REVIEWS

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Deficiencies and Excessive Human Complement System Activation in Disorders of Multifarious Etiology

Niedobory oraz nadmierna aktywacja układu dopełniacza człowieka w chorobach o różnorodnej etiologii

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Abstract

Complement is an integral part of the immune system protecting the host organism against invasion and proliferation of various microorganisms. It is also involved in the removal of the body's own damaged and altered cells. Activation of the complement system is a very precise process and it is strictly controlled by regulatory proteins present in both plasma and at host cells' surfaces. C3 protein plays a major role in the complement activation and generation of immune responses. Deficiencies of the C3 and other complement components, so-called early and late complement proteins, contribute to the emergence of recurrent bacterial, viral and fungal infections. The low level of mannose-binding lectin is also important. This protein plays a protective role in the early stages of infection and in the control of inflammation. Its deficit is one of the most common reasons for human immunodeficiency, observed in microbial infections as well as in autoimmune diseases such as rheumatoid arthritis. On the other hand, the excessive activation of complement proteins is often discovered to be the reason for many diseases. These include e.g. autoimmune diseases, Alzheimer's syndrome, schizophrenia, atypical hemolytic-uremic syndrome, angioedema, macular degeneration, and Crohn's disease **(Adv Clin Exp Med 2012, 21, 1, 105–114)**.

Key words: complement protein deficiencies, complement regulation, bacterial infections, MBL, C3 protein.

Streszczenie

Układ dopełniacza jest integralnym elementem odporności chroniącym organizm gospodarza przed wnikaniem i rozprzestrzenianiem różnorodnych drobnoustrojów. Bierze również udział w usuwaniu uszkodzonych i zmienionych komórek własnych organizmu. Aktywacja układu dopełniacza odznacza się precyzją i podlega ścisłej kontroli ze strony białek regulatorowych, znajdujących się zarówno w osoczu, jak i na komórkach makroorganizmu. Główną rolę w aktywacji komplementu i reakcjach odpornościowych odgrywa białko C3. Niedobory zarówno tego składnika, jak i pozostałych, tzw. wczesnych oraz późnych białek dopełniacza, sprzyjają pojawianiu się nawracających zakażeń bakteryjnych, wirusowych oraz grzybiczych. Duże znaczenie w podatności organizmu na choroby zakaźne mają również małe stężenia lektyny wiążącej mannozę. Białko to pełni ważną rolę ochronną we wczesnych stadiach zakażenia oraz regulacji procesu zapalnego. Z jednej strony jego deficyt to jeden z najczęściej występujących wśród ludzi niedoborów odporności, obserwowany zarówno w zakażeniach drobnoustrojami, jak i w chorobach autoimmunologicznych, np. reumatoidalnym zapaleniu stawów. Z drugiej strony, stale odkrywa się choroby i zespoły objawów, których podłoża upatruje się w nadmiernej aktywacji komplementu. Należą do nich m.in. choroby autoimmunizacyjne, zespół Alzheimera, schizofrenia, atypowy zespół hemolityczno-mocznicowy, obrzęk naczynioruchowy, zwyrodnienie plamki żółtej czy zespół Leśniowskiego-Crohna **(Adv Clin Exp Med 2012, 21, 1, 105–114)**.

Słowa kluczowe: niedobory białek dopełniacza, regulacja dopełniacza, zakażenia bakteryjne, MBL, białko C3.

Complement (C), together with the antibodies present in serum, phagocytic and cytotoxic cells, is an integral part of the immune system protecting the human body against the invasion and proliferation of various microorganisms. It is responsible, among others, for Gram-negative bacteria cells' lysis. In addition to the lytic activity, complement together with the IgM and IgG antibodies is involved in opsonization, resulting in more efficient phagocytosis of the antigen-antibody complexes bound

to protein C3b. Complement components C3a, C4a and C5a act as anaphylotoxins – mediators of inflammation, which cause increased permeability of blood vessels as a result of mast cell degranulation and histamine release [1, 2].

