Serum Autoantibodies in Patients With Alzheimer’s Disease and Vascular Dementia and in Nondemented Control Subjects

Oscar L. Lopez, MD; Bruce S. Rabin, MD; F. Jacob Huff, MD; Donald Rezek, MD; and Oscar M. Reinmuth, MD

Background and Purpose: In this study we sought to evaluate the clinical significance of serum autoantibodies to dementing processes.

Methods: We assessed 40 age-matched subjects: 10 patients with probable Alzheimer’s disease, 10 with possible Alzheimer’s disease with cerebrovascular disease, 10 with vascular dementia, and 10 nondemented control subjects. Serum from each subject was tested for the presence of antithyroglobulin antibody, thyroid antimicrosomal antibody, gastric anti-parietal cell antibody, anti-smooth muscle antibody, antinuclear antibody, rheumatoid factor, antineuronal antibody, and anticardiolipin antibody. In addition, we investigated the sera of these patients for the presence of an antivascular antibody directed against the vascular basement membrane proteoglycan antigen and for circulating immune complexes.

Results: Autoantibodies were present in 100% of the patients with possible Alzheimer’s disease with cerebrovascular disease, 80% of those with vascular dementia, 40% of those with probable Alzheimer’s disease, and 30% of the nondemented control subjects. The highest number of autoantibodies was observed in patients with vascular dementia and possible Alzheimer’s disease. Antinuclear antibody was present in 60% of vascular dementia patients and antineuronal antibody in 50% of these patients. However, no individual autoantibody could differentiate Alzheimer’s disease from cerebrovascular disorders. Immune complexes were detected in the serum of 20–30% of each patient group. Neither the patient nor the control sera was found to contain antiendothelial antibody.

Conclusions: Despite the relatively small number of individuals examined in each category, the elevated number of autoantibodies associated with possible Alzheimer’s disease with cerebrovascular disease and vascular dementia indicates a possible link between the presence of autoantibodies and cerebrovascular disorders in dementia.

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KEY WORDS • Alzheimer’s disease • autoimmunity • dementia

A variety of immunologic abnormalities have been demonstrated in Alzheimer’s disease (AD) patients, involving defective immune regulation and/or autoimmunity. Attempts to demonstrate a relation between AD and immunologic mechanisms have suggested that the amyloid substance in senile (neuritic) plaques may be derived from serum immunoglobulins (Ig), which could be explained by a leakage of serum proteins. In addition, it has been suggested that elderly subjects with cognitive deficits have higher levels of IgG and IgA. Interestingly, elevated titer of IgG in serum and cerebrospinal fluid have been demonstrated in multi-infarct dementia (MID) and not in AD, indicating a disruption of the blood–brain barrier (BBB) in patients with cerebrovascular disorders. Furthermore, histopathologic studies in MID and AD with MID have shown the presence of heavy deposits of serum proteins (IgG, C1q, C3c, and fibrinogen) exclusively in capillaries of layers I–IV of the neocortical gray matter, suggesting a defect of the cortical capillary system in patients with vascular disorders and the presence of antigen-antibody (Ag-Ab) complexes in the perivascular deposits. Whether these immunologic changes in MID are related to the dementing process have not been determined yet.

One possible approach to this problem is the study of serum autoantibodies against non–central nervous system tissue in patients with AD and vascular dementia (VD). Based on a common model of known autoimmune disease (e.g., diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis), patients who develop autoimmune disease frequently have autoantibodies to a variety of tissue other than the organs targeted. This approach may allow us to predict that the presence of non–central nervous system autoantibodies would reflect an autoimmune process in the cerebral tissue of these patients.

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vascular basement membrane proteoglycan antigen and went extensive screening, including medical, neurological, and laboratory procedures. Antibody to thyroglobulin and thyroid microsomal antigen (thyroid peroxidase) were investigated in sera of these patients for the presence of circulating immune complexes.

In the present study we further analyzed the clinical significance of those findings to determine whether the immune abnormalities are part of a subgroup of AD or are associated with cerebrovascular disorders. We examined the presence of serum autoantibodies in patients with probable AD,17 possible AD with CVD, andVD, and in normal elderly control subjects. In addition, we investigated the sera of these patients for the presence of an antivascular Ab directed against the vascular basement membrane proteoglycan antigen and for circulating immune complexes.

