Complement Deficiencies 8

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Core Messages

- Complement plays a role in the recognition, opsonization, and killing or clearance of invading microorganisms, immune complexes and altered host cells.
- There are three main pathways of complement activation: the classical pathway (C1 dependent), the lectin route (mannan-binding lectin/ficolin and MASP dependent), in which both C4 and C2 play a role, and the alternative pathway (Factor B, D, and properdin dependent).
- MBL deficiency occurs frequently and acts as a disease-modifying factor. All other complement deficiencies are rare and result in recurrent pyogenic infections or autoimmune disease reminiscent of systemic lupus erythematosus.
- Novel assays have made the diagnosis of complement deficiencies easier.
- C1INH (C1 inhibitor) replacement therapy is available for hereditary (or acquired) angioedema (HAE), and replacement therapy is being developed for MBL (mannan-binding lectin).
- Complement-targeted therapy (e.g., C1INH, soluble CR1, antibodies against C5, C5aR antagonists) will become important in the near future for adjuvant treatment in ischemia-reperfusion injury, transplantation medicine, and inflammatory disease.

8.1 Introduction

The complement system is an important part of innate and adaptive immunity [102, 103]. This system was discovered shortly before 1900 [39], but the first complement-deficient patient was described in 1960 [107]. The human complement system consists of more than 30 proteins, which are primarily produced in the liver and circulate in general in their inactive forms. When activated, they have several important biological functions, such as the recognition, processing, presentation and retention of foreign antigens, regulation of acquired immunity, and clearance of immune complexes and cellular debris such as apoptotic cells [8, 63, 106].

The complement system is activated via the classical (CP), lectin (LP) or alternative (AP) pathways [56, 81, 102, 103] (Fig. 8.1), which are initiated by different mechanisms [17, 73, 107]. This system forms an enzymatic reaction cascade of one component activating the next, resulting in an amplification process. Most complement proteins are produced in the liver by hepatocytes and secreted in plasma constitutively or induced by inflammatory cytokines during the acute-phase response. Some proteins, like C1q, C7 and factor D, are mainly produced extra-hepatically, e.g., C1q by macrophages and factor D by adipose and renal cells. Local synthesis of complement proteins by resident or infiltrating cells is pivotal to drive inflammatory processes.

During complement activation, fragments of C4 and C3 are deposited on pathologic or senescent targets for the purpose of opsonization, i.e., covering the surface with proteins to enhance uptake and breakdown by phagocytic leukocytes. The final step of complement activation implies release of C5a, a highly potent vasoactive peptide that promotes the inflammatory reaction, and formation of the terminal C5b-9 complement complex (TCC) that leads to lysis of certain Gram-negative bacteria like *Neisseria* species.

Complement deficiencies, acquired or hereditary, have been recognized for almost all of the known components of the complement system (Table 8.1). Acquired deficiency may be caused by infection or immune-complex disorders. Most inherited deficiencies of complement components are expressed in autosomal recessive patterns, whereas properdin deficiency is X linked [36]. The gene defects may give rise to a dysfunctional protein or to complete absence of the protein.

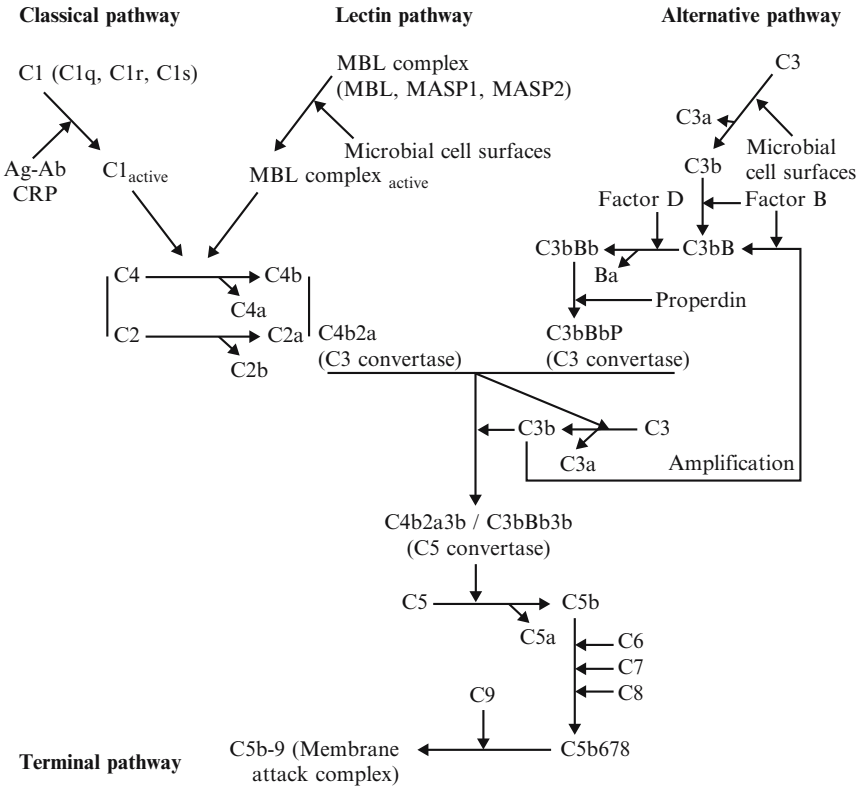

Fig. 8.1 Complement activation pathways

Parents of patients with complete deficiency of a complement component usually show heterozygous conditions, resulting in approximately half-normal levels of the protein [17, 106], and family studies are necessary to identify other affected family members [35].

