Selectin adhesion molecules in Behçet’s disease

Şeminur Haznedaroğlu, Yaşar Karaaslan, Yahya Büyükasık, Ali Koşar, Osman İ Özcebe, İbrahim C Haznedaroğlu, Şerafettin Kızıli, Semra V Dündar

Abstract

Objectives—The pathogenesis of Behçet’s disease (BD) is closely related to endothelial cells, leucocyte functions and autoimmunity. The aim of this study was to investigate circulating selectin adhesion molecules, which are known to play a significant part in the immune response especially by regulating interactions of the leucocytes with endothelium, in BD.

Methods—Plasma E-, L-, and P-selectin concentrations were evaluated in 11 patients with widespread BD (group I), 10 cases with merely mucocutaneous involvement (group II) and 15 age and sex matched healthy control subjects. The patients were newly or previously diagnosed cases not taking any drug for BD.

Results—Plasma concentrations of all selectins were significantly higher in group I compared with group II. E-selectin and P-selectin were significantly increased in each subgroup of patients compared with the healthy controls. L-selectin concentrations were higher than the controls only in group I.

Conclusions—Increases in the selectins in BD may be a direct consequence of the leucocyte, endothelium and platelet activations observed during the disease process. However, abnormal/increased selectin expression to various triggers should also be considered. More prominent increases in patients with extensive disease suggest that circulating selectin concentrations are related to disease severity.


Behçet’s disease (BD) is a chronic recurrent systemic vasculitis of unknown aetiology. Aetio-pathogenesis of this inflammatory process is controversial. A genetically determined autoimmune phenomenon has been suggested to play the major pathogenetic part. However, some authors believe that BD is not an autoimmune process but essentially a disorder of heightened inflammation. Selectins are adhesion molecules regulating interactions of the leucocytes, platelets and endothelial cells. These molecules are involved in leucocyte migration, homing and inflammation, all of which are essential components of the immune response. Circulating leucocytes bind to the selectins expressed by activated endothelium and thereby leucocyte migration occurs.

Neutrophil hyperfunction, especially increased chemotaxis, is a well described phenomenon in BD. Soluble mediators of the inflammation (for example, tumour necrosis factor α, interferon γ and interleukin 1) are well known inducers of adhesion molecule expression. The pathobiology of BD may be related to the selectins, because it is an inflammatory process in which leucocyte and endothelial abnormalities and autoimmunity are possibly involved. The aim of this study was to investigate plasma concentrations of the selectins in patients with BD and to search for a possible relation between disease severity and the selectin concentrations.

Methods

In an outpatient setting, consecutive BD patients with widespread disease (that is, active systemic and mucocutaneous involvements) were selected for assessment of plasma selectin concentrations (table 1). Selectin concentrations of these patients (group I) (M/F 4/7; mean (SD) age 32 (11); range 20–54 years) were compared with the concentrations of a second group of consecutive BD patients (group II) (M/F 5/5; mean age 37 (11); range 25–53 years) who had only mucocutaneous disease and to the concentrations of age and sex matched healthy volunteers (M/F= 6/9; mean age 31.3 (5.5); range 25–44 years). The patients were required to be newly diagnosed or previously recognised cases not taking any drug for BD. All patients were or had been diagnosed according to the criteria of the International Study Group for BD. They were referred to an ophthalmologist to be evaluated for eye involvement. The majority of the control subjects were department staff.

Blood samples were taken before any treatment for BD was started. Peripheral venous blood samples were taken between 8 and 10 am into 3.8% 1:9 trisodium citrate containing vacuum tubes without venous occlusion. The blood samples were centrifuged immediately at 2000 g for 15 minutes and then the plasmas were stored in several aliquotes at −70°C until assayed. Plasma E-selectin (Parameter Human E-selectin Immunoassay, R&D Systems Europe, Abingdon, UK), P-selectin (sP-selectin enzyme linked immunosorbent assay (ELISA), Bender MedSystems, Vienna, Austria) and L-selectin (sL-selectin ELISA, Bender MedSystems, Vienna, Austria) levels were measured by sandwich type ELISA. The intra-assay coefficient of variation was 6%, the inter-assay coefficient of variation 8%, computed from results of pathological plasma samples in our laboratory.

Plasma selectin concentrations between patient subgroups and controls were compared with the Mann-Whitney U test. Statistical significance was assigned to p values lower than 0.05.
Table 1  Clinical characteristics and selectin concentrations of individual patients at the time of blood sampling. The first 11 patients (group I) had widespread involvement. The remaining cases had only mucocutaneous disease (group II). Numbers of aphtae and locations of uveitis, arthritis and thrombosis are presented in parentheses

