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Increased expression of ADAMTS13 mRNA correlates with ischemic cerebrovascular disease in systemic lupus erythematosus patients

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Abstract

Objective: We investigated ADAMTS13 (a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13) messenger RNA levels as a biomarker of disease features in systemic lupus erythematosus.

Methods: We measured and compared messenger RNA (mRNA) levels of ADAMTS13 in peripheral blood cells in patients with systemic lupus erythematosus and healthy control subjects by whole-genome microarray. We retrospectively analyzed the correlations of ADAMTS13 mRNA expression with clinical features, laboratory parameters, therapeutic features, and disease activity (according to the Systemic Lupus Erythematosus Disease Activity Index). We also examined the association of three single nucleotide polymorphisms (rs4962145, rs2285467, and rs685523) of the *ADAMTS13* gene with patient characteristics.

Results: In 309 patients, the median ADAMTS13 mRNA expression levels were significantly higher in blood cells of systemic lupus erythematosus patients than in 23 healthy controls ($p = .03$). Notably, ADAMTS13 mRNA expression levels were significantly higher in systemic lupus erythematosus patients with a history of stroke ($p = .02$) or transient ischemic attack ($p = .02$). Among the three single nucleotide polymorphisms analyzed, rs2285467 was significantly associated with stroke ($p = .03$) and anticardiolipin antibodies ($p = .04$).

Conclusions: Increased expression of ADAMTS13 mRNA in blood cells is associated with the presence of ischemic cerebrovascular disease in systemic lupus erythematosus patients and suggests a potential role for ADAMTS13 in the pathogenesis of ischemic cerebrovascular disease in these patients.

Keywords

ADAMTS13, atherosclerosis, cardiovascular disease, gene polymorphism, systemic lupus erythematosus

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Introduction

ADAMTS13 protease, a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13, is known to cleave highly active, thrombogenic, ultralarge von Willebrand factor (vWF) multimers into less active, small-molecular-weight multimers, thereby controlling vWF-mediated platelet thrombus formation.[1] ADAMTS13, also known as vWF-cleaving protease, belongs to a recently described group of secreted metalloproteinase enzymes, the ADAM and matrix metalloproteinase families of proteases (ADAMTS).[2,3] Emerging evidence suggests that members of the ADAMTS protease family play important roles in disorders such as arthritis (ADAMTS4 and ADAMTS5),[4] arterial thrombosis (ADAMTS13),[5] and cancer (ADAMTS1).[6] Recent studies have just begun to establish roles for the ADAMTS proteases in atherosclerosis and inflammation (ADAMTS1, ADAMTS4, ADAMTS5, and ADAMTS8).[6–10]

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However, the biological function of most ADAMTS proteases is not yet well known.

Importantly, a deficiency of ADAMTS13 is associated with thrombotic thrombocytopenic purpura (TTP),[11–13] a potentially lethal syndrome that often occurs concurrently with systemic lupus erythematosus (SLE).[14] SLE is a chronic multisystem autoimmune disease with a broad range of clinical manifestations, including photosensitive rashes, discoid lesions, arthritis and arthralgia, renal disorders, cardiac and pulmonary disease, and central nervous system disorders. SLE has in common with TTP several pathogenic triggers and clinical findings (fever, central nervous system involvement, renal impairment, hemolytic anemia, and thrombotic events), although they are distinct entities.[15] While the pathogenic role of ADAMTS13 in TTP associated with SLE has been well investigated, information on ADAMTS13 and other clinical manifestations of SLE is limited.

On the basis of this background, we examined whether expression levels of ADAMTS13 mRNA (messenger RNA) in peripheral blood cells vary among different clinical, immunologic, and laboratory features in SLE patients, and whether ADAMTS13 mRNA expression levels depend on disease activity. We subsequently investigated whether ADAMTS polymorphisms predispose to any particular manifestation of SLE. We found that ADAMTS13 mRNA expression levels in blood cells are associated with the presence of ischemic cerebrovascular disease (stroke or transient ischemic attack (TIA)) in SLE patients without evidence of TTP and suggests a potential role for ADAMTS13 in the pathogenesis of ischemic cerebrovascular disease in SLE patients.