### Subjects and Methods

We examined sera from 40 age-matched subjects: 10 with probable AD, 10 with possible AD with CVD, 10 with VD, and 10 normal elderly control subjects who were participating in a longitudinal study of dementia at the University of Pittsburgh (Pa). Each subject underwent extensive screening, including medical, neurological, psychiatric, social work/nursing, and neuropsychological examinations. Computed tomographic (CT) scans (27 patients) or magnetic resonance imaging (MRI) (13 patients) of the head, electroencephalograms, chest roentgenograms, and appropriate laboratory and blood studies were completed. Each clinical diagnosis was reached after review at a consensus conference by two board-certified neurologists. No subject was depressive or had manic or hypomanic episodes before the onset of dementia. One patient with VD was medicated with beclomethasone. Four of the 40 subjects have since died, and autopsy was performed in two patients. One patient had “definite” AD17 and other AD with hemorrhagic infarcts in parietal and temporal lobes. Both patients died 2 years after the autoantibodies study was performed. The demographic characteristics of the subjects are shown in Table 1.

On the basis of the clinical diagnosis, we divided the patients as follows: Probable AD: This group met the NINCDS-ADRDA clinical criteria for probable AD.17 These were patients in whom the concomitant presence of a dementing process other than AD was excluded. Patients with evidence of infarction in two or more contiguous cuts of the CT or MRI scan were excluded from this group. Patients with a Hachinski Ischemic score of >4 were excluded. Possible AD with CVD: This group included patients with evidence of CVD in addition to the clinical diagnosis of AD. The diagnosis was based on a history of onset and progression of dementia consistent with AD but with a single clinical episode consistent with stroke or a single focal lesion in two or more cuts of the CT or MRI, interpreted as an infarction. Vascular dementia: This group included patients with clinical and/or radiological evidence of multiple infarctions contributing to dementia in which concomitant dementing processes other than CVD were excluded. The diagnosis was based on evidence of two or more infarctions, including clinical episodes of strokes and/or multiple focal lesions in the MRI or CT scan of the head.

The Hachinski Ischemic score was not used as an affirmative criterion for diagnosing possible AD with CVD or VD because it is known not to be specific for these disorders.21

Autoantibody titers were determined by different laboratory procedures. Antibody to thyroglobulin and thyroid microsomal antigen (thyroid peroxidase) were determined by the indirect hemagglutination procedure using kits purchased from Miles, Inc., Elkhart, Ind. A

### Table 1. Demographic Data for Patient and Control Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Probable Alzheimer's disease</th>
<th>Possible Alzheimer's disease + CVD</th>
<th>Vascular dementia</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (women:men)</td>
<td>6:4</td>
<td>5:5</td>
<td>3:7</td>
<td>6:4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>72.1±4.5</td>
<td>73.0±4.4</td>
<td>72.4±4.9</td>
<td>72.1±4.4</td>
</tr>
<tr>
<td>Mini-Mental State Examination score (range)</td>
<td>13.8±8.4</td>
<td>18.2±4.7</td>
<td>15.3±9.5</td>
<td>29.0±0.9</td>
</tr>
<tr>
<td>Hachinski Rating Scale score (range)</td>
<td>1.7±1.2</td>
<td>4.6±2.1</td>
<td>5.5±1.9</td>
<td>1.7±0.9</td>
</tr>
</tbody>
</table>

Values are mean±SD. CVD, cerebrovascular disease.

### Table 2. Autoantibodies in Alzheimer's Disease Patients, Normal Control Subjects, and Vascular Dementia Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>ANA (%)</th>
<th>SM (%)</th>
<th>Pariet (%)</th>
<th>TG (%)</th>
<th>Micro (%)</th>
<th>RF (%)</th>
<th>CL (%)</th>
<th>ANL (%)</th>
<th>Total antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable Alzheimer's disease</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (20)</td>
<td>6</td>
</tr>
<tr>
<td>Possible Alzheimer's disease + CVD</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>4 (40)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>3 (30)</td>
<td>3 (30)</td>
<td>14</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>6 (60)</td>
<td>3 (30)</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>3 (30)</td>
<td>5 (50)</td>
<td>20</td>
</tr>
<tr>
<td>Control</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>5</td>
</tr>
</tbody>
</table>

