The von Willebrand factor – ADAMTS-13 axis in malaria

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Abstract
Cerebral malaria (CM) continues to be associated with major morbidity and mortality, particularly in children aged <5 years in sub-Saharan Africa. Although the biological mechanisms underpinning severe malaria pathophysiology remain incompletely understood, studies have shown that cytoadhesion of malaria-infected erythrocytes to endothelial cells (ECs) within the cerebral microvasculature represents a key step in this process. Furthermore, these studies have also highlighted that marked EC activation, with secretion of Weibel-Palade bodies (WPBs), occurs at a remarkably early stage following malaria infection. As a result, plasma levels of proteins normally stored within WPBs (including high-molecular-weight von Willebrand factor [VWF] multimers, VWF propeptide, and angiopoietin-2) are significantly elevated. In this review, we provide an overview of recent studies that have identified novel roles through which these secreted WPB glycoproteins may directly facilitate malaria pathogenesis through a number of different platelet-dependent and platelet-independent pathways. Collectively, these emerging insights suggest that hemostatic dysfunction, and in particular disruption of the normal VWF–ADAMTS-13 axis, may be of specific importance in triggering cerebral microangiopathy. Defining the molecular mechanisms involved may offer the opportunity to develop novel targeted therapeutic approaches, which are urgently needed as the mortality rate associated with CM remains in the order of 20%.

KEYWORDS
ABO blood group, cerebral malaria, Plasmodium falciparum, platelets, von Willebrand factor

Essentials
- Cytoadhesion of infected erythrocytes is critical in cerebral malaria (CM) pathobiology.
- Markedly elevated plasma VWF levels represents an early hallmark feature of CM.
- Platelets directly impact malaria pathogenesis through multiple mechanisms.
- VWF–ADAMTS-13 axis targeting in CM may offer novel therapeutic opportunities.

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Von Willebrand factor (VWF) is a large multimeric plasma glycoprotein that plays key roles in normal hemostasis.\textsuperscript{1,2} VWF binds to exposed collagen at sites of vascular injury and subsequently is able to tether and activate platelets.\textsuperscript{3} In addition, VWF also functions as a carrier molecule for procoagulant factor VIII (FVIII), protecting it against early degradation.\textsuperscript{3} Under normal conditions, VWF biosynthesis in vivo occurs only in endothelial cells (ECs)\textsuperscript{4} and megakaryocytes.\textsuperscript{5} VWF synthesized within ECs is either secreted into the plasma or stored within Weibel-Palade bodies (WPBs).\textsuperscript{5} Following EC activation by a variety of different secretagogues, this stored VWF is actively secreted together with other WPB contents (including the VWF propeptide VWFpp and angiopoietin-2 [Ang-2]). Previous shear-based studies have demonstrated that ultra-large multimers (UL-VWF) secreted following EC activation becomes tethered on the cell surface to form elongated strings.\textsuperscript{6} This unwound VWF is able to bind platelets, leading to the formation of long platelet-decorated VWF strings. In normal plasma, formation of these strings is regulated by the zinc metalloprotease ADAMTS-13 which specifically cleaves VWF at the Tyr1605-MetM1606 bond within the A2 domain.\textsuperscript{7} Consequently, VWF circulates as a series of heterogeneous multimers, with the larger multimers having significantly enhanced functional capacity.\textsuperscript{1} The biological importance of ADAMTS-13 regulation of VWF multimer distribution is highlighted by the fact that inherited or acquired ADAMTS-13 deficiency triggers severe microangiopathic thrombosis in patients with thrombotic thrombocytopenic purpura (TTP).\textsuperscript{8}

