Altered Levels of Soluble Adhesion Molecules in Patients with Rheumatoid Arthritis Complicated by Peripheral Neuropathy

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ABSTRACT. ***Objective.*** To assess levels of 2 circulating soluble adhesion molecules, vascular cellular adhesion molecule (sVCAM) and E-selectin, in patients with rheumatoid arthritis (RA) complicated by peripheral neuropathy compared to RA patients with no neurological complications and healthy controls.

Methods. In total, 25 RA patients with peripheral neuropathy (detected by clinical examination and confirmed by electromyography and nerve conduction studies), 40 RA patients without peripheral neuropathy, and 25 controls were studied. Clinical and laboratory assessments of disease activity were carried out and levels of sVCAM-1 and E-selectin were measured by ELISA in each of the 3 groups.

Results. Levels of sVCAM-1 and sE-selectin were higher ($p < 0.001$) in RA patients with peripheral neuropathy than in patients without neuropathy and controls. Levels of sE-selectin and sVCAM-1 correlated positively with disease activity variables. Correlation was independent of age and sex.

Conclusion. Peripheral neuropathy in patients with RA is associated with increased endothelial cell activation evidenced by elevated serum levels of sVCAM-1 and sE-selectin in this group of patients. (J Rheumatol 2002;29:57–61)

Key Indexing Terms:
RHEUMATOID ARTHRITIS PERIPHERAL NEUROPATHY ADHESION MOLECULES

Rheumatoid arthritis (RA) is a systemic inflammatory disease of unknown etiology characterized by the manner in which it involves the joints. Rheumatoid disease is not confined to the locomotor system. Extraarticular features have been found in the cutaneous, cardiovascular, digestive, and nervous systems. Hematological and occular alterations have also been described[1]. Early reports showed that extraarticular features were found in 10–20% of patients with RA, and neurologic manifestations as a result of peripheral and central nervous system involvement are common[2].

It has been reported that RA can be complicated by peripheral neuropathy in 1–18% of patients. Peripheral nerve involvement in RA might be in the form of compressive neuropathy, which is by far the commonest, or vasculopathy, resulting in distal sensory and combined sensory and sensorimotor neuropathy[3]. Although the underlying pathology of rheumatoid neuropathy is not clear, humoral mechanisms such as the deposition of immune complexes and fixation of complement are thought to be important factors. Recently, it was found that patients with RA complicated with peripheral neuropathy develop antiganglioside antibodies to peripheral nerve antigens that may be exposed to the immune system as a result of vasculitic damage to the blood–nerve barrier[4]. In another research study antibodies against neuroblastoma cells were more prevalent in RA patients with peripheral neuropathy than in patients without peripheral nerve involvement[5].

The interaction of leukocytes with the vascular endothelium is pivotal to the inflammatory process and is mediated by multiple pairs of adhesion molecules. Adhesion molecule expression and affinity are regulated by inflammatory stimuli, e.g., cytokines, chemoattractants, bacteria, and viruses. Intercellular adhesion molecule-1 (ICAM-1) is constitutively expressed on both endothelial and circulating cells including leukocytes, and is upregulated by immune activation and inflammation. By contrast, vascular cell adhesion molecule-1 (VCAM-1) and E-selectin expression in normal tissue is undetectable or minimal[6,7]. In recent studies, increased soluble levels of E-selectin were found in patients with Guillain-Barré syndrome and vasculitic neuropathies[8]. Blann, *et al*[9] found higher levels of sE-selectin in their 2 groups of patients with vasculitis and RA compared to controls. In other reports serum sVCAM-1 was found at high levels in sera from patients with RA, and the levels correlated with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)[10]. More recently, Saleh, *et al*[11] suggested that the development of peripheral neuropathy in RA can be attributed to increased endothelial cell activation.

We investigated the hypothesis that in RA patients with peripheral neuropathy there is increased activation or injury to

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endothelial cells that may allow immune mediated damage to the peripheral nerves.

