# Defects of the Complement System

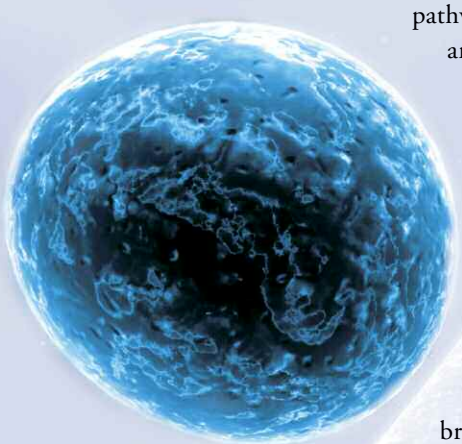
Missing or reduced elements of the complement system, a complex and essential part of the innate immune system, cause recurrent bacterial infections and predispose individuals to autoimmune disorders.

By Bob Geng, MD

**THE COMPLEMENT SYSTEM** is an essential part of our body's defense against infections. It helps the cells in our immune system to better recognize and capture bacteria, and can also lead to direct elimination of bacteria by destroying its cell membrane. There are many components to the complement system, and three distinct pathways in which it can be activated. In addition to its components, many regulatory proteins are involved in ensuring the normal functioning of the complement system.

Complement proteins are made in the liver and circulate in the bloodstream. They can be activated spontaneously (alternative pathway), by the molecules on the surfaces of pathogens directly (lectin pathway) or by the antibodies generated against specific pathogens (classical pathway). The nine main proteins involved in the classical pathway of activation are C1, C2, C3, C4, C5, C6, C7, C8 and C9. In the alternative pathway, factor B, factor D and properdin are involved in addition to components C3 and C5 through C9. In the lectin pathway, mannose-binding lectin (MBL) and mannan-binding lectin-associated protease 2 (MASP-2) are involved in addition to components C2 through C9.

Defects of the complement system are rare, but they can occur at crucial steps in each of the pathways of activation, as well as among the regulatory proteins. These deficiencies in complement components can be either inherited or acquired. This article will focus mainly on the inherited disorders, the way they may present, the method of diagnosis and treatment strategies, but it will also briefly touch on the essential aspects of acquired complement deficiencies.



## Inherited Disorders

Inherited disorders are deficient in components of the complement system. The clinical features of inherited disorders generally present as recurrent infections and/or autoimmune disorders. Infections include respiratory tract illnesses (sinusitis, bronchitis, pneumonia), meningitis and, in severe cases, sepsis. The bacteria involved are generally Streptococcus pneumonia, Haemophilus influenza type B and Neisseria meningitidis. The main autoimmune syndrome associated with inherited disorders is systemic lupus erythematosus (lupus). Lupus symptoms include joint pains, rash, fevers and various organ dysfunctions (lung, kidney, central nervous system, etc.).

Disorders in the classical pathway can include defects in the production of any component of the complement system. Deficiencies of components C1 through C4 can present with autoimmune complications and/or recurrent bacterial infections. The most common C1 disorder is C1q deficiency. C1q is one of the subcomponents of C1. C2 deficiency can be either partial or complete. Complete C2 deficiency is sometimes seen with IgG subclass deficiencies, as well as in conjunction with other autoimmune disorders. Partial C2 deficiency does not appear to have any clinical significance in most people. Complete C3 deficiency can lead to severe recurrent infections, as well as autoimmunity, but partial C3 deficiency does not appear to have any clinical significance. Deficiencies in the regulatory proteins factor H and/or factor I can lead to a secondary C3 deficiency. Total C4 deficiency often presents with early-onset lupus, and partial C4 deficiency can also predispose patients to the development of lupus. Often in cases of lupus, it can be difficult to discern whether a low C4 level is due to inherent deficiency in C4 or to increased amount of consumption secondary to the buildup of immune complexes as part of the disease process of lupus.

The components C5 through C9 form the membrane attack complex (MAC) that leads to direct destruction of bacteria. Deficiencies in any one of these components can predispose individuals to develop recurrent infections to Neisseria species. In the U.S., C5, C6 and C8 deficiencies are the most common among all MAC defects. C9 deficiency is most often seen in Japanese patients, and tends to be less severe than deficiencies in any of the other elements of the MAC because bacteria can still be destroyed by the components C5 through C8.