<table>
<thead>
<tr>
<th>Oral aphtae</th>
<th>Genital aphtae</th>
<th>Pathergy</th>
<th>Folliculitis</th>
<th>EN</th>
<th>Uveitis</th>
<th>Arthritis</th>
<th>VT</th>
<th>P-</th>
<th>E-</th>
<th>L-</th>
<th>Selectins (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39 (875) 713</td>
</tr>
<tr>
<td>2</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>89 (1115) 612</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>115 (1214) 811</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>51 (715) 269</td>
</tr>
<tr>
<td>5</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>108 (1785) 1305</td>
</tr>
<tr>
<td>6</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>152 (1318) 627</td>
</tr>
<tr>
<td>7</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>121 (1135) 720</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>107 (820) 754</td>
</tr>
<tr>
<td>9</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41 (1290) 725</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>107 (1200) 1625</td>
</tr>
<tr>
<td>11</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>157 (526) 820</td>
</tr>
<tr>
<td>12</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50 (510) 240</td>
</tr>
<tr>
<td>13</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18 (386) 185</td>
</tr>
<tr>
<td>14</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80 (780) 315</td>
</tr>
<tr>
<td>15</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45 (525) 219</td>
</tr>
<tr>
<td>16</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>86 (810) 779</td>
</tr>
<tr>
<td>17</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>47 (525) 480</td>
</tr>
<tr>
<td>18</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>86 (804) 278</td>
</tr>
<tr>
<td>19</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80 (705) 320</td>
</tr>
<tr>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42 (478) 375</td>
</tr>
<tr>
<td>21</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19 (315) 524</td>
</tr>
</tbody>
</table>

EN = erythema nodosum; VT = venous thrombosis.

Results

Plasma concentrations of all selectins were significantly higher in group I compared with group II (tables 1 and 2). Taken together, the patients with BD had significantly higher E- and P-selectin concentrations compared with the control group (table 2). L-selectin concentrations were also higher in the patients, but the difference was not statistically significant. E- and P-selectin concentrations were significantly increased in each subgroup of the patients compared with the control subjects. L-selectin concentrations were higher than the control group in group I, but not in group II.

Discussion

Focal neutrophil infiltration is an essential histopathological feature of BD. The pathergy reaction, histologically described as appearance of a sterile microabscess in the site of skin prick, is a clinical reflection of the non-specific neutrophil hyperactivity of BD. Endothelial injury and/or pathological activation, another characteristic of BD, can be observed even in patients without any clinical vascular involvement. High frequency of venous thromboembolism in BD suggests that the endothelial injury seen in these patients may have unique properties leading to thrombotic tendency. Platelet hyperactivity in relation to pathological eicosanoid pathway has also been suggested to occur in patients with BD. Platelets (P-selectin), platelets (P-selectin), and leucocytes (L-selectin). The main role of the selectin adhesion molecules is closely related to the immunological response: regulation of leucocyte trafficking and supporting leucocyte rolling. P-selectin has also specific roles in the inflammatory and haemostatic functions of the platelets. At the site of inflammation, endothelial cells are subjected to prolonged or repeated stimulation by many chemical mediators. Re-expression of functional P-selectin molecules on the endothelial cell surface by repeated stimulation with thrombin was shown. Increased plasma thrombin-antithrombin III complex and prothrombin fragment concentrations, which reflect intravascular thrombin generation in the prethrombotic state of BD have also been demonstrated. The association and pathophysiological relevance of the increased circulating thrombin and P-selectin concentrations during the pathological transition of Behçet endothelium remains to be elucidated.

In this study, we found that P- and E-selectin concentrations were increased in patients with BD compared with the healthy control subjects. L-selectin concentration was higher than the controls only in patients with widespread involvement. Plasma concentrations of the selectins were more prominently increased in BD patients with widespread involvement compared with those with only mucocutaneous disease. Increase of the selectins in BD reflects activation of the leucocytes and platelets, and injury/activation of the endothelium in these patients. More prominent increases in patients...
with systemic involvement suggest that these activations are associated with disease severity.

Increments of the selectin concentrations in BD may be simply a result of the leucocyte, endothelium and platelet activations related to the inflammatory process and/or haemostatic activation observed in these patients. However, a primary abnormality in selectin expression/secretion mechanisms should also be considered as a possible cause of the increased selectin concentrations. Non-specifically increased neutrophil migration attributable to abnormal/increased selectin expression of the blood cells and/or endothelium should be investigated as a possible pathogenetic mechanism in BD.

Colchicine has been shown to change quantitative and qualitative display of selectins on endothelial cells and neutrophils. Specifically, it has been suggested that colchicine may exert its prolymphatic effects on cytokine provoked inflammation by diminishing the qualitative expression of E-selectin on endothelium, and its therapeutic effects by diminishing the quantitative expression of L-selectin on neutrophils. Therapeutic effect of this agent in BD should rise the possibility of a selectin dependent mechanism in the pathogenesis of BD. Definitive roles of the selectin adhesion molecules in the aetiopathogenesis of the disease, and their modulation with the established treatment modalities are important issues that certainly deserve further elucidation.

13 Wilson AP, Ethiumino J, Beretterde DJ. Decreased prosta
15 Newman W, Beall LD, Carson CW, Hunder GG, Graven N, Randhawa ZI, et al. Soluble E-selectin is found in superna

Selectin adhesion molecules in Behçet's disease


doi: 10.1136/ard.59.1.61

Updated information and services can be found at:
http://ard.bmj.com/content/59/1/61

References
This article cites 19 articles, 4 of which you can access for free at:
http://ard.bmj.com/content/59/1/61#BBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Immunology (including allergy) (5144)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/