Complement: Deficiency Diseases

Secondary article

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Genetically determined deficiencies of the complement system result in an increased susceptibility to infection, rheumatic disorders, or angio-oedema.

Introduction

Although the complement system was first described at the turn of the twentieth century, it was not until 1960 that the first patient with a genetically determined complement deficiency was identified. Since then, deficiencies have been described for nearly all of the components of the complement system.

Pathophysiology

Individuals with genetically determined complement deficiencies have a variety of clinical presentations. Most patients present with an increased susceptibility to infection, others with a variety of rheumatic diseases, still others with angio-oedema, and in rare instances, patients may even be asymptomatic. The elucidation of the pathophysiological basis for the different clinical presentations of complement-deficient individuals has contributed to a better understanding of the physiological role of complement in normal individuals.

Increased susceptibility to infection

An increased susceptibility to infection is a common clinical finding in most patients with complement deficiencies. The kinds of infections relate to the biological functions of those components that are missing. For example, the major cleavage product (C3b) of the third component of complement (C3) is an important opsonic ligand. Therefore, patients with a deficiency of C3, or of a component of either of the two pathways that activate C3, are susceptible to infections caused by encapsulated bacteria for which opsonization is the primary host defence (e.g. *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae*). Similarly, C5–C9 form the membrane attack complex and are responsible for the bactericidal functions of complement. Thus, patients with deficiencies of C5, C6, C7, C8 or C9 are susceptible to *Neisseria* species since serum bactericidal activity is an important host defence against these organisms.

Rheumatic diseases

Patients with complement deficiencies may also develop a variety of rheumatic diseases. These include a disorder that resembles systemic lupus erythematosus (SLE) as well as glomerulonephritis, dermatomyositis, anaphylactoid purpura and vasculitis. The prevalence of these inflammatory disorders is highest in those patients with deficiencies of the classical activating pathway (C1, C4 and C2) and of C3. For example, approximately 80% of patients with C4 or C3 deficiency diseases and just over 30% of patients with C2 deficiency have had a rheumatic disorder. In contrast, fewer than 10% of patients with deficiencies of terminal complement components have rheumatic disorders. The most attractive hypothesis linking rheumatic diseases and complement deficiency diseases has to do with the role of the complement system in the clearance and processing of immune complexes. A number of studies have shown that the sera of patients with complement deficiencies have altered and/or reduced abilities to process immune complexes and that the inability of the patients' sera to process immune complexes *in vitro* correlates with their risk for developing a rheumatic disorder. For example, serum from patients with genetically determined deficiencies of Clq, C4, C2 and C3 fails to prevent the precipitation of immune complexes as they are forming, has a reduced ability to resolubilize complexes once they have formed, and does not support the binding of preformed immune complexes to C3b receptors on human erythrocytes. In contrast, the serum of patients with deficiencies of terminal components (C5–C9) are normal with respect to these activities.

Angio-oedema

Patients with a deficiency of one of the control proteins of the classical pathway, C1 esterase inhibitor (C1 INH), usually present with angio-oedema of the skin or mucous membranes (see below). The pathophysiological basis for

the development of angio-oedema in C1 INH deficiency is not fully understood, but appears to relate to the inability of C1 INH to inhibit the activation of both the complement system and the kinin system.

Asymptomatic

Some patients with genetically determined complement deficiencies are relatively asymptomatic, never having developed a serious infection or a rheumatic disorder. These asymptomatic patients are usually ascertained as a consequence of screening family members of complement-deficient patients who themselves have been ascertained because of clinical problems.

Specific Disorders

Most of the genetically determined deficiencies of the complement system are inherited as autosomal recessive traits. There are only two known exceptions: deficiency of C1 inhibitor has an autosomal dominant mode of inheritance, while properdin deficiency is inherited as an X-linked recessive disorder.

Clq deficiency

The first component of complement is composed of three distinct subunits, Clq, Clr and Cls. There appear to be two distinct forms of Clq deficiency. In one form, Clq cannot be detected by either functional or immunochemical analysis. In the other form, immunochemical Clq is present, but it lacks functional activity, i.e. it is dysfunctional. The dysfunctional C1q is antigenically deficient, and it does not interact with either immunoglobulin G (IgG) or its substrates, Clr and Cls.