Most of the inherited deficiencies are uncommon, but there are diverse ethnic and geographical influences on the prevalence of these deficiencies [17, 24, 25, 77, 92, 108]. For example, C9 deficiency is the most common complement deficiency in Japan, where it may occur in up to 0.1% of the population [30, 43], while it is rare in Western countries. On the other hand, C2 deficiency has a frequency of 0.01% in the USA, but it is unreported in Japan [24].

It is estimated that the prevalence of a hereditary complete complement component deficiency is 0.03% in the general population, excluding deficiency of mannan-binding lectin (MBL), which might be present in the homozygous form in as many as 3% of people [63].

Primary complement deficiencies are in particular associated with increased susceptibility to recurrent and invasive infections and with autoimmune disorders [25, 35]. Deficiency of C1 inhibitor (C1INH), the main inhibitor of the classical and lectin pathways of complement activation, leads to angioedema.

Patients with a deficiency of an early complement component in any of the activation pathways, which leads to decreased activation of C3, often manifest with recurrent pyogenic infections, principally with encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenza* type-b, because opsonization followed by phagocytosis is the main host defense against these organisms [35]. For deficiencies of terminal complement components (C5-9), recurrent systemic neisserial infection is the dominant manifestation, because clearance of these bacteria depends on C5b-9-mediated lysis [8, 93].

Autoimmune, systemic lupus erythematosus (SLE)-like diseases are associated with deficiencies of many complement components, but are typically seen with classical pathway component deficiencies, in particular with C1q deficiency [93].

Although complement deficiencies are uncommon in the general population, individuals with such deficiencies frequently suffer from serious diseases. Therefore, patients with recurrent or invasive bacterial infections, certain kidney diseases, familiar

Table 8.1 Characteristics of primary complement deficiencies

Complement components	Deficiency[a]	Gene	Inheritance	Associated features
Classical pathway	C1q	*C1Q*	AR	SLE, Rheumatoid disease, Infections
	C1r	*C1R*	AR	SLE, Rheumatoid disease, Infections
	C1s	*C1S*	AR	SLE, Rheumatoid disease, Infections
	C4	*C4A, C4B*	AR	SLE, Rheumatoid disease, Infections
	C2	*C2*	AR	SLE, Vasculitis, Polymyositis, Infections
Lectin pathway	MBL	*MBL2*	AR	Pyogenic infections
	MASP2	*MASP2*	AR	Pyogenic infections, SLE
Alternative pathway	Factor D	*CFD*	AR	Neisserial infections
	Properdin	*PFC*	XL	Neisserial infections
C3	C3	*C3*	AR	Recurrent pyogenic infections, Glomerulonephritis
Terminal pathway (Membrane attack complex)	C5	*C5*	AR	Neisserial infections, SLE
	C6	*C6*	AR	Neisserial infections, SLE
	C7	*C7*	AR	Neisserial infections, SLE, Vasculitis
	C8a	*C8α*	AR	Neisserial infections, SLE
	C8b	*C8β*	AR	Neisserial infections, SLE
	C9	*C9*	AR	Neisserial infections, SLE
Regulatory proteins	C1 inhibitor	*C1INH*	AD	Hereditary angioedema
	Factor I	*CFI*	AR	Recurrent pyogenic infections
	Factor H	*CFH*	AR	Hemolytic-uremic syndrome, Membranoproliferative glomerulonephritis[b]
	CD46	*CD46 (MCP)*	AR	Hemolytic-uremic syndrome, Glomerulonephritis
	CD55	*CD55*	AR	Inab blood group phenotype
	CD59	*CD59*	AR	Hemolysis pyogenic infections
	CD18	*ITGB2*	AR	Necrotic lesions, Omphalitis; Leukocyte adhesion deficiency type 1 (see Sect. 4.4 for more details)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked, *MBL* mannan-binding lectin, *MASP2* MBL-associated serine protease-2, *SLE* systemic lupus erythematosus
[a]Deficiency implies both complete genetic deficiency and genetic variants (polymorphisms) that predispose to the associated features
[b]Similar manifestations are seen with genetic variants of factor I, CD46, CD55, factor B, and C3

autoimmune features or angioedema should be tested for complement deficiencies [106].

Screening tests for complement component deficiency have traditionally included functional hemolytic tests for the classical (CH50 test) and alternative pathways (AH50 test, also called AP50 test). Low levels of CH50 or AH50 necessitate additional evaluation. If both CH50 and AH50 are low or absent, one or more of the terminal components (C5, C6, C7, C8, and C9) are missing. If the CH50 is low or absent but the AH50 is normal, a classical pathway component is missing, whereas if the AH50 is low or absent but the CH50 is normal, an AP component is missing [106].

Recently, a novel enzyme-linked immunosorbent assay (ELISA) has been developed for separately revealing deficiencies of CP (classical) LP (Lectin) or AP (alternative) pathways components [89]. This is a functional assay based on selective binding of CP

components to IgM, LP components to mannan and AP components to lipopolysaccharide (LPS). The read-out is common for the three pathways, namely detection of binding and activation of C9. From this functional complement screening test it can be deduced which components might be deficient; e.g., a MBL defect will be revealed by a low LP activity, a C2 defect will show low activity in both CP and LP, C3 or C5-C9 deficiencies will result in low activity in all three pathways. An advantage with this screening system is that properdin deficiencies consistently show low AP activity, which is not always the case for the hemolytic AH50 assay.