CVD, cerebrovascular disease; ANA, antinuclear antibody (Ab); SM, anti-smooth muscle Ab; Pariet, gastric anti-parietal cell Ab; Micro, thyroid antimicrosomal Ab; TG, antithyroglobulin Ab; RF, rheumatoid factor; CL, anticardiolipin Ab; ANL, antineuronal Ab.
<table>
<thead>
<tr>
<th>Case/age/sex by group</th>
<th>Medication</th>
<th>Systemic disease</th>
<th>Type of antibody</th>
<th>CT scan* or MRI† findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable Alzheimer’s disease patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/79/F</td>
<td>Nortriptyline, hydrochlorothiazide, triamterene</td>
<td>Hypertension</td>
<td>...</td>
<td>Normal*</td>
</tr>
<tr>
<td>2/76/F</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Normal†</td>
</tr>
<tr>
<td>3/71/F</td>
<td>Hydrochlorothiazide</td>
<td>Hypertension</td>
<td>Micro, ANA</td>
<td>Small infarction internal capsule, PWM†</td>
</tr>
<tr>
<td>4/72/M</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Volume loss*</td>
</tr>
<tr>
<td>5/62/M</td>
<td>Nortriptyline</td>
<td>Lithium</td>
<td>...</td>
<td>Volume loss*</td>
</tr>
<tr>
<td>6/71/F</td>
<td>Captopril</td>
<td>Hypertension</td>
<td>ANL</td>
<td>Normal*</td>
</tr>
<tr>
<td>7/71/F</td>
<td>Insulin</td>
<td>Diabetes mellitus</td>
<td>Pariet</td>
<td>Small cortical infarct§</td>
</tr>
<tr>
<td>8/70/M</td>
<td>Enalapril</td>
<td>Hypertension</td>
<td>ANA, ANL</td>
<td>Small infarction internal capsule, volume loss§</td>
</tr>
<tr>
<td>9/74/F</td>
<td>Tolbutamide</td>
<td>Diabetes mellitus</td>
<td>...</td>
<td>Normal*</td>
</tr>
<tr>
<td>10/75/F</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Volume loss*</td>
</tr>
<tr>
<td>Possible Alzheimer’s disease with CVD patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11/79/F</td>
<td>α-Methyldopa</td>
<td>Hypertension</td>
<td>AC</td>
<td>Volume loss, PWM†</td>
</tr>
<tr>
<td>12/75/M</td>
<td>Triazolam, isosorbide dinitrile</td>
<td>Pernicious anemia, ischemic heart disease</td>
<td>ANL, AC</td>
<td>Volume loss, PWMH†</td>
</tr>
<tr>
<td>13/72/M</td>
<td>Glipizide</td>
<td>Diabetes mellitus</td>
<td>Pariet, AC</td>
<td>PWM†</td>
</tr>
<tr>
<td>14/72/M</td>
<td>Propanolol</td>
<td>Ischemic heart disease</td>
<td>Pariet, ANL</td>
<td>Volume loss*</td>
</tr>
<tr>
<td>15/62/M</td>
<td>...</td>
<td>...</td>
<td>Pariet</td>
<td>Volume loss, infarct in left occipital lobe, PWMH†</td>
</tr>
<tr>
<td>16/72/F</td>
<td>Thorazine, α-methyldopa</td>
<td>Pernicious anemia, diabetes mellitus, hypertension, ischemic heart disease</td>
<td>Pariet, ANL</td>
<td>Normal*</td>
</tr>
<tr>
<td>17/76/F</td>
<td>Hydrochlorothiazide, triamterene</td>
<td>Hypertension</td>
<td>ANA</td>
<td>Infarction in left caudate nucleus, PWM†</td>
</tr>
<tr>
<td>18/75/F</td>
<td>Hydrochlorothiazide, triamterene</td>
<td>Hypertension</td>
<td>Micro</td>
<td>PWM†</td>
</tr>
<tr>
<td>19/74/M</td>
<td>Glipizide, digoxin</td>
<td>Diabetes mellitus, ischemic heart disease</td>
<td>RF</td>
<td>PWMH†</td>
</tr>
<tr>
<td>20/73/F</td>
<td>...</td>
<td>Asthma</td>
<td>TG</td>
<td>Aneurysm, anterior communicating artery, PWM†</td>
</tr>
<tr>
<td>Vascular dementia patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21/79/M</td>
<td>...</td>
<td>Peripheral vascular disease</td>
<td>...</td>
<td>Volume loss, infarcts in both parietal lobes and caudate nucleus*</td>
</tr>
<tr>
<td>22/76/M</td>
<td>...</td>
<td>...</td>
<td>ANA, ANL</td>
<td>Volume loss; infarcts in frontal lobes, corona radiata, and left temporal lobe; PWM‡</td>
</tr>
<tr>
<td>23/70/M</td>
<td>Haloperidol</td>
<td>Ischemic heart disease</td>
<td>TG, Micro, ANA, SM</td>
<td>Infarcts in right frontal lobe, PWM*</td>
</tr>
<tr>
<td>24/70/F</td>
<td>...</td>
<td>...</td>
<td>ANA, RF, ANL, AC</td>
<td>Infarcts in centrum semiovale and left caudate, PWM†</td>
</tr>
<tr>
<td>25/61/M</td>
<td>Phenobarbital, diphenhydantoin</td>
<td>Hypertension, seizures of adult onset</td>
<td>ANL, AC</td>
<td>Infarcts in caudate nuclei and midbrain, PWM*</td>
</tr>
<tr>
<td>26/71/M</td>
<td>Beclomethasone</td>
<td>Asthma, hypertension</td>
<td>...</td>
<td>Infarcts in left putamen, PWM*</td>
</tr>
<tr>
<td>27/76/F</td>
<td>...</td>
<td>...</td>
<td>ANA, SM</td>
<td>Multiple small infarcts in frontal lobes, PWM*</td>
</tr>
<tr>
<td>28/73/F</td>
<td>Insulin, desipramine</td>
<td>Diabetes mellitus</td>
<td>ANA</td>
<td>Volume loss, infarcts in centrum semiovale*</td>
</tr>
<tr>
<td>29/75/M</td>
<td>Procainamide</td>
<td>Ischemic heart disease</td>
<td>ANA, ANL, AC</td>
<td>Infarct in centrum semiovale, PWM*</td>
</tr>
<tr>
<td>30/73/M</td>
<td>Hydrochlorothiazide, triamterene</td>
<td>Hypertension</td>
<td>SM, ANL</td>
<td>Cerebellar infarct, PWMH†</td>
</tr>
</tbody>
</table>
positive titer was 100 for Ab to thyroglobulin and 400 for Ab to thyroid microsomes.