The complement system is made up of approximately 40 proteins of an enzymatic, receptor, and regulatory nature, which all participate in a very well-functioning immune system [3, 4]. Complement proteins are synthesized mainly by hepatocytes, monocytes/macrophages, and enterocytes [4, 5], as well as by adipocytes [6] and glial cells [7]. Most of these components circulate in the blood and other body fluids in an inactive form. They have been divided into early-reacting proteins of non-catalytic activity and late-reacting proteins, which form a so-called membrane attack complex (MAC) on the surface of a target cell membrane.

Complement activation is a cascade process in which the inactive proenzymes are converted into proteases, for which other proteins of the complement system are the reaction substrates [4, 5, 8]. Complement is activated on the classical, alternative and lectin pathways [4, 8] (Fig. 1).

The classical pathway of complement activation is triggered by the binding of a C1q component (Ca^{+2}-dependent lectin) to the antigen-IgG or antigen-IgM complex, which is a signal for C1r and C1s activation [4]. Active C1s compound (C1 proteinase) causes proteolytic cleavage of C4 and C2 to the "a" and "b" subunits. Components C4b and C2a bind to form an enzyme – C3 convertase (C4b2a) [5].

The alternative pathway of complement activation is triggered spontaneously and it does not require the participation of either antibodies or C1, C2 and C4 components [5] (Fig. 1). Therefore, it plays an important role in the early stages of bacterial infection, in fetal development, in newborns and infants, when the level of antibodies is low. Activators of this pathway include Gram-positive and Gram-negative bacteria (especially bacterial cell wall polysaccharides), viruses, and virus-infected cells, fungi, protozoa, some parasitic worms and cancer cells. The presence of protein C3b, which is obtained by the spontaneous hydrolysis of the ester bonds within the C3 molecule or as a result of classical pathway activation, is necessary for stimulation of the alternative pathway [9]. In the initial stage of activation, subunit C3b binds – in the presence of Mg^{+2} – to complement factor B. The resulting C3bB complex interacts with a protein D, which causes dissociation of a B molecule into Ba and Bb subunits. The Bb component combines with C3b, creating in this way C3 convertase (C3bBbP) stabilized by properdin (P). That is why the alternative complement route was formerly known as the properdin pathway [4, 5, 8, 9]. It might seem that everything is already known about the activation of the alternative pathway, but some new facts were recently presented by Kemper et al [10]. This paper shows that properdin has the ability to bind to early apoptotic T cells. This results in complement activation, leading to C3b opsonization and ingestion by phagocytic cells. The recognition of dying T cells by properdin protects the human body from harmful inflammatory and autoimmune reactions. This interesting discovery deserves further and more detailed investigation.

The lectin route of complement activation is also antibody independent. It involves – in the presence of Ca^{+2} – the attachment of mannose binding lectin (MBL) to the sugar residues present on the surface of various pathogens, such as bacteria, viruses, fungi and protozoa [4, 11]. MBL is also able to bind non-sugar ligands, such as phospholipids, outer membrane proteins of *Neisseria* spp., and the DNA of apoptotic cells [12]. MBL circulates in serum in complexes with MASP-1, MASP-2, MASP-3 (MBL-associated serine proteases) and sMAP (small MBL-associated protein, MAP-19) (Fig. 1). Formation of a MBL polysaccharide complex triggers conversion of serine protease proenzymes into their active forms. MASP-1 cleaves C3 and C2 and MASP-2 splits C4 and C2 complement components. As a result of these interactions C3 convertase (C4b2a) is created [12, 13]. MASP-3 function is likely to regulate the activity of MASP-2, while the role of sMAP is still not fully understood [4, 12].

In the further stages of complement activation, the C5 convertases of the classical and lectin pathways (C4b2a3b) and the alternative route (C3bBb3b) resulting from the activation of complement proteins cascade, causing proteolysis of factor C5 into C5a and C5b subunits. The C5a component acts as an anaphylotoxin, while the C5b fragment sequentially joins other complement components (C6, C7, C8, and C9) to form the membrane attack complex C5b-9 (MAC) on the surface of a target cell. MAC damages the bacterial cell membrane by the creation of channels or pores, leading to electrolyte imbalance and metabolism disturbances, resulting in cell death [4, 5].