Measurement of the fragments formed during the enzymatic reaction cascade is another useful technique for evaluating the complement system activity [80]. C4a and C4d are used for determination of CP or LP activation, Bb is measured for evaluating AP activation, and C3a, iC3b, C5a, and soluble C5b-9 can be used to determine terminal pathway activation [106].

Individual components of the complement system can be measured by immunochemical methods, including immunoprecipitation assays such as nephelometry, radial immunodiffusion, radioimmunoassay (RIA), and ELISA techniques [106]. In certain cases, functional assays are required for further evaluation, despite the presence of normal amounts of component protein detected by immunochemical assays [74].

Although definite managements for complement deficiencies are restricted, most complement-deficient patients would undoubtedly benefit from a correct diagnosis [93]. In the case of C1INH deficiency, it is crucially important to make the diagnosis, since this is a potentially life-threatening disease that can be effectively treated.

If a complement deficiency is identified, management focuses on the associated disease, such as infection or autoimmunity. Prevention of infections by vaccination and immediate treatment with appropriate antibiotics are incredibly important. In some of these patients, antibiotic prophylaxis might be considered, and special attention should be given to vaccination against encapsulated organisms such as *Streptococcus pneumoniae, Haemophilus influenzae* and *Neisseria* species. Also, early recognition and management of autoimmune diseases are necessary [17, 106]. In the case of C1INH deficiency, prophylactic treatment with danazol is indicated, as well as acute treatment with C1INH concentrate. In atypical hemolytic uremic syndrome, plasma replacement may be considered.

8.2 Deficiencies of Classical Pathway Components *(C1q/C1r/C1s Deficiencies, C4 Deficiency, C2 Deficiency)*

8.2.1 Definition

The classical pathway (CP) is typically activated by immune complexes that contain immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies (subclasses IgG1, IgG2, and IgG3) bound to the antigen, but may also be initiated by other agents, such as C-reactive protein (Fig. 8.1). C1 is composed of three subunits: C1q, C1r, and C1s. C1q must bind to two adjacent Fc regions of antibodies (CH2 domain of IgG and CH3 domain of IgM) in an immune complex to initiate the complement cascade. The binding of C1q to an immune complex leads to enzymatic activation of the serine protease C1r, which then cleaves and activates the serine protease C1s [16, 33, 88]. C1s cleaves C4 into C4a and C4b, and C4b forms covalent linkages with the immune complex (e.g., a cell coated with antibodies). C2 attaches to the immune complex or to C4b bound to the cell surface, and then C1s cleaves C2 into C2a and C2b. The C2a and C4b on the target cell surface form the classical pathway C3 convertase (C4bC2a) that cleaves C3 into C3a and C3b. C3b deposits on the target, where it serves as an opsonin (capable of binding to the CR1 receptor on phagocytes) or is further cleaved to iC3b as another opsonin (capable of binding to the CR3 receptor on phagocytes). Moreover, C3b also interacts with C4bC2a to form the C5 convertase [52]. All three complement activation pathways (CP, LP and AP) share the same terminal C5-C9 activation sequence (Fig. 8.1).

Complement activation via the classical pathway effectively opsonizes antibody-coated pyogenic bacteria such as encapsulated *Streptococcus pneumoniae* and *Haemophilus influenzae* strains, as well as other cells coated with antibodies. Furthermore, C1q is particularly important for clearance of apoptotic cells, thereby contributing to tissue homeostasis and renewal. A defect in this mechanism predisposes to SLE-like disease.

8.2.2 Etiology

Classical pathway deficiencies (C1, C4, and C2) are inherited in an autosomal recessive pattern. The genetics

of C1 and C4 deficiency are complex, involving multiple genes for each component. C1q [encoded by *C1Q* (OMIM*20550, +120570, *120575)], C1r [encoded by *C1R* (OMIM+216950)], and C1s [encoded by *C1S* (OMIM+120580)] are required for C1 function; thus, if any one subunit is missing, the complex cannot form.

C4 exists in humans in two forms, C4A (acidic) and C4B (basic), encoded by different, coexisting genes [*C4A* (OMIM+120810) and *C4B* (OMIM*120820)] [109], so all four alleles must be deleted or defective to give total C4 deficiency. Moreover, both genes may be present in multiple copies and contain numerous polymorphisms.

C2 deficiency (*C2,* OMIM+217000) is the most common homozygous CP component deficiency, with an incidence of 1 case per 10,000–20,000 individuals [71, 76, 97]. However, the incidence of C2 deficiency in patients with rheumatologic disorders, such as SLE, is much higher and approaches 1%. [4, 44]. The female-to-male ratio is approximately 1 to 1 in C1q or C4 deficiency, but is 7 to 1 in C2 deficiency [77].