The most common clinical presentation of either form of Clq deficiency has been a lupus-like syndrome. The clinical manifestations of SLE in patients with Clq deficiency are not markedly different from those seen in complement-sufficient individuals, although the age of onset is somewhat earlier and the disease can be very severe with significant central nervous system (CNS) and renal disease. Patients with Clq deficiency also have an increased susceptibility to bloodborne infections with pyogenic organisms, such as sepsis and/or meningitis, presumably due to their inability to generate opsonically active C3b via activation of the classical pathway.

Clr/Cls deficiency

The genes encoding Clr and Cls map to the short arm of chromosome 12, are separated by only 9.5 kb and are highly homologous. Genetically determined deficiency of Clr is characterized by a marked reduction of Clr (less than 1% of normal) and a moderate reduction of Cls (20–50% of normal). The basis for the association of the moderately reduced levels of Cls with the absence of Clr in these patients is unknown, although it may relate to their close structural and functional similarity. Interestingly, one patient has been described in which Cls is markedly reduced while Clr levels are 50% of normal.

Most Clr/Cls-deficient patients have presented with SLE, although isolated glomerulonephritis has also been described. In addition, some patients have been ascertained as part of family studies and have been clinically well.

C4 deficiency

There are two loci (C4A and C4B) within the major histocompatibility complex that encode for C4. Although the products of the two loci share some functional, structural and antigenic characteristics that identify them as C4, they differ sufficiently with respect to electrophoretic mobility, molecular weight of the α chain, specific epitopes and functional haemolytic activity to allow their separate identification. Patients with total C4 deficiency are homozygous deficient at both loci and have severely depressed serum levels of both antigenic and functional C4 (less than 1%). Those serum activities that depend on C3 and C5–C9 and can be mediated via activation of the alternative pathway, such as opsonic, chemotactic and bactericidal activities, are present but are not generated to the same degree or as quickly as in normal sera because of a lack of an intact classical pathway.

The predominant clinical manifestation of complete C4 deficiency has been an SLE-like illness, characterized by photosensitive skin rashes, renal disease and occasionally arthritis. Although some patients have an increased susceptibility to infection, these are patients in whom the SLE-like illness is also present.

Although complete C4 deficiency is rare, individuals who are homozygous deficient for either C4A or C4B are relatively common. Approximately 1% of the population is homozygous deficient in C4A and 3% of the population is deficient in C4B. As mentioned, C4A and C4B differ somewhat in function; C4A binds more efficiently to proteins and C4B binds more efficiently in carbohydrates. Individuals who lack C4A are missing the isotype that interacts most efficiently with proteins, and therefore might not be able to clear protein-containing immune complexes normally and be more susceptible to immune complex diseases such as SLE. In fact, the prevalence of homozygous C4A deficiency in SLE is between 10% and 15%, a prevalence at least 10 times higher than that in the general population. Individuals who are deficient in C4B lack the isotype that is more efficient in interacting with polysaccharides and therefore might not be able to assemble the classical pathway C3-cleaving enzyme on bacterial poly-

saccharide capsules and be more susceptible to bloodborne bacterial infections. In fact, the prevalence of C4B deficiency is increased in children with bacteraemia and meningitis.

C2 deficiency

Genetically determined C2 deficiency is the most common of the inherited complement deficiencies, occurring in 1 in 10 000 in Caucasian populations. The gene for C2 lies within the major histocompatibility complex (MHC) and is associated with a conserved MHC haplotype, HLA-B18, C2*QO, Bf*S, C4A*4, C4B*2 and DR*2. Because of its linkage disequilibrium with the conserved haplotype, it is not surprising that over 95% of C2-deficient individuals are homozygous for the same mutation, a 28 base pair deletion that results in premature termination of transcription. Complement-mediated serum activities, such as opsonization and chemotaxis, are present in patients with C2 deficiency, presumably because their alternative pathway is intact, although they are not generated as quickly nor to the same degree as in individuals with an intact classical pathway.