Patients and methods

Patients and clinical assessment

This study was carried out in accordance with research protocols approved by institutional review boards of Mayo Clinic, Rochester, Minnesota; University of Minnesota School of Medicine, Minneapolis, Minnesota; and Johns Hopkins University School of Medicine, Baltimore, Maryland. Informed consent was provided by all study participants. Peripheral blood samples were obtained from patients who fulfilled at least four criteria of the American College of Rheumatology for SLE[16,17] and healthy controls. Patients included in this study were enrolled from the Hopkins Lupus Cohort[18] under the auspices of the Autoimmunity Biomarkers Collaborative Network.[19] Data were collected retrospectively for all patients regarding the presence or absence of each individual American College of Rheumatology criterion for SLE;[16,17] signs and symptoms associated with organ-system involvement; presence or absence of SLE-associated autoantibodies, including antinuclear antibody, anti-Ro, anti-LA, anti-Sm, anti-RNP, anti-dsDNA, antiphospholipid, and anticardiolipin antibodies; clinical laboratory tests; medication profile; and the SLE Disease Activity Index (SLEDAI).[20] Subsequently, history of major cardiovascular risk factors (smoking, diabetes, and hypertension) was obtained from all SLE patients. Samples were collected and studied from an array of patients ranging from those with newly diagnosed disease to those with a longstanding diagnosis. Data were collected using the REDCap system.[21]

ADAMTS13 gene expression

Total RNA was isolated from whole blood collected in tubes treated with an RNA stabilization agent (PAXgene; PreAnalytiX, Hombrechtikon, Switzerland) and stored at −80°C until RNA isolation. RNA was isolated using an RNA-purification kit (PAXgene Blood RNA kit) following the manufacturer's instructions and subjected to an on-column DNase I treatment. Labeled complementary RNA was generated from total RNA using the manufacturer's protocol (Illumina TotalPrep RNA Amplification Kit; Life Technologies, Grand Island, NY) using manufacturer's protocol. The labeled complementary RNA was hybridized to expression arrays (Illumina Human WG-6v2 BeadChip; Illumina, San Diego, CA). Data quality assessment and quantile normalization were performed (Illumina Genome Studio software). To reduce noise contributed by genes expressed at very low levels, expression values that had a detection p value higher than .1 were replaced with the minimum detectable expression value for that gene ($p < .1$).

Genotyping

Three polymorphisms from ADAMTS13 (rs4962145, rs2285467, and rs685523) were genotyped (Illumina Human Hap550v3 Genotyping BeadChip) at the Feinstein Institute for Medical Research, Manhasset, New York. These data were generated as part of a genomewide association study to identify risk loci associated with SLE.[22]

Statistical analysis

Descriptive statistics (means, medians, ranges, percentages, etc.) were used to summarize the data. The χ^2 test was used for discrete variables, and the Kruskal–Wallis test was used to compare continuous variables between groups (e.g. with and without SLE, with and without certain patient characteristics, and genotypes). Spearman rank correlation methods were used to examine potential associations between ADAMTS13 levels and continuous characteristics (e.g. SLEDAI).

Results

Patient clinical features and their correlation with ADAMTS13 mRNA expression

The study included 309 subjects with SLE (280 women, 29 men), with a mean ± SD age of 44.1 ± 12.5 years. All patients in the study were White. The mean ± SD disease duration was 13.8 ± 9.6 years. The range of SLEDAI scores was from

Table 1. Patient characteristics (N = 309).

Characteristic	Value[a]
Female sex	280 (91)
Age, mean ± SD (years)	44.1 ± 12.5
White race	309 (100)
SLE duration, mean ± SD (years)	13.8 ± 9.6
SLEDAI, mean ± SD (range)	1.8 ± 2.7 (0–14)
Skin involvement[b]	241 (78)
Arthritis[b]	224 (72)
Serositis[b]	149 (48)
Renal disorders[b]	183 (59)
Neurologic disorders (seizures or psychosis)[b]	4 (1)
Hemolytic anemia[b]	28 (9)
Leukopenia[b]	184 (60)
Thrombocytopenia[b]	66 (21)
Anti-dsDNA positive[b]	163 (53)
Anti-Sm positive[b]	25 (8)
Antiphospholipid[b]	182 (59)
Antinuclear antibodies[b]	293 (95)
Lupus anticoagulant	95 (31)
Anti-RNP	32 (11)
Cardiovascular risk factors	
Smoking (former or current)	115 (37)
Hypertension	125 (41)
Diabetes	24 (8)
Medications	
Any DMARD (current use at study visit)	219 (71)
Plaquenil	203 (66)
Cyclophosphamide	16 (5)
Methotrexate	14 (5)
Chloroquine	6 (2)
Dapsone	11 (4)
Prednisone	136 (55)

DMARD: disease-modifying antirheumatic drug; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; anti-RNP: anti-ribonucleoprotein.
[a]Values are number (percentage) unless indicated otherwise.
[b]The American College of Rheumatology revised classification criteria for SLE, adapted from Hochberg.[17]