8.2.3 Clinical Manifestations

Deficiency of an early CP component (C1, C4, or C2) usually does not predispose patients to severe infections, as is observed in patients with a deficiency of properdin, C3, or a terminal component. Patients with a CP component deficiency may present with mild infections, which is common in patients with C2 deficiency [22, 25], but more frequently they develop autoimmune syndromes, particularly SLE [8, 12, 66, 75, 76, 98, 104, 106]. Increased prevalence of atherosclerosis and cardiac diseases has also been reported for C2 deficiency [45].

The incidence of SLE in patients with CP component deficiency is 90% for C1q, 75% for C4, 55% for C1r and C1s (deficiency usually involves both C1r and C1s) and 20% for C2 deficiency [71, 77, 97]. Thus, individuals with total deficiency of C1q have the highest occurrence of SLE and the most severe manifestation of the disease [65]. Partial C4 deficiency is also associated with SLE, and 15% of patients with SLE display C4A deficiency [5, 7].

In patients with CP component deficiency, in particular C1q, clearance of immune complexes and apoptotic cells is impaired, which might explain the development of SLE in these patients [13, 77].

8.2.4 Diagnosis

The traditional CH50 assay, based on hemolysis of sensitized sheep erythrocytes, or the novel ELISA screening assay for all pathways [89], can be used to detect CP deficiency. Absence or decrease of CH50 in the presence of normal AH50 means that at least one of the early components of CP is missing or low [78]. Complete deficiencies of C1q, C1r or C1s will give a low CP activity, but a normal LP and AP activity in the ELISA screening test. Complete deficiency of C4 or C2 will give low CP and LP activity, whereas AP activity will be normal.

Identification of the missing component follows from recovery of complement activity in either of these tests after addition of a purified component and by immunochemical tests or gene sequencing of the component in question.

Specific components of the CP (C1q, C1r, C1s, C2 and C4) can be evaluated by functional and immunochemical tests. Also, C4a and C4d are measured for determination of CP activation [106].

8.2.5 Management

Treatment of patients with complement deficiencies is based on their manifestations. Identification and management of autoimmune diseases in patients with deficiencies of the early components of CP are necessary. Also, recurrent infections in these patients should be managed with appropriate antibiotic therapy and vaccination [17, 106].

8.3 Deficiencies of Lectin Pathway Components *(MBL Deficiency, MASP2 Deficiency)*

8.3.1 Definition

The lectin pathway (LP) (Fig. 8.1) functions like the CP, but in this pathway certain lectins [e.g., mannan-binding lectin (MBL, encoded by *MBL2*, OMIM*154545) and ficolins] bind to a carbohydrate moiety on microorganisms instead of antibody binding to a microbial antigen [42, 47]. Then the MBL-associated serine protease-2, MASP2 [encoded

by *MASP2* (OMIM*605102)] and probably MASP1 (encoded by *MASP1)*, which are analogous to C1r and C1s, cleave C2 and C4, forming C3 convertase (C4bC2b). The terminal components of complement are then activated as in CP [8, 61, 73].

8.3.2 Etiology

MBL deficiency is common, with a 5% frequency in the homozygous form in the general population (MBL <100 ng/ml) and with 30% of the population carrying variant alleles with correspondingly reduced MBL concentration (<400 ng/ml) [63]. Thus, MBL deficiency is one of the most common protein deficiencies described in humans. Recently, it was claimed that this genetic evolution represent heterosis, implying that there is an advantage of being heterozygous [37]. Thus, a complete deficiency might increase infection susceptibility, whereas high levels of the protein may lead to host tissue damage caused by excessive complement activation ("the double-edged sword").

8.3.3 Clinical Manifestations

Deficiency of MBL has been related to an increased frequency of pyogenic infections, including pneumococcal infection and sepsis, particularly in children and neonates. This may be explained by the "window" period from 6–18 months of life, in which antibodies from the mother have disappeared and those of the child are still insufficient, and therefore immune defense is reduced. Normally, MBL deficiency is not associated with an increased incidence of infections, but MBL may be of importance as a redundancy protein in immunosuppressed patients, e.g., those treated with cytostatics or irradiation for malignancy or after HIV (human immunodeficiency virus) infection. MASP2 deficiency has recently been reported and may present with increased susceptibility to infection or autoimmunity [96]. A deficiency in LP may lead to autoimmune diseases [77], but may also modify the progress of a disease to be more benign, as seen in rheumatoid arthritis patients [32], or to be more serious, as seen in cystic fibrosis [31]. A 2- to 3-fold increased incidence in MBL deficiency has been reported in patients with SLE [48]. Some studies have shown that MBL deficiency is related to cardiovascular disease, in which a deficiency might be either beneficial or detrimental [69, 86]. Thus, at present, hardly any conclusions can be drawn with respect to the clinical consequences of being MBL-deficient.

8.3.4 Diagnosis

The activity of the MBL pathway can be assessed with the screening ELISA [89]. MBL deficiency and MASP2 deficiency will cause low LP activity, whereas CP and AP activities will be normal. A functional assay of MBL binding and capacity to activate C4 has also been described, in which the amount and function of later complement components are not of importance [74]. Further analysis includes immunochemical quantitation of MBL and genotyping of MBL and MASP2.

8.3.5 Management

Patients with recurrent infections may benefit from antibiotic prophylaxis and immunization with polyvalent pneumococcal vaccine [106]. Purified MBL for therapeutic use as substitution therapy is under development [100], but the indication for such treatment is at the moment unclear.

