Monoclonal Gammapathies in Alzheimer Disease

To the Editor:

It has been suggested that disorders of immunoregulatory mechanisms may be responsible for the amyloid deposits in senile plaques (SP) in subjects with Alzheimer disease (AD). Increased concentrations of serum IgG and IgA in such subjects have been found by several groups (1, 2). However, they did not mention whether some of the sera contained monoclonal components.

We examined serum immunoglobulins in 20 AD patients (5 men, 15 women), ages 71–94 years, who were observed for at least 6 months. The diagnosis of AD was based on Diagnostic and Statistical Manual of Mental Disorders (DSM III) criteria and on the International Classification of Diseases.

The diagnostic protocol included clinical history, psychological and neurological examination, laboratory screening tests, electroencephalography, Sandor Clinical Assessment Geriatric (SCAG), Mini Mental State (MMS), and Hachinski Scale. Two patients underwent a brain scan by computerized tomography.

The control group consisted of 40 age-matched patients, 10 men and 30 women, none of whom had any neurological disorder.

We excluded demented patients with focal neurological diseases, cardiovascular disorders, diabetes, thyroid diseases, hyperlipidemias, hypertension, history of trauma or head injury or intoxication, Parkinson disease, alcoholism, or psychiatric disorders. None of the patients had diseases that affect serum concentrations of protein or immunoglobulins.

In all 60 patients we measured serum IgG, IgA, IgM, haptoglobin, transferrin, albumin, and prealbumin. In 5 of the 20 AD patients, protein electrophoresis on agarose gel revealed the presence of a monoclonal component in the immunoglobulin area, whereas no monoclonal component was observed in the control group. This difference was statistically significant (chi-square test: P > 0.001).

The monoclonal components in these patients, determined by immunofixation electrophoresis, were three IgG, one IgG κ, and one IgM λ. Interestingly, these five findings of monoclonal components in the AD patients were all present on admission and remained virtually unchanged throughout the patients’ hospitalization—18 months to 7 years.

In addition, these five patients showed the following characteristics: a normal k/λ ratio, no Bence Jones protein, hemoglobin >100 g/L, normal concentrations of albumin and total serum protein, IgG monoclonal serum protein <30 g/L (individual values of 18.4, 23.8, 22.8, and 20.1 g/L) and IgM monoclonal serum protein <15 g/L (actual value 3.2 g/L), and no osteolytic lesions.

Because none of the patients showed clinical and (or) laboratory signs suggesting myeloma and amyloidosis during the long periods of observation, we consider that rectal and bone biopsy were unnecessary. The above changes were classified as monoclonal gammapathy of undetermined significance (MGUS).

The results for the other serum proteins (Table 1) are in keeping with malnutrition often present in these patients. The increase of serum IgG and immunoglobulins, which we and others (1, 2) have described in AD patients, suggests that amyloid deposits in the central area of senile plaques (3, 4) might derive from immunoglobulins or other serum proteins. Indeed, as shown with specific antisera, amyloid contains IgG, immunoglobulin light chains, IgM, IgA, fibrinogen, and albumin (5, 6).

Although MGUS can be found in the population at large and in elderly subjects, the frequency of 25% found in our group of AD patients is much higher than 1% and 3%, respectively, seen in these groups. Similar findings in the elderly have already been reported (7).

These results lead us to conclude the following:

- the monoclonal component always reflects an immunological disease;
- IgG is the immunoglobulin most frequently seen in the central areas of senile plaques (3, 4) and represents the monoclonal component in four of our five positive cases;
- the monoclonal components in four of our five AD patients were λ, as they frequently are in amyloidosis (7, 8)— unlike the monoclonal components of many other diseases, where the κ type is prevalent.

On the basis of these observations, we suggest that some immunological disorders that lead to the overproduction of monoclonal components might be related to the pathogenesis of amyloid deposits in senile plaques of AD patients.

References


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Table 1. Concentrations of Various Proteins in Serum of AD Patients and Control Subjects

<table>
<thead>
<tr>
<th>Protein</th>
<th>AD (n = 20)</th>
<th>Control (n = 40)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>15.41 ± 4.22</td>
<td>11.18 ± 3.35</td>
<td>0.0002</td>
</tr>
<tr>
<td>IgA</td>
<td>3.55 ± 1.26</td>
<td>2.98 ± 1.63</td>
<td>0.04</td>
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<tr>
<td>IgM</td>
<td>1.73 ± 0.91</td>
<td>1.05 ± 0.67</td>
<td>0.003</td>
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<tr>
<td>Transferrin</td>
<td>2.33 ± 0.60</td>
<td>2.59 ± 0.59</td>
<td>0.09</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>1.61 ± 0.53</td>
<td>1.32 ± 0.60</td>
<td>0.03</td>
</tr>
<tr>
<td>Albumin</td>
<td>31.67 ± 5.12</td>
<td>38.05 ± 3.93</td>
<td>0.00004</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>0.169 ± 0.055</td>
<td>0.224 ± 0.067</td>
<td>0.002</td>
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</tbody>
</table>

* Wilcoxon test.