Original paper

ADAMTS13 deficiency and immunological abnormalities in patients with systemic sclerosis

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Abstract

Introduction: Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disorder characterized by immunological deviations and generalized microvascular damage.
Aim: To determine the serum level of the von Willebrand factor cleaving protease (ADAMTS13) in 39 SSc patients and healthy controls.
Material and methods: ADAMTS13 serum level was determined in 39 SSc patients and 11 healthy controls. Complete history of the patients was recorded and thorough clinical, rheumatological, and dermatological examinations were performed.
Results: The serum levels of ADAMTS13 were significantly lower in SSc than in normal controls (455.47 ±128 vs. 702.01 ±142 ng/ml, $p < 0.00001$). However significant correlations among serum ADAMTS 13 levels and organ changes were not found in SSc patients.
Conclusions: We demonstrate a decreased serum level of ADAMTS13 in SSc patients, which may contribute to the vessel microangiopathy observed in systemic sclerosis.

Key words: systemic sclerosis, ADAMTST13.

Introduction

The pathogenesis of systemic sclerosis is still unknown, although immunological deviations, generalized microcirculation disorders and progressive tissue fibrosis may have an important role in initiating and perpetuating the disease [1]. At present the role of initial morphological and functional markers of systemic sclerosis in microvascular structural damage have been put forward. ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motives) is a zinc-containing metalloprotease that is involved in cleavage of von Willebrand factor and is synthesized by endothelial cells and megakaryocytes [2]. Deficiency of von Willebrand factor cleaving protease (ADAMTS13) may contribute to endothelial injury followed by vessel damage and subsequent fibrosis [3, 4]. However, in the pathogenesis of systemic sclerosis (SSc) there is considerable mechanistic overlap, and the vessel injury and fibrosis probably have multifactorial causation but ADAMTS13 may play an important role as a co-factor.

Aim

Thus, the aim of the study was to evaluate the concentration of the ADAMTS13 and attempt to evaluate their role in the pathogenesis of SSc. An attempt was also made to assess the relationship between the concentration of the selected parameters and the diagnosed organ changes as well as vascular disorders observed in capillaroscopy.

Material and methods

Blood samples were obtained from 39 SSc patients (37 females and 2 male; 29 limited systemic sclerosis (lcSSc), 10 diffuse systemic sclerosis (dcSSc) according to the criteria of LeRoy [5] and 11 healthy individuals, all participants have signed informed consent approved by the Ethical Committee. All SSc patients fulfilled the criteria of the American College of Rheumatology (1980) [6]. The control group consisted of 11 randomly selected healthy subjects with no systemic diseases or on medica-

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tion. All samples were taken between 7:00 and 9:00 a.m. The samples were centrifuged and the obtained sera were stored in aliquots at –20°C until analyses. Clinical, laboratory and treatment data were collected at the time when the blood samples were drawn. Drugs, including corticosteroids and immunosuppressants, were authorized but stopped 24 h before blood collection. All patients with SSc were taking vasodilators and some of them corticosteroids (15 patients: 9 with lcSSc, 6 with dcSSc) or/and methotrexate (4 patients: 3 with lcSSc, 1 with dcSSc) or/and cyclophosphamide (5 patients: 3 with lcSSc, 2 with dcSSc). The patient characteristics are presented in Table 1.

Clinical assessment

An extensive clinical profile was established for each SSc patient [7]. The history and complete physical examination were obtained from each patient. The patients were evaluated for the cardiac (diagnosed by Holter, ECG, echocardiography and cardiological consultation), pulmonary (chest RTG, high-resolution computed tomography (HRCT) scan of thorax and pulmonary consultation), esophageal (esophageal scintigraphy), renal and hematological (blood test, bone marrow biopsy if needed) involvement. Cardiovascular changes included abnormal cardiac rhythm or documented fibrosis of myocardium. Pulmonary involvement was defined as the presence of ground glass or honeycombing appearances that suggest lung fibrosis. Esophageal changes were diagnosed on the basis of impaired transit in scintigraphy. Renal involvement was found if serum creatinine was above 100 µmol/l, significant proteinuria – above 500 mg for 24 h (after excluding other causes) or documented renal crisis in the past. Hematological involvement was diagnosed in case of leukopenia or anemia, after excluding other causes. Medical history of the disease (onset of Raynaud's phenomenon and skin sclerosis), ulcerations in finger tip pulp and the medications in the past and at present were also considered. Duration of the disease has been established since the skin sclerosis.

Levels of ADAMTS13 were determined by quantitative colorimetric sandwich ELISA kits (R&D Systems, Minneapolis, MN, USA) strictly according to the manufacturer's instructions.