It is worth noting that some additional complement activation pathways were recently discovered. The first one is called the "C2-bypass", whereby the direct lysis (omitting C2 and C4 proteins) of a C3 component by an MBL/MASP-2 complex occurs [15]. Therefore, MBL/MASP-2 can be responsible not only for the lectin route of complement activation, but as suggested by some authors, by direct lysis of factor C3 of the alternative pathway [15, 16] (Fig. 1). In another way of

complement activation, proteolytic enzymes kallikrein and thrombin, proteins belonging to the serine proteases family, are involved. Kallikreins are present in the cells of exocrine glands, the neutrophils and body fluids. They contribute to kinin and plasmin synthesis [17, 18]. Thrombin is involved in the conversion of fibrinogen into fibrin, and therefore, as well as kallikrein, it stimulates the processes of blood coagulation [19]. Both proteins can stimulate the complement system, causing direct lysis of components C3 and C5 [17] (Fig. 1).

The Major Role of Protein C3 in Complement Activation

The protein C3 plays a major role in the activation of the complement system and the organism's immune responses [5, 20, 21]. At the level of this component, all the complement activation pathways are linked together (see Fig. 1).

As a result of the proteolytic action of classical and lectin (C4b2a) and alternative pathways (C3bBbP) C3 convertases, protein C3 is broken down into two subunits: a smaller C3a – of anaphylotoxin nature and a bigger – C3b, which binds to the target cell's membrane. The C3b component is involved in both the lytic reactions and the opsonization process.

Subunit C3b, together with factor iC3b (a lytically inactive form of C3b) opsonize the antigen, which enables its immunophagocytosis by leukocytes carrying on their surface receptors for these complement components (CR1 for C3b and CR3 for iC3b). Some C3b molecules act as components of the alternative pathway's C3 convertase and take part in strengthening (amplification) of the complement system activation in this way. As a result of combining the agent C3 with C3 convertases, C5 convertases are formed, and subsequently so-called late proteins of the complement system (C5-C9) are activated [5, 20, 21].

For the reasons stated above, the protein C3 is essential in the macro-organism's resistance against infections caused by bacteria, protozoa, fungi and some viruses. The participation of component C3 in anti-infectious immunity has been confirmed by observations of close correlation between genetic deficiency or absence of this protein and recurrent bacterial infections [21, 22].

