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Serum endothelial adhesion molecules levels correlate with lesion burden in multiple sclerosis patients treated with interferon beta-1b

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Abstract

The levels of serum-soluble intracellular adhesion molecule-1 and soluble endothelial-leukocyte adhesion molecule-1, and the Gadolinium-enhanced T1-weighted MRI were studied in a group of patients with relapsing–remitting multiple sclerosis treated with interferon beta-1b and compared to a non-treated control group. The levels of serum-soluble intracellular adhesion molecule-1 and soluble endothelial-leukocyte adhesion molecule-1 increased, after three months treatment, as compared to baseline and the non-treated MS patients. A significant correlation was found in the treated group between serum-soluble endothelial-leukocyte adhesion molecule-1 and the lesion area in the Gadolinium-enhancing (T2 weighted scan) MRI.

Keywords: Multiple sclerosis; MRI; sICAM-1; sELAM-1

1. Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS). There is evidence suggesting that this process may be caused by activated T cells crossing the blood–brain barrier (BBB) to mediate the immune response in the CNS. Adhesion molecules are involved in the migration and accumulation of lymphocytes into the CNS (Kahaleh, 1990; Male et al., 1990; Wong et al., 1994). Soluble forms of many adhesion molecules, including the intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and, endothelial-leukocyte adhesion molecule (ELAM-1) can be elevated in inflammatory, infectious and malignant diseases, and also in MS (Cannella et al., 1995; Hartung et al., 1994; Rieckmann et al., 1997; Shimizu et al., 1991; Sobel et al., 1990). Soluble adhesion molecules correlate with disease activity, at least, in patients with relapsing–remitting forms of MS (RR–MS) (Hartung et al., 1993; Sharief et al., 1993; Tsukada et al., 1993). Gadolinium(Gd)-enhancing lesions on cerebral magnetic resonance images (MRI) are a marker of breakdown of the BBB and correlate with disease activity (Evans et al., 1997; Filippi et al., 1995, 1996; Katz et al., 1993; Smith et al., 1993).

The purpose of this work was to study the levels of serum sICAM-1 and sELAM-1, and its possible correlation with Gd-enhanced MRI lesions and with the clinical outcome in RR–MS patients treated with IFN beta-1b in comparison to a non-treated control group.

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2. Patients and methods

Sixteen patients with active RR–MS (all of which fulfil the criteria of the Spanish Health Service), were divided into two groups and agreed and signed their informed consent to participate in this open, controlled study. Eight patients were treated with 8 MIU of IFN beta-1b subcutanously every other day, and an equal number of patients chose not be treated and served as a control group. Two patients belonging to the control group started treatment after 6 months. The demographic data are summarized in Table 1. Blood sampling was taken by venopuncture, serum was extracted and frozen at −80°C at baseline, and at 1, 3, 6, 9 and 12 months. MRI was performed with and without Gd-enhancement at baseline, and every 3 months until the 12th month. The time interval between the venopuncture and MRI study was always less than 48 h.

The concentration of sICAM-1 (T Cell Diagnostics, Inc. USA) and sELAM-1 (Bender MedSystem, Vienna, Austria) in serum were determined by ELISA as instructed by the manufacturers.

MRI was done with a General Electric/Siemens/Philips 0.5/1/1.5 Tesla Sigma scanner. The pulse frequencies were as follows: T1 weighted imaging-reception time, 600 ms; echo delay, 25 ms; T2-weighted imaging-repetition time, 2500 ms; echo delay, 30 and 80 ms. The scans were obtained with 5 mm slice thickness with no interslice time gap. Gd-DTPA (Schering; Berlin, Germany) was administered intravenously at a dose of 0.2 mM/kg, followed by a 5 ml flush with physiological saline. The imaging protocol consisted of T2 weighted images that were obtained prior to Gd administration. T1 weighted imaging were achieved before and 5 min after intravenously administered Gd. A repositioning protocol was used at every examination. Details of the imaging protocols are published elsewhere (Paty, 1993).

Clinical examination was performed regularly at baseline, and every 3 months, always one or two days before MRI examination. The results in the EDSS and functional system scales were documented at every visit. Patients were also examined for adverse reactions, concomitant diseases and medications at every visit.