The clinical manifestations of C2 deficiency have varied from individuals who have either rheumatic diseases and/or an increased susceptibility to infection to individuals who are asymptomatic. Approximately 40% of C2-deficient individuals develop SLE or discoid lupus. Patients with C2 deficiency express many of the characteristic features of lupus, although severe nephritis, cerebritis and aggressive arthritis are less common than in complement-sufficient SLE patients. Cutaneous lesions are common in C2-deficient patients with lupus and many have a characteristic annular photosensitive rash. Patients with C2 deficiency and SLE have a lower prevalence of anti-DNA and antinuclear antigen antibodies than do other SLE patients, but their incidence of anti-Ro antibodies is higher. A variety of other rheumatic disorders have also been described in C2 deficiency, including glomerulonephritis, inflammatory bowel disease, dermatomyositis, anaphylactoid purpura and vasculitis. Approximately 50% of C2-deficient patients have an increased susceptibility to bloodborne infections (e.g. sepsis, meningitis, arthritis and osteomyelitis) caused by encapsulated organisms (e.g. pneumococcus, *H. influenzae* and meningococcus).

C3 deficiency

Patients with C3 deficiency generally have less than 1% of the normal amount of C3 in their serum. Those serum activities either directly dependent on C3 (opsonization) or indirectly dependent on C3 because of its role in the activation of C5–C9 (chemotaxis and bactericidal activity) are also markedly reduced. The clinical manifestations of C3 deficiency include both an increased susceptibility to infection and rheumatic disorders. The infections have included pneumonia, bacteraemia, meningitis and osteomyelitis caused by encapsulated pyogenic bacteria. The rheumatic disorders have varied from limited clinical involvement, such as arthralgias and vasculitic skin rashes, to a more extensive clinical picture consistent with systemic lupus erythematosus. Interestingly, as with some other complement-deficient patients, C3-deficient patients may not have serological evidence of lupus. Membranoproliferative glomerulonephritis has also been seen in C3-deficient patients. The renal disease may reflect the role of C3 in immune complex clearance.

C5 deficiency

The sera of patients with C5 deficiency are unable to generate normal amounts of chemotactic or bactericidal activity. As expected, serum opsonic activity is intact, since the activation of C3 can proceed without the participation of C5.

Although the initial patient identified as C5 deficient had SLE and membranoproliferative glomerulonephritis, subsequent patients have been ascertained because of either meningococcal meningitis or disseminated gonococcal infections. A few C5-deficient patients have been asymptomatic, having been ascertained as part of family studies.

C6 deficiency

C6 deficiency has been reported in nearly 100 individuals, many of whom are of African descent. The most common form of C6 deficiency is characterized by absent or nearly absent levels of C6 ($< 1\%$ of normal), whether it is assessed immunochemically or functionally. The only abnormality relating to their serum complement system is a marked deficiency of serum bactericidal activity. A subtotal deficiency of C6 (C6SD for C6 subtotal deficiency) has also been described which is characterized by serum levels of C6 that are 1–2% of normal. This truncated C6 protein has a lower molecular weight and although it can be incorporated into the membrane attack complex, it functions less efficiently.

The major clinical manifestation of complete C6 deficiency has been disseminated neisserial infections. While most patients have had meningococcal sepsis and meningitis, others have had disseminated gonococcal infections. Patients with C6SD do not appear to have an increased susceptibility to infection.

C7 deficiency

Only a few patients with C7 deficiency have been identified. Most individuals have severely reduced levels of C7 ($< 1\%$). Serum bactericidal activity is markedly reduced.

A second type of C7 deficiency has been described in which the quantity of C7 is diminished but not absent. The C7 that is present exhibits an altered isoelectric point. Interestingly, this form of C7 deficiency, termed subtotal C7 deficiency (C7SD), has been seen primarily in association with C6SD (see above).