### 1.1 Emerging roles for VWF in inflammation and sepsis

Beyond its pivotal role in maintaining physiological hemostasis, recent data have demonstrated that VWF also plays important roles in inflammation.\textsuperscript{9} In particular, VWF has been shown to bind to both granulocytes and macrophages.\textsuperscript{10-12} A number of leukocyte receptors and VWF domains have been implicated in modulating these binding interactions (Figure 1). Specific leukocyte receptors reported to bind to VWF include the low-density lipoprotein receptor-related protein-1; the scavenger receptor class A member I\textsuperscript{12}; the macrophage galactose-type lectin\textsuperscript{14,15}; Siglec-5\textsuperscript{16} and the Galectins-1 and -3.\textsuperscript{17} In addition to this in vitro data, studies in animal models support the hypothesis that VWF plays direct roles in inflammation that may be platelet-dependent or -independent in nature.\textsuperscript{18} For example, Petri et al.\textsuperscript{19} demonstrated that pretreatment with anti-VWF blocking antibodies resulted in significantly attenuated leukocyte recruitment in murine models of thioglycollate-induced experimental peritonitis and keratinocyte-derived chemokine-stimulated cremaster muscle, respectively. Thus, VWF not only binds to leukocytes but can also modulate extravasation in a platelet-dependent manner. Furthermore, Hillgruber et al.\textsuperscript{20} showed that VWF-blocking antibodies also significantly reduced neutrophil recruitment in murine models of immune complex–mediated vasculitis and contact dermatitis. Interestingly, in these cutaneous inflammation models, the ability of anti-VWF antibodies to inhibit leukocyte recruitment was shown to be platelet independent. Recent studies have demonstrated
that VWF is also involved in both NETosis and complement activation. The concept that VWF is involved in inflammatory responses is further supported by data from murine sepsis experiments. In particular, significantly improved overall survival was observed in VWF−/− mice compared to wild-type controls in a cecal ligation puncture model. Finally, recent studies have suggested that dysfunction of the VWF–ADAMTS-13 axis may also be important in the pathogenesis of the characteristic pulmonary microangiopathy seen in patients with severe COVID-19.

1.2 | VWF and ADAMTS-13 in human malaria

Markedly elevated VWF and ADAMTS-13 levels have been consistently reported in patients with malaria (Table 1). Plasma VWF antigen (VWF:Ag) levels correlate with disease severity, so that the highest levels (in the range 300-500 IU/dL) are typically seen in children with cerebral malaria. However significant increased VWF:Ag levels are also a feature of mild to moderate Plasmodium falciparum malaria in both adults and children. More modest increases in plasma VWF:Ag levels have also been observed in patients with Plasmodium vivax malaria. Within Weibel-Palade bodies, mature VWF:Ag is stored in equimolar amounts with VWF propeptide. Studies have demonstrated that plasma VWFpp levels are also markedly elevated in children with cerebral malaria (CM) and again correlate with disease severity (Table 1). Collectively, these data suggest that severe malaria results in fulminant EC activation, with resultant WPB secretion leading to high plasma VWF concentrations (Figure 2). The mechanism(s) through which malaria infection causes such profound EC activation remain poorly defined. However, studies performed in healthy volunteers infected with P. falciparum showed that the increase in plasma VWF:Ag and VWFpp was present from an early stage following parasite infection when infected erythrocyte (IE) levels were <0.001%. In contrast to the elevated plasma VWF levels observed in patients with severe malaria, studies suggest that ADAMTS-13 levels are significantly reduced (Table 1). Furthermore, polymorphisms in ADAMTS-13 have been associated with malaria severity. Importantly, however, reported reductions in ADAMTS-13 activity in severe malaria have been relatively modest, with plasma levels typically remaining above 30% of normal levels. Previous studies suggest that these ADAMTS-13 levels should be adequate to prevent accumulation of abnormal UL-VWF. Nonetheless, the VWF:ADAMTS-13 ratio in children with CM is greatly increased. In addition to these quantitative variations, plasma levels of several putative ADAMTS-13 functional inhibitors (including interleukin-6 and free hemoglobin) are also significantly increased in malaria. Given these findings, it is perhaps unsurprising that abnormal UL-VWF (similar to those seen in TTP) have been reported in children with cerebral malaria (Table 1). Moreover, several studies have reported that the plasma VWF circulating in patients with severe malaria exists in an active conformation that allows shear-independent binding to platelets.

