

Complement
deficiency

Complement deficiency

hello@piduk.org
0800 987 8986
www.piduk.org

About this booklet

This booklet provides information on complement deficiency. It has been produced by the PID UK Medical Advisory Panel and Patient Representative Panel to help answer the questions patients and their families may have about this condition but should not replace advice from a clinical immunologist.

Contents

Summary	3
What is a complement deficiency?	3
What causes complement deficiency?	4
What are the signs and symptoms?	5
How is complement deficiency diagnosed?	6
Associated health complications	6
Treatment	7
Immunisation	7
Glossary of terms	8

Summary

Complement is a group of more than 30 different proteins that are involved in a biochemical pathway, called the complement pathway. This pathway plays a critical role in inflammation, which serves as a defence against some bacterial and viral infections. The term complement deficiency is used when proteins are missing or do not function properly.

Complement deficiencies are rare and will cause people to have different symptoms depending on which complement protein is affected. Most complement deficiencies have a genetic cause and family members of those affected may need to be tested.

Treatments for complement deficiency depend on the complement protein affected. People who are more susceptible to bacterial infections might need to take daily antibiotics and be vaccinated to improve their protection against specific infections.

What is a complement deficiency?

Complement is the term used to describe a group of over 30 proteins that kill micro-organisms and assist other cells of the immune system to fight infection. Complement proteins also play an important role in inflammation.

Complement proteins are made mainly in the liver and then secreted into the blood. They are numbered C1 to C9, and there are other supporting proteins that are also considered to be complement proteins (e.g. C1 inhibitor, properdin, factor B, factor D, factor H and factor I).

The proteins form part of a tightly regulated pathway that is designed to kill invading microbes whilst limiting damage to other body tissues. When the complement proteins encounter bacteria, a virus, an immune complex, damaged tissue or other substance not usually present in the body, the complement proteins become 'activated' and act in a coordinated way. This activation is often referred to as a cascade reaction and is likened to the falling of a row of dominoes because the process must occur in a specific order.

Complement deficiency results when any of the proteins that make up the complement pathway are missing or do not work properly. Because each protein has a different role in the pathway, each complement deficiency has different symptoms and treatments.

Cells of the immune system



Complement system

Innate immunity

- Marking pathogens for destruction (opsonization)
- Breaking them down (lysis)
- Inflammation
- Cell activation

Disposal system

- Clearing of immune complexes and dying cells

Adaptive immunity

- Enhancing antibody responses
- Promoting T-cell responses
- Eliminating self-reactive B-cells
- Enhancing immunological memory

The complement system acts on different cells of the immune system to ensure the effective elimination of infectious microorganisms.

What causes complement deficiency?

Most complement deficiencies have a genetic cause. They are often inherited (passed down between generations) but can arise for the first time in an affected individual. People with genetic causes of complement deficiencies have DNA that does not enable a working form of the affected protein to be made. The way in which complement deficiencies are inherited is complex, so speak to your doctor if you have any questions.

In some medical conditions, such as infection, blood cancers and autoimmune conditions, and some types of kidney problems, complement proteins can be 'used up' and their levels become low. These conditions are referred to as acquired complement deficiencies.

What are the signs and symptoms?

The signs and symptoms depend on the type of complement deficiency, as changes in different complement proteins can have very different symptoms.

Low levels of mannose-binding lectin (MBL) are common, and patients often do not have any symptoms. By itself, a low level of MBL does not cause a major immunodeficiency. See our separate booklet on MBL deficiency.

C1 inhibitor deficiency includes the conditions hereditary angioedema (HAE) and acquired angioedema. C1 inhibitor is a protein that helps to regulate the complement pathway and regulates production of a chemical called bradykinin. People with reduced C1 inhibitor may have high levels of bradykinin, which can cause tissue swellings called angioedema. They may also get episodes of severe abdominal pain caused by swelling of the gut. The organisation HAE UK offers support and advice on the symptoms, management and treatment of C1 inhibitor deficiencies.

People with defects in proteins in the early parts of the complement pathway (proteins C1-C4) may be more likely to develop autoimmune diseases, such as systemic lupus erythematosus (also called lupus, or SLE). They may also be susceptible to infections with encapsulated bacteria, such as pneumococcal and neisseria species, that can cause severe infections, including pneumonia and meningitis. Low but not absent C4 is very common and is not usually associated with any major health problems. Antibodies against C3 or C4 can occur and are called nephritic factors because they are associated with kidney disease.

People with defects in proteins in the later parts of the complement pathway (proteins C5-C9) are also susceptible to infection with encapsulated bacteria (bacteria that are surrounded by a coating that helps protect them and evade immune responses).

When complement factors B or D are reduced, this may predispose those affected to recurrent infection. Rarely, changes that lead to over-activity of factor B and factor D may cause a disorder called atypical haemolytic uraemic syndrome (aHUS), characterised by excessive destruction of red blood cells. Factor H and factor I genetic mutations can also cause this disorder.

Sometimes people may have complement abnormalities detected on blood tests before they have any symptoms.

How is complement deficiency diagnosed?

Complement deficiencies are usually diagnosed by performing special blood tests in people who have symptoms of disease. Sometimes these blood tests have to be repeated to make sure the result is accurate. Complement proteins are often reduced due to infection or because the blood sample didn't get to the lab quickly enough. The results may also be confirmed by genetic testing. Sometimes relatives of people affected are also tested for the condition.

Associated health complications

People with reduced C1 inhibitor may have tissue swellings.

