[Frontiers in Bioscience 9, 1654-1659, May 1, 2004]

SOLUBLE ADHESION MOLECULE LEVELS, NEUROPSYCHIATRIC LUPUS AND LUPUS-RELATED DAMAGE

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1. ABSTRACT

Nervous system dysfunction may occur in as many as 80% of patients with Systemic Lupus Erythematous (SLE) at some point in their disease course. Upregulation of adhesion molecules has been linked to acute SLE-related disease activity and chronic damage. We evaluated the relationship between soluble adhesion molecule levels and neuropsychiatric lupus (NPSLE) manifestations using the American College of Rheumatology (ACR) case definitions to investigate for evidence of a link between upregulation of adhesion molecules and NPSLE manifestations. Sera from the initial study visit of 133 SLE patients enrolled in the San Antonio Lupus Study of Neuropsychiatric Disease (SALUD) and 40 controls were evaluated for soluble adhesion molecule levels (VCAM-1, ICAM-1 and E-selectin) and antiphospholipid antibodies. A subset of 57 SLE patients were evaluated for soluble adhesion molecule levels and antiphospholipid antibodies on two subsequent study visits, as well. NPSLE manifestations at the time of sera ascertainment were recorded using ACR case definitions and SLE-related acute activity and damage were measured. Elevated levels of all three soluble adhesion molecules were seen in SLE patients compared to normal control values. Soluble VCAM-1 levels correlated with measures of current disease activity, NPSLE manifestations and deep venous thrombosis. Persistently positive levels of ICAM-1 and VCAM-1, but not E-selectin were association with increased SLE-related damage. Elevated levels of all soluble adhesion molecule levels correlated with abnormal levels of antiphospholipid antibodies, which are associated with some NPSLE manifestations and have been shown to upregulate adhesion molecule expression.

2. INTRODUCTION

Neurological dysfunction may occur in as many as 80% of patients with Systemic Lupus Erythematosus (SLE) (1-5). Neuropsychiatric SLE-related (NPSLE) syndromes encompass a wide spectrum of features including strokes, seizures, peripheral neuropathy, dementia, psychosis, anxiety and depression. The American College of Rheumatology (ACR) has published case definitions for nineteen different NPSLE syndromes to help standardize case reporting (6). The etiology of NPSLE manifestations is not well understood, and is likely to be heterogeneous. Medications and toxic or metabolic abnormalities due to systemic organ failure can affect nervous system functioning in patients with SLE (2,3). In addition, a nervous system-directed immune-mediated process can also occur resulting in clinically symptomatic nervous system dysfunction (7-9). Many of these processes also involve abnormal endothelial-white blood cell interactions, which allow proteins or cells access to the central nervous system (CNS).

Discovering the factors that regulate endothelial-white blood cell interactions and lymphocyte trafficking into the CNS is of considerable importance in furthering our understanding of NPSLE. The expression of adhesion proteins on endothelial cells appears to up-regulate, and facilitate lymphocyte entry into the CNS in many autoimmune diseases (10-17). Shedding of the active from of these molecules occurs, and soluble levels can be measured in both serum and cerebrospinal fluid (CSF) (18, 19). Although adhesion molecules have been implicated as serological markers in SLE patients with skin disease (20), renal disease (21, 22) and other non-nervous system organ involvement (22-24), few other studies have evaluated soluble adhesion molecule levels in relationship to NPSLE manifestations.

3. METHODS

3.1. Patient Population

The patient sample consisted of 133 participants in the San Antonio Lupus Study of Neuropsychiatric

Table 1. Demographic Features of Systemic Lupus Erythematosus (SLE) and Control Subjects

	SLE Subjects N=133	Control Subjects N=40
Gender		
Men	8 (6%)	12 (30%)
Women	125 (94%)	28 (70%)
Ethnicity		
Hispanic	77 (58%)	24 (60%)
African American	10 (7.5%)	1 (3%)
Non-Hispanic White	42 (31.5%)	15 (37%)
Other	4 (3%)	0
Age (mean – range)	42 years - range: 19-69 years	38.4 years – range 20-69 years
Educational Level (mean – range)	12 years – range: 0-20 years	14.6 years – range 8-22 years

Disease (SALUD), a longitudinal study designed to characterize the spectrum and define important risk factors for specific neuropsychiatric lupus syndromes (NPSLE). The details about the study methodology and baseline subject characteristics have already been published (19). Briefly, patients were eligible to participate if they met the ACR criteria for the diagnosis of SLE (25). No effort was made to either include or exclude patients with neurological, cognitive, or psychiatric illness. Informed consent was obtained from all study participants. Control subjects were healthy friends and family members of subjects enrolled in SALUD. Study visits were completed at the Frederic C. Bartter General Clinical Research Center and not as part of clinical care. The following information was obtained each study visit for SLE subjects: general medical, neurologic and rheumatologic history, neurological exam, rheumatologic exam, SLE disease activity (26), SLE Damage index (27), psychiatric evaluation using the SCID (28) and a computerized neurocognitive test (29). The following information was collected from control subjects: medical history, computerized neurocognitive test (29).