A number of clinical presentations have been associated with C7 deficiency. As with the other deficiencies of terminal components, systemic neisserial infections have occurred in most reported cases of C7 deficiency. Individual patients have also presented with lupus, rheumatoid arthritis, scleroderma and pyoderma gangrenosum. Finally, there have been a few patients with C7 deficiency who have been clinically well.

C8 deficiency

Native C8 is composed of three chains (α, β and γ). The α and γ chains are covalently joined to form one subunit (C8αγ), which is joined to the other subunit composed of the β chain (C8β) by noncovalent bonds. Each of the C8 polypeptides is encoded by separate genes. In one form of C8 deficiency, patients lack the C8αγ subunit, while in the other form, the C8β subunit is deficient. Deficiency of C8β is more common in white populations while C8αγ deficiency is more common in Africans. Eighty-six percent of C8β null alleles are due to a C-T transition in exon 9 producing a premature stop codon, suggesting a founder effect. The molecular basis of C8αγ deficiency has been identified in three patients. In five of the six null alleles, an intronic mutation alters the splicing of exons 6 and 7 of C8A and creates a 10-bp insertion that generates a premature stop codon. In either C8αγ deficiency or C8β deficiency, C8 activity is markedly reduced and there is a marked reduction in bactericidal activity.

The clinical presentation of C8 deficiency has been similar to the other deficiencies in terminal complement components. Meningococcaemia, meningococcal meningitis and disseminated gonococcal infections have predominated, but SLE has also rarely been seen.

C9 deficiency

Only a few patients with C9 deficiency have been identified in Western populations but it appears to be the most common complement deficiency in Japan with a prevalence of 0.036–0.095%. The lysis of bacteria can be mediated by a membrane attack complex composed of C5b-8 and is not, therefore, strictly dependent on C9. As a result, the sera of patients with C9 deficiency possess some bactericidal activity, although the rate of killing is significantly reduced.

The first few individuals with C9 deficiency were asymptomatic, suggesting initially that C9 deficiency was not associated with any clinical problems. However, most subsequent patients with C9 deficiency presented with systemic meningococcal infections. In addition, an epidemiological study of C9 deficiency in Japan provided strong evidence for a relationship between C9 deficiency and meningococcal sepsis and meningitis.

Factor I deficiency

Factor I controls the assembly and expression of the alternative pathway enzyme that activates C3. Factor I deficiency is characterized by uncontrolled activation of C3 via the alternative pathway because, in the absence of factor I, there is no control imposed on the formation and expression of the alternative pathway that activates C3. Patients with factor I deficiency, therefore, have a secondary consumption of C3 resulting in markedly reduced levels of native C3 in their serum. Most of the C3 is not in its native form, but rather in the form of its inactive cleavage product, C3b. Those serum activities that directly or indirectly depend on the availability of native C3 (opsonic activity, chemotactic activity and bactericidal activity) are reduced in patients with factor I deficiency.

The most common clinical expression of factor I deficiency is an increased susceptibility to infection. As with primary C3 deficiency (see above), infections have included both localized infections on mucosal surfaces, as well as systemic infections. The organisms most commonly responsible for these infections have been encapsulated pyogenic bacteria, such as the streptococcus, pneumococcus, meningococcus and *H. influenzae* organisms, for which C3 is an important opsonic ligand. In addition to problems with infection, some patients have had elevated levels of circulating immune complexes. There have as yet been no reports of patients with factor I deficiency developing chronic renal disease as has been the case with C3 deficiency. However, there has been one report of a transient illness resembling serum sickness and characterized by fever, rash, arthralgia, haematuria and proteinuria.

Properdin deficiency

Properdin deficiency is the only complement deficiency that is inherited as an X-linked recessive trait. Properdin acts to stabilize the alternative pathway enzymes that activate C3 and C5. The serum of patients with properdin deficiency is therefore unable to activate C3 via the alternative pathway. There are a number of forms of properdin deficiency. In one form, affected males have markedly reduced levels of properdin ($< 1\%$ of normal), while in another form, properdin is present but in reduced amounts (10% of normal). A third form of properdin deficiency has been described in which properdin is present in normal concentrations but is dysfunctional.

