Complement Studies in Adipose Patients Treated with Intestinal Bypass

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ABSTRACT. Seventeen consecutive patients subjected to jejunoileostomy for obesity have been investigated for complement abnormalities and cryoglobulinaemia. The study took place 1-91 years after the operation. A concomitant clinical examination revealed recurrent arthritis in 6 (30%) of the patients. In 6 of the patients complement abnormalities were found, as activation of the classical pathway in 3 and activation of the alternative pathway in another 3 could be suspected from immunochemical data. One patient showed activation of both the classical and the alternative pathway. Two of the patients with arthritic symptoms belonged to the group showing activation of the alternative pathway. It is suggested that deficient inactivation of bacterial products from intestinal bacteria (lipopolysaccharides) have a role in the complement abnormalities found. No patient exhibited the cryoprotein complexes found earlier in this type of patients.

Jejunoileal bypass for morbid obesity has become an accepted form of treatment (2, 5, 9, 10). The operative mortality is low (1-2%) and the weight reduction is often satisfactory (2). However this operative procedure may be followed by several complications, at either an early (intractable diarrhoea, electrolyte imbalances) or a late stage (hepatic insufficiency, urinary calculi, renal tubular acidosis and arthritis). The severity of the late complications has in some cases led to reoperation with elimination of the bypass, and subsequent resolution of clinical symptoms has been observed (11, 13). However, the exact significance of the late complications is still unknown, as is the pathogenesis.

The most frequent complication is recurrent arthritis, observed in 13-30% of the cases (2, 11). Generally a tenosynovitis involving wrists and fingers is found but greater joints can be affected. Rheumatoid factors or antinuclear antibodies are not found. In a recent paper Wands et al. (13) analysed 3 patients with severe arthritis following intestinal bypass. They were able to demonstrate that activation of complement took place through both the classical and the alternative pathway in the patient's serum during bouts of arthritis. Furthermore, in connection with arthritic symptoms cryoprotein complexes were found. These complexes consisted of immunoglobulins and complement components. It was shown that the immunoglobulin had antibody activity against certain intestinal bacteria (e.g. E. coli). Reoperation was necessary in one patient whose arthritic symptoms cleared and cryoprotein complexes could no longer be detected. During resolution of symptoms in two other patients and in two controls without arthritis, no cryoprotein complexes were found.

STUDY BASE

The study population comprised 17 consecutive patients, 16 females, subjected to jejunoileostomy for morbid obesity since Oct. 1966. Their mean age was 38 years (range 22-63). For all but one patient the operative procedure was the same. An end-to-end anastomosis was established between the distal aspect of the oral 36 cm of jejunum and the ileum 12 cm from the coecum. The remaining 90% of the small bowel closed orally remained in situ (9). Biopsy specimens of the liver taken from 11 patients showed slight to moderate fatty infiltration in 8. However, liver function was judged normal from measurements of albumin, coagulation factors, ASAT and alkaline phosphatase.
The examination for complement abnormalities took place 1–94 years after the operation. A concomitant clinical examination and history showed that 6 of the patients could be classified as having recurrent arthritis, involving fingers with periodical swelling, redness and morning stiffness. These patients will be referred to as the group with arthritic symptoms. Blood samples of 35 ml were taken at 10 a.m. in the supine position for analysis of plasma proteins (including complement components), antibodies against DNA, antinuclear antibodies and rheumatoid factors. Cryoproteins were investigated on blood drawn at 37°C, and serum was isolated at the same temperature. Analysis was performed as described by Nakamura (8).

Control sera. Control values for complement components were obtained from 20 healthy persons studied for 6 months, as described in detail elsewhere (3). Normal values for complement ratios (C3/C4, C3/C3PA and C3PA/C4) were determined from these control individuals. All control values given are mean ±2 S.D.

RESULTS

Complement studies. In general, we found no significant changes in the mean values of the complement components in the total group of patients. However, we observed a tendency to low serum levels of C1q and C4 (Fig. 1). Furthermore, a significant elevation of C1INA was documented, especially in the patients with arthritic symptoms. The mean values cannot be used to decide whether activation of complement is present and to answer this question we studied the ratio between certain complement components and compared these with the ratios of the control persons. The ratios studied, together with our interpretation, are shown in Table I. Fig. 2 indicates that complement activation takes place in some of the patients. Three patients showed activation of the classical pathway (C3/C4 ratio elevated), while another 3 showed activation of the alternative pathway (C3/C3PA ratio elevated). One of the patients with activation of the classical pathway displayed a normal C3PA/C4 ratio, indicating a concomitant activation of the alternative pathway. Arthritic symptoms were found in two of the patients showing activation of the alternative pathway, while none of the patients showing activation of the classical pathway had arthritic symptoms.