8.4 Deficiencies of Alternative Pathway Components (*Factor D Deficiency, Properdin Deficiency*)

8.4.1 Definition

The alternative pathway (AP), which plays an important role in innate immune defense, is a spontaneously activating system that does not require a trigger, an antigen-antibody complex or a lectin [8, 51]. C3 in plasma is continuously cleaved at a low rate (C3 tick-over), and the AP is initiated by the formation of $C3(H_2O)$ (Fig. 8.1) [72]. The C3 convertase is initiated when factor B binds to $C3(H_2O)$. Then factor D, itself always active, cleaves factor B to produce the first AP C3 convertase $C3(H_2O)Bb$, which cleaves C3 into C3a and C3b. If C3b binds to a cell surface that lacks complement regulators, it

results in rapid activation of the complement cascade. C3b binding to factor B, followed by cleavage by factor D, generates the second C3 convertase C3bBb. Properdin stabilizes the C3bBb complex. This complex may activate many C3 molecules, which can combine with factor B, be activated by factor D and thus form additional C3 convertases. In this way, amplification of complement activation can occur, not only from the AP, but also from the CP and the LP. After the C3 convertase cleaves another C3 bound to the convertase, C3b combines with the C3 convertase complex to form the AP C5 convertase, thus activating the terminal pathway as in CP and LP [1, 3, 101, 106]. The AP and the amplification loop are controlled by the action of inhibitory proteins present on membranes and in plasma [1, 3, 54, 101, 106]. Recently, it was shown that properdin, the only known positive regulator of complement activation, may also act as a recognition molecule for lipopolysaccharide and initiate AP activation [49, 94]. This may explain the increased susceptibility to neisserial infection in properdin deficiency and the fact that properdin deficiency is more easily detected in the AP functional ELISA assay than in previous hemolytic assays.

8.4.2 Etiology

Early alternative pathway deficiencies of factor D (encoded by *CFD*, OMIM*134350) and properdin (encoded by *PFC*, OMIM*300383) are rare. Total homozygous deficiency of factor D has been described [9, 95]. Properdin deficiency (OMIM#312060) is more frequently found and is the only complement deficiency that is X-linked. So far, all reported cases of properdin deficiency involve males [106].

8.4.3 Clinical Manifestations

AP component (properdin, factor D) deficiency, especially the lack of properdin, is associated with severe, fulminant infections by *Neisseria gonorrhoeae* or *Neisseria meningitides,* with a high mortality rate, and has not been associated with autoimmunity [8, 23]. In some families with properdin deficiency, invasive infections have been documented in several patients [92].

8.4.4 Diagnosis

The traditional AH50, based on the lysis of rabbit erythrocytes, has been used for screening of AP component deficiencies, but is hampered by not always detecting properdin deficiency. This problem does not occur with the ELISA screening assay [89]. A defect in AP components (factor B, factor D or properdin) will yield low AP activity with normal CP and LP activity. Alternative pathway components can be further evaluated by functional and immunochemical tests, and by gene sequencing.

8.4.5 Management

Patients with deficiencies of AP components should be vaccinated with tetravalent meningococcal vaccine, particularly important in properdin-deficient persons [93]. Early antibiotic treatment is mandatory.

8.5 Deficiency of Complement Component C3

8.5.1 Definition

C3 is the most important protein of the complement system, and its activation has an important role both in innate and in adaptive host defense [87]. Although each pathway of the complement system is activated differently, they come together at the point in which enzymatic reactions lead to the proteolytic cleavage of C3 that generates C3b and C3a. C3b is in general necessary for formation of C5 convertases, although a novel pathway of thrombin-mediated C5 activation has recently been described [40]. C3b is covalently attached to the surface of a microorganism and then acts as a ligand for complement receptors (CR1, CR3 and CR4) present on phagocytic cells [53]. This is the most important mechanism of complement defense against infection. C3a binds to its receptor (C3aR) on mast cells and basophils as an anaphylatoxin, and triggers these cells to release inflammatory mediators, such as histamine [21].

8.5.2 Etiology

C3 deficiency (*C3*, OMIM+120700) is rare and is inherited in an autosomal recessive pattern [106].

8.5.3 Clinical Manifestations

Primary and secondary deficiencies of C3 result in severe, recurrent pyogenic infections early in life, because of ineffective opsonization of pathogens [5, 15, 84]. In these patients, the infections are mainly caused by gram-negative bacteria, such as *Neisseria meningitidis, Enterobacter aerogenes, Haemophilus influenzae* and *Escherichia coli* [50]. Some patients with C3 deficiency may also develop membranoproliferative glomerulonephritis without systemic features of SLE [19, 28, 58, 71, 77, 97, 105]. Acquired C3 deficiency occurs in factor H or factor I deficiencies, or in the presence of C3 nephritic factor [106].

8.5.4 Diagnosis

C3 can be measured functionally and quantitatively. In the screening tests for complement activity, it will show reduced CP, LP and AP activity. Also, measurement of C3a, iC3b, and C5a can be used to determine C3 activation [106].

8.5.5 Management

Patients with C3 deficiency may benefit from early or prophylactic antibiotic therapy and vaccination. Also, autoimmune diseases should be identified and treated in these patients.