Assessment of the classical pathway function should always begin with an assay of the CH50 (total hemolytic complement), which measures the ability of a patient's serum to destroy sheep red blood cells. The

value reported indicates the degree of dilution of the patient's serum that can still destroy 50 percent of the sheep red blood cells. An elevated CH50 indicates high level of activity of the classical pathway of the complement system, but does not have any specific clinical meaning except suggesting the presence of active inflammation and immune activation. An undetectable CH50 can indicate the complete deficiency of any component of the system. However, given the fact that cell lysis (a process in which a cell is broken down or destroyed as a result of some external force or condition) can still occur without C9, even a complete deficiency of C9 may yield only a low but still detectable CH50 measurement. If the CH50 is low, then measurements of specific components can be performed. If the initial CH50 is low, the first thing to do is to repeat the test to rule out the possibility of an error from poor handling of the serum specimen since the CH50 can be reduced after prolonged exposure to room temperature.

*The clinical features of inherited complement disorders generally present as recurrent infections and/or autoimmune disorders.*

Defects of the alternative pathway are extraordinarily rare. The most common defect of the alternative pathway is Properdin deficiency, which is an X-linked disorder (the gene only occurs on the X chromosome) that affects only males. Fewer than five cases have been reported for deficiency in factor D, and there is one reported case of factor B deficiency. Alternative pathway defects present with recurrent respiratory tract infections, meningitis and/or sepsis secondary to Streptococcus pneumonia or Neisserial species. Unlike the assessment of the classical pathway, the alternative pathway can be assessed by an assay called the AH50, which is not commonly available. If the AH50 is very low, then possibility of Properdin, factor B and factor D deficiency should be considered.

Management of patients with classical and alternative pathway defects requires persistent vigilance for infections, early initiation of antibiotics and adequate vaccinations. Patients should be taught to recognize early warning signs of severe infection such as stiff neck, rash, fevers, severe respiratory tract symptoms, etc. They need to seek medical attention right away from professionals who understand the significance of these disorders. Patients should receive all necessary vaccines, and are not at higher risk of developing adverse reactions from live viral vaccines. Complement deficient patients need to be vaccinated against the encapsulated bacteria such as Streptococcus pneumonia, Haemophilus influenza B and Neisseria meningitidis because they are at a higher risk of developing recurrent infections to these organisms. However, when these patients receive vaccines, they should be given protein-conjugated (i.e., Prevnar) rather than purely polysaccharide vaccines (i.e., Pneumovax) in order to mount a more robust immune response. Plasma replacement therapy is rarely done for complement deficient patients mainly because it is not practical and carries an increased risk of transmitting bloodborne illnesses. There is very limited experience or evidence of success, and it is currently not part of the standard of care.

The most common defect in the lectin pathway of complement activation is deficiency in MBL, a protein that attaches onto the surface of bacteria and triggers the activation of the complement cascade. MBL levels can be directly measured and are generally defined as being deficient when the level in the blood is lower than 500ng/ml. In many individuals, MBL deficiency is asymptomatic (since the other pathways of complement activation are still intact), but in some people, it can lead to recurrent bacterial infections. However, deficiency in MBL can predispose individuals to develop more severe symptoms if they have chronic inflammatory conditions. In addition, MBL deficiency in addition to another known defect of the immune system can lead to more severe and frequent bacterial infections. Both recombinant (synthetically made) and plasma-derived MBL products are commercially available, but are still currently under research investigation as a form of replacement therapy. The most likely indication for this investigational therapy may be patients diagnosed with MBL deficiency plus another known defect of the immune system who are suffering from severe acute bacterial infections.

## Acquired Disorders

Some patients acquire complement deficiency as a consequence of another illness. There are a series of conditions that can lead to acquired disorders of the complement system. The

most common cause of acquired complement deficiency is lupus, which in half of all cases will result in a reduced level of C2, C3 and C4. Lupus is a disease associated with an increased amount of immune complex formation (antibody-antigen complexes), which accelerates the consumption of complement factors. Another condition associated with an increased amount of immune complex buildup is cryoglobulinemia. Cryoglobulins are proteins in the blood that will precipitate (separate out) at temperatures cooler than normal body temperature. Cryoglobulinemia can be a result of chronic viral hepatitis infection or can occur without any identifiable cause. Complement deficiency from cryoglobulinemia generally present with low C2 and C4 levels without a significant decrease in C3 levels.

Another acquired condition that leads to complement deficiency is the development of an autoantibody (an abnormal antibody that recognizes and targets normal elements in the body) called C3 nephritic factor, which leads to an overactivation and excessive consumption of C3. This condition leads to low C3, low factor B and low AH50, all of which indicate an alternative pathway defect. Since the classical pathway is not affected, the C4 level is usually normal. The presence of C3 nephritic factor often leads to the development of membranoproliferative glomerulonephritis (a severe form of kidney disease) during childhood, as well as an increased number of bacterial infections.

Since all complement proteins are made in the liver, severe liver disease can lead to a decreased production of those complement proteins resulting in lower levels in the blood. In patients with alcoholic liver disease, C3 and C4 levels may be reduced. However, liver disease would have to be quite advanced before seeing appreciably lower complement levels in the blood, so other conditions need to be considered for significantly low levels in patients with mild liver dysfunction.