Antinuclear Ab, anti-smooth muscle Ab, and gastric anti-parietal cell Ab were determined by indirect immunofluorescence on sections of mouse stomach and kidney using slides purchased from Kallestad Laboratories, Austin, Tex. A titer of 40 was considered positive.

Antiendothelial Ab was detected by immunofluorescence using fresh-frozen monkey heart sectioned at 4 μm on a cryostat and fixed in cold (4°C) acetone for 30 seconds. Sera were tested at a 1:10 and a 1:40 dilution and incubated for 30 minutes at room temperature. A goat anti-human fluorescein-labeled anti-IgG was then coated onto 96-well, flat-bottomed microtiter plates. After blocking unbound sites with bovine serum albumin, patient and control sera were added to coated and uncoated wells, after which IgG antibody binding was detected by adding goat anti-human IgG conjugated with alkaline phosphatase. Color development was by p-nitrophenylphosphate, and a reaction was considered positive when the optical density of the color in the well containing antigen was 2.5 times that of the uncoated well.

One-way analysis of variance (ANOVA) and a contrast analysis were used to analyze Mini-Mental State scores24 and Hachinski Rating Scale scores.29 Simple χ² and McNemar’s test for paired categorical data were used to analyze contingency tables.

**Results**

The patients had been matched by age. The ANOVA and post hoc comparisons with subject groups and the Mini-Mental State scores revealed a significant statistical difference between patient groups (e.g., probable AD, possible AD with CVD, and VD) and normal control subjects (F_{3,39}=10.15, p<0.001), and there was no difference among patient groups. ANOVA and post hoc comparisons within subject groups and the Hachinski Rating Scale revealed that possible AD with CVD and VD differed significantly from probable AD and normal control subjects (F_{3,39}=12.63; p<0.001), and there was no difference between possible AD with CVD and VD (Table 1).

Immune complexes were detected in the sera of 20–30% of each patient group. There were no significant differences between groups. Neither the patients nor control sera were found to contain antiendothelial antibody.

Autoantibodies were present in 10 of 10 (100%) possible AD with CVD patients, in 8 of 10 (80%) VD patients, in 4 of 10 (40%) probable AD patients, and in 3 of 10 (30%) normal control subjects (Table 2). There was a significant statistical difference when we compared the proportion of patients with autoantibodies between the groups with cerebrovascular disorders (possible AD with CVD and VD) and the groups without those characteristics (normal control subjects and probable AD) (χ²=12.91, df=1, p<0.001).