1.3 | VWF strings modulate cyto-adhesion of malaria-infected erythrocyte

Plasmodium falciparum–infected erythrocytes are able to adhere to ECs lining the cerebral microvasculature. This active sequestration plays a critical role in the pathogenesis of CM. A number of different EC surface receptors have been implicated in modulating IE binding, including CD36, intercellular adhesion molecule 1, thrombomodulin, endothelial protein C receptor, and P-selectin. These receptors are able to bind to parasite-related ligands expressed on the IE surface, most notably P falciparum erythrocyte membrane protein 1 (PfEMP1). Given the early increase in plasma VWF levels associated with P falciparum infection, together with the presence of UL-VWF multimers, Bridges et al. investigated whether VWF might play a direct role in facilitating IE cytoadhesion to EC. In a flow-based assay, they demonstrated that platelet-decorated VWF strings could tether fluorescently labeled P falciparum IE. In contrast, platelet-decorated VWF strings did not bind to uninfected erythrocytes, nor to erythrocytes infected with immature P falciparum ring-stage parasites that fail to express PfEMP1. Furthermore, IE binding was ablated in the presence of anti-CD36 or anti-VWF A1 domain monoclonal antibodies. Together, these findings suggest that under physiological shear conditions, UL-VWF strings tethered on EC surfaces can bind to platelet glycoprotein Ib via the VWF A1 domain. Subsequently, CD36 on the platelet-decorated strings facilitates IE binding by interacting with PfEMP1 (Figure 3). The authors hypothesized that stores of high-molecular-weight multimers (HMWM)-VWF secreted from WPBs following acute EC activation might be particularly important in enabling IE sequestration during the early stages of malaria infection in the period before the biosynthesis of other EC adhesion molecules can be upregulated.

1.4 | VWF in murine experimental CM

The combination of markedly elevated plasma VWF levels, alteration in the normal VWF–ADAMTS-13 ratio, and the presence of pathological UL-VWF raises the intriguing possibility that VWF may play direct roles in the pathobiology of CM. Several recent studies have investigated this idea in a number of different murine malaria models. O’Regan et al. studied VWF in a murine model of experimental cerebral malaria (ECM) in which C57BL/6J mice were infected with Plasmodium berghei ANKA. Following infection, mice became progressively unwell, developing ECM features, with most mice dying after 6 to 7 days. In keeping with the findings observed in patients with severe malaria, P berghei infection was associated with a significant increase in murine plasma VWF:Ag levels. Moreover, this marked increase in VWF levels was an early feature in the disease course, being observed before significant numbers of P berghei–infected erythrocytes were visible in the circulation. Angiopoietin-2 (Ang-2) is another protein that is stored in WPBs and actively secreted following acute EC activation. Significantly increased plasma Ang-2 levels were seen in C57BL/6J mice following...
inoculation with *P. berghei*, which further supports the concept that EC activation and WPB secretion are consistent features in both human and murine CM. Although plasma ADAMTS-13 levels were not significantly reduced in the murine ECM model, abnormal ultra-large multimers were again observed. Importantly, subsequent studies demonstrated that the clinical features of ECM progressed significantly more slowly and that overall survival was significantly longer in VWF−/− mice compared to wild-type controls.

More recently, Kraisin et al. used this same ECM model but assessed the effect of using lower initial infecting doses of *P. berghei*. They confirmed that plasma VWF:Ag levels and Ang-2 levels were both significantly elevated following *P. berghei* infection. In keeping with O’Regan et al., ADAMTS-13 levels remained within the normal range in malaria-infected mice. In this ECM model using reduced *P. berghei* doses, a subtle reduction in clinical signs was again seen in VWF−/− mice in the late stages of the disease, but no significant improvement in overall survival was observed. Cumulatively, these murine ECM data are consistent with human clinical findings in demonstrating that marked EC activation and WPB secretion represent hallmark features of CM. However, the findings also highlight the inherent limitations of the murine ECM model.