3.2. Serologic Assays

Soluble adhesion molecule and autoantibody testing was performed on stored sera collected at the first study visit for all SLE patients and controls. A subset of 57 SLE patients had soluble adhesion molecule and antiphospholipid antibody testing performed on 2 additional visits approximately 1 year apart to test for the relationship between changes in these tests and clinical change. The subset was selected as follows: all subjects with sVCAM-1 levels > 800ng/dl (high positive, number=30) and a random sample of subjects with normal sVCAM-1 levels (number=27) on sera tested at the first study visit.

Soluble ICAM-1, sVCAM-1 and sE-Selectin determinations were performed using antigen capture immunoenzymometric assay (ELISA) kits (R&D Systems) according to the manufacturer's instructions. All samples were tested in duplicate and were repeated if the coefficient of variation was greater than 20%. Cut-off values to define abnormal protein levels were based on the mean plus 2 standard deviation of the control subjects for all soluble adhesion molecule levels: ICAM-1 > 291.3 ng/ml, VCAM-1 was > 701.8 ng/ml and E-Selectin > 86.5 ng/ml. These were not significantly different from control values provided by the manufacturer. Soluble adhesion molecule levels were defined as persistently positive in the subset of patients with repeated testing if elevated on at least 2 of the 3 visits.

Anticardiolipin (aCL) IgG and IgM values were also obtained from the serum samples using enzyme-linked immunosorbent assay (ELISA) kit (APHL Louisville APL Diagnostics, Inc.). Cut-off values to define abnormal aCL levels were defined as IgG = 15 GPL units and IgM = 15 MPL units where one unit is defined as approximately one microgram of affinity purified aCL antibody per ml of serum. Beta-2-glycoprotein 1 (B_2 GP1) IgG and IgA antibodies were measured using an ELISA kit (QUANTA Lite INOVA Diagnostics, Inc.). Cut-off values to define abnormal anti- B_2 GP1 levels were defined as greater than 20 units for both classes.

3.3. Statistical Methods

Independent t-tests were used to examine whether mean values for soluble adhesion molecule and antibody levels differed between SLE and control subjects and to examine whether the relationship between abnormal adhesion molecule levels and NPSLE manifestations was statistically significant when compared to the relationship between normal adhesion molecule levels and NPSLE manifestations. Correlations were used to determine strength of association between abnormal adhesion molecule levels and clinical and serologic variables. Repeated measures analysis was used to evaluate the relationship between changes in soluble adhesion molecule levels and clinical and other laboratory features over time. The Bonferonni adjustment was used to correct for multiple comparisons.

4. RESULTS

The demographic features of the SLE and control subjects included in this report can be found in Table 1. Table 2 lists the results for soluble adhesion molecule, aCL and anti-B_2 GP1 levels for the initial study visit for SLE and control subjects. Control subjects differed significantly from SLE subjects for mean levels of aCL IgG ($p=0.001$), anti-B_2 GP1 ($p=0.001$), and all soluble adhesion molecule levels (sICAM, sVCAM and sE-selectin all $p<0.000$).

Using data obtained from the entire cohort at visit 1, the presence of an abnormal sVCAM-1 level was

Table 2. Soluble Adhesion Molecule, Anticardiolipin antibody (aCL) and Anti-β-2-glycoprotein 1 (anti-β2-GP1) Levels in SLE and Control Subjects

Antibody and Soluble Adhesion Molecule levels expressed as mean +/- SD	SLE Subjects (N=133)	Control Subjects (N=40)
aCL IgG	8.7 +/-35.8	1.5 +/-1.8 (p=0.001)
aCL IgM	9.7 +/- 60.5	2.3 +/-3.6 (NS)
Anti-B2 GP1 IgG	8.7 +/-13.5	3.6 +/-2.6 (NS)
Anti B2 GP1 IgA	45.1 +/-102.8	12.4 +/-11.5 (p=0.001)
Soluble ICAM-1	336.3 +/-121.8	200.4 +/- 45.5 (p<0.000)
Soluble VCAM-1	714.8 +/- 358.4	524.1 +/- 88.8 (p<0.000)
Soluble E-selectin	69.0 +/-38.3	50.9 +/-17.8 (p<0.000)

Cut-off values for an abnormal level are as follows: aCL IgG and IgM > 15; anti-β2-GP1 IgG and IgA >20; soluble ICAM-1 > 291.3; soluble VCAM-1 > 701.8; soluble E-selectin > 86.5

associated with a history of stroke (p = .0024), high anti-double stranded DNA titers and low serum complement levels (p < .0001) and one or more psychiatric illnesses (p < .000).

