Archives of Disease in Childhood, 1978, **53**, 417–419

Serum complement components in Henoch-Schönlein purpura

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SUMMARY Serum levels of C1q, C4, C3, C5, factor B, and properdin were measured in patients with Henoch-Schönlein purpura (HSP). In the cases of acute HSP, 9 of 23 (39%) had a low CH50, and 5 of 17 (30%) a low properdin; C1q, C4, and C3 levels were not depressed. In 10 cases with chronic nephritis following HSP, complement components were normal except for 2 with reduced C4 and one with low properdin. These findings confirm that complement activation occurs in HSP; the low serum levels of properdin in the acute group indicate that there is activation of the alternative pathway in these patients.

Activation of complement is thought to cause tissue damage in Henoch-Schönlein purpura (HSP). Complement components are found in affected skin (Baart de la Faille-Kuyper *et al.*, 1973; Asamer *et al.*, 1974) and glomeruli (Berger, 1969; Urizar and Herdman, 1970), circulating breakdown products of C3 are detectable in plasma (Shulman *et al.*, 1971), a minority of patients have low serum levels of complement components (Levy *et al.*, 1976), and patients' sera inhibit the formation by lymphocytes of rosettes with complement-coated sheep erythrocyte-antibody complexes (Smith *et al.*, 1975). The demonstration of properdin (a protein of the alternative pathway of complement) in affected glomeruli (Evans *et al.*, 1973) and the occurrence of HSP in 2 patients with C2 deficiency (Sussman *et al.*, 1973; Gelfand *et al.*, 1975) point to the activation of complement via the alternative pathway. We present the results of measurement of serum concentrations of complement components in patients with HSP, including the first observations of low properdin levels.

Materials and methods

HSP was defined as the typical rash with any two of the other three major manifestations of the disease, namely joint involvement, microscopic haematuria and/or proteinuria, and gastrointestinal involvement shown by abdominal pain and/or melaena.

Patients were divided into two groups. *Acute:* 23 patients with active disease studied within 30 days of onset (mean age 7·2 years, range 3–13 years). *Chronic nephritis*: 10 patients with a previous episode of HSP occurring 6 months to 11 years previously (mean age 4·0 years) and with microscopic haematuria and/or proteinuria >0·5 g/24 h at the time of study (mean age at onset of HSP 7·7 years, range 5–17 years). 23 fit children admitted for elective surgery for noninflammatory benign conditions (mean age 8·1 years, range 4–14 years) were used as controls. Sera were stored at −70°C with 0·1% sodium azide.

Complement components. CH50 was estimated by the 50% haemolysis time assay; serum levels of C1q, C3, and properdin by radial immunodiffusion, and of C4, C5, and B by haemolytic techniques (Lachmann *et al.*, 1973; Martin *et al.*, 1976). Measurements were made using a pool of normal human serum as a reference, individual results being expressed as a percentage of this and the values of the controls then being used to calculate a mean and standard deviation for a population of normal children. All measurements were made in duplicate.

Anticomplementary activity. Test sera were heated at 56°C for 10 minutes, then incubated with an equal volume of 10% guinea-pig serum (GPS) for 30 minutes at 37°C. This mixture was assayed for CH50 value as described above and compared with 10% GPS diluted with an equal volume of phosphate-buffered saline, pH 7·4.

Received 10 October 1977

Antisera. The antiproperdin antiserum was a gift from Professor D. K. Peters (Royal Postgraduate Medical School, London). All other antisera were obtained commercially (Behringwerke).

Results (Fig.)

The main abnormalities occurred in the acute group in which 9/23 (39%) had a low CH50 and 5/17 (30%) a low properdin. One patient had a very low serum level of factor B (confirmed by radial immunodiffusion) but this subsequently returned to normal. Low C1q, C4, or C3 levels were not a feature of this group; on the contrary, C4 and C3 were found in several cases to be greater than normal.

In the patients with chronic nephritis following HSP, complement components were for the most part normal, except for 2 patients with low C4 and one with low properdin; a raised C4 was found in several cases. There was no correlation between clinical manifestations of disease or its severity and any abnormal complement levels. Anticomplementary activity was detected in only one case. This patient had acute HSP with very low B and low C3 levels; all abnormalities returned to normal with clinical improvement.