Thrombocytopenia is a common finding in patients with severe malaria. In addition, postmortem samples from children with fatal malaria have demonstrated accumulation of both platelets and leukocytes within occluded cerebral microvasculature. Since VWF plays a key role in regulating platelet tethering, studies have investigated whether it may also be important in malaria-induced thrombocytopenia. However, data from the murine ECM experiments have demonstrated that thrombocytopenia is similar in VWF−/− mice compared to controls. Thus, it appears that thrombocytopenia in malaria is occurring through VWF-independent pathways. Similarly, VWF can also bind to leukocytes and has been implicated in playing a role in neutrophil extravasation. Although cerebral leukocyte recruitment is also a hallmark feature in murine ECM, Kraisin et al. showed that this process was not affected by VWF deficiency. Additional research studies will thus be required to elucidate the biological mechanisms through VWF influences the pathogenesis of cerebral malaria in vivo.

### Table 1: Examples of studies investigating VWF–ADAMTS-13 axis in human and murine malaria pathogenesis

| Study              | Malaria type | Patient age | Patient numbers | Plasma VWF:Ag (median, % local normal) | Plasma VWFpp (median, % local normal) | Plasma ADAMTS13 activity (median, % local normal) | VWF multimers | Additional comments |
|--------------------|--------------|-------------|-----------------|----------------------------------------|---------------------------------------|-------------------------------------------------|--------------|---------------------|
| **Human malaria**  |              |             |                 |                                        |                                       |                                                 |              |                     |
| Hollestelle et al, 2006 | *P. falciparum* | Children (0.5-6 y) | CM (n = 26) Severe (n = 73) | CM – 281 Severe – 249 Mild – 245 | CM – 331 Severe – 260 Mild – 220 | NR | NR | VWFpp levels correlate with disease severity |
| Larkin et al, 2009 | *P. falciparum* | Children (0.5-6 y) | CM (n = 13) Severe (n = 20) | CM – 340 Severe – 310 | NR | CM – 63 Severe – 56 | UL-VWF multimers | ADAMTS-13 inhibition |
| de Mast et al, 2009 | *P. falciparum* and *P. vivax* | Children and Adults (2-37 y) | P. falc (n = 26) P. vivax (n = 16) | P. falc – 290 P. vivax – 200 | NR | P falc – 13.5 P vivax – 13.3 | UL-VWF multimers | VWF in active conformation |
| Lowenberg et al, 2010 | *P. falciparum* | Adults (22-51 years) | Severe (n = 30) Mild (n = 12) | Severe – 415 Mild – 310 | Severe – 580 Mild – 480 | Severe – 36 Mild – 88 | NR | None |
| Graham et al, 2016 | *P. falciparum* | Children (1-10 y) | Severe (n = 180) | Severe – 339 | NR | Severe – 90 | UL-VWF multimers | VWF in active conformation |
| Barber et al, 2015 | *P. falciparum* and *P. vivax* | Adults (17-52 y) | Severe PF (n = 21); severe PV (n = 9) | Severe PF – 508; severe PV – 358 | NR | Severe PF – 34; severe PV – 61 | NR | None |
| **Murine malaria** |              |             |                 |                                        |                                       |                                                 |              |                     |
| O’Regan et al, 2016 | *P. berghei* ANKA | N/A | N/A | CM – 240 | NR | Normal | UL-VWF multimers | Mild protective effect in VWF−/− |
| Kraisin et al, 2019 | *P. berghei* NK65-E | N/A | N/A | ARDS -190 | NR | Normal until late stages | Reduced HMWM late stages | Parasitemia higher in VWF−/− |
| Kraisin et al, 2019 | *P. berghei* ANKA | N/A | N/A | CM –140% | NR | Normal | Reduced HMWM late stages |