People with defects in the early complement pathways are more likely to get autoimmune conditions, such as SLE.

People with certain complement deficiencies are susceptible to infections caused by encapsulated bacteria.

People with blood cancers, such as lymphoma, may get acquired complement deficiencies, although this is very rare.

The table below summarises the health problems associated with complement deficiency.

Complement deficiency	Health complication
Deficiencies of early C components (C1, C2, C4)	Systemic lupus erythematosus (SLE), including the neonatal onset form in C1q deficiency
	Glomerulonephritis - inflammation of the kidney's blood vessels
	Polymyositis - inflammation of the muscles
C1 inhibitor	Hereditary angioedema
C3 and factor B	Severe bacterial infections
Factor I, C6 and C8	Severe neisserial infections

Treatment

Treatment depends on the type of complement deficiency. C1 inhibitor deficiencies may be treated by a range of different medications, including C1 inhibitor replacement, Lanadelumab; tranexamic acid; hormones; and drugs such as icatibant that block the action of bradykinin. People with these conditions need to avoid particular drugs for blood pressure (ACE inhibitors). Medications that contain oestrogen, such as some contraceptives, can make the condition worse. The support group HAE UK has information on all the treatments available to patients affected by C1 deficiency.

If patients have autoimmune conditions, such as SLE, they may need to be treated with steroids and other immunosuppressants.

If patients are more susceptible to bacterial infections, they might need to take daily antibiotics and be vaccinated to improve their protection against specific infections. They should seek medical advice early if they are unwell. This is because, if they get an infection, it can progress rapidly, with fewer signs than in people with normal complement function.

Immunisation

Patients with complement deficiencies can usually have all vaccines without any problems. Vaccination is an important part of protecting patients with certain complement deficiencies. If you have a complement deficiency, you should check with your doctor before taking live vaccines, such as the MMR vaccine or the yellow fever vaccine, especially if you are on immune-suppressive drugs. If you are travelling abroad, you should seek advice about any vaccinations needed a few months before you travel.

'The time leading up to and just after diagnosis was awful. However, with the right medicine, it gets easier to deal with. If someone had told me six years ago that we would be able to travel around Asia, I wouldn't have believed them. But that's what we did last year, and Isaac continues to be a very happy child who just gets on with enjoying life.'

Mum to Isaac, who was diagnosed with C2 complement deficiency in 2013.

Support groups

PID UK is the main support organisation in the UK for anyone affected by a primary immunodeficiency disease. Call our helpline on 0800 987 8986 or visit our website at www.piduk.org

HAE UK (<http://www.haeuk.org>) offers support and expert advice to families affected by hereditary angioedema and acquired angioedema. Call them on 07975 611787 or email support@haeuk.org

Reference

European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA)
Complement Guideline: Deficiencies, Diagnosis, and Management.
Nicholas Brodzski, Ashley Frazer-Abel, Anete S. Grumach, Michael Kirschfink, Jiri Litzman, Elena Perez, Mikko R. J. Seppänen, Kathleen E. Sullivan and Stephen Jolles.
Journal of Clinical Immunology (2020) May; 40: 576–591.
<https://doi.org/10.1007/s10875-020-00754-1>

Glossary of terms

acquired angioedema - when another disease causes reduced functioning of the C1 inhibitor protein, leading to tissue swellings.

acquired complement deficiency - when another disease causes changes in the function of the complement pathway.

angioedema - the medical term for types of tissue swellings.

antibody - a type of protein that is produced by white blood cells.

atypical haemolytic uraemic syndrome (aHUS) - a condition in which red blood cells are broken down inappropriately by the complement pathway. It can cause low levels of red blood cells and kidney problems.

autoimmunity - when the body fails to recognise body tissues and damages them.

bradykinin - a hormone that causes inflammation in the body; it can cause swelling by making blood vessels leaky.

C1 inhibitor - a complement protein that inhibits the action of the protein C1. Low C1 inhibitor levels can cause episodes of swelling or abdominal pain.

complement - proteins that form a biochemical pathway to fight infections.

encapsulated bacteria - bacteria that are surrounded by a coating that helps protect them and evade immune responses.

hereditary angioedema - a genetic condition that can cause tissue swellings.

immunosuppressants - drugs that reduce the activity of the immune system.

live vaccine - a vaccine that contains a living but modified version of a bacterium or virus.

meningitis - inflammation or infection of the membrane that covers the brain.

MMR vaccine - the vaccine against the infections mumps, measles and rubella.

neisseria - a group of bacteria that cause meningitis and sepsis.

pneumococcus - a bacterium that can cause infections, including pneumonia.

systemic lupus erythematosus (SLE) - an autoimmune condition that can have a wide range of symptoms.

About Primary Immunodeficiency UK

**Primary Immunodeficiency UK
(PID UK) is a national organisation
supporting individuals and families affected
by primary immunodeficiencies (PIDs).**

We are the UK national member of the International Patient Organisation for Primary Immunodeficiencies (IPOPI), an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

Our website at www.piduk.org provides useful information on a range of conditions and topics, and explains the work we do to ensure the voice of PID patients is heard.

If we can be of any help, please contact us at hello@piduk.org or on **0800 987 8986**, where you can leave a message.

Support us by becoming a member of PID UK. It's free and easy to do via our website at www.piduk.org/register or just get in touch with us. Members get monthly newsletters.

PID UK is reliant on voluntary donations. To make a donation, please go to www.piduk.org/donate

hello@piduk.org
0800 987 8986
www.piduk.org



AmDel
Medical
A James Lyon & Co. Company