malaria parasite sequestration: CD36 is the major receptor, but cerebral pathology is unlinked to sequestration. Proc. Natl. Acad. Sci. U.S.A 2005;102:11468–11473. [PubMed: 16051702]
7. Cabrales P, et al. Murine cerebral malaria is associated with a vasospasm-like microcirculatory dysfunction and survival upon rescue treatment is markedly increased by nimodipine. Am. J. Pathol. Jan 28;2010
8. Martins YC, et al. Characterization of cerebral malaria in the outbred Swiss Webster mouse infected by *Plasmodium berghei* ANKA. Int. J. Exp. Pathol 2009;90:119–130. [PubMed: 19335550]
9. Faille D, et al. Platelet-endothelial cell interactions in cerebral malaria: the end of a cordial understanding. Thromb Haemost 2009;102:1093–1102. [PubMed: 19967139]
10. Weinberg JB, et al. Arginine, nitric oxide, carbon monoxide, and endothelial function in severe malaria. Curr. Opin. Infect. Dis 2008;21:468–475. [PubMed: 18725795]
11. Desruisseaux MS, et al. Cerebral malaria, a vasculopathy. Am. J. Pathol. Jan 21;2010
12. Beare NA, et al. Perfusion abnormalities in children with cerebral malaria and malarial retinopathy. J. Infect. Dis 2009;199:263–271. [PubMed: 18999956]