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Blood-Brain Barrier and Cerebral Malaria: The Road So Far

Mauro Prato[1,2]*

[1]Dipartimento di Neuroscienze, Università di Torino, Torino, Italy
[2]Dipartimento di Scienze della Sanità Pubblica e Pediatriche, Università di Torino, Torino, Italy

Cerebral Malaria (CM) is a life-threatening complication of *falciparum* malaria, associated with high mortality rates, as well as neurological impairment in surviving patients [1]. According to the World Health Organization (WHO) clinical criteria, CM is defined as a potentially reversible, diffuse encephalopathy causing a Glasgow coma score of 11/15 or less, often associated with fitting, in the absence of other factors that could cause unconsciousness such as coexistent hypoglycemia or other CNS infections [2]. Children from areas endemic for malaria or non-immune adults traveling from developed countries are at higher risk to develop CM. On the contrary, CM is rarely encountered in >10-year-old patients who have been exposed to *Plasmodium falciparum* since birth. Mortality ranges from 15-30%, and 11% of children display neurological deficits upon discharge [1].

The pathophysiological mechanisms underlying CM are not fully understood so far. *P. falciparum* is unique in that it causes mature infected red blood cells to sequester and adhere to cerebral microvascular beds. However, *P. falciparum* appears to remain in the vascular space without ever entering the brain parenchyma, in contrast to other encephalitis-causing pathogens, such as *Trypanosoma spp* or *Toxoplasma gondii* [3], thus raising question of how intravascular *Plasmodium* parasites are capable of inducing such a devastating neural dysfunction in CM. Several authors have implicated blood-brain barrier (BBB) damage as one of the underlying mechanisms of CM, with leaky BBB allowing toxic compounds to enter the brain and cause neurological dysfunction [4-7]. The BBB is constituted of cerebral vascular endothelial cells, which do not form a rigid structure, but rather a dynamic interface with a range of physical, biochemical and immune properties and functions, built from effective inter-cellular junctions and cell-matrix adhesion molecules, enzymes, and trans-endothelial transport systems [8]. In particular, BBB integrity is dictated by tight junctions between adjacent endothelial cells, forming a network of strands composed by several proteins, including junctional adhesion molecules, claudins (mainly -1 and -5) and occludin, which interact with cellular actin through cytoplasmic proteins such as zonula occludens-1 [9].

However, there is much discrepancy on the entity of BBB damage between animal and human models of CM thus far. As recently reviewed [7], a strong BBB breakdown is recurring in mouse CM models; however, data on increased BBB permeability in human CM are somehow less evident, generally suggesting the occurrence of only mild BBB impairment, characterized by a relevant degree of tight junction disruption, but lacking molecule exchange between serum and cerebral-spinal fluid. The relevance of murine CM models for studying CM pathophysiology has been a topic of big debate in the recent years, since murine CM displays obvious differences and some similarities to the clinical and pathological features of human CM [10,11]. A recurring issue concerns the degree of iRBC sequestration in the brain and other organs of *P. berghei* ANKA–infected mice. Although recent data find increased iRBC accumulation during murine CM in multiple organs including the brain, *P. berghei* infection is generally acknowledged to promote marked accumulation of leukocytes, which is in stark contrast with human CM [11]. Additionally, mouse studies suggesting associations between high levels of cytokines and CM have been recently challenged by works showing that high levels of pro-inflammatory cytokines such as TNF-α are poor indicators of human CM in African children [10]. Thus, future experimental studies on alternative animal models (non-human primates and other mouse models) are encouraged and urgently necessary to better understand the pathological processes underlying human infection [10,11].

Another interesting point emerging from clinical data is that the BBB appears more impaired in children than in adults [7]. Since CM often strikes children at a critical time in brain development, Hawkes and colleagues have nicely hypothesized that developmental changes in the cerebral vasculature may account for some of the differences in disease presentation and outcome between children and adults [12]. The brain develops within an environment that is different from that of the rest of the body, and the developing brain possesses a number of unique features not generally present in the adult [13]. Interestingly, certain genes coding for influx/efflux proteins are expressed at much higher levels early in development than in the adult, and there is physiological evidence that these transport systems are functionally more active in the developing brain [13]. How such differences between the pediatric and adult BBB can affect CM pathogenesis and correlate with enhanced BBB permeability in pediatric CM is still unknown, and future research aimed at shedding light on this topic will certainly be useful.

Finally, experimental evidence has recently implicated a specific family of host proteolytic enzymes known as matrix metalloproteinases (MMPs) in CM pathogenesis [7,14-17]. MMPs can process a large repertoire of substrates, including pro-inflammatory molecules, tight junctions, and hemostatic factors [18,19] and could play an active role during CM development by modulating the inflammatory response and the BBB function. Clearly, the idea of using broad spectrum or specific MMP inhibitors as adjuvant therapy in CM appears intriguing. Unfortunately, in the last two decades, a large number of synthetic MMP inhibitors have gone through clinical trials as anti-cancer and anti-arthritis drugs, but largely failed due to serious side effects [20,21]. Nevertheless, the side effects of MMP inhibitors were associated with long-term treatment, whereas the time course of drug administration in CM therapy should be reasonably shorter than cancer therapy. Moreover, several artemisinins, currently used for primary therapy of uncomplicated malaria, have displayed MMP-inhibiting properties [22]. Thus, combinations of MMP inhibitors with anti-malarials could justify lower therapeutic doses of both drugs, thereby reducing their potential side effects whilst still enhancing anti-MMP properties by drug synergy. Although the effects of MMP inhibitors in CM have

*Corresponding author: Mauro Prato, Department of Neuroscience, University of Turin, Corso Raffaello 30, 10125, Torino, Italy, Tel: 39-011-6708198; Fax: 39-011-6708174; E-mail: mauro.prato@unito.it

been scarcely investigated so far, evidence showing improved survival of CM mice after treatment with broad-spectrum MMP inhibitor BB-94 appears promising [23]. Future research aimed at determining the exact contribution of each MMP to BBB damage during CM could yield novel insights to develop new adjuvant therapy approaches.

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