Significant positive correlations were seen across all visits between soluble VCAM-1 levels and SLE Disease Activity Index (r=.141, p=0.027), ICAM-1 levels and aCL IgG (r=.200, p=0.02) and E-selectin levels and aCL IgG (r=.304, p<0.001), anti-B2GP1 IgG (r=.312, p<0.001) and anti-B2GP1 IgA (r = .170, p=0.009).

There were no differences in mean levels of any soluble adhesion molecule over time (data not shown). There were significant differences in all soluble adhesion molecule levels between Mexican American patients and Caucasian (sICAM-1, p=<0.001; sVCAM-1, p=0.012; sE-Selectin, p=0.002) and African American patients (sICAM-1, p=0.04; sVCAM-1, p=0.001), with higher levels seen in Mexican Americans. There was a significant interaction of all soluble adhesion molecule levels by age, with the highest levels seen in the oldest age group (sICAM-1, p=0.032; sVCAM-1, p=0.012; E-Selectin, p=0.005).

There were 27 patients with persistently positive sICAM-1 levels and 30 who had 1 or fewer positive sICAM-1 levels over the 2-year period. Persistently positive sICAM-1 levels were associated with higher SLE Damage Index scores (p=0.001) and higher B2-GP1 IgG antibody levels (p=0.008). There were 31 patients with persistently positive sVCAM-1 levels and 26 with 1 or fewer sVCAM-1 levels over the 2-year period. Persistently positive sVCAM-1 levels were associated with higher SLE Damage Index scores (p=0.006), higher aCL IgG (p=0.03), aCL IgM (p-0.032), B2-GP1 IgG (p=0.001) and B2-GP1 IgA (p=0.001) antibody levels. There were 12 patients with persistently positive sE-Selectin levels and 45 who had 1 or fewer positive sE-Selectin levels over the 2-year period. A persistently positive sE-Selectin level was not associated with greater SLE-related activity or damage or levels of any of the antiphospholipid antibodies.

Lupus patients with hypertension had higher mean levels of sICAM-1 (p=0.008) and sVCAM-1 (p=0.004). Those with diabetes mellitus had higher mean levels of sICAM-1 (p=0.026). Mean levels of sVCAM-1 were higher in patients with a history of blood clots in any location (p=0.001), deep venous thrombosis (p=0.011), and any arterial thrombosis (p=0.021).

Abnormal soluble adhesion molecule levels over the 2-year follow-up period were associated with increased SLE disease activity measured by the SLE Disease Activity Index: higher frequency of renal disease associated with sICAM-1 (p=0.03) and higher frequency of abnormal anti-double stranded DNA titers and low serum complement levels associated with sVCAM-1 (0=0.013).

5. DISCUSSION

Adhesion molecules are crucial for cellular communication between immunocompetent cells, and play a key role in cellular activation and adhesion (18). ICAM-1 supports the adhesion of all leukocytes and is expressed in activated endothelial cells, smooth muscle cells and in human atherosclerotic lesions. VCAM-1 supports the adhesion of monocytes, lymphocytes, and eosinophils but not neutrophils and is expressed in macrophages, activated endothelial cells and atherosclerotic lesions (19). VCAM-1 is also influential in the recruitment of leukocytes to sites of inflammation (19). E-selectin arbitrates the adhesion of neutrophils, monocytes, and some memory T-cells to vascular endothelium, hence is important in the regulation of inflammatory and immunological events at the vessel wall. Initial binding of leukocytes to E-selectin is thought to trigger the recruitment and activation of additional adhesion molecules to the site of inflammation (31).