Table 1
Clinical and demographic characteristics of MS patients

	Treated group ($n = 8$)	Control group ($n = 8$)
Sex (F:M)	5:3	5:3
Mean age (years)	38.8	28.1
Mean age at disease onset (years)	31.2	23.5
Mean disease duration (years)	7.6	5.6
Mean entry EDSS score (range)	2.9	2.1
Yearly relapse rate at baseline	0.87	0.73

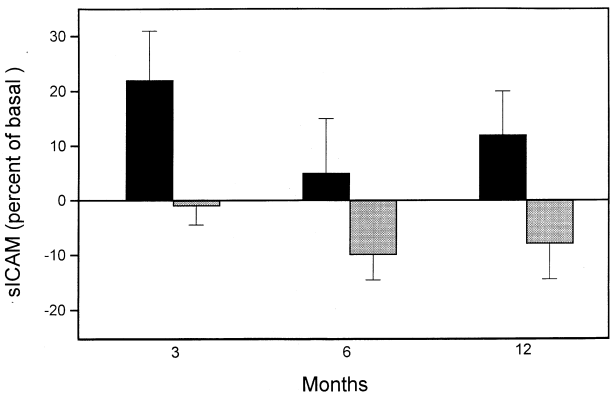

Fig. 1. Longitudinal analysis of the serum sICAM-1 in MS patients. sICAM-1 concentrations were determined in serum (see Section 2) at the indicated intervals in IFN beta-1b treated (■) and non-treated (▩) MS patients.

3. Results

3.1. sICAM-1 and sELAM-1 analysis

The longitudinal analysis of the levels of serum sICAM-1 and sELAM-1 in both groups of patients were analyzed at baseline, and at 3, 6, and 12 months. Values of sICAM-1 were 198.6 ± 34 ng/ml (mean ± SD) for treated patients and 180.6 ± 38 ng/ml (mean ± SD) in the control group. Serum sICAM-1 values were over baseline after 3, 6 and 12 treatments whereas in the control group the serum sICAM-1 remained below baseline for the 12-month period. The mean serum sELAM-1 value at the baseline was 48 ± 21 ng/ml (mean ± SD) for the treated patients, and 34 ± 16 ng/ml (mean ± SD) for the controls. In the treated group, serum sELAM-1 increased after 3 months in comparison to the control group, 6.66 ± 40.4 vs 0.51 ± 17.5 respectively. The most evident increase in the levels of serum sELAM-1 in the treated group was found at the 6th month (see Figs. 1 and 2).

3.2. MRI finding

T2 weighted images were analysed and the results are summarised in Table 2. In five out of eight treated patients, a reduction in the MRI burden was noticed. By contrast, in the control group, in four out of six patients there was a clear increase in the MRI burden. The difference between the treated and the control groups (omitting the values of the patients who did not complete the 12-month follow-up) for the baseline

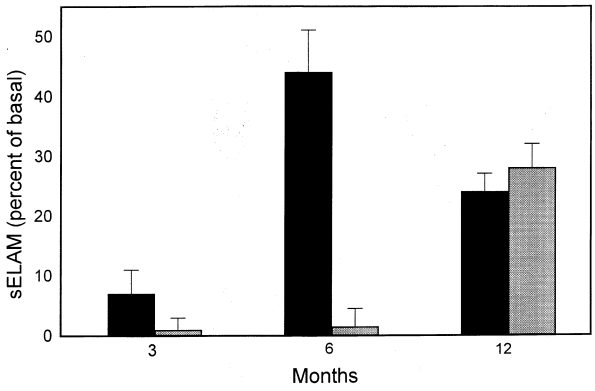

Fig. 2. Longitudinal analysis of the serum sELAM-1 in MS patients. sELAM-1 concentrations were determined in serum (see Section 2) at the indicated intervals in IFN beta-1b treated (■) and non-treated (▩) MS patients.

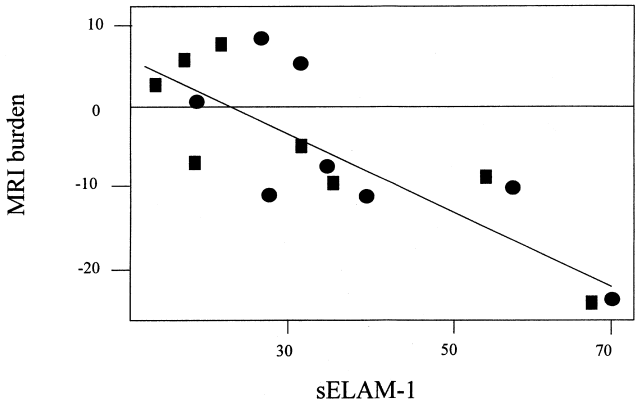

Fig. 3. Correlation between serum sELAM-1 and lesion area. MS patients were treated with IFN beta-1b for 12 months and the lesion area (T2 weighted scans) and serum sELAM-1 were measured as indicated in Section 2. sELAM-1 at the 3rd and at 12th months and the percentage of change of lesion were plotted from the linear regression parameters ($P = 0.01$, 3rd month; $P = 0.02$, 12th month).

and 12-month lesions areas, using the Fisher's exact test, was statistically significant ($P = 0.04$). The mean increase of lesion area (mm^2) in T2 weighted scans after 12 months for the control group was 27.55, whereas the treated group had a mean decrease of −5.26.