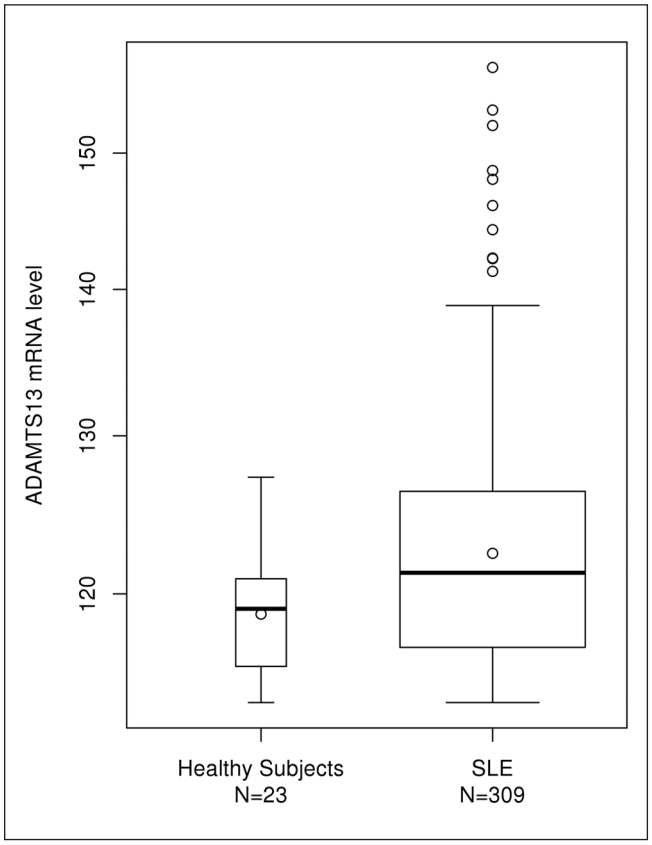

Figure 1. Comparison of *ADAMTS13* gene expression for 23 healthy control subjects and 309 patients with SLE.
SLE: systemic lupus erythematosus; ADAMTS13: a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13.
The y-axis represents *ADAMTS13* gene expression. The horizontal bars indicate medians. ADAMTS13 mRNA expression levels were significantly higher in SLE patients (median, 121.3 (25th, 75th quartile, 116.8, 126.4)) than in healthy controls (median, 119.1 (25th, 75th quartile, 114.8, 121.3)).

0 to 14, and the mean was 1.8 ± 2.7. Clinical and demographic characteristics of the 309 SLE patients are shown in Table 1. The study also included 23 healthy controls (16 women, 7 men), with a mean ± SD age of 38.7 ± 10.0 years.

The most common manifestations included skin involvement (241 patients), arthritis (224 patients), leukopenia (184 patients), and renal disorders (183 patients). Seizures and/or psychosis associated with SLE were found in 4 patients. Ischemic stroke and TIA were observed in 11 and 5 patients, respectively; in 3 patients, TIA preceded stroke. Clinical features of TTP were observed in 5 SLE patients. A total of 16 SLE patients were antinuclear antibody negative; 219 patients were currently being treated with one or more disease-modifying antirheumatic drugs, such as antimalarials, methotrexate, cyclophosphamide, and dapsone, either alone or in combination with corticosteroids at the time of the blood draw. A total of 250 patients had a history of previous corticosteroid treatment.

Correlation of ADAMTS13 mRNA expression with clinical features in SLE patients

The results of measuring and comparing ADAMTS13 mRNA levels in peripheral blood cells showed that the median ADAMTS13 mRNA expression levels were significantly higher in the 309 SLE patients (median, 121.3 (25th, 75th quartile, 116.8, 126.4)) than in the 23 healthy controls (median, 119.1 (25th, 75th quartile, 114.8, 121.3)) ($p = .03$) (Figure 1).

Table 2 classifies SLE patients according to the presence or absence of clinical features of SLE. No significant differences were found between ADAMTS13 mRNA expression levels and skin manifestations, arthritis, serositis

Table 2. *ADAMTS13* gene expression by clinical features.[a]