We found elevated levels of ICAM-1, VCAM-1 and E-selectin in our cohort of SLE patients as compared to normal control values. Others studies have also detected elevated levels of one or more of these when compared to controls (16, 18, 20, 21, 23, 24, 32-36). High levels of all soluble adhesion molecule levels were found in Mexican American lupus patients, as compared with Caucasian and African American lupus patients and Mexican American control subjects. This suggests that the upregulation of adhesion molecules in Mexican American lupus patients may account for some of the ethnic differences in disease expression that have been previously described (37). We also found that all soluble adhesion molecule levels increased significantly with age. This finding does not explain the higher levels in Mexican American lupus patients, however, as Mexican Americans were

significantly younger than Caucasians and no different in age as compared to African Americans in the study (data not shown).

We systematically evaluated the relationship between soluble VCAM-1, ICAM-1 and E-selectin molecule levels and nervous system manifestations defined by the ACR NPSLE case definitions, in addition to evaluating their importance in acute SLE activity and SLE-related damage. An abnormal level of soluble VCAM-1 at the first study visit was associated with a history of stroke and the presence of one or more psychiatric manifestations in this cohort. These findings support two other small studies that found a relationship between soluble adhesion molecule levels and neurological disease. Baraczka and colleagues previously described the appearance of new neurological symptoms in association with an increase in serum sVCAM-1 levels (18). Spronk and colleagues also found elevated levels of sVCAM-1 in 7 patients with some type of CNS involvement (22).

We also found a relationship between both sVCAM-1 and sICAM-1 levels and levels of autoantibodies that have been associated with NPSLE manifestations, namely antiphospholipid antibodies (aPL) (24). These antibodies constitute a heterogenous family that includes antibodies directed against negatively charged phospholipids, including aCL and anti-B2-GP1 (38). The antiphospholipid syndrome (APS) is defined as episodes of thrombosis or recurrent fetal loss in the presence of moderate titers of aCL IgG or aCL IgM on at least two occasions six or more weeks apart (39). APS is considered primary if it occurs in a patient without SLE or other collagen vascular disease and secondary if it occurs in people with SLE.

Antiphospholipid antibodies can activate endothelial cells, leading to the upregulation of adhesion molecules and adherence of leukocytes (40). There is also evidence from animal knock out models that aPL may require the upregulation of adhesion molecules to lead to thrombosis, and possibly other NPSLE manifestations (41). Kaplanski and colleagues evaluated the relationship between soluble adhesion molecules (ICAM-1, VCAM-1 and E-selectin) in 61 patients with primary APS, SLE with APS and SLE with APS in comparison to 48 control patients with thrombosis unrelated to APS and 18 healthy control subjects (24). They found elevated sVCAM-1 in patients with primary APS, SLE with APS and SLE without APS compared to the healthy volunteer and thrombosis control groups. When patients with primary APS and SLE with APS were divided into two groups based on severity and frequency of thrombosis, sVCAM-1 levels were increased in the groups with greater severity and more frequent thromboses. The primary APS group with cerebral arterial thrombosis, fetal loss or renal vein thrombosis had increased sVCAM-1 levels when compared to primary APS patients without these manifestations. This work supports our findings of an association between increased sVCAM-1 levels and thrombotic manifestations, including stroke. Kaplanski and colleagues did not study the association between soluble adhesion molecule levels and other neurological manifestations (24). Prior studies finding an association between elevated sVCAM-1 levels and neurological manifestations did not evaluate for aPL (18, 22).

Other studies have reported a correlation between soluble adhesion molecule levels and SLE-related disease activity (20, 23, 36). Several studies have reported a relationship between active renal disease and increased levels of soluble adhesion molecules (21, 24). High sICAM-1 levels were seen in our cohort with acute SLE-related renal disease, as well.

We also found that persistently positive sICAM-1 and sVCAM-1 levels over a 2-year period was associated with higher SLE-related damage scores than in the group without persistently high levels. This supports the results from another study reporting that persistently elevated levels of one or more adhesion molecules is associated with increased morbidity and mortality in patients with SLE (42). It is possible that conditions leading to a chronic increase in adhesion molecule levels may also result in cumulative SLE-related damage.

In summary, our data suggest that elevated levels of one or more soluble adhesion molecules are both markers for current SLE-related activity, including NPSLE manifestations, and for cumulative SLE-related damage. Taken together, these data suggest that up-regulation of adhesion molecule expression may be important in the mechanism of some NPSLE manifestations and may also be a predictor for neurological and non-neurological SLE-related disease activity and cumulative damage.

6. ACKNOWLEDGEMENTS

The project was supported by an award from National Institute of Neurological Disorders and Stroke (R01 NS35477) and from the National Center for Research Resources (M01RR 01346-19).

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Key Words: Systemic Lupus Erythematosus, Adhesion Molecules, Neuropsychiatric Disease

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