

ADAMTS13 in clinical patho-physiology

Latest scientific evidence



ADAMTS13 activity and the risk of thrombotic thrombocytopenic purpura relapse in pregnancy.

Raman R et al., Br J Haematol. 2011 Jan 31. [Epub ahead of print]

Summary:

Thrombotic thrombocytopenic purpura (TTP) associated with pregnancy accounts for 12–31% of TTP cases and is associated with high rates of obstetric complications. Some reports have noted that women who initially present with idiopathic TTP are more likely to relapse during a pregnancy compared to those who presented initially with TTP in association with a pregnancy (25% vs. 12%) while deficient pre-pregnancy ADAMTS13 activity has been utilized to determine this risk by others. The authors demonstrate that severely deficient (<2.5%) ADAMTS13 activity during pregnancy predicts a high risk of relapse and identifies patients in which the risk/benefit ratio justifies prophylactic therapy. Such a correlation may exist irrespective of the circumstances of the initial TTP episode (idiopathic versus pregnancy-associated).

The authors conclude that pregnant patients with a previous TTP episode should have ADAMTS13 activity assessed pre- and throughout pregnancy to identify those at greatest risk of relapse.

Pregnancy-associated thrombotic thrombocytopenic purpura with anti-centromere antibody-positive Raynaud's syndrome.

Watanabe R et al., Intern Med. 2010;49(12):1229-1232.

Summary:

The authors report the case of a 32-year-old woman with microangiopathic hemolytic anemia, thrombocytopenia, and a slightly elevated serum creatinine level with anti-centromere antibody-positive Raynaud's syndrome in the early puerperal period.

Thrombotic thrombocytopenic purpura (TTP), scleroderma renal crisis (SRC), and hemolysis, elevated liver enzyme levels, and a low platelet count (HELLP) syndrome displaying common symptoms were considered in the differential diagnosis. The measurement of ADAMTS13 activity and its inhibitor level led to the diagnosis of TTP. She was successfully treated by plasma exchange and high-dose prednisolone and angiotensin-converting enzyme inhibitor.

An accurate diagnosis of TTP is challenging when symptoms occur in perinatal women or patients with signs of SSc. Therefore, the most important laboratory data to guide the correct choice of treatment is ADAMTS13 activity and its inhibitor level.

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Von Willebrand Factor and ADAMTS13: A Candidate Couple for Preeclampsia Pathophysiology.

Stepanian A et al., Arterioscler Thromb Vasc Biol. 2011 Apr 21. [Epub ahead of print]

Summary:

Preeclampsia is the most frequent medical complication during pregnancy. The pathogenesis involves inadequate cytotrophoblast invasion with subsequent abnormal placentation, resulting in placental hypoperfusion and ischemia with microthrombotic lesions.

This study is the first to suggest a link between ADAMTS13 deficiency and Preeclampsia. The authors could demonstrate that Preeclampsia is associated with decreased levels of ADAMTS13, independently of VWF. This decrease is quantitative, occurs early, and seems to be dependent on inflammation. The results suggest that ADAMTS13 could participate in the pathophysiology of preeclampsia.

Von Willebrand factor antigen and ADAMTS13 activity assay in pregnant women and severe preeclamptic patients.

Zhang D et al., J Huazhong Univ Sci Technolog Med Sci. 2010 Dec;30(6):777-780.

Summary:

The authors analyzed von Willebrand factor (vWF) levels and ADAMTS13 activity in pregnant and severe preeclamptic women in order to shed light on the prothrombotic state in severe preeclampsia.

In conclusion, plasma ADAMTS13 activity is normal in severe preeclampsia despite the increased vWF:Ag levels. Prothrombotic state is involved in the pathogenesis of severe preeclampsia, as a result of endothelial injury.

Changes in von Willebrand factor and ADAMTS13 during IVF.

Westerlund E et al., Blood Coagul Fibrinolysis. 2011 Mar;22(2):127-131.

Summary:

During *In vitro fertilization* (IVF), circulating estradiol concentrations are strongly increased, and this may have direct effects on hemostasis.