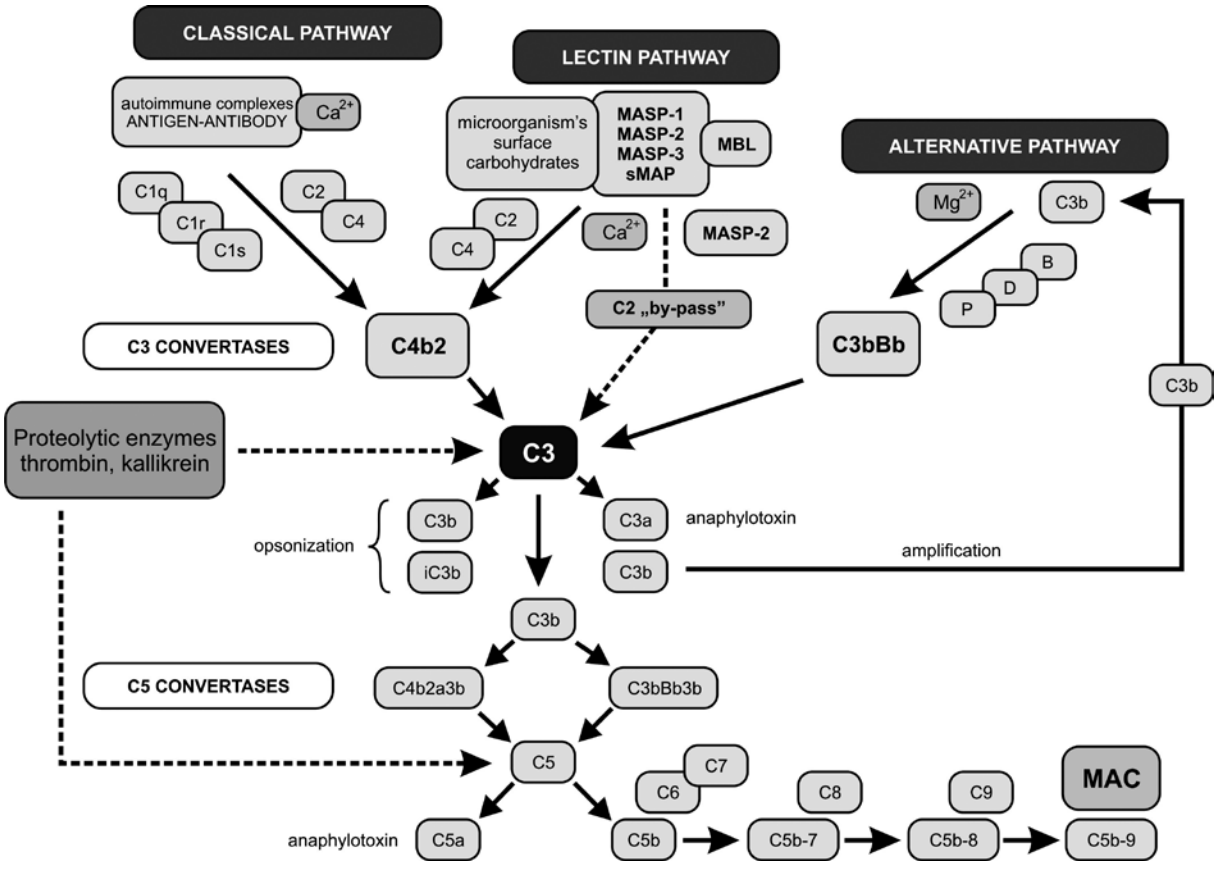

Fig. 1. Complement activation pathways [4, 9, 10, 19, 21, 22]

Ryc. 1. Drogi aktywacji układu dopełniacza [4, 9, 10, 19, 21, 22]

Table 1. Regulatory proteins of the human complement system [1–3, 5, 8, 22]

Tabela 1. Białka regulatorowe układu dopełniacza człowieka [1–3, 5, 8, 22]

Regulatory protein (Białka regulatorowe)	Name (Nazwa)	Function (Funkcja)
Serum (Surowicze)	C1INH (C1-inhibitor, serpin)	inhibition of C1r and C1s; removal of MASP-1 and MASP-2 from active MASP/MBL complexes
	α2-macroglobulin	regulation of MASP/MBL complexes activity
	factor I (fI)	control of C3 and C5 convertases activity (breakdown of the α chains in C3b and C4b molecules – in cooperation with appropriate co-activators)
	C4BP (C4-binding protein)	fI co-activator (participation in the inactivation of the classical pathway convertase C3)
	factor H (fH)	fI co-activator (participation in the inactivation of the alternative pathway convertase C3)
	C3INA (C3-inactivator)	inactivation of C3a
	factor S (fS, vitronectin)	preventing the incorporation of C5b-7 complexes in the membrane
	clusterin	
Cellular (Komórkowe)	DAF (Decay Accelerating Factor, CD55)	shortening the half-life of the classical and alternative pathways
	MCP (Membrane Cofactor Protein, CD46)	supporting C3b and C4b degradation by fI
	CR1 (CD35)	control of C3 and C5 convertases activity through the distribution of C3b and C4b
	CR2 (CD21)	regulation of antibody synthesis by B cells
	CR3 (CD11b/CD18)	phagocytosis supporting
	CR4 (CD11c/CD18)	
	HRF (Homologous Restriction Factor, CD59)	blocking of MAC formation by binding C8 and C9
	MIRL (Membrane Inhibitor of Reactive Lysis)	blocking C9 attachment and MAC creation

Regulatory Proteins of the Complement System

It should be kept in mind that complement system activation and MAC creation are very precise processes, strictly controlled by regulatory proteins present in plasma and the macro-organism's cells (Table 1). These proteins have an inhibitory nature and they exert their effects mainly by shortening the half-life of C3 and C5 convertases [5]. Factors present on the cells' surface are responsible for catching the complement components. This allows the body's own cell defense against complement activation by microorganisms. Properdin is virtually the only complement stabilizing factor.

Abnormalities in complement system functioning, associated with both deficiencies and excessive activation of its components and regulatory proteins, may be responsible for the occurrence of pathological syndromes [3, 22].

