Significance of serum complement levels in patients with gastrointestinal disease

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SUMMARY Levels of the serum complement components, C3 and C4, in patients with Crohn’s disease, ulcerative colitis, and miscellaneous gastrointestinal disorders were compared with those of normal blood donors. Significant increases of both components were found in all three patient groups, the highest being in patients with Crohn’s disease. Generally, levels of C3 and C4 were lower in patients with inactive rather than active Crohn’s disease and ulcerative colitis.

These results provide some evidence in support of an immunological basis for inflammatory bowel disease. However, in view of the frequent elevation of C3 and C4 in other gastrointestinal diseases, it is equally possible that the complement components are behaving as acute phase proteins.

Material and methods

Serum C3 and C4 levels were measured in three serial groups: 39 patients with CD, 35 with UC, and 70 other patients investigated in a gastrointestinal unit (gastrointestinal controls, Table 1) and also in a group of 100 normal blood donors. The diagnosis of CD and UC was based on accepted clinical, radiological, and pathological criteria; disease activity was determined using the criteria of Truelove and Witts (1955) for UC and of De Dombal et al. (1974) for CD, taken in conjunction with the results of serum levels of albumin and orosomucoid.

Serum albumin was determined by a standard autoanalytical technique (Northam and Widdowson, 1967) and serum orosomucoid by a M-Partigen Immunodiffusion plate (Behringwerke AG, West Germany); serum C3 and C4 levels were measured by the modified single diffusion technique of Mancini et al. (1965) using monospecific antisera.

Statistical analysis was performed by calculating fiducial limits based on Student’s t distribution, as described by Bliss (1967) for samples with unequal variances.

Results

The mean (± 1 SD) levels of serum C3 and C4 in the four groups of subjects, together with the p value for the difference between these means, are shown in Table 2, and the results for individual patients are presented in Figures 1 and 2.
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Comparison between C₃ and C₄ levels in each of the three patient groups showed significant differences, the CD group having the highest mean values. In addition, the mean C₃ and C₄ values in these three patient groups, which included the gastrointestinal control group, were significantly higher than in the normal controls. Of 10 CD patients with a C₃ level within the normal control range (mean ± 2 SD), only four had active disease. The complement levels in two of these four patients were measured at a time when they were extremely ill with CD, and both have subsequently died of their disease. Complement levels in patients with inactive disease tended to be lower than in those with active disease; 10 out of 11 (C₃) and nine out of 11 (C₄) patients with inactive CD had levels below the mean of the CD group, while seven out of 13 (C₃) and nine out of 13 (C₄) with inactive UC had levels below the mean of their group. Concurrent elevation of both C₃ and C₄ in individual patients occurred in about 50% of cases. The diagnoses of the gastrointestinal control patients with elevated C₃ and/or C₄ levels are listed in Table 1.

There was no correlation between serum orosomucoid levels and levels of C₃ or C₄ in either CD or UC, in serial samples taken from individual patients.

**Discussion**

Our results clearly indicate an altered complement metabolism with respect to C₃ and C₄ complement components in CD and UC. Only 16% of patients with active disease had complement values within the normal control range, and, in addition, levels of...
both components were lower in quiescent CD and UC.

These findings are in keeping with the results reported by Thayer and Spiro (1963) for total haemolytic complement in UC, elevated values being found in active disease. Subsequently, Feinstein et al. (1976) and Hodgson et al. (1977) found the serum factor B level to be raised in both conditions, particularly in CD, and remission of the inflammatory bowel disease was associated with a fall in this level. Hodgson et al. (1977) also reported significantly elevated levels of serum C3 in CD and an elevation of serum Clq in both CD and UC. In contrast, Teisberg and Gjone (1975) and Ward and Eastwood (1975) were unable to demonstrate significant elevation of C3 or C4 in inflammatory bowel disease (except for C4 in CD in the latter study).

In spite of these varying results there is additional evidence of altered complement activity in inflammatory bowel disease, namely (i) C3 conversion as shown by the presence of C3 breakdown products in blood (Teisberg and Gjone, 1975), (ii) the presence of low titres of immunoonconglutinins reflecting continuing complement activation (Pepys et al., 1977), and (iii) an increased fractional catabolic rate as well as synthetic rate of the C3 component (Hodgson et al., 1977).

With respect to mechanisms, it has been postulated that the site of complement activation is within the gut mucosa itself, initiated by antigen-antibody reactions. However, it is equally possible that the high titres of C3 and C4 demonstrated in this study represent acute phase reactants. C3, C4, C5, C6, and factor B are known to be 'acute phase' proteins of acute inflammation (Schutte et al., 1974; Lachmann, 1975). Both C3 and factor B originate in the liver, as do other acute phase proteins; these include orosomucoid, which is elevated in active CD (Cooke et al., 1958). Nevertheless, in our patients with active CD comparison of serial C3 or C4 levels with orosomucoid levels showed no correlation.

Additional evidence that C3 and C4 behave as acute phase reactants is suggested by the elevated values found in patients with gastrointestinal disease other than inflammatory bowel disease, and in hospital patients without immunological disorders in the report from Hodgson et al. (1977). It is difficult to explain the cause of raised complement levels in seven out of 14 patients who, after intensive
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investigation, including jejunal biopsy and barium studies, were classified as having an irritable bowel syndrome, and this finding is perhaps worthy of further study.

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References


Requests for reprints to: Dr P. Asquith, The Alastair Frazier and John Squire Metabolic and Clinical Research Unit, East Birmingham Hospital, Birmingham B9 5ST.
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