Note: Abbreviations: CM, cerebral malaria; HMWM, high-molecular-weight multimers; N/A, not applicable; NR, not reported; PF, *Plasmodium falciparum*; PV, *Plasmodium vivax*; UL-VWF, ultra-large VWF multimers; VWFpp, VWF propeptide.
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1.5 | VWF in experimental malaria-associated respiratory distress syndrome

Malaria-associated acute respiratory distress syndrome (MA-ARDS) has been associated with both *P. falciparum* and *P. vivax* infections.\(^{55,56}\) To further investigate roles for the VWF–ADAMTS-13 axis in malaria pathogenesis, Kraisin et al.\(^{57}\) used an established mouse model of MA-ARDS in which C57BL/6J mice were infected with a different type of *P. berghei* parasite (PbNK65). Consistent with the murine ECM data, significantly elevated plasma VWF:Ag levels were seen in wild-type mice infected with PbNK65 from an early stage before significant numbers of IEs were visible in peripheral blood smears.\(^{57}\) Plasma ADAMTS-13 antigen levels remained within the normal range, but a significant reduction in plasma ADAMTS-13 activity levels was observed suggesting that ADAMTS-13 function may be inhibited in MA-ARDS. Finally, despite the reduction in ADAMTS-13 activity, a reduction in HMWM-VWF was observed in late-stage MA-ARDS mice.\(^{57}\) Although recent studies have reported that plasmin can cleave VWF,\(^{58}\) the loss of HMWM in MA-ARDS was shown to be plasmin independent.\(^{57}\)

In the murine ECM model, VWF deficiency was associated with a partial protective effect.\(^{48}\) Interestingly, in the MA-ARDS model, the opposite effect was observed, whereby overall survival was actually significantly reduced in VWF−/− mice compared to wild-type controls.\(^{57}\) Subsequent studies demonstrated that this reduced survival was due to markedly increased PbNK65 parasitemia levels in the VWF−/− mice. The biology through which VWF impacts parasitemia levels in this model remain unclear, but interestingly reticulocyte counts were also increased in VWF−/− animals.\(^{57}\) Overall, this alternate murine model of severe malaria clearly further supports the hypothesis that the VWF–ADAMTS-13 axis is important in disease pathogenesis. Furthermore, it seems likely that VWF may have multifactorial effects that impact different stages in the malaria disease journey.\(^{29,53}\)

1.6 | Platelet-induced killing of malaria parasites

Postmortem studies performed on children with CM have reported significant platelet accumulation within the cerebral microvasculature.\(^{54}\) Levels of thrombocytopenia have also been shown to correlate with increased severity of malaria infection, higher parasite density, and worse clinical outcomes.\(^{52,53}\) Accumulating recent data suggest that platelets impact malaria pathobiology through a number of different mechanisms. For example, platelets can play roles in facilitating IE clumping,\(^{59}\) IE cytoadhesion to ECs, and IE sequestration.\(^{6,52}\) In
addition, platelets may contribute to EC activation and inflammatory responses in severe malaria infection. Besides these deleterious effects, several studies have reported an intriguing role for platelets in killing intraerythrocytic malaria parasites.\(^60,61\) This platelet-induced malaria killing process was most marked for \(P\) \textit{vivax} but has also been observed for a number of different human malaria species (including \(P\) \textit{falciparum} and \(P\) \textit{malariae}).\(^62\) The molecular mechanisms involved remain poorly understood but appear to require platelet-IE adhesion, as well as platelet CD36 and platelet factor-4.\(^61\) Given the key role played by VWF in modulating platelet function under shear, further studies investigating the VWF–ADAMTS-13 axis in this context will be interesting.