The most common clinical manifestation of properdin deficiency has been fulminant meningococcaemia and

meningococcal meningitis, emphasizing the importance of the alternative pathway in host defence against meningococci. These patients appear to have a particularly high mortality rate (75%) compared to complement-sufficient patients or patients with deficiencies of terminal complement components. SLE and discoid lupus have also been described in isolated patients.

C1 esterase inhibitor deficiency

A genetically determined deficiency of C1 esterase inhibitor (C1 INH) is responsible for the clinical disorder hereditary angio-oedema (HAE). C1 inhibitor deficiency is inherited in an autosomal dominant fashion. There are at least two forms of C1 INH deficiency. In the most common form (type I), which accounts for about 85% of patients, the serum of affected individuals is deficient in both C1 INH protein (5–30% of normal) and C1 INH activity. In the less common form (type II), which accounts for the remaining 15% of patients, a dysfunctional protein is present in normal or elevated concentrations, but its functional activity is markedly reduced. The pathophysiological mechanisms by which the absence of C1 INH activity leads to the angio-oedema characteristic of the disorder are still incompletely understood. Neither the mediators responsible for producing the oedema nor the mechanisms initiating their production have been clearly identified, although evidence implicates both the complement system and the kinin system in the pathogenesis of the oedema.

The clinical symptoms of HAE are the result of submucosal or subcutaneous oedema. The lesions are characterized by noninflammatory oedema associated with capillary and venule dilation. The three most prominent areas of involvement are the respiratory tract, skin and gastrointestinal tract.

Attacks involving the upper respiratory tract represent a serious threat to the patient with HAE. Before the use of impeded androgens to prevent such episodes, pharyngeal oedema occurred at least once in nearly two-thirds of the patients. The patients may initially experience a 'tightness' in the throat and swelling of the tongue, buccal mucosa and oropharynx follow. In some instances, laryngeal oedema, accompanied by hoarseness and stridor, progresses to respiratory obstruction and represents a life-threatening emergency. Attacks usually progress for 1–2 days and resolve over an additional 2–3 days.

Attacks involving the skin may involve an extremity, the face or genitalia. The oedema may vary in size from a few centimetres to involvement of a whole extremity. The lesions are pale rather than red, usually not warm, and are characteristically nonpruritic. There may be a feeling of tightness in the skin caused by accumulation of subcutaneous fluid, but there is no pain.

The gastrointestinal tract can also be affected by HAE. In fact, gastrointestinal involvement is especially common in children with HAE. Symptoms are secondary to oedema of the bowel wall and may include anorexia, dull aching of the abdomen, vomiting and crampy abdominal pain. Abdominal symptoms can occur in the absence of concurrent cutaneous or pharyngeal involvement.

The onset of symptoms referable to HAE occurs in more than half the patients before adolescence, but in some patients, symptoms do not occur until adulthood. Even though trauma, anxiety and stress are frequently cited as events that initiate attacks, more than half of patients cannot clearly identify an event that initiated an attack. Dental extractions and tonsillectomy can initiate oedema of the upper airway, and cutaneous oedema may follow trauma to an extremity.

Therapy of HAE is divided into two categories: prophylaxis of attacks and treatment of attacks. Long-term prevention of attacks may be indicated in those patients who have had laryngeal obstruction or have suffered frequent and debilitating attacks. Antifibrinolytic agents such as ε-amnocaproic acid (EACA) have been used with some success in the long-term prevention of attacks. More recently, impeded androgens such as danazol and stanozolol, which have attenuated androgenic potential, have been found to be useful in long-term prophylaxis of HAE. These agents have not been used extensively in children, however, because of their androgenic effects. They act by stimulating the synthesis of functionally intact C1 INH by the normal gene. In some instances, patients may need short-term prophylactic therapy (e.g. before oral surgery). In these circumstances, danazol therapy may be initiated one week before surgery or EACA the day before surgery.

A number of drugs have been used in an attempt to interrupt an attack of HAE once it has begun. Adrenaline, antihistamines and corticosteroids are of no proven benefit. However, recent trials with partially purified C1 INH are encouraging.

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