Editorial Focus

Clinical insights from observations on ADAMTS13 deficiency in liver cirrhosis

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Ten years ago ADAMTS13 (*A disintegrin and metalloprotease with thrombospondin 1-like repeats*) exploded into the awareness of haematologists when a severe deficiency of ADAMTS13 was associated with thrombotic thrombocytopenic purpura (TTP) (1, 2). ADAMTS13 is an enzyme in normal plasma required for proteolysis of von Willebrand factor (VWF) following its secretion from endothelial cells; the absence of ADAMTS13 in the circulation leads to abnormally large multimers of VWF which may spontaneously bind to circulating platelets and result in microvascular thrombosis. As may occur with strikingly original observations that reveal clear pathogenetic mechanisms for a critical illness, it was initially assumed that ADAMTS13 would tell the whole story of TTP: severe ADAMTS13 deficiency would be both necessary and sufficient to cause TTP, and documentation of severe ADAMTS13 deficiency would be both sensitive and specific for identifying patients with TTP. However, as may also occur, more experience and less selectivity of patients have resulted in a more realistic understanding of the role of ADAMTS13.

The observations by Uemura et al. (3) in this issue of *Thrombosis and Haemostasis* are an excellent example of our expanding knowledge about ADAMTS13. Initially severe ADAMTS13 deficiency was considered to be an abnormality specific for TTP (4). Subsequent studies reported that severe ADAMTS13 deficiency may also occur in patients with sepsis and disseminated intravascular coagulation (5, 6). Uemura et al., following their previous observation that ADAMTS13 is synthesized in hepatic stellate cells (7), have now clearly documented that patients with severe liver disease may also have severe ADAMTS13 deficiency (3). Their observation is convincingly demonstrated by multiple experiments. The severity of ADAMTS13 deficiency was related to the severity of liver disease. ADAMTS13 activity also correlated with many clinical and laboratory parameters that describe the severity of liver disease. Deficient ADAMTS13 activity was confirmed by documentation of parallel deficiencies of ADAMTS13 antigen and also by the presence of abnormally large VWF multimers.

What is the clinical importance of these observations? Although a deficiency of ADAMTS13 activity creates a prothrombotic state (8, 9), this may not be apparent because of the coagulation factor deficiencies and thrombocytopenia that also occur in liver disease. In the study of Uemura et al. (3), five patients with end-stage liver disease had undetectable ADAMTS13 but only one had the clinical syndrome of TTP. Could the four other patients with undetectable ADAMTS13 but absence of clinical features of TTP have an indolent prothrombotic state with risk for future complications? The authors speculate that these four patients may have had "subclinical" TTP. Could a deficiency of ADAMTS13 synthesis and secretion by the liver have a more localized prothrombotic in the liver itself? The authors propose that ADAMTS13 deficiency could contribute to the common occurrence of portal and hepatic vein thrombosis in patients with advanced liver cirrhosis. These observations are important not only for a better understanding of the systemic manifestations of severe liver disease; they are also important to stimulate questions concerning the role of ADAMTS13 in other disorders.

To return to TTP, which was the beginning of the ADAMTS13 story, these observations may suggest new perspectives about TTP. For example, we have thought that TTP occurs in discrete episodes, and that patients are either critically ill or in complete remission. However, could the intensity of TTP be variable? Does "subclinical" TTP exist? Persistent absence of ADAMTS13 activity following remission from TTP may increase the risk for a recurrent acute episode (10), but examples of chronic, smoldering TTP, as opposed to intermittent acute episodes, are not currently recognized. However, in the era before effective treatment, patients were described who had chronic TTP manifested by intermittent neurologic abnormalities and purpura (11). With more careful long-term follow-up of patients following their recovery from an acute episode, continuing, subtle manifestations of TTP may become apparent.

We have also thought that TTP is a disorder characterized by systemic microvascular thrombosis. However, could the anatomic manifestations of TTP in some patients be selective? Pre-

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vious experience has suggested that microvascular thrombosis may occur less frequently in the liver and lungs than elsewhere (12). But rather than specific organs being spared, could there be clinical situations in which specific organs are targeted by TTP? Thrombotic microangiopathies caused by multiple etiologies may be localized to the kidney (13), but none of these disorders are currently known to be associated with severe ADAMTS13 deficiency. However, patients with congenital absence of ADAMTS13 may develop progressive renal failure in the absence of overt acute episodes of TTP (14, 15).

The observations of Uemura et al. (3), as with all original clinical observations, are important not only for the disease that was studied but also for stimulating questions and creative insights that can help to understand other disorders.

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