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Editorial (concerning B.S. Joly et al. ADAMTS13 conformation is closed in non-immune acquired thrombotic thrombocytopenic purpura of unidentified pathophysiology (uTTP)

A third form of thrombotic thrombocytopenic purpura ?

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In this issue of Haematologica a highly provocative Research Letter by B.S. Joly et al. on behalf of the French Reference Center for Thrombotic Microangiopathies (CNR-MAT) reiterates the existence of a so-far largely disregarded - not to say «scotomized» - form of acquired thrombotic thrombocytopenic purpura (TTP) (1). Since its first description by Moschcowitz in 1924, TTP has attracted the interest of numerous clinicians and researchers over the past 100 years; the development of our knowledge on the pathophysiology and more recently new therapeutic advances in this previously mostly fatal disease are a major success story of modern scientific medicine (for review see 2).

TTP specialists usually distinguish two pathophysiologically distinct forms of TTP : i) a very rare hereditary or congenital TTP (cTTP) or Upshaw-Schulman syndrome caused by biallelic mutations of the *ADAMTS13* gene leading to a severe constitutional deficiency of the Von Willebrand factor-cleaving metalloprotease ADAMTS13 and ii) an acquired, autoimmune TTP (iTTP) associated with autoantibody-mediated severe ADAMTS13 deficiency (3,4).

Whereas in plasma from healthy subjects, from patients with hemolytic uremic syndrome or sepsis, the ADAMTS13 circulates in a closed conformation whereby the two CUB domains interact with the spacer domain, the ADAMTS13 in acute iTTP plasma adopts an open conformation allowing cryptic epitopes in the spacer domain to be recognized by specific monoclonal antibodies (5). Thus, an open ADAMTS13 conformation, i.e. a conformation index > 0.5, was suggested to be a specific hallmark of acute acquired, autoantibody-mediated TTP (5) . A follow-up study initiated by the group of K. Vanhoorelbeke in Kortrijk showed that isolated IgG anti-ADAMTS13 autoantibodies purified from iTTP plasmas were able to induce an open conformation of ADAMTS13 in normal plasma (6). Furthermore, using a large multicentric iTTP cohort with plasma samples obtained during acute TTP episodes and during remission, a conformation index > 0.5 was not only confirmed to be present in the acute disease phase but also in almost all iTTP samples in remission with an ADAMTS13 activity ≤50% and even in 38% of remission samples with normalized ADAMTS13 activity > 50% (6). Therefore, an open ADAMTS13 conformation was proposed as a specific biomarker for both manifest and subclinical iTTP.

In 2016, the French Reference Center for Thrombotic Microangiopathies had reported a cross-sectional analysis of all 939 adult patients admitted with a first episode of acute thrombotic microangiopathy (TMA) with severe ADAMTS13 deficiency between 1999 and 2013 (7). From 772 patients data and blood samples at admission were available: 378 (49%) had idiopathic TTP and 394 (51%) had non-idiopathic TTP, defined as TTP associated with various clinical conditions such as infections, autoimmune diseases, pregnancy, cancer, organ transplantation or drugs. Pathophysiologically, three distinct forms of TTP were delineated: 585 (75%) had iTTP (defined by the presence in plasma of free IgG anti-ADAMTS13 autoantibodies measured by a commercial assay), 21 (3%) had cTTP with biallelic *ADAMTS13* mutations, and 166 (22%) had acquired TTP of unknown cause (uTTP), defined by the absence of IgG anti-ADAMTS13 antibodies (7). Of note, 345/378 (91%) idiopathic TTP cases had iTTP whereas only 240/373 (64%) non-idiopathic acquired TTP cases were classified as iTTP (displaying free anti-ADAMTS13 autoantibodies), and the remaining 133 non-idiopathic cases with lacking autoantibodies were denoted as acquired TTP of unknown cause (uTTP).

The present Research Letter by Joly et al. (1) now focuses on the ADAMTS13 conformation in acquired TTP of unknown pathophysiology, tentatively called uTTP. The authors selected a new cohort of 125 adult patients with a first acute non-idiopathic TTP (ADAMTS13 activity <10% of normal) enrolled in the French TMA Registry in the years 2012-2016. Fourty-nine of the 125 non-idiopathic TTP patients had measurable anti-ADAMTS13 IgG antibodies and were classified as iTTP whereas 76 had no free anti-ADAMTS13 IgG and constituted the group of interest, i.e. the uTTP cases. Comparing the uTTP with the iTTP patients, the former were older, had less female preponderance, had more often associated cancers and less often accompanying autoimmune diseases. Clinical presentation in both groups was similar except for more prevalent renal abnormalities in uTTP. Laboratory features showed less severe thrombocytopenia, higher creatinine values and higher ADAMTS13 antigen levels in uTTP compared to iTTP cases (1). ADAMTS13 conformation index, measurable in 59/76 uTTP and in 30/49 iTTP patients with ADAMTS13 antigen levels of ≥ 0.03 µg/mL displayed an open conformation in 23/30 (76%) iTTP but only 8/59 (13.6%) uTTP patients.

The study by Mariotte et al. (7) and the present Research Letter (1) suggesting the existence of a third pathophysiologic form of TTP besides the well established iTTP and cTTP raise scientifically and practically important questions. What might be the pathophysiology of uTTP ? And what is the most appropriate therapy for this provisional entity ? Obviously, uTTP is associated with an acquired severe ADAMTS13 deficiency and several surviving patients may recover normal ADAMTS13 activity. In contrast to most iTTP cases displaying a CI > 0.5, 51/59 (86.4%) uTTP patients of the present cohort showed a closed ADAMTS13 conformation. Could acquired alterations (deglycosylation, oxidation, proteolysis, high cytokine levels, other factors) during inflammatory reactions severely compromise ADAMTS13 activity ? Or are IgM and/or IgA anti-ADAMTS13 autoantibodies (8), not assessed by commercial IgG anti-ADAMTS13, responsible for uTTP ? Alternatively, could still IgG anti-ADAMTS13 be causative, all bound within circulating IgG-ADAMTS13 complexes (9,10) leaving no detectable free antibodies ?

Evidently, concerted multicentric efforts would be ideal to clarify the nature of uTTP. Such exemplary country-wide collaborative cohorts as provided by the French Reference Center for Thrombotic Microangiopathies will be instrumental to unravel the pathophysiology and thereby to establish whether therapeutic plasma exchange with plasma replacement, corticosteroids, other immunosuppressant drugs and caplacizumab (2) are the optimal measures also for uTTP.

In brief, the research on TTP must go on.

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