MATERIALS AND METHODS

Patients with RA diagnosed according to the American College of Rheumatology revised criteria[12] were consecutively enlisted from those attending rheumatology and rehabilitation and internal medicine outpatient clinics at Ain Shams University Hospitals. They were subjected to full rheumatological and neurological assessment and accordingly they were classified into 2 groups. Group 1 comprised 25 RA patients with peripheral neuropathy, and group 2 comprised 40 RA patients without peripheral neuropathy. The diagnosis was confirmed by motor and sensory nerve conduction and needle electromyography (EMG) studies (Dantec keypoint™). The conduction study included the sensory and motor conduction velocities as well as response amplitude of median and ulnar nerves in the upper limb, and anterior and posterior tibial nerves in the lower limb. This was measured by conventional methods using surface electrodes. Needle EMG was done for the abductor pollicis brevis in the upper limb and for the tibialis anterior muscle in the lower limb to detect neuropathic weakness as a result of axonal involvement. The following measures of RA disease activity were recorded according to Mallya and Mace[13]: Duration of early morning stiffness, Ritchie articular index (RAI), which was calculated from a count of 53 joints counted separately, with tenderness graded from 0 to 3[14], in addition to 10 cm visual analog scale for pain. Patients were considered in activity if they had active disease for at least 4 weeks, defined by the presence of at least 3 of the following criteria: ≥ 6 tender joints, ≥ 3 swollen joints, morning stiffness > 44 min, and ESR > 28 mm/h[15]. Also, patients were examined for the presence of extraarticular manifestations and vasculitis. Plain chest radiograph was done for each patient to rule out the presence of radiologic lung manifestations. Twenty-five healthy volunteers of matched age and sex who were asymptomatic for vascular disease and who had normal neurological examination and normal nerve conduction studies were assessed as a control group. They were recruited from office workers in Ain Shams University Hospitals. Exclusion criteria for all subjects were malignancy, renal or hepatic disease, metabolic diseases such as diabetes mellitus, and treatment with corticosteroid or cytotoxic therapy.

Informed consent was given by all patients and controls.

Blood samples were taken for estimation of ESR (Westergren), complete blood count (CBC), CRP (latex agglutination kit, Omega Diagnostics, Alloa, Scotland, UK; detection limit 6 mg/l), and RF (latex and Rose Waaler tests). Complement 3 and 4 were measured by single immunodiffusion kits (Bioscientifica SA, Buenos Aires, Argentina). To measure adhesion molecule levels: (1) blood was obtained and allowed to clot at room temperature; (2) serum was withdrawn after centrifugation for 10 min; (3) soluble VCAM-1 and E-selectin were measured using monoclonal antibody based ELISA kits from R&D Systems (Minneapolis, MN, USA) according to the manufacturer's instructions. In brief, microtiter plates (Immunolon, Nunc, Roskilde, Denmark) were coated with specific antibody (anti-E-selectin, anti-VCAM), in 0.1 M carbonate buffer at pH 8.9. Diluted serum was added to the wells followed by a second biotinylated antibody. Each assay was calibrated using the appropriate recombinant soluble molecule (R&D Systems).

Statistical analysis. Data were revised, coded, and tabulated on a personal computer. Normally distributed data were presented as mean ± standard deviation, while skewed nonparametric variables were described using the median and interquartile range. Two groups' means comparison was performed using the Student t test if data were normally distributed; Mann-Whitney test was used with nonparametric distribution of data. Spearman's correlation was used to test correlation of adhesion molecules to other laboratory and disease activity variables. In all tests, p value was set at 0.05 using Statistical Package for Social Sciences, v.6.

