

## Thrombotic Microangiopathies: Role of ADAMTS-13

Salman Naseem Adil, Farheen Karim

Section of Haematology, Department of Pathology, Aga Khan University, Karachi.

Thrombotic microangiopathy (TMA) refers to conditions that cause microvascular thrombosis and result in microangiopathic haemolytic anaemia with presence of fragmented red cells on peripheral blood, thrombocytopenia and end organ damage. Syndromes most commonly associated with thrombotic microangiopathy are thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS).<sup>1</sup> TMA may occur in other disorders, such as malignant hypertension, scleroderma, systemic lupus erythematosus, preeclampsia, radiation nephropathy, renal allograft rejection, HIV infection, disseminated malignancies and disseminated intravascular coagulation (DIC). TTP is a fatal thrombotic microangiopathy if not treated appropriately. Using a variety of approaches and case definitions the incidence of TTP has been estimated to be 2-7 per million person-years. The pentad of signs and symptoms of TTP include thrombocytopenia, microangiopathic haemolytic anaemia, neurological abnormalities, renal failure and fever.<sup>2</sup>

TTP is caused by deficiency of a von Willebrand factor cleaving protease that was identified in 1996 and as the thirteenth member of the ADAMTS family of enzymes was named as ADAMTS-13 (A disintegrin and metalloprotease with thrombospondin type-1 motives).<sup>3</sup>

ADAMTS-13 is released from the liver and is required for cleavage of the ultra large von Willebrand factor multimers. Von Willebrand factor is released from the storage granules known as weibel-palade bodies of the endothelial cells in the form of ultra large multimers. The ultra large von Willebrand factor (ULvWF) is the hyperactive form of vWF. It is not only very large in size, but it also binds platelets with greater affinity that results in spontaneous platelets aggregation.<sup>4</sup> After release, these ULvWF undergo rapid proteolysis by ADAMTS-13 that converts these highly thrombotic forms to smaller less adhesive forms which are haemostatically critical.<sup>5</sup>

Deficiency of ADAMTS-13 results in failure of cleavage of ULvWF multimers. These ULvWF multimers due to their thrombotic potential cause excessive platelet aggregation, resulting in widespread platelet rich thrombi which in turn results in the development of thrombotic microangiopathy.<sup>6</sup>

Acquired TTP occurs due to autoantibodies to ADAMTS-13 resulting in severe ADAMTS13 deficiency, whereas, hereditary TTP previously known as Schulman-

Upshaw syndrome or chronic relapsing TTP is a result of mutations in the ADAMTS-13 gene. ADAMTS13 activity levels are <10% (or <5%, depending on the assays used) of normal control in patients with acute TTP.<sup>7</sup> A severe deficiency of ADAMTS-13 activity is a specific finding for most patients with a diagnosis of thrombotic thrombocytopenic purpura (TTP) but is not present in those with a diagnosis of haemolytic uraemic syndrome. This finding is important because distinguishing between TTP and HUS is often not possible due to the frequently overlapping clinical and laboratory features of the two disorders.

While looking into the role of ADAMTS13 in common diseases associated with thrombotic microangiopathies, it has been found that apart from classical TTP, mild to moderate ADAMTS-13 deficiency is also present in liver cirrhosis,<sup>8</sup> malignancies,<sup>9</sup> sepsis,<sup>10</sup> connective tissue diseases like systemic lupus erythematosus (SLE)<sup>11</sup> and disseminated intravascular coagulation.<sup>12</sup> Low ADAMTS-13 levels have been associated with poor survival rate and higher in-hospital mortality in severe sepsis and DIC.<sup>13,14</sup>

The precise analysis of ADAMTS13 antigen and activity levels in disease states offers insight into the roles of ADAMTS13 in thromboembolic diseases. Severe ADAMTS-13 deficiency with activity of <5% of the normal is a specific finding for acute classical TTP. However, it does not have a solo diagnostic value for TTP. ADAMTS-13 activity can also be used as a diagnostic and prognostic marker in patients with sepsis and DIC.

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