Taking advantage of the fact that patients and control subjects were matched by age, we compared groups using McNemar’s test for paired categorical data. The proportion of VD patients with autoantibodies was not

### Table 3. Continued

<table>
<thead>
<tr>
<th>Case/age/sex by group</th>
<th>Medication</th>
<th>Systemic disease</th>
<th>Type of antibody</th>
<th>CT scan* or MRI† findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondemented controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31/78/M</td>
<td>Digoxin, furosemide</td>
<td>Polymyalgia, rheumatica, ischemic heart disease</td>
<td>TG, Micro, RF</td>
<td>PWMH†</td>
</tr>
<tr>
<td>32/76/M</td>
<td>Nitroglycerine</td>
<td>Ischemic heart disease</td>
<td>...</td>
<td>Normal†</td>
</tr>
<tr>
<td>33/72/M</td>
<td>Hydrochloorthizide, triamterene</td>
<td>Hypertension</td>
<td>...</td>
<td>PWMR*</td>
</tr>
<tr>
<td>34/72/M</td>
<td>Hydrochloorthizide, triamterene, digoxin</td>
<td>Hypertension, ischemic heart disease</td>
<td>...</td>
<td>Volume loss†</td>
</tr>
<tr>
<td>35/62/F</td>
<td>Hydrochloorthizide</td>
<td>Hypertension</td>
<td>...</td>
<td>Normal†</td>
</tr>
<tr>
<td>36/69/F</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Volume loss†</td>
</tr>
<tr>
<td>37/75/F</td>
<td>Thyroxine, nitroglycerine</td>
<td>Hypothyroidism, ischemic heart disease</td>
<td>SM</td>
<td>Volume loss†</td>
</tr>
<tr>
<td>38/71/F</td>
<td>...</td>
<td>Hypertension</td>
<td>...</td>
<td>PWMH†</td>
</tr>
<tr>
<td>39/75/F</td>
<td>Nitroglycerine</td>
<td>Ischemic heart disease</td>
<td>ANL</td>
<td>Normal†</td>
</tr>
<tr>
<td>40/71/F</td>
<td>Cimetidine</td>
<td>...</td>
<td>...</td>
<td>PWMH†</td>
</tr>
</tbody>
</table>

PWM, periventricular white matter; PWMH, periventricular white matter hyperintensities on magnetic resonance imaging (MRI); AD, Alzheimer’s disease; CVD, cerebrovascular disease; VD, vascular dementia; Micro, thyroid antimicrosomal antibody (Ab); ANA, antinuclear Ab; ANL, antineuronal Ab; Pariet, gastric anti-parietal cell Ab; AC, anticardiolipin Ab; RF, rheumatoid factor; TG, antithyroglobulin Ab; SM, anti-smooth muscle Ab.

*CT findings.
†MRI findings.
‡Subjects with pathological diagnosis: AD (case 2), AD with hemorrhagic infarcts in temporal and parietal lobes (case 12).
§Patients with evidence of possible infarction in two or more contiguous cuts of CT scan were excluded from this group.
significantly different from that of probable AD patients \((p=0.21)\), possible AD with CVD patients \((p=0.5)\), and nondemented control subjects \((p=0.12)\). However, the proportion of patients with possible AD with CVD with autoantibodies was significantly different from nondemented control subjects \((p=0.01)\) and probable AD patients \((p=0.03)\), and no significant difference was seen when we compared them with VD patients \((p=0.5)\). It is important to note that the low number of patients in each group may give a low statistical power to this analysis.

Table 3 shows the relation between serum autoantibodies and medication, systemic diseases, and neuroradiological findings.

No relation was observed between medication and the presence of autoantibodies. The proportion of patients with systemic disease that could affect the integrity of the cerebral blood vessels, such as hypertension, diabetes mellitus, and ischemic heart disease (atherosclerosis), was similar among groups. The diagnosis of ischemic heart disease required a history of documented myocardial infarction and/or an abnormal electrocardiogram for the presence of ischemic changes or arrhythmias. Hypertension was diagnosed by previous history and/or systolic blood pressure of >140 mm Hg and diastolic of >90 mm Hg at the moment of the physical examination.