The present study was aimed to study possible changes in ADAMTS13 during IVF and whether changes in VWF during IVF are related to changes in ADAMTS13. The authors analyzed von Willebrand factor antigen, von Willebrand factor ristocetin cofactor activity, factor VIII and ADAMTS13 antigen and activity levels in plasma from women (n=31) undergoing IVF treatment.

The increments in estradiol and factor VIII during IVF were paralleled by an increase in von Willebrand factor antigen and activity, and a decrease in circulating ADAMTS13 antigen and activity, respectively. This could in part explain why these patients have an increased risk of thrombotic events.

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ADAMTS13--marker of contractile phenotype of arterial smooth muscle cells lost in benign nephrosclerosis.

Bockmeyer CL et al., Nephrol Dial Transplant. 2010 Oct 5

Summary:

Hypertensive nephrosclerosis alone and in combination with other renal diseases is a leading cause of terminal renal insufficiency. Histologic lesions manifest as benign nephrosclerosis with arteriolar hyalinosis and later fibrosis. Hyalinosis is considered to consist of plasma insudation possibly containing procoagulant factors like von Willebrand factor (VWF).

Therefore, it is speculated that ADAMTS13 expression in VSMCs might play a role in this context.

The authors demonstrated for the first time that ADAMTS13 is expressed in arterial and arteriolar VSMCs throughout the human organism. The role of ADAMTS13 expression in VSMCs is probably cleavage of endothelium-derived VWF multimers permeating into the arterial walls. ADAMTS13 can be considered a marker of the contractile phenotype that is lost in the chronic, fibrotic lesions of bN. Loss of ADAMTS13 and accumulation of VWF exclusively in fibrotic arteriolar lesions could contribute to fibrosis.

ADAMTS13--more than just TMA and TTP.

Amann K. Nephrol Dial Transplant. 2011 Apr 29. [Epub ahead of print]

Editorial comment on the results from Bockmeyer et al.

Pivotal role of ADAMTS13 function in liver diseases

Uemura M et al., Int J Hematol. 2010 Jan;91(1):20-29.

The liver is a major source of clotting and fibrinolytic proteins, and thus plays a central role in hemostasis regulation. Patients with advanced liver diseases tend to bleed because of reduced plasma levels of several clotting factors and thrombocytopenia, but they also experience thrombotic complications.

ADAMTS13 is produced exclusively in liver cells, and cleaves highly multimeric von Willebrand factor (VWF). Deficiency of ADAMTS13 results in accumulation of unusually large VWF multimers (UL-VWFM) in plasma. This promotes platelet clumping under high shear stress and leads to disturbed microcirculation. Decreased ADAMTS13 activity may be involved not only in microcirculatory disturbances, but also in the subsequent progression of liver injuries, eventually leading to multiorgan failure.

Taken together, ADAMTS13 may play an important role in the patho-physiology of liver diseases, and insights into ADAMTS13 regulation may provide a basis for the development of novel therapies.

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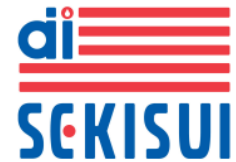
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Severe transient ADAMTS13 deficiency in pneumococcal-associated hemolytic uremic syndrome.

Pelras S et al., *Pediatr Nephrol.* 2011 Apr;26(4):631-635.

Summary:

The authors report the case of a critically ill 2-year-old girl with invasive pneumococcal disease associated hemolytic uremic syndrome (p-HUS) whose condition was complicated by severe ADAMTS13 deficiency, without detectable inhibitor, in a context of multiple organ failure. The patient recovered with supportive treatment, and ADAMTS13 activity normalized without plasmatherapy.

Thrombotic microangiopathy: new insights.

Benz K and Amann K, *Curr Opin Nephrol Hypertens.* 2010 May;19(3):242-247.

Summary:

In this study new aspects and insights into the epidemiology, pathogenesis and typical morphology of kidney involvement in thrombotic microangiopathy (TMA) are discussed.

