



CHAPTER

13

Complement Deficiencies

Complement is the term used to describe a group of serum proteins that are critically important in our defense against infection. There are deficiencies of each of the individual components of complement. Patients with complement deficiencies encounter clinical problems that depend on the role of the specific complement protein in normal function.

Definition of Complement Deficiencies

Complement is the term used to describe a group of serum proteins that are critically important in our defense against infection (see chapter titled *The Immune System and Primary Immunodeficiency Diseases*). The complement system includes at least 30 proteins. The first nine of these proteins were given numbers as their names, such as C1, C2, C3, etc. As more proteins were discovered they were named with letters, such as Factor B and Factor D. Still, others were given more descriptive names such as C1 Inhibitor.

These proteins act together to provide critical help in our defense against infection in a number of ways. One of the proteins, C3, acts to coat bacteria so that the bacteria are more easily ingested, or eaten, by white blood cells. Others, C5, C6, C7, C8 and C9, assemble on the surface of a certain kind of bacteria and punch holes in the bacteria, causing them to rupture and die. Finally, small fragments of two of the complement proteins, C3 and C5, can cause an increase in blood supply and the attraction of white blood cells to local areas of infection, both of which are needed to clear an infection.

The complement proteins act in a cascade, one protein activating or stimulating the next in a specific sequence of reactions, much like a series of standing dominoes pushing each other over. A protein that recognizes the invading microorganism, such as immunoglobulin

(antibody) often starts the cascade of complement proteins. There are 3 known major pathways of complement activation. These are the *classical pathway*, the *lectin pathway*, and the *alternative pathway*. The classical pathway, the first to be discovered, is triggered by the interaction of antibodies (immunoglobulin) with microorganisms, such as bacteria. In the lectin pathway, Mannose Binding Lectin (MBL) binds to the sugars on a bacterial surface and activates the complement system. Like the lectin pathway, the alternative pathway doesn't need antibody or immunoglobulin to be activated. These three complement pathways all lead to the activation of the components of complement, although each does so in a slightly different way.

Some proteins of the complement system regulate the degree to which the system is activated and keep it under control so it doesn't activate excessively and overreact to invading microorganisms. The control, or regulatory, proteins such as C1 Inhibitor (C1INH) are also critically important in stopping the complement system from over reacting to trivial stimuli, such as minor trauma.

There are deficiencies in each of the individual components of complement. For example, there are individuals deficient in C2, individuals deficient in C3, individuals deficient in C5, individuals deficient in C1 Inhibitor, etc.

Clinical Presentation of Complement Deficiencies

Deficiencies of the Third Component of Complement (C3) and those proteins of the complement system that activate C3

The third component of complement (C3) is the protein that coats bacteria and makes them more susceptible to being eaten by a certain kind of white blood cell, phagocytic cells (see chapter titled *The Immune System and Primary Immunodeficiency Diseases*). Patients who are deficient in C3 or the proteins that are necessary to activate C3 (e.g. C1, C2 and C4)

are susceptible to a variety of bacterial infections. Although patients with deficiencies of C3, C1 or C4 are quite rare, patients with deficiencies of C2 are more common, occurring as frequently as 1 in 10,000 in the general population.

Interestingly, these patients also have a higher than expected prevalence of some so-called "autoimmune diseases" such as systemic lupus erythematosus (SLE or Lupus) or rheumatoid arthritis. Although the reasons for this association of these autoimmune diseases with these complement system deficiencies are unknown, some complement deficient patients may have more difficulty with autoimmune diseases than they do with infection.

Clinical Presentation of Complement Deficiencies continued

Deficiencies of C5, C6, C7, C8 or C9

Individuals who are deficient in any one of these components of complement are only susceptible to one family of bacteria. This includes the organism that causes an important form of meningitis, *Neisseria meningitidis*, and the organism that causes gonorrhoea, *Neisseria gonorrhoeae*. These late acting complement proteins are involved in forming holes in membranes. It is thought that the hole-forming complement proteins may be significant in protecting against these organisms. Although patients deficient in any of these components possess the opsonic protein, C3, it does not appear to be sufficient to provide protection against these specific organisms.

Deficiency of C1 Inhibitor

There are individuals who are missing, or have an abnormality of, the C1 inhibitor, a significant regulator of the complement system. C1 inhibitor has been shown to have inhibitory activity in the complement system, the clotting system, the kinin generating system (a system that generates another inflammatory peptide, Bradykinin), and the fibrinolytic system (the system that dissolves blood clots). Patients with C1 inhibitor deficiency often have the illness, Hereditary Angioedema. Angioedema refers to swelling in tissues under the skin or mucus membranes that are not itchy. This swelling can affect the hands, feet, bowel, mouth and airway. When the swelling affects the skin, there is localized swelling, usually without any redness or itching. If the swelling affects the wall of the bowel, it causes extreme abdominal pain. The swelling of the airways can be especially serious since the swelling can compromise the patient's ability to breathe. The swelling, or angioedema, usually lasts up to three days.

Diagnosis of Complement Deficiencies

A variety of laboratory tests are used to diagnose patients with deficiencies of individual complement proteins or components. Initially, the ability of the patient's complement system to function as a whole is examined by seeing if the whole cascade is capable of punching a hole in red blood cells. There are different ways to test the integrity of the whole cascade, but the most common is CH50 assay (see chapter titled *Laboratory*

Tests). If the integrity of the cascade is abnormal, a search is made to determine which of the components is not present or not functioning in the proper fashion. Tests of individual components are relatively sophisticated and not performed in every laboratory. These tests check for either the presence of the individual complement protein in the patient's blood serum or for the ability of the individual complement proteins to function properly.

Inheritance of Complement Deficiencies

Most of the complement proteins and regulators are inherited as autosomal recessive genes; this means that there are two copies of each gene present, one contributed by each parent (see chapter titled *Inheritance*). There are two exceptions:

1. A deficiency of Properdin, is inherited as an X-linked recessive trait.
2. C1 Inhibitor Deficiency (or Hereditary Angioedema) requires the presence of only one abnormal gene out of the two genes for this protein to produce the disease. When the presence of one abnormal gene "dominates" over the normal gene, it is called autosomal dominant inheritance. In this case, the presence of the one normal gene does not produce sufficient C1 inhibitor to prevent patients from having Hereditary Angioedema attacks.

Treatment of Complement Deficiencies

Deficiencies of the Third Component of Complement (C3) and those proteins of the complement system that activate C3 and Deficiencies of C5, C6, C7, C8 or C9

At this time, it is not possible to replace the missing components of the complement system. In general, these proteins have rapid turnover and often must be made by the body on a daily basis. Therefore, long-term replacement therapy is not an option since injections of highly purified components would be required almost every day and the proteins are difficult to purify. Patients with abnormalities that are associated with a high frequency of infection are usually helped by immunization when available and, occasionally, are treated with prophylactic antibiotics.

Deficiency of C1 Inhibitor

There has been extensive research in recent years on the treatment of Hereditary Angioedema and there are a number of companies developing therapies for this illness. For several decades it has been known that impeded androgens can be highly effective in treating patients with Hereditary Angioedema. Impeded androgens, such as Danazol or Oxandrolone, are androgens in which the masculinizing effect of the drug is minimized. In Europe, the plasma protein that is deficient in Hereditary Angioedema, C1 inhibitor, reliably terminates attacks and is available for therapeutic administration. It appears that it will become available in North America as well.

Expectations for Complement Deficiency Patients

Most patients with complement deficiencies can expect to become productive adults if they are recognized as having the deficiency and treated early and vigorously.