8.6 Deficiencies of Terminal Pathway Components *(C5-9 Deficiencies)*

8.6.1 Definition

The cleavage of C5, a process common to all three pathways, results in the products C5a and C5b [106]. The C5b formed by the convertase initiates the formation of the terminal C5b-9 complement complex (TCC) by subsequently binding C6 and C7. If there is a lipid membrane close to this event, C5b-7 will insert and subsequently engage C8 and one or more C9 molecules. This membrane complex is frequently termed the membrane attack complex (MAC) and can lyse certain microorganisms, such as *Neisseria* species, and other target cells if they are not protected by regulatory proteins [41, 52, 79]. In sublytic doses, C5b-9 will induce cell activation. If there is no lipid membrane present, C5b-7 may bind the soluble regulator proteins vitronectin and clusterin. C8 and C9 then bind to this complex to form the soluble form of TCC (sC5b-9), which can be detected as activation product in the fluid phase. C5a, generated irrespective of the fate of C5b-9, is an anaphylatoxin and a potent chemotactic factor that can trigger inflammatory cells to release their vasoactive mediators [41, 79].

8.6.2 Etiology

Terminal complement component deficiencies [*C5* (OMIM+120900), *C6* (OMIM+217050), *C7* (OMIM+217070), *C8* (OMIM+120950, +120960), and *C9* (OMIM+120940)] are inherited in an autosomal recessive fashion [106]. C9 deficiency is the most common complement deficiency in Japan, where it occurs in up to 0.1% of the population [30, 43], but it is uncommon in Western countries.

8.6.3 Clinical Manifestations

Terminal complement component deficiencies typically lead to recurrent systemic infections by *Neisseria gonorrhoeae* or *Neisseria meningitides,* because the bactericidal function of C5b-9 is important in defense against neisserial infections. The meningococcal serogroups W-135 and Y are particularly common in these patients [25, 84]. Also, some autoimmune findings have been reported in patients with deficiency of the terminal components [28, 71, 77, 97].

8.6.4 Diagnosis

In patients with terminal component deficiencies, CP, LP and AP activities are low in functional complement screening tests. Components can further be

measured by functional or immunochemical methods. C8 is made up of 3 chains that are encoded by different genes. Because C8 requires all 3 chains to be functional in the C5b-9 complex, assays that measure only the protein can be misleading, whereas the functional assay is diagnostic [106].

8.6.5 Management

Patients with terminal complement component deficiencies may benefit from vaccination with the polyvalent meningococcal vaccine, and early antibiotic treatment is essential [106].

8.7 Deficiencies of Complement Regulatory Proteins *(C1 Inhibitor Deficiency, Factor I Deficiency, Factor H Deficiency, CD46 Deficiency, CD55 Deficiency, CD59 Deficiency)*

8.7.1 Definition

Activation of the complement system is very tightly controlled through the action of complement inhibitors. Regulators control via blocking the initiation of the cascade, by preventing amplification of the C3 convertase and formation of the C5 convertase, and by inhibiting the assembly of the terminal C5b-9 complex [18, 62].

C1INH is an inhibitory protein that regulates the classical pathway by covalently attaching to $C1r_2$-$C1s_2$. Then C1INH disassembles the complex into $C1rC1s(C1INH)_2$ complexes, dissociates it from C1q and stops activation of the CP [90, 110]. If not inhibited, a single activated C1s can cleave numerous molecules of C4. Thus, deficiency of C1INH leads to uninhibited formation of C4b and C4a and, as a result, to consistently low C4 concentrations in the circulation. C1INH also blocks active sites of MASPs and so prevents excessive activation of the LP [18]. C1INH deficiency is usually regarded as a complement disease, since diagnosis is based on C1INH and C4 levels. However, the pathophysiology is caused by bradykinin release, due to lack of inhibition by C1INH of the kallikrein-kinin system.

Complement factor I is one of the most important regulators of the complement activation. It cleaves cell membrane-associated C3b into iC3b, C3d, and C3dg, and similarly cleaves C4b. Factor I requires the presence of several cofactor proteins, such as C4-binding protein (C4BP), complement factor H, complement receptor-1 (CR1) and complement membrane cofactor protein (MCP, CD46), to properly perform its regulatory functions [3, 55, 64, 101].

C4BP and factor H are potent soluble inhibitors of CP, LP and AP, respectively, by serving as cofactors for factor I. Factor H promotes conversion of C3b to iC3b by factor I and displaces Bb from the alternative pathway C3 convertase (C3bBb) [6].

C4BP regulates the CP by inhibiting the assembly of the C4bC2a complex. Decay-accelerating factor (DAF, CD55), CD46 and CR1 are membrane regulators corresponding to the fluid-phase regulators C4BP and factor H. These regulators act as inhibitors at the C4/C3 level by serving partly as cofactors for factor I and partly by dissociating the C3 and C5 convertases [57].

Complement protectin (CD59) is a cell-membrane protein that binds C8 and C9 and so prevents insertion of C8 and C9 into the C5b-9 complex, thereby protecting host cells against lysis. In the fluid phase, vitronectin and clusterin in plasma bind to C5b-7 and render the subsequent fluid-phase sC5b-9 complex water soluble [106].

Thus, excessive complement activation at the surface of tissue cells of the host is kept in check by several soluble and cell-associated regulatory proteins that are not present on microorganisms.

CD11b/CD18 (CR3) and CD11c/CD18 (CR4) are adhesion molecules present on phagocytic cells. They bind iC3b and serve as important receptors for phagocytosis of complement-opsonized particles.