RESULTS

Twenty-five RA patients with peripheral neuropathy were compared to the RA control group (40 patients). There were no significant differences in age, sex, RA disease duration, prescription of disease modifying drugs, ESR, or CRP (Table 1). Clinical assessment revealed that of the 25 patients with RA and peripheral neuropathy, 14 had active RA and 5 had extraarticular manifestations in the form of nodules and pulmonary complications (interstitial pulmonary fibrosis and pleural effusion). There was no other form of nervous system involvement. No vasculitis was detected on clinical examination. Nineteen of 25 patients were taking disease modifying drug therapy in the form of methotrexate (MTX), hydroxychloroquine, and sulfasalazine. Similarly in the RA control group of 40 patients, 10 had extraarticular manifestation of RA (nodules, pulmonary complications), and 29/40 were taking second line drug therapy in the form of MTX, hydroxychloroquine, sulfasalazine, and gold. Antirheumatics were not thought to have contributed to the neuropathic disease in any patient. Twenty-three of the 25 patients with RA and peripheral neuropathy had axonal involvement, while demyelination neuropathy was observed in only 2 patients. This was diagnosed according to Gilliat[16], that is, in peripheral neuropathies with pure axonal degeneration the conduction velocity is reduced by < 40% of the normal mean, while in demyelination the conduction velocity is often slowed by > 40% of the normal mean[17].

Comparison between the 3 groups (RA with neuropathy, control RA, and controls; Table 2) revealed highly significant difference between the groups for sE-selectin ($p < 0.001$) and sVCAM-1 ($p < 0.001$). RA patients with neuropathy had significantly higher levels of serum sVCAM-1 and sE-selectin than patients without neuropathy and controls. Patients with RA with neuropathy had significantly lower levels of complement 3 and 4 compared to the control RA group. For all indices measured, we found no difference between the sexes. Comparison between patients with active and inactive RA

Table 1. Baseline criteria of the subjects included in this study.

Variable	RA, Neuropathy Mean ± SD	RA, Without Neuropathy Mean ± SD	p
Male: female	6:19	8:32	NS
Age, yrs	51.68 ± 6.13	53.1 ± 10.0	NS
Duration of RA, yrs	8.5 ± 3.3	7.8 ± 2.9	NS
Clinical indices			
RAI*	6.0 (3.0–9.5)	4.5 (1–11.75)	NS
Morning stiffness, h	1.46 ± 0.9	1.42 ± 1.18	NS
Clinical vasculitis	Nil	Nil	
Other extraarticular manifestations (%)	5/25 (20)	10/40 (25)	NS
Lab indices			
ESR, mm/h	44.88 ± 16.91	45.85 ± 21.65	NS
CRP, mg/l*	12.0 (6-30)	9.0 (6-36)	NS

RAI: Ritchie Articular Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.*Median (interquartile range).

Table 2. Serum levels (mean ± SD) of adhesion molecules and complement level in RA patients with peripheral neuropathy versus control groups.

Variable	RA, Neuropathy	RA, Without Neuropathy	Healthy Controls
sE-selectin, ng/ml	63.84 ± 12.80**	45.8 ± 12.90*	31.36 ± 7.58
SVCAM-l, ng/ml	1161.88 ± 82.11**	816.48 ± 124.99*	526.48 ± 87.30
Complement 3, mg/dl	91.64 ± 10.03†	102.02 ± 11.70*	82.88 ± 17.0
Complement 4, mg/dl	23.36 ± 4.94†	35.17 ± 6.20*	22.6 ± 8.3

** Levels significantly higher than those in RA controls and healthy controls. * Levels significantly higher than those in healthy control group. † Levels significantly less than RA control group.

showed that adhesion molecule levels were elevated in the active group. The sVCAM-1 level was significantly higher in patients with active RA with peripheral neuropathy ($p < 0.05$), while the level of E-selectin, although higher in patients with active RA with peripheral neuropathy, was insignificant in comparison with patients with inactive RA complicated by peripheral neuropathy (Table 3). Table 4 shows correlations of adhesion molecule levels to disease activity measures as well as laboratory indices in RA patients we studied. It shows that levels of sVCAM and E-selectin correlated significantly with all variables studied.