**Discussion**

The present study indicates that serum autoantibodies were present in 100% of the patients with possible AD with CVD, 80% of those with VD, and 40% of those with probable AD and in 30% of normal control subjects. No individual autoantibody could differentiate AD from cerebrovascular disorders or demented patients from control subjects. However, antinuclear Ab was present in 60% of VD patients and antineuronal Ab in 50%. Assays to detect the presence of antiendothelial Ab and circulating immune complexes did not differentiate the patient groups. No relation was observed between medication and systemic disease and the presence of autoantibodies. However, one patient with VD was medicated with beclomethasone, which could have a suppressive effect on some autoantibodies. 25

Antinuclear and antineuronal antibodies were more frequent in VD patients than in the other groups examined. It is possible that the antineuronal Ab occurs after tissue damage associated with vascular occlusion. Antigens from damaged tissue may enter the systemic circulation and stimulate an Ab response. Whether such Ab interferes with normal cell function and contributes to the dementia observed in these patients could not be determined by these studies. Antineuronal Ab has been associated with neuropsychiatric manifestation in systemic lupus erythematosus patients. 26-29 The mechanisms involved in the antineuronal Ab clinical manifestations are unknown. However, its presence in the serum and cerebrospinal fluid of systemic lupus erythematosus patients indicated a BBB dysfunction. Although the clinical significance of antineuronal Ab in non-systemic lupus erythematosus patients is less well demonstrated, the presence of antineuronal Ab in the serum of VD patients may also indicate a BBB dysfunction and an underlying cerebral immunological process.

The role of antinuclear Ab in VD is less clear than that of antineuronal Ab. It has been reported that antinuclear Ab increases with age, and some authors linked its presence to the aging process. 30 However, in systemic lupus erythematosus patients the presence of antinuclear Ab has been associated with cerebral infarction, especially when it is accompanied with antiphospholipid antibodies. 31

Atherosclerotic angiopathy 32 and cerebral amyloid angiopathy 33 with secondary vascular changes (i.e., infarcts and hemorrhages) may be partially or wholly responsible for deficits in the permeability of the BBB. 34,35 and the transudation of serum proteins to the central nervous system in VD or in AD with CVD. 10 Similarly, cerebral angiopathies may also explain the presence of central nervous system autoantibodies in the serum of demented patients. In addition, it has been demonstrated that the degree of permeability was as pronounced in MID as in VD patients. 34 indicating that cerebral softenings per se were not the only cause of BBB dysfunction. In our study, subjects showed no symptoms or signs of cerebral ischemic events within 6 months before the serum examination. Thus, it seems unlikely that infarcts could have caused increased BBB permeability. Furthermore, autoantibodies were most common in patients with CT scans or MRI of the head that reflected chronic vascular disorders, either evident ischemic infarcts or periventricular white matter lesions. 36,37 Interestingly, three of the four patients with probable AD with autoantibodies showed small cerebral infarcts in neuroradiological studies. None of these patients had transient ischemic attacks or episodes of loss of consciousness from cardiovascular problems. These findings indicate the importance of small-vessel disease in dementia processes and suggest an association with the presence of circulating autoantibodies.

One possibility examined in this study is that circulating autoantibodies may reflect a predisposition to develop autoantibodies to vascular endothelial cells. Fillit et al 3 previously used immunofluorescence to detect antiendothelial Ab in patients with dementia. The authors found that six of 16 AD patients examined had an antivascular Ab and suggested that an autoimmune injury to the BBB by antivascular Ab may play a role in the pathogenesis of dementia by permitting the passage of injurious substances into the brain. However, assays to detect the presence of antiendothelial Ab were negative in all groups examined in this study. Another possibility examined involved the presence of immune complexes that deposit in the vessel walls, activate the complement system, and lead to vessel damage, as suggested by Alafuzoff et al. 11 However, we failed to reveal a difference in the frequency of immune complexes between various groups studied.

Although demented patients with cerebrovascular disorders met our criteria for either CVD or VD, questions may arise about low scores and the lack of statistical difference between both groups on the Hachinski Rating Scale. This brings to light a current problem in the classification of cerebrovascular disorders in an ambulatory population with dementia who have not suffered major ischemic or hemorrhagic lesions on the brain. Some such patients have clinical evidence of stroke for which there are no corresponding focal neuroradiological lesions at the time of the examination, whereas others have focal lesions on the CT or MRI scan.
of the brain for which no focal neurological signs or history of stroke can be established. These observations suggest that there is a multifactorial etiology of VD.

Infarcts may be involved, especially in the etiology of VD. Amongst the examined individuals, 17 of 49 demonstrated autoantibodies had small cerebral infarcts, indicating the presence of a cerebrovascular disorder but without clinical manifestation of CVD. Despite the relatively small number of individuals examined in this study, the presence of autoantibodies may indicate a link between an autoimmune process and CVD in dementia.

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Autoantibodies in AD and Vascular Dementia

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