and usually less than 20×10^9/L—this is because drug-dependent antibodies usually recognize glycoprotein (GP) IIb/IIIa and/or GPIb/IX antigen targets,[7,8] and these high copy number membrane surface GPs ensure that a high proportion of sensitized platelets are cleared. Finally, there should not be an alternative explanation for thrombocytopenia more highly probable than DITP.

The clinician should also be aware that many drugs beyond the 2 dozen listed do cause DITP. For example, the Milwaukee laboratory has identified at least 10 patients with suspected DITP as having ceftriaxone-dependent platelet-reactive antibodies,[1,6] a causal relationship also supported by data mining.[1] Inexplicably, however, no individual case reports of ceftriaxone-induced DITP exist.[4,5]

Another example: 4 years ago, the authors of this Inside *Blood* commentary jointly observed a 39-year-old male burn victim in whom acute, severe thrombocytopenia (platelet count nadir, 12×10^9/L) began 1 week after beginning a course of mirtazapine (tetracyclic antidepressant), and in whom no other convincing explanation was found; the thrombocytopenia quickly resolved after stopping mirtazapine. A PubMed search ("mirtazapine" and "thrombocytopenia") yielded a single report[9] of mirtazapine-induced DITP, and in which mirtazapine-dependent GPIIb/IIIa-reactive antibodies were identified. The existence of this single published report, in our view, strongly supported the plausibility of a diagnosis of mirtazapine-induced DITP in our patient, even though we could not detect mirtazapine-dependent antibodies in our patient's serum by flow cytometry (in vitro testing for drug-dependent antibodies is relatively specific, but, unfortunately, not always very sensitive[7]). However, as only one ("probable") report of mirtazapine-induced DITP currently exists,[9] and as no such case has undergone serologic verification by the Milwaukee laboratory,[6] mirtazapine failed on 2 counts to meet the authors' criteria for inclusion within the list of 24 drugs.[1] Encouragingly, AERS data mining did identify mirtazapine as a possible cause of DITP.[1]

Between these 2 extremes of putative DITP due to ceftriaxone and mirtazapine—the former almost attaining the top tier and the latter meeting only the novel data-mining category—there undoubtedly exist many other drugs that cause DITP. The strongest candidates are those for which laboratory evidence of drug-dependent antibodies exist,[6] followed by those for which reasonably convincing clinical evidence has been tabulated.[4,5] By these standards, 106 drugs (beyond those 24 listed) meet this level of culpability.[1] The contribution of Reese et al—including the searchable online data supplement—is a valuable "one-stop" resource for clinicians. Their 3-pronged approach of careful evaluation of clinical observations,[4,5] laboratory detection of drug-dependent antibodies,[6] and, now, data mining of spontaneously generated AERS reports,[1] will help focus attention on those drugs that really cause DITP.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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● ● ● THROMBOSIS & HEMOSTASIS

Comment on Feys et al, page 2005

ADAMTS13 Alone

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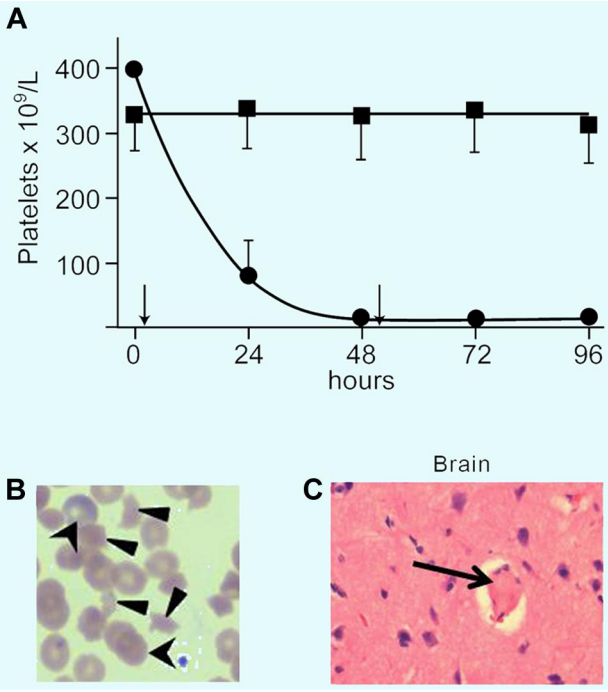
Whether ADAMTS13 deficiency alone is sufficient to cause an acute episode of TTP or whether additional prothrombotic conditions are also required has been uncertain—until now.

The discovery of the plasma protease, ADAMTS13, and its function to cleave the newly synthesized, ultra-large multimers of von Willebrand factor (VWF) changed the landscape of thrombotic thrombocytopenic purpura (TTP), providing insights for etiology and pathogenesis.[1] Severe ADAMTS13 deficiency can be acquired, caused by an autoantibody that inhibits ADAMTS13 function, or very rarely it can be caused by a mutation of the *ADAMTS13* gene. A severe deficiency of ADAMTS13 activity, either acquired or congenital, is strongly associated with acute episodes of TTP. However, there are multiple observations that people can have severe ADAMTS13 deficiency, either acquired or congenital, without clinical signs of TTP.