## Disorders of Regulatory Proteins

Regulatory proteins help activate and control the complement system. Defects in C1 inhibitor, factor H, factor I, CD55 (decay accelerating factor) and CD59 have been associated with human disease.

The deficiency of C1 inhibitor level or function leads to the development of hereditary angioedema (HAE). The extensive review of HAE, including its diagnosis, pathogenesis and treatment is beyond the scope of this article. In addition to C1 inhibitor being involved in the complement system, it is also involved in the kinin pathway that regulates the production of a potent vasodilator called bradykinin. Deficient level or function of C1 inhibitor ultimately leads to an excessive amount of production of bradykinin, which in turn leads to severe swelling. The swelling can occur in the extremities, on the face, the lips, tongue, throat or abdomen. A bradykinin-mediated angioedema is not associated with any hives, and does not respond to antihistamines, steroids or epinephrine. HAE can be treated either acutely or prophylactically by plasma-derived C1 inhibitor replacement therapy (Berinert or Cinryze, respectively). Antifibrinolytics and androgens were used more commonly for HAE in the past, but due to the rise of newer and more efficacious drugs, they are less commonly used today. For acute treatment of attacks, direct bradykinin receptor blockers (Icatibant) and kallikrein inhibitor (Ecallantide) have been shown to be efficacious in the treatment of HAE.

Factor H and I are elements that control and regulate the activation of C3. Therefore, if there is a complete deficiency (homozygous deficiency) in either one of these factors, an excessive amount of C3 would be consumed via the alternative pathway, and those patients would present similar to patients who have a C3 deficiency. The most common symptoms are recurrent bacterial infections. Partial deficiency (heterozygous deficiency) would predispose individuals to develop nondiarrheal hemolytic uremic syndrome, the HELLP syndrome (a pregnancy-related condition that is associated with kidney injury, anemia, low platelets and high liver enzymes) and age-related macular degeneration.

The cell surface proteins CD55 and CD59 protect our own blood cells from being damaged by the complement system. They block the activation of C3 and prevent the assembly of the C5 to C9 membrane attack complex from injuring our own cells. However, when someone is deficient in either one of those cell surface proteins, the complement system is no longer inhibited, which results in the destruction of the cell. Red blood cells are particularly vulnerable to this deficiency, which is why the main disease that results from this condition is paroxysmal nocturnal hemoglobinuria (PNH). In PNH, episodes of uncontrolled destruction of red blood cell occurs leading to significant anemia and to the presence of hemoglobin (the oxygen binding molecule in red cells) in the urine. Furthermore, PNH can predispose individuals to the development of low platelet counts and blood clots in the veins. Blood transfusions are important to prevent the anemia from becoming dangerous for patients, and oral steroids can be effective on an episodic basis to decrease the amount of red cell destruction, but long-term use of steroids is not advised due to the significant amount of side effects. In addition to blood transfusions and close monitoring of the blood cell counts, there is a targeted treatment medication called Eculizumab that has been shown to be effective. Eculizumab is a monoclonal antibody that targets C5 and prevents the initiation of the membrane attack complex, therefore preventing the destruction of the cell. Clinical studies of Eculizumab have shown that it is a safe treatment, and that it has significantly decreased the amount of red cell destruction and prevents the development of venous blood clots.

## An Essential Part of the Immune System

The complement system is an essential part of the innate immune system that protects against recurrent infections. A normal complement system also regulates the process of inflammation in the body. It is a complex system that can malfunction when any particular component of the system is missing or reduced. When it malfunctions, individuals become vulnerable to not only bacterial infections, but also become predisposed to the development of autoimmune diseases. Complement disorders are rare and complex. Improving education about them will help increase awareness, as well as result in better care for patients.

**BOB GENG**, MD, MA, studied medicine at Washington University School of Medicine in St. Louis, where he also completed his residency training in internal medicine. He is currently a third-year fellow in allergy and immunology at UCLA Medical Center. Dr. Geng received his bachelor and master of arts in Georgetown University's School of Foreign Service.

### References

1. Wen, L, Atkinson, JP, Giclas, PC. Clinical and laboratory evaluation of complement deficiency. *J Allergy Clin Immunol*, 2004;113(4):585.
2. Liszewski, MK, Atkinson, JP. Inherited disorders of the complement system. *Uptodate*, August 2014.
3. Sullivan, KE, Winkelstein, JA. Chapter 21: "Deficiencies of the Complement System." Editors Stiehm, ER, Ochs, HD, Winkelstein, JA. *Immunologic Disorders in Infants & Children 5th Edition*. Elsevier. Philadephia, 2004; pages 652-683.