3.3. Correlation between adhesion molecules and MRI

The results in the treated group indicated that the levels of serum sICAM-1 at the 3rd month correlated inversely with the number of Gd-enhancing lesions in the MRI ($r = 0.496$, $P = 0.05$). However, this association was not found at 6 and 12 months. We also found in the treated group, a statistically significant ($P = 0.01$) correlation between the values of sELAM-1, and the percentage of lesion change, when the lesion area was measured with T2 weighted scans (see Figs. 3 and 4).

Table 2
Lesion areas (mm^2) in T2 weighted scans for the treated and non-treated MS patients[a]

	Baseline	12 months	Difference
Treated patients			
1	325.66	295.8	−29.81
2	121.7	11.8	−9.95
3	50.41	51.05	−2.96
4	300.35	228.2	−72.12
5	1341.2	1209	−133
6	353.97	381.4	27.43
7	134.03	141	6.99
8	105.22	106.9	1.63
Control patients			
9	683.27		
10	188.06	125.6	−62.47
11	157.14	214.3	57.16
12	259.8	387.4	127.56
13	141.49	141.4	−0.06
14	130.01	239.4	109.42
15	115.27	148.7	33.38
16	254.09		

[a] The lesion areas were measured at baseline (initial value) and after 12 months in Interferon beta-1b treated and non-treated (control) MS patients. Values are given in mm^2 and were measured in T2 weighted MRI.

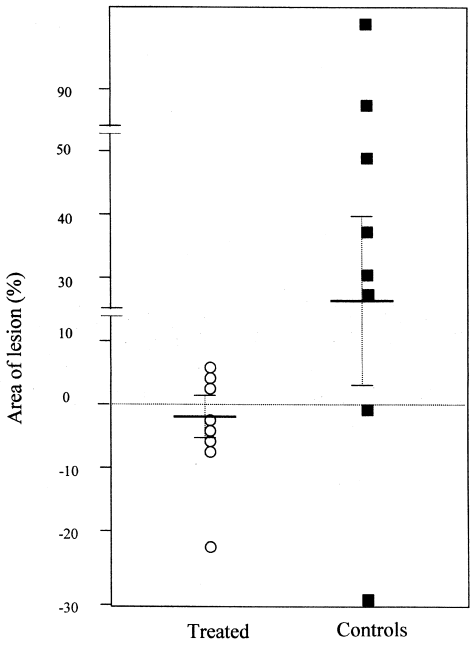

Fig. 4. Comparison of lesion area in control versus treated MS patients. MS patients were either treated (○) or non-treated (■) for 12 months. The area of lesions was determined by T2 weighted scans. Results, given as a percentage of change, refer to within individual variations between the initial and the 12th month values.

4. Discussion

The interaction between adhesion molecules and their respective receptors seems to be a primary event in the initiation of the pathogenesis of the MS in the CNS. It has been suggested that serum and CSF sICAM-1 may act as a marker of inflammatory activity in MS. As opposed to ICAM-1, which is found on T cells, monocytes/macrophages and endothelial cells, ELAM-1 is found on the vascular endothelial cells. Increased ELAM-1 levels have been described in the sera of patients with neurovascular pathologies, but the role of this molecule in the pathogenesis of MS is still not clear (Dore Duffy et al., 1995; Soilu-Hännien et al., 1995). The exact mechanism of action of IFN beta-1b in MS is not known although several processes seem to be involved: (a) down regulation of T-lymphocyte activation; (b) inhibition of HLA expression (Shimizu et al., 1992); (c) antigen presentation to T-lymphocytes; (d) reduction of IFN-gamma production; (e) increase in TGF-beta production and; (f) improvement in suppressor T lymphocyte function.

Our results show an increase of the serum levels of both adhesion molecules sICAM-1 and sELAM-1, especially in the treated group; this up regulation was more evident at the 3rd month for sICAM-1 and at the 6th month for sELAM-1. The results also showed a significant correlation between the lesion area as measured by T2 weighted scans, and sELAM-1 after 3 and 12 months. Serum sICAM-1 values, although slightly raised, were within normal ranges during the period of treatment. This contrasted with serum sELAM-1 levels which remained in the pathological range in most of the patients. It seems pertinent to point out that ELAM-1 may be a specific marker for the activation of endothelial cells. The up regulation of serum sICAM-1 and sELAM-1, the clinical evolution and the decrease in the number of Gd-enhanced lesions suggest two possibilities: (1) IFN beta-1b might counteract the catabolism of the adhesion molecules (decreased clearance); (2) in the course of the inflammatory process, the adhesion molecules shed from the surface of endothelial cells or lymphocytes, and appear as soluble molecules in serum. The adhesion molecules might then interact with their natural ligands, therefore acting as physiological inhibitors of activated cells. It might be argued that IFN beta-1b increases the levels of serum sICAM-1 and sELAM-1, and therefore blocks the respective lymphocyte receptors and decreases the inflammatory process. The results of the correlation between the T2 weighted scans and sELAM-1 after 12 months of treatment seems to point to sELAM-1 as a potential marker of efficacy of the IFN beta-1b.

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