

THROMBOTIC THROMBOCYTOPENIC PURPURA AND THE ROLE OF ADAMTS13 AS A KEY ENZYME IN THE PATHOGENESIS OF TTP

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Thrombotic thrombocytopenic purpura (TTP) is one of the most serious and life-threatening form of thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, severe thrombocytopenia, and multiple organs damage due to VWF-platelet aggregations in the arterioles and capillaries of end organs. The thrombi are found most extensively in the heart, brain, kidney, pancreas, spleen, mesentery and adrenal glands. Thrombocytopenia results from consumption of platelets in the thrombotic process, while erythrocyte fragmentation and hemolysis result from mechanical injury induced by abnormally high shear stress in the microvasculature. Pathophysiology involves the absence of von Willebrand factor cleaving enzyme (ADAMTS-13), resulting in unusually large von Willebrand multimers. These multimers lead to platelet aggregations, microthrombi and subsequent thrombocytopenia. About 35% of

adult patients have idiopathic (acquired) TTP due to formation of antibodies/inhibitors against ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13). These patients develop severe ADAMTS13 deficiency and acute TTP. The inhibitors are primarily IgG but less often IgM. The plasma ADAMTS13 activity level is less than 10% or 5% in acute TTP. Inherited form of TTP is also described in children due to mutations of ADAMTS13 gene located on the long arm of chromosome 9. An ADAMTS13 level >10% excludes the diagnosis of TTP. Early diagnosis of TTP is essential to initiate appropriate treatment. The first-line therapy for acute TTP is based on daily therapeutic plasma exchange supplying deficient ADAMTS13. Immune modulators are humanized anti-CD20 monoclonal antibody rituximab.

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