The Role of Deficiencies and Excessive Activation of Complement Proteins in Various Diseases

Innate immune mechanisms including the complement system are the first line of a higher organism's defense against infective agents coming from the external environment [3, 5]. Im-

pairment of these basic mechanisms can cause a diverse spectrum of diseases. The reasons for the complement system malfunctioning may be different. They are often the result of mutations in genes encoding the complement cascade proteins or regulatory proteins.

Disorders of Complement System Activation in Infectious Diseases

In patients with deficiencies of complement proteins, the greater susceptibility to infections and the occurrence of recurrent bacterial infections are often observed [5, 22] (Fig. 2). A key component of the complement cascade – protein C3 – plays a primary role in the resistance of the host organism to bacterial, viral, fungal, and parasitic infestations.

The results of numerous research studies confirm the correlation between C3 deficiency and recurrent infections caused by both Gram-negative (e.g. *Neisseria* spp., *Haemophilus influenzae*) and Gram-positive (e.g. *Streptococcus pneumoniae*) bacteria [21, 23]. The particular susceptibility to infections in patients with C3 deficiencies is strictly related to the major role of this component in both the lytic serum properties and opsonophagocytosis [23, 24].

Deficiencies of the late complement proteins involved in the creation of the MAC are related to the occurrence of meningococcal infections. In patients displaying a deficiency of even one of the proteins belonging to the group of C5-C8, recurrent systemic infections, meningitis, purulent otitis media and bacteremia, usually of severe intensity, may occur [3, 22]. Meningococcal and other bacterial infections are also linked with properdin deficiency [25].

The absence of the C3INA factor, which controls the activity of C3, in the clinical picture resembles the state of agammaglobulinemia and promotes the recurrence of bacterial infections. It is also observed that the deficiencies of the alternative pathway's factors B, D, P, and H, lead to increased susceptibility to infections caused by *Neisseria* spp., *Proteus* spp., and *Pseudomonas* spp. bacteria [22, 24].

Since the first case, in 1968, of a girl with atopic dermatitis suffering from recurrent bacterial infections and disorders of phagocytosis was described, MBL has been considered to be a very important component of innate immunity and is used in the treatment of various diseases [20, 26]. MBL plays an essential protective role in the early stages of infection, before the development of effective hu-

