Complement activation profiles in disease

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Complement is an acute-reacting non-specific effector system. Activation and consumption of individual components of this multicomponent system occur secondarily to specific complement fixing events. The complement system is therefore an indirect and imprecise diagnostic tool and can be used clinically only as a general indicator of the severity of a particular disease or as a monitor of its progress. An exception is the case of the very rare inherited complement deficiencies where examination of the system does become directly diagnostic.

The 11 proteins of the classical pathway, three additional ones of the alternative pathway, and three natural inhibitors can be measured either immunochemically using the appropriate specific antibody or functionally by the appropriate haemolytic assay. At present only a limited number of activation and consumption profiles can be considered to be clinically useful.

Immune complex diseases

The commonest changes are those seen in overt circulating immune complex disease where the early components of the classical pathway C1, C4, C2, and C3 are variably but often much reduced when measured by both immunochemical and haemolytic titration. Haemolytic C6 and C7 almost never fall outside the normal range, though C5 may be reduced. The prime example of a disease demonstrating this profile is clinically severe systemic lupus erythematosus (SLE) when it presents or during relapse, and identical changes are seen in some cases of mixed connective tissue disease and rheumatoid vasculitis (Table 1). Some investigators (West *et al.*, 1973; Whaley *et al.*, 1979) have shown marked falls in factor B, properdin, and the control protein β_1H in active SLE, and they interpret these findings as evidence for triggering of the feedback cycle in such cases.

The immune complex profile of complement consumption is seen in several infectious diseases and is particularly associated with a 'serum sickness'-like phase of the infection (Alpert *et al.*, 1971; Meyer zum Büschenfelde *et al.*, 1978). Not surprisingly,

Table 1 *Diseases showing early classical complement pathway (C1423) activation and consumption*

Systemic lupus erythematosus
Rheumatoid vasculitis
Mixed cryoglobulinaemia
Postheterologous protein injections
Leucocytoclastic vasculitis and urticaria
Poststreptococcal glomerulonephritis
Shunt nephritis
Acute bacterial endocarditis
Postgonococcal and postmeningococcal septicaemia
Pneumococcal septicaemia
Subacute bacterial endocarditis
Prodromal phase of hepatitis B virus infection
'Post' rubella syndrome
Acute phase of infectious mononucleosis
Malaria (during schizogony)
Cryptococcaemia

large amounts of circulating complement-fixing immune complexes are found in the circulation at this time. Examples of bacterial and viral infections in which these associations may be seen are listed in Table 1. C1423 complement component consumption is an almost invariable accompaniment of post-streptococcal nephritis and shunt nephritis (Strife *et al.*, 1976; Harkiss *et al.*, 1979), though in post-streptococcal nephritis there is often a disproportionate fall in C3 and C4 concentrations in relation to C1 and C2 (West *et al.*, 1973).

The incidence of these changes in the other examples in Table 1 is not yet established since it is based on small numbers of observations by the author and others. Complement changes suggestive of classical pathway activation occur at the time of the serum sickness-like illness reported to develop 5-10 days after meningococcal or gonococcal septicaemia (Greenwood *et al.*, 1976). A rather different association between neisserial infections and complement occurs in rare patients with inherited total deficiencies of C6, C7, or C8. 'Classical' serum sickness with pronounced C1423 consumption is still occasionally seen and can, for example, follow the injection of heterologous antiserum (Nielsen *et al.*, 1978).

Two subtle variations of the basic immune complex complement profile have recently been recog-

nised. Tarantino *et al.* (1978) showed selective loss of C142 with essentially normal C3 concentrations in a large series of mixed cryoglobulinaemias. This slightly anomalous finding may be partly explained by the efficient fixation of C1 and C4 in the cold but the strong temperature dependence of the C42 complex as a C3 convertase.

Agnello *et al.* (1971) described an unusual immune complex disease with the features listed in Table 2. Several other cases (Marder *et al.*, 1976; Geha and Akl, 1976) with identical complement changes have since been reported and their clinical similarity suggests that this may be a unique syndrome. The C1q binding and consuming agent may be an unusual IgG molecule binding to C1q via its Fc end (Marder *et al.*, 1978). But there seems to be some overlap between this syndrome and other cases presenting with chronic urticaria, arthritis, and leucocytoclastic vasculitis which have typical C1, C4, C2 and C3 consumption, variable amounts of circulatory immune complexes, and cryoglobulins (McDuffie *et al.*, 1973; Soter *et al.*, 1974; Soter, 1977).