8.7.2 Etiology

Hereditary C1INH deficiency (OMIM#106100) is inherited via an autosomal dominant trait [59], which affects about 1:50,000 persons [46]. More than 100 mutations in the complement component 1 inhibitor (*C1INH*) gene (OMIM*606860) have been reported in unrelated patients, and about 20% of patients represent new mutations (no family history) [11, 14, 20, 26, 68, 70]. C1INH deficiency is typically caused by heterozygous mutations, and although one recent report [10] has demonstrated homozygosity, it is generally thought that complete C1INH deficiency is incompatible with life. Deficiencies of factor I (*CFI*, OMIM*217030), factor H (*CFH*, OMIM+134370), CD46 or membrane cofactor protein (*MCP*, OMIM+120920), CD55 (*CD55*,

OMIM*125240), and CD59 (*CD59*, OMIM+107271) are inherited as autosomal recessive traits.

Uncontrolled complement activation by autoantibodies (C3-nephritic factor, C3NeF) or complete factor H deficiency may result in membranoproliferative glomerulonephritis (MPGN) type II. Heterozygous factor H, factor I, factor B or MCP (CD46) mutations are associated with atypical familial hemolytic uremic syndrome (aHUS) but rarely result in hypocomplementemia because it is the localized complement activation only that cannot be checked. In these diseases and in age-related macula degeneration, factor H and other regulatory proteins are not necessarily deficient, but can also be of certain predisposing genotypes.

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder characterized by hemolysis, cytopenias, infections, and venous thrombosis. Somatic mutations of the phosphatidylinositol glycan, class A (*PIGA*) gene (OMIM+311770) disturb lipid-anchorage of several surface membrane proteins to hematopoietic cells, among which are the complement regulatory proteins CD55 and CD59.

8.7.3 Clinical Manifestations

Deficiency of any one of these inhibitors results in extensive complement utilization, leading to an inappropriate inflammatory response, damage to self-tissue, and depletion of C3 or other components downstream of the missing control protein [106].

Heterozygous deficiency of C1INH results in hereditary angioedema (HAE) [27], which is characterized by recurrent episodes of facial (Fig. 8.2), truncal, and extremity edema that spontaneously subsides in 48–72 h [18, 27, 29]. The patients may have life-threatening laryngeal edema, and in some patients swelling of the bowel wall results in severe colicky abdominal pain, nausea, and vomiting that mimics acute abdominal syndromes [32, 48]. Symptoms usually arise spontaneously, but in some patients they may be triggered by mild trauma, drugs such as angiotensin-converting enzyme inhibitors, or possibly by psychological stress [2, 29]. Also, in HAE, chronic activation of the complement system leading to depletion of CP proteins may result in appearance of autoimmune disorders, specifically SLE [8], although

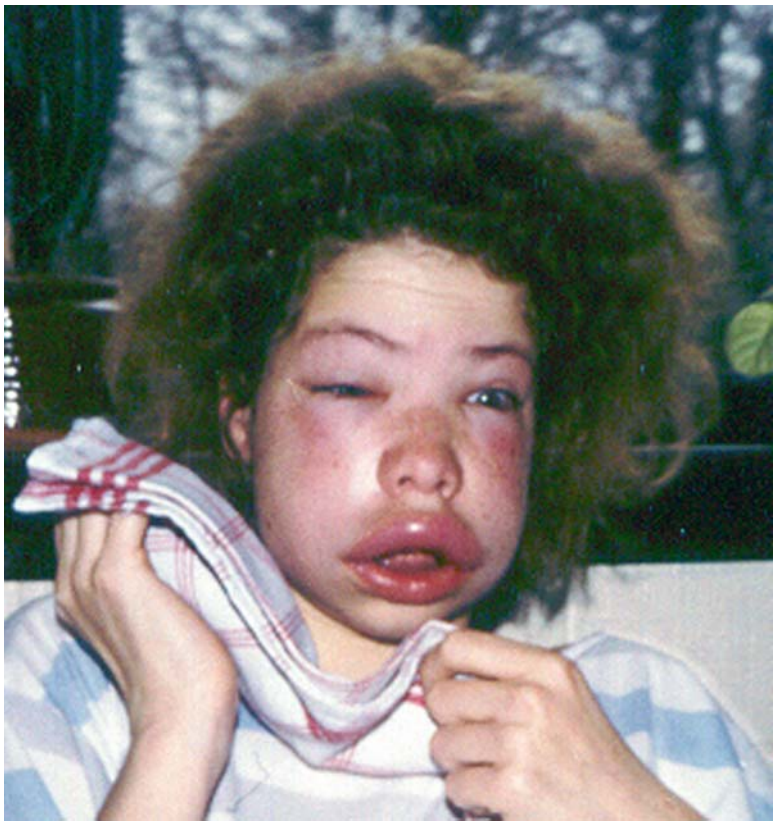

Fig. 8.2 Hereditary angioedema patient during an angioedema attack. (Picture obtained with permission from the Netherlands Organization of Patients with HAE-QE)

this has been disputed [2]. Acquired C1INH deficiency is a rare condition, usually presenting after the second decade of life, and is often related to underlying conditions such as autoimmune and lymphoproliferative disorders with the presence of anti-C1INH autoantibodies [59, 91].