Acquired severe ADAMTS13 deficiency can be documented in approximately one-third of patients diagnosed with TTP.[2] Some of these patients may continue to have severe ADAMTS13 deficiency after an apparent complete recovery with no clinical signs of TTP. Whether persistent ADAMTS13 deficiency during remission predicts a subsequent relapse remains uncertain.[2] In some patients, acute episodes of TTP are apparently preceded (perhaps "triggered"?) by an inflammatory condition (such as pregnancy, pancreatitis, or an infection) but whether "trigger" conditions precede acute episodes of TTP occasionally, often, or always is unknown.

The occurrence of acute episodes of TTP in patients with congenital severe ADAMTS13 deficiency may also be unpredictable. Some patients present with manifestations of TTP in infancy while others, even in the same family with the same genetic abnormality, may not have clinical signs of TTP until they are adults, or may never have clinical manifestations of TTP.[3]

It was predicted based on clinical observations, that mice with deletions of the *ADAMTS13* gene would manifest the clinical features of TTP, but they did not.[4,5] Additional stresses, such as Shiga toxin,[4] a procoagulant infusion,[5] or use of a mouse strain with



Clinical features of TTP induced by anti-ADAMTS13 antibody in a baboon. (A) The development of sustained, severe thrombocytopenia after 2 infusions of anti-ADAMTS13 antibody (circles, with infusions indicated by arrows; squares represent infusion of a control immunoglobulin). (B) The development of microangiopathic hemolytic anemia in the affected baboons (narrow arrowheads indicate schistocytes; broader arrowheads indicate polychromatophilic red cells). (C) A section of brain with a capillary thrombus (hematoxylin and eosin stain; special stains documented that the thrombus contained platelets and VWF). Professional illustration by A. Y. Chen.

high concentration of plasma VWF[4] were required to provoke the manifestations of TTP.

The sum of these clinical and experimental observations has supported the idea that ADAMTS13 deficiency may merely be a risk factor, albeit a powerful risk factor, but not an independent cause for TTP. This is why the observations of Feys and colleagues[6] are so important. They produced severe ADAMTS13 deficiency in baboons by infusion of inhibitory monoclonal antibodies developed against human rADAMTS13. The ADAMTS13 deficiency alone caused almost all of the characteristic clinical features of TTP in all baboons studied: severe thrombocytopenia and microangiopathic hemolytic anemia with microvascular thrombi composed of platelets and VWF in kidneys, brain, heart, and spleen, but not in lungs—the common pathologic pattern of TTP (see figure). One characteristic feature of untreated TTP that did not occur in the baboons was death. Even with prolonged antibody infusions causing severe thrombocytopenia and anemia with evidence of myocardial ischemia, the baboon "never became noticeably ill."[6p2008]

The conclusion of these observations is clear—ADAMTS13 deficiency alone can cause TTP. But how do we interpret the observations that acute episodes of TTP in our patients sometimes seem to require a "trigger" condition? Could this be merely a quantitative issue? Could patients with undetectable ADAMTS13 activity by current assays still have sufficient activity to prevent the spontaneous development of TTP? Or could baboons be qualitatively distinct from humans, with greater sensitivity to ADAMTS13 deficiency because of occult inflammation? In addition, how do we interpret the observations that the baboons "never became noticeably ill"? Could this also be a quantitative issue, with fewer microthrombi occurring in the affected organs than occur in humans? What provides protection against the continuing microvascular thrombosis? There are no answers yet for these questions.

Beyond the clear conclusion that ADAMTS13 deficiency alone can cause the clinical manifestations of TTP, the baboon model for TTP has great promise for additional value. An imperative goal for the management of patients with TTP is to develop treatment that is more effective, more accessible, and safer than plasma exchange. The introduction of plasma exchange was life-saving, resulting in survival rates of 80%[7] compared with previous survival of only 10%.[8] Treatment must be more effective, because the survival rate has not changed in the past 20 years; 20% of patients with TTP still die.[2] Treatment must also be more accessible. Plasma exchange procedures require specialized instruments, personnel, and insertion of a dialysis catheter, things that are not available at all times in all places. Treatment must also be safer because plasma exchange has a high frequency of serious complications. In 249 consecutive patients treated with plasma exchange for TTP from 1996 to 2008, 64 (26%) patients had 83 major complications and 7 (2.8%) died.[9] The baboon model developed by Feys and colleagues[6] will be immediately important for developing better treatments for patients with TTP.

To summarize, the article by Feys and colleagues[6] is simple in concept, important for better understanding of the pathogenesis of TTP, and critical for developing better treatments for patients with TTP.

Conflict-of-interest disclosure: The author is a consultant for Baxter Inc for development of rADAMTS13. ■

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