DISCUSSION

Interest in soluble forms of the adhesion molecules is growing. Increased levels of adhesion molecules following cytokine stimulation of endothelial cells suggest a role in acute and/or chronic inflammation as well as in connective tissue diseases[18]. Although the biological significance of the soluble forms is unclear, one function may be to enhance or inhibit the interaction between leukocytes and the cell surface forms of the molecules, i.e., a form of regulation. Another is that binding of soluble adhesion molecules may promote or inhibit the activation of leukocytes before they interact with the endothelium[19]. We examined whether levels of soluble adhesion molecules were elevated in patients with RA complicated by peripheral neuropathy compared to RA patients without neurological complications. Our results revealed that a significantly higher proportion of RA patients with peripheral neuropathy had elevated serum levels of sE-selectin and sVCAM-1 compared to RA patients without neuropathy and healthy controls. It was interesting to find significantly lower complement 3 and 4 levels in the RA group with peripheral neuropathy. This would suggest an active vasculitic process. Our results agreed with those reported by Saleh, *et al*[11], who found significantly elevated sE-selectin and sVCAM-1 levels in RA patients with peripheral neuropathy compared to an RA control group and healthy controls. In addition they found no significant difference in serum levels of sVCAM-1 and sE-selectin between RA patients with peripheral neuropathy and patients with vasculitis uncomplicated by neurological disease. To rule out the hypothesis that activity of the disease may confound the effect of peripheral neuropathy on adhesion molecules, we classified the patients in this work into 2 groups, active and nonactive, and the effect of peripheral neuropathy on the level of sVCAM and E-selectin was tested in each group. In both groups there was significant difference on comparing the level of adhesion molecules and complement ($p < 0.001$). This confirms that peripheral neuropathy has a

Table 3. Comparison between patients with active and nonactive RA of disease activity variables and adhesion molecule levels.

Variable	RA with PN		RA without PN	
	Active RA, n = 14	Nonactive RA, n = 11	Active RA, n = 18	Nonactive RA, n = 22
RAI**	9 (7–12.5)*	3 (2.0–4.0)†	12.5 (8.7–18.2)*	1 (1.0– 3.2)
Morning stiffness, h	2.0 ± 0.78*	0.77 ± 0.47	2.5 ± 0.79*	0.52 ± 0.5
Visual analog scale, cm	7.25 ± 1.34*	3.636 ± 1.29	7.58 ± 1.48*	2.82 ± 1.47
ESR, mm/h	55.07 ± 12.92*	31.91 ± 11.79	65.11 ± 16.83*	30.09 ± 7.92
CRP, mg/l**	24 (12–48)*	6 (0–6.0)	36 (21–48)*	6 (0–6.0)
Complement 3, ng/dl	88.571 ± 8.72	95.55 ± 9.74†	91.72 ± 5.0	110.46 ± 8.20
Complement 4, ng/dl	20.79 ± 4.46††	26.55 ± 3.53†	30.78 ± 4.56	39.77 ± 3.22
SVCAM	1201.8 ± 78.5*††	1111.0 ± 55.5†	922.89 ± 90.84*	729.41 ± 68.44
E-selectin	64.86 ± 12.65††	62.55 ± 13.51†	50.11 ± 14.58	42.27 ± 8.98

PN: peripheral neuropathy, RAI: Ritchie Articular Index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. *Significant difference comparing active RA to nonactive RA with and without PN ($p < 0.05$), ** median (interquartile range), †† significant difference comparing active RA with PN to active RA without PN ($p < 0.001$), † significant difference comparing nonactive RA with PN to nonactive RA without PN ($p < 0.001$).

Table 4. Correlation of VCAM and E-selectin to disease activity variables and laboratory tests in patients with RA.

	s-VCAM				E-selectin			
	Active RA		Nonactive RA		Active RA		Nonactive RA	
	PN	No PN	PN	No PN	PN	No PN	PN	No.PN
Disease duration	NS	NS	NS	NS	NS	NS	–0.59	NS
RAI	NS	0.778	0.653	0.805	0.585	NS	NS	0.423
Morning stiffness	NS	0.899	NS	0.723	NS	NS	NS	NS
VAS	NS	0.785	NS	0.878	NS	NS	NS	0.554
ESR	0.661	0.671	NS	0.562	NS	NS	NS	0.417
CRP	0.542	0.560	NS	0.722	NS	NS	NS	0.496
C3	NS	–0.764	NS	–0.833	NS	NS	NS	–0.679
C4	NS	–0.730	NS	NS	NS	NS	NS	–0.485

RAI: Ritchie Articular Index, VAS: visual analog scale, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, C3: complement 3, C4: complement 4, PN: peripheral neuropathy.

significant effect on level of adhesion molecules regardless of disease activity.