Statistical analysis

Statistical significance was analyzed by non-parametric Mann-Whitney test, Kruskal-Wallis test, Student's *t*-test and *Spearman's* rank correlation test. *P*-values less than 0.05 were considered significant.

Results

Mean ADAMTS13 serum levels were decreased in SSc patients compared to healthy controls (455.47 ±128 vs. 702.01 ±142 ng/ml, $p < 0.00001$). However serum levels of ADAMTS13 were not different between lSSc and dSSc. Significant correlations between serum levels of ADAMTS13 and organ changes were not found in SSc patients, as well as serum levels of ADAMTS13 and duration of the Raynaud's phenomenon or disease, skin involvement or taking immunosuppressive drugs. Interestingly, the Kruskal-Wallis test in SSc subsets showed that ADAMTS13 serum levels were associated with elevated antinuclear antibodies (ANA) (Table 2).

Discussion

The data obtained in our study showed decreased plasma levels of ADAMTS13 in SSc patients. Molecular mechanism of hemostatic balance and thrombotic microangiopathies is still poorly understood. However, pathogenesis of SSc may be initiated in the vasculature, hence reduced activity of ADAMTS13 may additionally promote a prothrombotic function of von Willebrand factor (VWF) and can be an important factor triggering progression of blood vessel damage and consequent fibrosis [8]. Studies suggested also that endothelial cells secrete ADAMTS13, although its impact on vasculature has not been established [9, 10].

Table 1. Clinical characteristics of 39 patients with systemic sclerosis

Parameter	Number/percentage or mean ± SD		
	SSc	lcSS	dcSS
Age at study [years]	55 ±10.9	56 ±12.01	53 ±7.42
Age of onset [years]	42 ±9.79	41 ±9.94	45 ±8.88
Duration of the skin sclerosis [years]	8 ±6.18	9 ±6.50	6 ±4.72
Female/male ratio	37/2 (5%/95%)	28/1 (96%/4%)	9/1 (90%/10%)
Limited/diffuse SSc	29/10 (74%/26%)		
ANA:	100%		
Anti-topoisomerase I	55%	47%	80%
Anti-centromere	18%	24%	0%
U1RNP	15%	21%	0%
Ro-52	21%	21%	20%
Duration of the RP [years]	13 ±7.19	15 ±7.06	7 ±4.70
Organ involvement	85%	83%	90%
Cardiac involvement	79%	83%	70%
Pulmonary involvement	33%	31%	40%
Esophagus involvement	61%	59%	70%
Renal involvement	13%	7%	30%
Pitting scars	69%	69%	70%

Table 2. Serum levels of ADAMTS13

Parameter	Statistical data	SSc (n = 39)	Investigated groups		Control group (n = 14)
			lcSSc (n = 29)	dcSSc (n = 10)	
ADAMTS13 [ng/ml]	$\bar{x}$	466.47	468.45	460.74	702.01
	Range (min.–max.)	211–768	211–768	276–672	478–1028
	SD	128.03	136.56	105.57	142.36
ANA		**1/640 (n = 7)**	**1/1280 (n = 12)**	**1/2560 (n = 20)**	
	$\bar{x}$	538.88	439.05	468.12	
	Range (min.–max.)	394–768	211–672	125.46	
	SD	146.41	276–764	131.08	
Ro-52		**Present (n = 9)**	**Absent (n = 30)**		
	$\bar{x}$	538.87	448.77		
	Range (min.–max.)	433–695	211–768		
	SD	101.95	133.21		

Moreover Mannucci *et al*. has not found anti-ADAMTS13 in SSc patients or in the investigated systemic lupus erythematosus (SLE) groups [11], suggesting that some other changes may be decreasing the level of ADAMTS13 in autoimmunological connective diseases, as endothelium damage. Scheja *et al.* study has suggested that von Willebrand factor (vWF) propeptide may be useful in the assessment of disease activity in SSc [12]. However in our study, relationships between ADAMTS13 and organ involvement, as well as prominent markers of endothelial injury, as Raynaud's phenomenon or finger tips ulcers were not observed.

This study seems to confirm the correlation between immunological abnormalities and decreased ADAMTS13 serum levels suggesting that reduced activity of ADAMTS13 is contributing to enhance the prothrombotic function of VWF and may play a role in microangiopathy and secondary fibrosis.

Conclusions

In this study, we demonstrated that ADAMTS13 serum levels are decreased in SSc and associated with the elevated antinuclear antibody level in SSc patients and presence of Ro-52 antibodies. Taken together our data further underscore the role of dysregulated hemostasis in SSc.

Conflict of interest

The authors declare no conflict of interest.

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