Clinical feature	Patients without characteristic		Patients with characteristic		*p* value
	No.	ADAMTS13 level	No.	ADAMTS13 level	
Thrombocytopenia	243	121.3 (116.8, 126.4)	66	121.4 (115.7, 126.4)	.85
Hemolytic anemia	281	121.2 (116.7, 126.3)	28	123.2 (116.2, 128.0)	.55
Proteinuria	209	120.8 (116.2, 126.3)	100	122.3 (117.4, 126.4)	.27
Hematuria	232	120.8 (115.8, 126.3)	77	122.4 (118.4, 127.7)	.12
Thrombotic thrombocytopenic purpura	304	121.3 (116.8, 126.4)	5	115.2 (115.1, 118.1)	.17
Stroke	**298**	**121.0 (116.6, 126.3)**	**11**	**126.5 (121.3, 129.2)**	**.02**
Transient ischemic attack	**154**	**121.6 (116.6, 127.4)**	**5**	**126.6 (126.3, 137.8)**	**.02**
Myocardial infarction	301	121.3 (116.8, 126.4)	8	123.1 (117.2, 125.2)	.82
Increased liver function tests	196	120.9 (115.8, 126.2)	113	121.6 (117.5, 127.2)	.13
Smoking (former or current)	194	121.4 (117.2, 126.1)	115	121.1 (116.8, 126.0)	.86
Hypertension	184	121.3 (116.5, 126.4)	125	121.3 (116.9, 126.4)	.70
Diabetes	285	121.2 (116.8, 126.2)	24	124.7 (116.7, 129.5)	.18
DVT	268	120.9 (116.5, 126.2)	41	125.0 (118.4, 128.5)	.057

ADAMTS13, a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13; DVT: deep vein thrombosis.
[a]Values in the table are median (25th, 75th quantile). Bold type indicates a statistically significant result.

(pleuritis or pericarditis), renal disorder (hematuria, persistent proteinuria, or cellular casts), neurologic disorder (seizures or psychosis), hematologic disorder (hemolytic anemia, leukopenia, or lymphopenia), and thrombocytopenia. In addition, no significant differences were found between ADAMTS13 mRNA expression levels and TTP manifestations (p = .17). We found that ADAMTS13 mRNA expression in blood cells did not correlate with disease activity (SLEDAI) (p = .71). Notably, ADAMTS13 mRNA expression levels were significantly higher in SLE patients with a history of ischemic stroke (p = .02) or TIA (p = .02) than in those without stroke or TIA.

No significant differences were observed between ADAMTS13 mRNA levels in the 26 SLE patients with coronary artery disease compared with those without coronary artery disease (p = .35). No association was found between ADAMTS13 mRNA levels and presence of cardiovascular risk factors (smoking, hypertension, and diabetes).

Plasma ADAMTS13 activity has been found to correlate with serum aspartate aminotransferase and alanine aminotransferase in patients with liver diseases,[22] suggesting that plasma ADAMTS13 activity may reflect hepatocellular damage. We found no significant differences between ADAMTS13 mRNA in SLE patients with elevated liver function test results compared with SLE patients with normal liver function (p = .13).

Patient clinical features and ADAMTS13 polymorphisms

In a subgroup of 261 patients enrolled in this study, polymorphism rs2285467 was significantly associated with stroke (p = .03) (Table 3) and anticardiolipin antibodies (p = .04) (data not shown), and rs685523 was associated with hemolytic anemia (p = .03) (Table 3). No other SLE clinical features were differentially represented in the genotype distribution of each ADAMTS13 polymorphism.

Discussion

In this study, we demonstrated by whole-genome microarray that ADAMTS13 mRNA expression levels were higher in SLE patients than in healthy controls. ADAMTS13 mRNA expression levels significantly correlated with the presence of ischemic stroke or TIA. It is well recognized that patients with SLE are at a five- to six-fold increased risk of myocardial infarction and stroke compared with the general population.[23–25] The pathogenic mechanisms underlying this increased risk of cardiovascular disease are not fully understood. It is increasingly accepted that accelerated atherosclerotic disease appears to be a major underlying mechanism of cardiovascular disease among SLE patients and in patients with other autoimmune diseases.[26,27] Whether this accelerated atherosclerosis and premature cardiovascular disease arise through the same or different mechanisms from those in the general population without SLE remains unclear. The risk of cardiovascular disease in SLE patients seems to be independent of traditional cardiovascular risk factors.[28] To our knowledge, decreased plasma ADAMTS13 activity (usually <5% of normal), which results in accumulation of prothrombotic, ultralarge vWF multimers in the blood circulation, has been the main pathophysiologic mechanism by which ADAMTS13 is linked to the development of thrombotic diseases. In a recent study, decreased plasma ADAMTS13 activity was implicated as a risk factor for pediatric stroke.[29] Our data were analyzed retrospectively; therefore, we could not determine the ADAMTS13 and vWF activity in plasma. However, we did not anticipate a

Table 3. Association between ADAMTS13 gene polymorphisms and selected clinical characteristics (n = 261).[a]