Table 2 *Hypocomplementaemic vasculitis urticaria syndrome*

Recurrent urticaria and angioedema
Necrotising vasculitis
Arthralgia
Low C1q, normal C1r, and C1s
Normal C1 esterase inhibitor
Low molecular weight C1q precipitins

The discussion so far has related to observations using immunochemical or haemolytic measurements of complement in serum. Metabolic studies of carefully purified undenatured radioiodinated single components may provide the best evidence for part of the complement system participating in a pathological process. Increased catabolic rates are sometimes recorded even when static serum concentrations are normal. For example, the catabolic rate of C3 is significantly raised in hereditary angioedema even though the serum level is normal (Ruddy *et al.*, 1975). Metabolic studies are widely used in clinical research but rarely used routinely since they are expensive, time-consuming, and have ethical implications.

Detailed analyses of immunochemically identified breakdown or activation products of complement components—for example, C1 and C3—have not so far been totally successfully exploited in clinical medicine, though techniques continue to improve (Perrin *et al.*, 1975; Laurell *et al.*, 1978; Thompson *et al.*, 1978).

Nephritic factor and mesangiocapillary glomerulonephritis

A disease with a unique complement consumption profile is the form of mesangiocapillary glomerulonephritis clinically associated with partial lipodystrophy and histologically associated with intramembranous dense deposits in the glomerular basement membranes. Most of the patients have very low though not absent C3, normal or low immunochemical factor B levels, low haemolytic factor B levels, and increased catabolic rates for C3 and factor B (Charlesworth *et al.*, 1974; Sissons *et al.*, 1976). Other complement components including C1, C4, and C2 are normal (Thompson and White, 1973). The complement changes can now be explained by an unusual IgG molecule (nephritic factor) which stabilises the alternative pathway C3 convertase (C3bBb). It may do this as an immunoglobulin-like molecule, an autoantibody that is elicited to a neodeterminant in the assembled convertase (Davis *et al.*, 1977; Scott *et al.*, 1978). The presence of nephritic factor is usually demonstrated in a simple assay in which, on mixing with normal serum, it converts native C3 (β_1C) to C3c (β_1A). The conversion products are detected by Laurell electrophoresis.

Inherited complement deficiencies

Many of the patients with these deficiencies suffer from diseases secondary to the deficiency state. Homozygous C1, C4, and C2 deficient patients present with SLE, SLE-like syndromes, or moderate to severe glomerulonephritis. In individual cases followed for some time it appears that during disease activity (Day *et al.*, 1973) components in the classical pathway preceding the deficient component are low—for example, low C1, C4 in C2 deficiency—while components after the deficient component are normal—for example, normal C3 in C2 deficiency. Appropriate treatment and remission may be associated with a return of all components to normal except for the congenitally absent one. The very rare C3b inactivator-deficient patients are a special case. C3b-inactivator protein (with β_1H) normally restrains the 'natural' tickover rate of the alternative pathway. In its absence large amounts of stable C3b, Bb are formed, C3 is broken down to C3b, and the feedback cycle runs down to exhaustion. These patients have no intact native haemolytic C3 or factor B (Thompson and Lachmann, 1977). Complement profiles in C3, C5, C6, C7, and C8 deficiency are generally reported as normal apart from the congenitally absent component.

The commonest inherited complement deficiency

is lack, or relative lack, of the control protein, C1 esterase inhibitor. People with this autosomal dominant condition present with angioedema of the face or limbs or signs of gastrointestinal obstruction. Typically during an attack functionally active C1 can be demonstrated directly in the patient's serum and C4 and C2 are reduced to zero (Donaldson and Rosen, 1964). C3 levels remain normal, an observation which allows clear distinction between angioedema and immune complex diseases.

A secondary angioedema syndrome (Caldwell's syndrome) is now recognised as a rare complication of lymphoma, chronic lymphocytic leukaemia, and macroglobulinaemia (Caldwell *et al.*, 1972; Day *et al.*, 1976; Schreiber *et al.*, 1976; Casali *et al.*, 1978). C1 esterase inhibitor falls to low levels, apparently stoichiometrically consumed by excessive amounts of active C1 which, in turn, is fixed and activated by an unusual cold-reacting antigen-antibody complex. In both the primary and secondary syndrome the definitive diagnosis rests on finding functionally low (less than 30%) or absent C1 esterase inhibitor.

Gram-negative septicaemia

Many agents apparently activate complement by antibody-independent mechanisms, though so far the mode of action of most of these agents has been evaluated only by *in-vitro* tests. *In-vivo* studies of antibody-independent complement changes have been limited to lipopolysaccharides (endotoxins) and in man in particular to changes observed in Gram-negative septicaemia. Although the haemodynamic changes which accompany Gram-negative septicaemia are complex and ill understood, a few experimental clinical studies have attempted to correlate alternative pathway activation and consumption with shock and mortality. However, there has been little general attempt by clinicians to use complement changes as a prognostic indicator. Recently, Whaley and colleagues (unpublished) have shown significant correlations between falls in C3, factor B, and the alternative pathway control protein β_1H and an unfavourable outcome in Gram-negative septicaemia.

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