Immunoglobulins. Three patients, none of whom had arthritis, had a slightly elevated serum level of

Table I. Normal values for complement ratios and the interpretation of elevated or low ratios

<table>
<thead>
<tr>
<th></th>
<th>C3/C4</th>
<th>C3/C3PA</th>
<th>C3PA/C4</th>
<th>Activation of classical pathway</th>
<th>Activation of alternative pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal values</td>
<td>0.80–1.76</td>
<td>0.74–1.42</td>
<td>0.59–1.89</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Activation of classical pathway</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activation of alternative pathway</td>
<td>Normal</td>
<td>or low</td>
<td>High</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table II. Certain plasma proteins (μmol/l) in 17 patients following intestinal bypass for obesity (mean ± S.D.) and normal values

<table>
<thead>
<tr>
<th></th>
<th>Patient values</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>512±60</td>
<td>510–740</td>
</tr>
<tr>
<td>α-1-glycoprotein</td>
<td>18±4.8</td>
<td>12.2–27</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>20.8±9.9</td>
<td>2–35</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>12.7±3.4</td>
<td>7.0–14.5</td>
</tr>
<tr>
<td>α-2-macroglobulin</td>
<td>4.4±1.25</td>
<td>1.3–4.1</td>
</tr>
</tbody>
</table>
Complement studies after intestinal bypass

IgG, while IgA levels were normal. IgM showed a tendency to be low but was generally within the normal limit (Fig. 3).

Other plasma proteins. Albumin was slightly decreased, as shown in Table II. Rather low levels were found in 7 patients (mean±S.D. 451±22 μmol/l). There was no correlation between low levels of albumin and complement abnormalities. Acute phase reactants (α-1-glycoprotein and haptoglobin) were normal, while fibrinogen was elevated in 4 patients (mean±S.D. 17.6±3.0 μmol/l). This was not correlated to low albumin levels or complement abnormalities. The non-specific protease inhibitor α-2-macroglobulin was substantially elevated in 10 patients (mean±S.D. 5.2±0.8 μmol/l). In 5 out of 6 patients showing complement activation, α-2-macroglobulin was elevated indicating an inflammatory reaction.

Antinuclear antibodies and rheumatoid factors. Antinuclear antibodies were seen in 3 patients and rheumatoid factors in 1 patient. There was no correlation between these findings and complement abnormalities or arthritis.

DNA antibodies. None of the patients showed elevated titres of DNA antibodies; the observed mean value was 0.09±0.02 (S.D.).

Cryoproteins. Except for insignificant cryofibrinogenæmia and one instance of IgG cryoglobulin (0.09 mg protein/ml), no cryoproteins were found.

DISCUSSION

The finding of circulating cryoprotein complexes in patients with arthritis following intestinal bypass operations for morbid obesity, and the coexisting complement activation (13) have important pathogenetic bearings on diseases such as rheumatoid arthritis and the arthritides in various intestinal diseases (ulcerative colitis, Crohn's disease and Whipple's disease). As strongly indicated in the study by Wands et al. (13) on only 3 patients with active arthritis, intestinal bacteria play an important role in certain arthritic conditions. It has been supposed that gramnegative bacteria or at least bacterial lipopolysaccharide can pass the intestinal epithelium (12) but in healthy persons the reticuloendothelial system in the liver is able to inactivate lipopolysaccharide (6). However, when hepatic function is compromised, as in some adipose patients (2) both before and after bypass procedures, or when the load of lipopolysaccharide is heavy (6), the liver is unable to eliminate the toxic molecule, and serum factors such as complement and certain esterases (1) are important in the clearance process. When degradation is insufficient, we suggest that circulating complexes supervene, such as found by Wands et al. (13). One might expect complement abnormalities to be present in the absence of overt symptoms if our hypothesis concerning intestinal bacteria in the pathogenesis of arthritis in these patients is correct.

In agreement with this, we found complement activation to be probable in at least 6 patients (30%). In 3 patients activation occurred through the classical pathway, in 2 through the alternative pathway and in 1 patient through both these pathways. Of the 3 patients showing activation through the alternative pathway, a history of recurrent

Fig. 2. Complement ratios (arbitrary units) in 17 patients following intestinal bypass for obesity. Symbols as in Fig. 1.

Fig. 3. Immunoglobulin levels (g/100 ml) in sera from 17 patients following intestinal bypass for obesity. Symbols as in Fig. 1.
Arthritis was documented in 2. Complement inactivator (C1INA) was elevated in 11 patients, including 5 of the 6 with arthritis, perhaps indicating an increased turnover of complement components not reflected in the ratios investigated. A further argument could be the substantial elevation of the non-specific protease inhibitor (α-2-macroglobulin) in 8 of these 11 patients.

That intestinal bacteria are involved is also suggested in occasional reports of remission of arthritis in bypass-operated patients following broad-spectrum antibiotics (tetracycline) and the striking response of the symptoms in Whipple's disease following treatment with tetracycline.

The high incidence of arthritis (30%) in the present patients may be explained by the long observation time (more than 9 years in some patients) and we would like to point out that only one of our patients had incapacitating arthritis for longer periods. This patient also suffered from nephrocalcinosis and underwent a renal biopsy which did not show deposition of immune complexes in glomeruli. In accordance with earlier reports on arthritis in such patients (11), we have not found rheumatoid factors or X-ray changes compatible with rheumatoid arthritis except in one patient probably suffering from rheumatoid arthritis prior to the operation. None of our patients exhibited elevated titers of DNA antibodies. We were unable to find significant cryoprotein complexes (13) in any of our patients, which can be explained by the fact that none of them had an active arthritis at the time of the investigation.

REFERENCES