Characteristics									
Polymorphism[b]	Thrombocytopenia	Hemolytic anemia	Proteinuria	Hematuria	TTP	Stroke	TIA	MI	Hypertension
rs4962145									
AA (n = 257)	60 (23)	25 (10)	84 (33)	192 (75)	4 (2)	7 (3)	5 (4)	7 (3)	104 (40)
GA (n = 24)	3 (13)	2 (8)	11 (46)	18 (75)	1 (4)	1 (4)	0 (0)	0 (0)	9 (38)
GG (n = 5)	2 (40)	1 (20)	3 (60)	2 (40)	0 (0)	1 (20)	0 (0)	0 (0)	1 (20)
p value	.31	.72	.20	.21	.62	.09	.81	.67	.63
rs2285467[c]									
AA (n = 256)	60 (23)	25 (10)	84 (33)	65 (25)	4 (2)	7 (3)	5 (4)	7 (3)	105 (41)
GA (n = 5)	2 (40)	1 (20)	3 (60)	3 (60)	0 (0)	1 (20)	0 (0)	0 (0)	2 (40)
p value	.39	.45	.20	.08	.78	**.03**	.73	.71	.96
rs685523									
AA (n = 3)	0 (0)	0 (0)	2 (67)	2 (67)	0 (0)	0 (0)	0 (0)	0 (0)	2 (67)
AG (n = 54)	8 (15)	10 (19)	21 (39)	11 (20)	2 (4)	3 (6)	1 (3)	1 (2)	23 (43)
GG (n = 246)	58 (24)	18 (7)	76 (31)	62 (25)	3 (1)	8 (3)	4 (3)	7 (3)	97 (39)
p value	.24	**.03**	.24	.18	.42	.68	.96	.88	.59

ADAMTS13, a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13; MI, myocardial infarction; TIA, transient ischemic attack; TTP, thrombotic thrombocytopenic purpura.

[a]Values are number (percentage) unless indicated otherwise. Statistically significant results are shown in bold.

[b]The number in parentheses indicates the number of patients positive for AA, GA, and GG in the genotypic distribution of each polymorphism.

[c]No patient had the GG genotype for rs2285467.

deficiency of ADAMTS13 activity in our SLE patients with ischemic cerebral events since our results showed an upregulation of ADAMTS13 mRNA, which could result in normal or increased plasma ADAMTS13 concentration.

Atherosclerotic plaque disruption with subsequent thrombus formation is a key event that leads to atherothrombosis. Recent studies showed that ADAMTS13 could modulate thrombus formation in atherosclerotic coronary arteries, where it was found colocalized with platelet-rich thrombi.[30] ADAMTS13 shares homology and domain structures with members of ADAMTS proteases. ADAMTS proteases are a multidomain, secreted, extracellular zinc metalloproteinase family with 19 members in humans. These proteases are known to cleave a wide range of proteins in the extracellular matrix. In recent years, there has been growing evidence concerning the role of several members of ADAMTS proteases in the pathogenesis of atherothrombosis. These proteases act by breaking down key proteoglycans of the arterial walls such as versican and brevican.[7] For instance, Wågsäter et al.[10] have demonstrated that levels of ADAMTS4 and ADAMTS8 mRNAs are at a three-fold increase in macrophage-rich areas of atherosclerotic lesions, and their expressions can be upregulated by the proinflammatory cytokines interferon γ and tumor necrosis factor α. Moreover, a recent report also demonstrated an association of four ADAMTS genes (ADAMTS2, ADAMTS12, ADAMTS13, and ADAMTS17) in conjunction with extracellular matrix components with susceptibility for pediatric stroke.[31] In our study, we found that ADAMTS13 polymorphism rs2285467 was significantly associated with stroke.

To our knowledge, this is the first study to associate ADAMTS13 mRNA expression in peripheral blood cells with ischemic stroke in SLE patients and suggests a potential role for the ADAMTS13 gene in ischemic cerebrovascular disease in SLE patients. Nevertheless, it remains to be determined whether the upregulation of ADAMTS13 is beneficial or detrimental to the process of cerebral atherothrombosis and whether ADAMTS13 has a role in the process of regeneration of brain function after focal brain ischemia. Therefore, further studies are required to better understand the physiologic and pathologic function of this protease in ischemic cerebrovascular injury. As this function becomes more clearly defined, new therapeutic targets may emerge.

Declaration of conflicting interests

The authors have no conflicts of interest.

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Appendix 1

Notation

ADAMTS13	a disintegrin-like and metalloprotease with thrombospondin type 1 motif, member 13
mRNA	messenger RNA
SLE	systemic lupus erythematosus
SLEDAI	systemic Lupus Erythematosus Disease Activity Index
TIA	transient ischemic attack
TTP	thrombotic thrombocytopenic purpura
vWF	von Willebrand factor