Discussion

These results confirm that complement activation is a feature of acute HSP, and the finding of low properdin levels in 30% of the acute patients indicates that the alternative pathway is involved. This accords with the presence of properdin in affected glomeruli (Evans *et al.*, 1973) and in cryoglobulins detected in the sera of these patients (Garcia-Fuentes *et al.*, 1977).

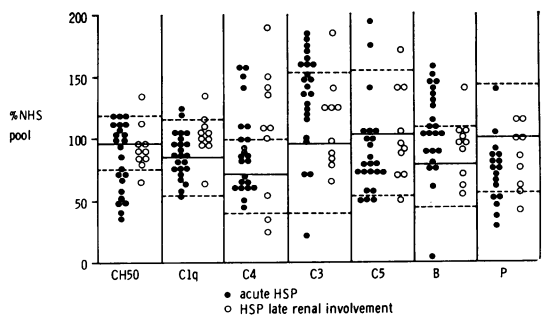

Fig. *Serum levels of complement components in patients with Henoch-Schönlein purpura (HSP). Sera for properdin (P) measurements were available in only 17 of the acute group (●) and 9 of the group with chronic nephritis (o). NHS = normal human sera.*

Despite the low values of CH50 in the acute group, there was no evidence that the early classical pathway was involved in that C1q, C4, and C3 levels were not depressed; unfortunately, we were not able to estimate serum C2. A minority of patients in the chronic nephritic group had low C1q and C4 levels. In the only other systematic study of complement profiles in HSP, Levy *et al.* (1976) found more convincing evidence that the classical pathway is involved. Of their 32 acute cases, serum C1q was low in 11 and C4 was low in 6, and of 14 cases with chronic nephritis following HSP, C1q was depressed in 3 and C4 in 4. The same workers' finding that factor B serum levels were low in both groups indicates that the C3b feedback pathway was being activated. Clearly, reduced serum levels of complement components are not a consistent or prominent feature of HSP and definition of their involvement would be attained more precisely by complement turnover studies.

This approach would also help to clarify the significance of the raised C1q, C4, C3, C5, and factor B noted in some cases by us and by Levy *et al.* (1976). The serum level of a complement component reflects both its catabolism and synthesis, and these measurements greater than normal may occur in patients in whom there is hypercatabolism, yet synthesis has increased to an extent that overcompensates for the tendency to lower the serum level.

The factors causing complement activation *in vivo* in HSP are presumably immune complexes. The detection of cryoglobulins in patients' sera (Garcia-Fuentes *et al.*, 1977) and of deposits in glomeruli of patients with nephritis (Heaton *et al.*, 1977) provide indirect evidence that HSP is an immune complex disease, and recently immune complexes have themselves been found in the sera of patients with HSP (Levinsky and Soothill, 1977). IgA was present in these immune complexes and in a high proportion of isolated cryoglobulins, and has been demonstrated by immunofluorescence in skin (Baart de la Faille-Kuyper *et al.*, 1973) and glomeruli (Berger, 1969). Since aggregated IgA has been shown to activate complement via the alternative pathway (Götze and Müller-Eberhard, 1971), these findings taken together suggest that this is the pathway by which the complement system is involved in HSP. On the other hand, there is a recent report of IgA activating the early classical pathway (Iida *et al.*, 1976), and both the immune complexes and cryoglobulins detected in this disease contain IgG and/or IgM, which can activate the classical pathway. Cryoglobulins isolated from both groups of patients activated complement *in vitro*, but all did so via the classical pathway, and none activated the alternative pathway directly (Garcia-Fuentes *et al.*, 1977). Nonetheless, the

alternative pathway may have been recruited indirectly *in vivo* in these patients since classical pathway activation may itself lead to activation of the alternative pathway (Nicol and Lachmann, 1973).

The financial support of the British Council for M.G-F., the Medical Research Council for A.M., and the Wellcome Trust for D.G.W. is gratefully acknowledged.

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