Hypothesis of mechanism of thrombocytopenia in severe dengue, providing clues to better therapy to save lives

The clinical consequence of dengue virus infection is 'dengue fever' or 'severe dengue'. Severe dengue is life-threatening from bleeding (dengue haemorrhagic fever, DHF), hypovolemic shock (dengue shock syndrome, DSS) or severe organ impairment (hepatic, renal, cardiac, pulmonary, brain). Bleeding results from microangiopathy, while platelet numbers are insufficient to block the bleeding points. Shock results from capillary plasma leakage from vascular to extracellular spaces. Organ failure is presumably due to microangiopathy resulting in impaired perfusion. While dengue fever is relatively inconsequential, severe dengue has a significant fatality rate. Thrombocytopenia is common in dengue fever and severe dengue, reaching a nadir by 4–6 days of onset of fever; platelet counts normalize in subsequent days.

Clinicians often find thrombocytopenia worrisome and transfuse platelets, occasionally repeatedly, in the hope of preventing severe dengue. Current guidelines from the World Health Organisation (WHO) for management of dengue advise against the use of 'prophylactic' platelet transfusions. The use of fresh-packed red cells or fresh or fairly fresh whole blood is advocated in the case of major bleeding[1].

It is important to know the mechanism of thrombocytopenia in dengue in order to design appropriate intervention. While hemophagocytosis[2] or bone marrow suppression[3] are possible explanations, we propose that endothelial sequestration of platelets could be the dominant mechanism of thrombocytopenia in patients with severe dengue.

Endothelial sequestration is caused by platelet adherence to von Willebrand factor (vWF), expressed on vascular endothelial cells. Increased vWF expression, if associated with a significant reduction in its rate of cleavage, may result in increased expression on endothelial surfaces of ultra-large (uncleaved) vWF multimers, which avidly entrap platelets. This sequence would lead to two downstream effects: platelet plugs in the microcirculation and low platelet counts in peripheral blood. Microcirculatory platelet plugs within an organ can lead to organ failure.

The disease thrombotic thrombocytopenic purpura (TTP) is a microangiopathy usually affecting brain or kidney. The mortality rate used to be >90% before it was recognized >40 years ago that plasma exchange or transfusion of fresh frozen plasma (FFP) or cryosupernatant reduced the mortality to 13% (refs 4 and 5). In 1998, deficiency of vWF cleaving protease was established as the pathway of TTP[6]. It was later named as ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 domain 13)[7]. ADAMTS13 deficiency leads to the formation of extremely adhesive ultra-large vWF multimers and predisposes to platelet microthrombi[5]. ADAMTS13 deficiency may result from inadequate production due to genetic factors[7]; alternatively, it may be an acquired deficiency as a consequence of neutralizing anti-ADAMTS13 antibody formation[8]. Supplementation of ADAMTS13 by way of transfusion of FFP or cryosupernatant has resulted in dramatically improved survival of patients with TTP. Recombinant ADAMTS13 is now being developed to treat patients with TTP[9].

There is emerging evidence that dengue is also associated with imbalance of vWF and ADAMTS13 (refs 10–12). In a study of 42 children with dengue infections (20 with dengue fever and 22 with DHF), endothelial activation, raised vWF and low ADAMTS13 levels in plasma were documented. In DHF patients, plasma vWF antigen level was significantly elevated, while platelet counts and plasma ADAMTS 13 levels were significantly lower compared to dengue fever patients. Abnormal vWF multimers were seen only in DHF patients. Plasma vWF antigen level was the best indicator of progression to DHF[10].

Imbalance of vWF and ADAMTS13 is reported to correlate with inflammatory markers and with organ failure also in patients with sepsis[13]. A study of critically ill children with thrombocytopenia-associated multi-organ failure syndrome documented the presence of vWF-mediated thrombotic microangiopathy. Seven non-survivors had thrombocytopenia-associated multi-organ failure, reduced plasma ADAMTS13 activity, and vWF-rich microvascular thromboses at autopsy. Intensive plasma exchange can replenish ADAMTS13 activity and reverse organ failure in such patients[14].

Imbalance of ADAMTS13 and vWF is now recognized in a variety of acute and chronic thrombocytopenic syndromes[15–18]. Further studies are needed to see if therapeutic manipulations to correct the imbalance of vWF : ADAMTS 13 in these situations favourably influence the natural history of such illnesses.

According to our hypothesis of the pathway to thrombocytopenia and pathogenesis of severe dengue as platelet sequestration, we propose the following three steps in the management of patients with severe dengue:

1. Avoid platelet transfusion in patients with dengue infection, as more platelets will adhere to the extremely adhesive ultra-large vWF multimers, worsening platelet plug formation and organ failure.
2. If platelet transfusion is felt essential in a patient with serious haemorrhage, then we should provide ADAMTS13 first (by transfusing FFP/cryosupernatant), followed by platelet transfusion. The ADAMTS13 supplementation should cleave vWF multimers, thus further reducing platelet plug formation. The obvious alternative is to give recombinant ADAMTS 13.
3. Plasma exchange in order to dilute out excess vWF also needs to be considered in patients with severe dengue.

A randomized controlled trial of FFP transfusion in patients with dengue infection showed an increase in platelet counts after 12 h; however, this study was not designed to evaluate survival in severe dengue[19]. Prophylactic platelet transfusions are ineffective in acute uncomplicated dengue as well as in severe dengue[20,21]. Among 60 patients with severe dengue who received prophylactic transfusions, 15 received FFP transfusions only, six received platelet concentrate transfusions only, and 39 received both[21]. This study was not designed to evaluate a protocol of transfusing FFP prior to platelet transfusion in dengue

patients, as being proposed in step 2 above. Transfusion of fresh whole blood to treat severe bleeding in dengue patients is suggested in the WHO guidelines[1]. It is possible that this benefit may be explained by providing ADAMTS13 supplementation.

We urgently need studies measuring survival after applying the above three-step policy in patients with early signals of severe dengue (steps 1 and 2) or established severe dengue (step 3). Research is also necessary to assess the utility of plasma exchange or FFP transfusion to prevent progression to severe dengue.

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