In thrombotic thrombocytopenic purpura (TTP) and typical and atypical haemolytic uraemic syndrome (HUS) the kidney shows characteristic vascular changes due to endothelial damage, that is, TMA. Renal involvement in TMA should be differentiated from other diseases by clinical and morphological techniques and in particular by immunohistological/immunofluorescence and electron microscopy.

Recent genetic and molecular studies have shed more light on the underlying pathogenesis in atypical HUS, that is, disturbances of various aspects of the complement system, and in TTP, that is, vWF regulation by ADAMTS13, which are also helpful in the differential diagnosis.

Thrombotic microangiopathies: new insights and new challenges.

Zipfel PF et al., *Curr Opin Nephrol Hypertens.* 2010 Jul;19(4):372-378.

Summary:

Thrombotic microangiopathies (TMAs) manifest as a spectrum of related disorders in the form of thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS).

The authors summarize the recent developments in this rapidly progressing field. New data on both diseases support more and more the relatedness of the disorders and reveal related pathomechanisms, which, however, manifest in different organs. TTP develops primarily at neurological sites, and also in the kidney, and HUS is a kidney disease. In TTP thrombi formation occurs subsequently to the release of multimers of von Willebrand factor (vWF), and in HUS endothelial cell damage is considered the reason for complement and platelet activation leading to thrombus formation.

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The balance between von-Willebrand factor and its cleaving protease ADAMTS13: biomarker in systemic inflammation and development of organ failure?

Claus RA et al., Curr Mol Med. 2010 Mar;10(2):236-248.

Summary:

In proinflammatory conditions, ADAMTS13 activity decreases due to various mechanisms, (i) down regulation on a transcriptional level, (ii) proteolytic degradation, and (iii) consumption due to the high substrate level. Marked dysbalance as found in patients with severe sepsis or septic shock results in substantial amounts of plasma ULVWF. This level of dysbalance is negatively correlated with platelet count and positively correlated with the severity of inflammation and the degree of organ failure.

This review investigates and highlights the activity of Willebrand factor (VWF) and its cleaving protease as biomarkers of the development of multiple organ dysfunction in infectious and noninfectious systemic inflammatory response syndrome.



Reduced ADAMTS13 in children with severe meningococcal sepsis is associated with severity and outcome.

Bongers TN et al., Thromb Haemost. 2010 Jun;103(6):1181-1187.

Summary:

Multiple organ failure is a common feature of pediatric meningococcal sepsis and is associated with an imbalance of coagulation and fibrinolysis. This is partly due to an increased secretion of prothrombotic ultra-large von Willebrand factor (VWF) as the result of vascular endothelial damage. Another important factor that may contribute is ADAMTS13, which converts VWF into smaller, less active, VWF multimers and thus influences VWF activity in plasma.

The authors showed that levels of ADAMTS13 are strongly reduced and levels of VWF are strongly increased in children with meningococcal sepsis and that these levels are associated with severity and outcome of the disease, likely by promoting the formation of microthrombi in these affected children.

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Prognostic value of plasma von Willebrand factor-cleaving protease (ADAMTS13) antigen levels in patients with coronary artery disease.

Miura M et al., Thromb Haemost. 2010 Feb 2;103(3). [Epub ahead of print].

Summary:

This study provides evidence that low plasma ADAMTS13 as well as high VWF antigen level is a useful predictor of future major adverse cardiac and cerebrovascular events (MACCE) and cardiac and cerebro-vascular thrombotic events in patients with coronary artery disease (CAD).

The authors examined the changes and the prognostic value of plasma VWF-cleaving protease (ADAMTS13) levels in patients with CAD (n= 225) and patients without CAD (n=100).

The CAD patients had higher VWF and lower ADAMTS13 antigen levels when compared to the control group. During the follow-up period 20 MACCE occurred in the patients with CAD. CAD patients with high plasma VWF antigen levels were significantly more likely to develop MACCE.

Eight cardiac and cerebrovascular thrombotic events [acute coronary syndrome (n=4) and cerebral infarction (n=4)] occurred in CAD patients with both high plasma VWF and low ADAMTS13 antigen levels.

Levels of von Willebrand factor and ADAMTS13 determine clinical outcome after cardioversion for atrial fibrillation.