### 1.7 VWF and ABO blood group in malaria

During its biosynthesis within EC or megakaryocytes, VWF undergoes complex posttranslational modification that includes significant N- and O-linked glycosylation.\(^63\) As a result, complex carbohydrate structures make up >20% of the final VWF monomeric mass.\(^64\) Plasma VWF is unusual compared to most other circulating glycoproteins in that it carries covalently linked ABO(H) blood group determinants as terminal sugar residues on both its N- and O-glycan chains.\(^65\) In contrast, however, VWF synthesized within megakaryocytes and stored within platelet alpha granules does not express these terminal ABO(H) structures.\(^66,67\) Interestingly however, ABO(H) determinants are expressed on a number of platelet membrane glycoproteins, including glycoprotein Ib, IIA, IIIa, IV, and \(\mathrm{V}\).\(^65\) The presence of ABO carbohydrate structures on both plasma VWF and platelet surface glycoproteins has direct biological significance. Numerous previous studies have demonstrated that ABO blood group has a major effect on plasma VWF:Ag levels.\(^68,69\) Indeed, ABO has been estimated to account for 30% of total genetic variability in VWF levels.\(^70\) Individuals in blood group O typically have plasma VWF:Ag levels that are 20% to 30% lower than those in non-O subjects.\(^69\) Among the non-O groups, VWF levels are highest in rare group AB individuals. This major effect of ABO on VWF levels is thought to be predominantly attributed to enhanced VWF plasma clearance in group O individuals.\(^71,72\) In addition to this quantitative effect on VWF levels, studies have also suggested that ABO blood group can also influence hemostatic functions of both VWF\(^73\) and platelet receptors.\(^74\) In particular, ABO determinants have been shown to regulate the susceptibility of VWF to proteolysis by ADAMTS-13, with significantly enhanced cleavage of group O VWF.\(^75,76\)

With respect to malaria, the major effects of ABO blood group in modulating VWF antigen and function in vivo are interesting given that studies have shown that individuals in blood group O have milder \(P\) \textit{falciparum} disease and less severe outcomes compared to
group A individuals. ABO blood group also affects plasma levels of procoagulant FVIII, with significantly higher levels in non-O individuals. This is important because local thrombin generation, loss of the endothelial protein C receptor, and disruption of the protein C anticoagulant pathway have also been implicated in malaria pathogenesis. Cumulatively, these data have led to the proposal that P falciparum may have exerted a selective genetic pressure in favor of group O, which is consistent with the current geographic distribution of ABO blood groups with increased group O prevalence in malaria-endemic regions. Based on the current evidence, it seems likely that ABO effects upon VWF and FVIII levels are likely to be important contributors in modulating this ABO effect on malaria susceptibility. Given that marked endotheliopathy has also been shown to play a key role in the pathogenesis of severe COVID-19, it is also interesting to note that a significant effect of the ABO group in regulating susceptibility to severe COVID-19 has also been reported.

2 | ISTH CONGRESS REPORT

Although platelets play a critical role in malaria pathogenesis, the mechanisms responsible for the significant thrombocytopenia that is associated with both human and murine malaria remain poorly defined. At the XXIX Congress of the ISTH (Philadelphia, PA, USA, July 17-21, 2021), Singh et al. used flow cytometry to characterize circulating platelets in healthy volunteers experimentally infected with P falciparum (PB0759). By day +10 following infection, a significant thrombocytopenia and a reduction in mean platelet volume were observed in malaria-infected subjects compared to controls. In addition, a reduction in platelet sialylation was also present in malaria cases. These findings are important given that terminal sialic acid expression plays a key role in protecting both platelets and plasma glycoproteins against premature clearance.

3 | CONCLUSIONS AND FUTURE DIRECTIONS

In summary, accumulating data over recent years have clearly demonstrated that both platelets and acute EC activation play critical roles in the pathogenesis underlying severe malaria. These effects have been observed in both patients infected with malaria and a variety of different murine models. Elucidating the precise molecular mechanisms involved, and how the importance of these mechanisms varies through the course of malarial illness, will require further studies. In view of the huge global morbidity and mortality that continue to be associated with severe malaria, these studies are urgently needed to address an important unmet clinical need. Improved understanding of the mechanisms involved may facilitate the development of novel treatment strategies.
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