The role of sVCAM and E-selectin in the pathogenesis of rheumatoid peripheral neuropathy is unknown. Like von Willebrand factor, sE-selectin is a specific endothelial product and increased levels of it reflect damage to the endothelium[20]. Moreover, it is likely that these adhesion molecules may play a significant role in the emigration of mononuclear cells found in nerve biopsy specimens from these patients. Supporting this theory are the findings of Panegyres, *et al*[21], who found increased expression of ICAM-1 and MHC class I and class II antigens in vasculitic lesions in nerve and muscle from patients with different clinicopathological entities. This was confirmed by the findings of Ashour, *et al*[22], who studied sural nerve biopsies from patients with nonsystemic vasculitic neuropathy. They found vasculitic effects in the form of intramural and perivascular infiltration by inflammatory cells, with necrosis of vasa nervosa denoting active vasculitis in patients with RA. Axonal degeneration was also found in their patients with peripheral neuropathy, evidenced by prominent myelin digestion chambers. Moreover, Saleh, *et al*[11] reported that antiendothelial cell antibodies (AECA) may play a role in the pathogenesis of neuropathy associated with RA. They suggested that AECA may induce functional changes on endothelial cells with resultant binding of T cells or immune complexes capable of endothelial injury.

It was of interest that RA patients with peripheral neuropathy showed no evidence of clinical vasculitis, yet had elevated levels of soluble adhesion molecules. This may imply that the etiopathogenesis of peripheral neuropathy can be attributed to a localized form of vasculitis, where only the vessels in the proximity of peripheral nerves are involved. Supporting this theory is our finding of significantly lower complement levels in RA patients with peripheral neuropathy. As well as Panegyres, *et al*[21], Pallis, *et al*[23] showed that in patients with systemic lupus erythematosus, expression of VCAM and E-selectin was found in blood vessels of biopsy specimens of skeletal muscles with mononuclear cell infiltration.

The levels of sVCAM-1 and sE-selectin were higher in patients with active RA regardless of peripheral nerve involvement. This confirms the findings of Conn, *et al*[3], Mason, *et al*[10], and Blann[20], who found that elevated levels of cVCAM-1, cICAM, and sE-selectin were significantly increased ($p < 0.001$) in RA patients compared with the control group. Moreover, Janssen, *et al*[24] also found close correlation between sVCAM levels and disease activity, thus they assumed that this may be a useful method of monitoring the disease. More interesting were their findings of persistently elevated sVCAM levels in 2 patients with apparently mild disease activity who subsequently had a major relapse, implying that measurement of these soluble adhesion molecules may have an advantage over existing measures of disease activity in detecting subclinical disease activity. In addition, it has been reported by Carson, *et al*[25] that as E-selectin is found only on activated endothelium, it should be a very specific marker of endothelial activation or damage. If these data are confirmed, this would justify the early institution of therapy, before organ damage occurs. Similarly, monitoring of sVCAM and sE-selectin levels may be helpful in assessing disease activity and response to therapy in vasculitis, as the failure of soluble adhesion molecule levels to normalize may reflect continued disease activity, and may allow new therapies to be developed using a reduction in sVCAM and sE-selectin levels as a surrogate marker of adequate response to treatment[26].

sVCAM-1 and sE-selectin were found at higher levels in sera from patients with RA with peripheral neuropathy compared to RA patients without neuropathy. In the absence of systemic vasculitis, these findings would suggest that peripheral neuropathy is the result of a localized nonsystemic form of vasculitis associated with increased endothelial cell activation and/or injury. These markers might be useful for assess-

ing and monitoring progression of RA neuropathy. New therapeutic tools directed against these adhesion molecules may ameliorate vascular damage in RA neuropathy.

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