Homozygous and heterozygous factor H deficiency is most commonly associated with either aHUS or MPGN [6, 60, 82, 85, 99]. The factor H mutations in patients with aHUS or in patients with age-related macula degeneration do not always lead to a decreased concentration or functional decrease of factor H in standard assays. In particular for aHUS, this is also the case for several of the components of AP and their regulators (factor B, C3, factor I, CD46, CD55). The majority of patients with aHUS presents with normal C3, C4, and hemolytic complement levels. Only the homozygous factor H or factor I deficiencies and the autoantibody C3NeF may cause complete secondary C3 deficiency through C3 consumption, which in turn predisposes patients to severe pyogenic bacterial infections [8].

A subgroup of aHUS patients showing persistent activation of the AP was found to carry mutations in the gene encoding factor B, a zymogen that carries the catalytic site of the AP convertase (C3bBb). Functional analyses demonstrated that the aHUS-associated factor B mutations were gain-of-function mutations that result in enhanced formation of the C3bBb convertase or increased resistance to inactivation by complement regulators. [34]. Thus, in case of gain-of-function factor B, homozygous factor H or factor I deficiency, and C3NeF, the individuals will show very low levels of C3 and factor B, whereas in primary C3 deficiency factor B will be normal (as well as factor H and factor I).

Compound heterozygous and homozygous mutations in CD46, a transmembrane complement regulator, are also related to aHUS [67, 83]. In contrast to the transmembrane regulator CD46, DAF and CD59 are linked to the outer leaflet of the erythrocyte membrane by means of a phospho-inositol-glycan moiety. In case of a defect in the synthesis of this anchor, the erythrocytes are highly susceptible to complement-mediated cell lysis, leading to hemolytic attacks and hemoglobinuria in PNH-patients. The *CD55* (*DAF*) mutations, designated as Inab phenotype in the Cromer blood group system, result in a complete loss of the protein on all cells, including erythrocytes. The clinical spectrum ranges from normal health to unexplained chronic intestinal disease. The Inab phenotype is unassociated with clinically evident hemolytic disease.

Leukocyte adhesion deficiency type 1 (LAD-1) is caused by a genetic defect in CD18, implying that CR3 (CD11b/CD18) and CR4 (CD11c/CD18) are not expressed. This leads to a reduced phagocytic activity to particles opsonized with iC3b, and thus to increased infectious susceptibility (see Sect. 4.4 for more details).

8.7.4 Diagnosis

Diagnosis of HAE can be made by measuring the plasma concentration of C4 and C1INH, which are strongly decreased in type I HAE, as well as the functional plasma C1INH activity, which is decreased in both type I and type II HAE (type II is a functional defect) [35, 46]. The quantity of C1-inhibitor protein is assessed immunochemically (in type I HAE usually <30% of mean normal adult level). Further distinction can be made by gene sequencing.

Plasma levels of regulatory proteins such as factor H and factor I can be measured immunochemically, and levels of MCP (CD46) expression can be tested on blood cells by flowcytometry. When complement consumption is not apparent, gene analysis is needed as direct proof of a deficiency and may be required to exclude or confirm a diagnosis of familial or recurrent aHUS. Most of the heterozygous missense mutations in factor H cluster within the tail of the protein (domains SCR19 and SCR20), a region that is critical to control activation of complement on cell surfaces but not required to regulate complement activation in plasma.

Currently, about 50% of patients with aHUS can be shown to carry heterozygous mutations in one of the genes encoding complement control proteins. Apart from the more prevalent factor H mutations, both factor I mutations as well as MCP deficiency have been defined to contribute about 10% each.

More than 20 different mutations in MCP have now been identified in patients with aHUS. Many of these mutations have been functionally characterized and have helped to define the pathogenic mechanisms leading to aHUS development. Over 75% of the reported mutations cause a reduction in MCP expression, due to homozygous, compound heterozygous or heterozygous mutations. In addition, genetic analysis of CD55, factor B and C3 is needed to assess possible predisposition for aHUS.

Diagnosis of PNH and LAD-1 is made by flowcytometric measurement of CD55/CD59 and CD18, respectively.

8.7.5 Management

HAE patients have been successfully treated with replacement of C1INH by infusion of intravenous fresh frozen plasma or C1INH concentrate, especially at the time of attacks [46, 106]. The androgen danazol is used for prevention of episodes of HAE. This anabolic steroid increases the circulating levels of normal functional C1INH in HAE [46].

Plasma exchange or plasma transfusions to replace the missing soluble regulatory components has been tried in several patients with factor H or factor I deficiency, and was successful in about one-third of these patients [6]. It does not work in the MCP mutation group, but these patients have a better prognosis than factor H-mutated and factor H-nonmutated patients.

In general, curative treatment of a congenital complement deficiency is only possible with liver transplantation, which is, however, not a preferred therapy. In case of factor H deficiency, renal transplantation often ends in relapses of HUS, in contrast to the situation with MCP mutations. Combined liver/kidney transplantation for patients known to have factor H mutations has not been successful to date. On the other hand, renal transplantation is a particularly viable therapy specifically for atypical HUS patients with MCP mutations [106].

PNH patients may be symptomatically treated with good results with a monoclonal antibody blocking C5, thereby reducing the lysis [38]. These patients should receive neisserial vaccine for the known increased risk of such infections when the terminal pathway is nonfunctional.

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