von Willebrand factor cleaving protease-ADAMTS 13

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TITLE	von Willebrand factor–cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic–uremic syndrome.
AUTHORS	Furlan M, Robles R, Galbusera M, *et al.*
JOURNAL	The New England Journal of Medicine. 1998;339(22):1578-1584. doi: 10.1056/NEJM199811263392202.

In 1988, Furlan and colleagues published an article in *The New England Journal of Medicine*[1] that was to be start of an extraordinary journey. von Willebrand factor cleaving protease (vWF CP) had recently been described as the enzyme responsible for the cleavage of vWF.[2] It was more than a decade later that vWF CP was confirmed as ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13).[3]

Why was this paper so important? Analysis of vWF CP levels differentiated four clinical groups. The cohort was large: 53 patients and samples taken, mainly before plasma exchange, and run in triplicate. The patients had a clinical diagnosis of thrombotic thrombocytopenia purpura-hemolytic uremic syndrome (TTP-HUS). Within the TTP group, the presence of an inhibitor was investigated using a multimeric assay and a Bethesda-based approach, using three dilutions of patients' plasma with normal plasma and incubating for 10 minutes at 37°C. Finally, affinity chromatography confirmed the antibody as IgG.

Patients in the TTP cohort were categorized into those having antibody-mediated disease (now known as immune TTP) or congenital TTP. All had a severe vWF CP deficiency, in contrast to HUS cases in which vWF CP levels were essentially normal.

In more detail, the normal range of vWF CP was derived from 120 control samples. Of the 53 patients, 30 had TTP and 23 had HUS. In non-familial TTP, 20 of the 24 patients had a severe deficiency of vWF CP and four cases had moderately reduced levels. Twenty cases had an inhibitor to vWF CP and in the five cases investigated further, the antibodies were IgG. Of the four cases with no inhibitor identified, three presented in pregnancy and the fourth was a case of thrombotic microangiopathy in a patient who had undergone an allogeneic transplant. In five patients vWF CP returned to normal in remission. In all familial TTP cases, vWF CP was severely deficient and no inhibitor was

Patient N (time of sample)	16(A)	17(A)	18(A)	19(A)	20(A)	21(A)	22(A)	23(A)	24(A)	25(A)	25(R)	26(A)	26(R)	27(A)	27(R)	28(A)	28(R)	29(A)	29(R)	30(A)
Inhibitor — U/mL	0.2	0.0	1.0	0.1	0.5	0.3	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Diagnosis	TTP	TTP	TTP	TTP	TTP	TTP	TTP	TTP	TTP	HUS	HUS	HUS	HUS	HUS	HUS	HUS	HUS	HUS	HUS	HUS

Figure 1. Activity of von Willebrand factor–cleaving protease and the level of its inhibitor in patients with non-familial thrombotic thrombocytopenic purpura or non-familial hemolytic-uremic syndrome. Plasma samples were collected during an acute event (A) and/or remission (R). TTP: thrombotic thrombocytopenic purpura; HUS: hemolytic-uremic syndrome. Figure adapted and reproduced, with permission, from Furlan M, *et al.*[1]

identified. In relation to mortality, there were eight acute deaths, six among patients with TTP and two among those with HUS, but no deaths in the familial cohort.

How do these findings relate to our understanding of TTP and HUS? Before the identification of vWF CP, it was difficult to differentiate TTP and HUS. However, the publication by Furlan *et al*. not only provided confirmation that the two conditions were separate entities but also the underlying pathogenesis for TTP (Figure 1). Multimeric analysis was a long, difficult research assay, but it paved the way for newer assays, performed in routine laboratories with results possible in 30 minutes. The algorithm for investigation of TTP, despite newer and quicker assays, still follows that laid out in the Swiss publication. Diagnosis and treatment pathways have improved driven by education, based on this landmark publication, ensuring that TTP (and HUS) are taught in medical school and postgraduate curricula. . Progress in therapy, derived from vWP CP (ADAMTS 13) levels, has shortened time to remission, with the use of caplacizumab and immunosuppression in the acute setting. Follow-up ADAMTS 13 monitoring and rituximab therapy prevent relapse of TTP. More recently, recombinant ADAMTS 13 has been licensed for congenital TTP, completing the cycle from laboratory discovery, through clinical trials to prophylactic patient care.[4]

Disclosures

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