Freyenhofer MK et al., Thromb Haemost. 2011 Mar;105(3):435-443.

Summary:

Patients with atrial fibrillation (AF) exhibit higher plasma vWF and lower ADAMTS13 antigen levels compared to controls. Little is known about vWF and ADAMTS13 in AF patients treated with cardioversion (CV). Thus the authors investigated the alterations of plasma vWF and ADAMTS13 after CV and evaluated the predictive value of these parameters for recurrence of AF.

The vWF/ADAMTS13-ratio significantly increases after cardioversion after CV; this suggests that endothelial dysfunction occurs early after CV. Therefore, the authors speculate that the endothelium, represented by the vWF/ADAMTS13-ratio, plays a crucial role in producing a pro-thrombotic milieu after successful CV. Since ADAMTS13 plasma concentration and the vWF/ADAMTS13-ratio are independently associated with rhythm stability, these indexes might be used for prediction of recurrence of AF.

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ACTIFLUOR™ ADAMTS13

Activity assay, # 812

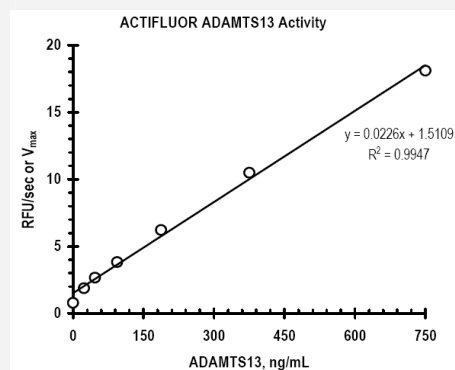


Principle of the assay

ACTIFLUOR ADAMTS13 is a FRET assay that measures the amount of ADAMTS13 activity in human plasma. A citrated plasma sample is assayed for ADAMTS13 protease activity using recombinant VWF86-ALEXA FRET substrate. Proteolytic cleavage of the VWF86-ALEXA FRET substrate by ADAMTS13 uncouples the ALEXA fluorochromes resulting in an increase in fluorescence. The increase in fluorescence over time (V_{max}) due to cleavage of the substrate by ADAMTS13 is monitored at 37°C using a spectrofluorometer (Ex=485 nm; Em=535 nm).

A standard curve is constructed using normal plasma with a known concentration of ADAMTS13. The ADAMTS13 activity in the plasma is determined by interpolation of the V_{max} values from the standard curve.

Standard curve



Key Features

- **Format:** 48-well format
- **Assay Time:** 20 minutes
- **Sample Type:** citrated human plasma
- **Sample Volume:** 20 μ L to perform duplicate analysis
- **Assay Range:** 0 - 750 ng/ml
- **Sensitivity:** 3 ng/ml (< 5% normal)
- **Values:** results expressed as ADAMTS13 conc. [ng/ml]
- **Precision:** intra-assay CV = 4.1 %, inter-assay CV= 4.4 %
- **IVD, CE-marked**

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ADAMTS13 / vWF Assays and Reagents



ASSAYS	Assay type	Format	Product #
ACTIFLUOR™ ADAMTS13 Activity kit	Fluorometric assay	48 tests	812
IMUBIND® ADAMTS13 kit	ELISA	96 tests	813
IMUBIND® ADAMTS13 Autoantibody kit	ELISA	96 tests	814
IMUBIND® vWF ELISA kit	ELISA	96 tests	828
IMUBIND® vWF Activity ELISA kit	ELISA	96 tests	885
IMUCLONE™ vWF:CB activity ELISA kit	ELISA	96 tests	59203
ANTIBODIES	Known Applications	Amount	Product #
anti-human ADAMTS13 mAb	ELISA	250 µg	3305
anti-human ADAMTS13 mAb	Western blot Immunoprecipitation Functional inhibition	250 µg	3312
anti-human vWF mAb	Western blot, Immunoprecipitation	500 µg	ESvWF-8
PROTEINS	Source	Amount	Product #
human vWF	native	100 µg	2041
human vWF, Factor VIII free	native	100 µg	2042

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