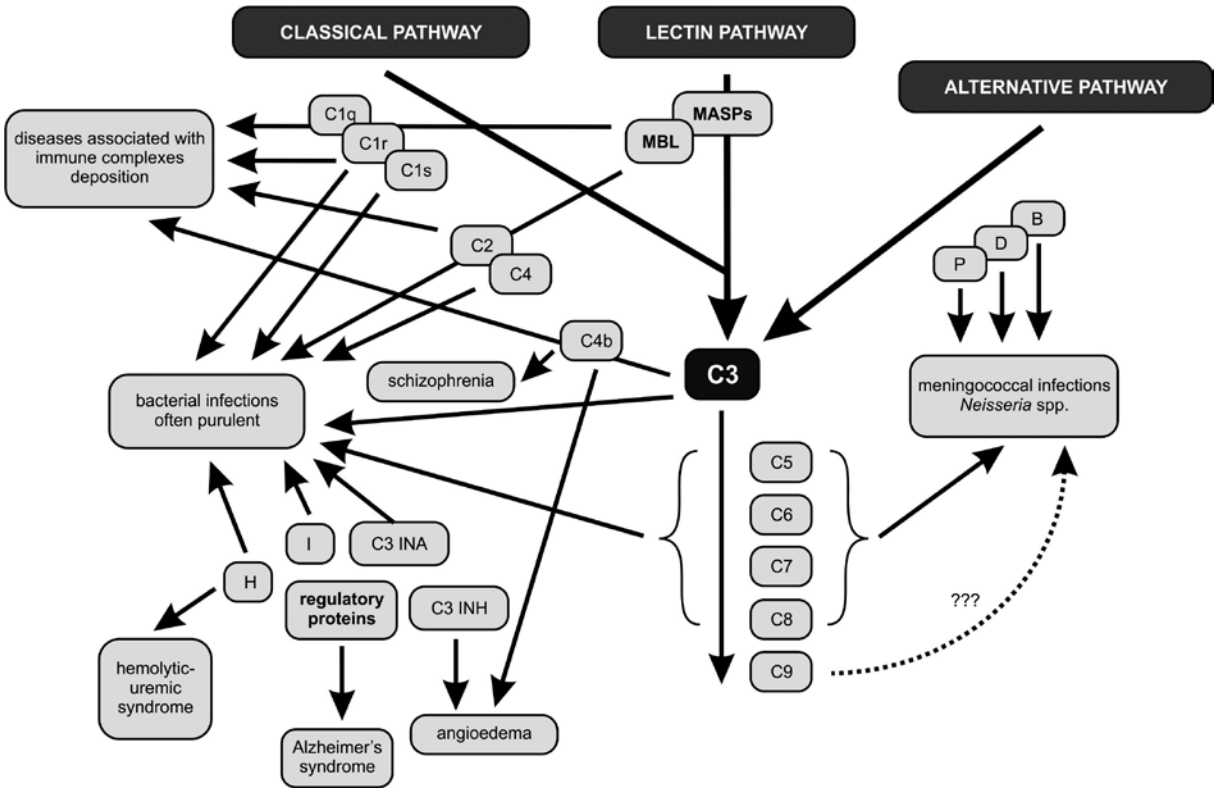

Fig. 2. Complement system deficiencies and related disorders [6, 26, 39, 46, 60, 61]

Ryc. 2. Niedobory białek układu dopełniacza i związane z nimi schorzenia [6, 26, 39, 46, 60, 61]

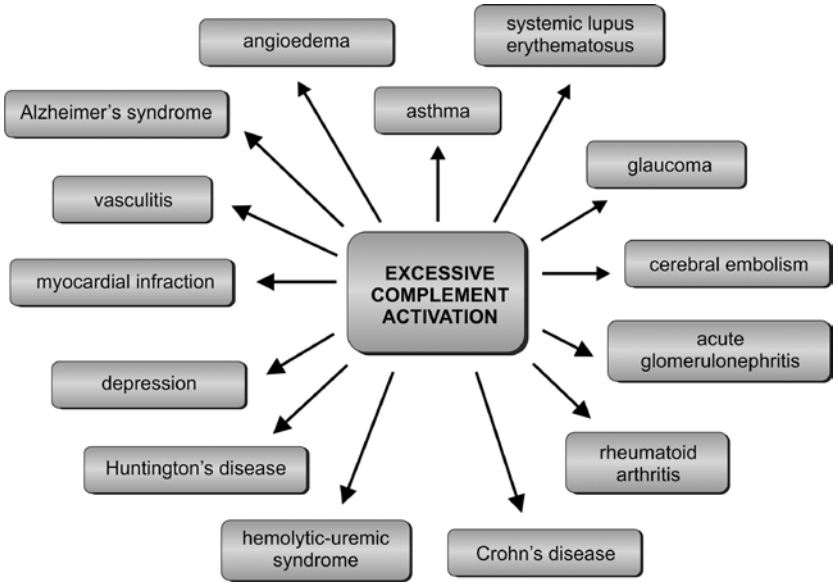

Fig. 3. Selected diseases and syndromes associated with excessive complement activation [6, 28, 29, 39, 40, 46, 60, 61]

Ryc. 3. Niektóre choroby i zespoły związane z nadmierną aktywacją układu dopełniacza [6, 28, 29, 39, 40, 46, 60, 61]

moral and/or cellular immunity responses. The deficit of this protein – one of the most common among human immune deficiency – may contribute to increased susceptibility to infectious diseases in childhood, as well as in adulthood [27, 28].

MBL occurs in serum in different concentrations, varying between populations, different age groups and among certain individuals. MBL presence in the serum at birth supports the hypothesis of its fundamental role in innate responses against a broad spectrum of pathogens. MBL is also involved in the regulation of the inflammatory processes through its impact on the increase or decrease of the level of cytokines secreted by cells [27, 29]. This collectin also plays an important role in opsonophagocytosis, providing an efficient defense against pathogenic microorganisms [29]. MBL together with complement component C1q and pulmonary surfactant protein A facilitate phagocytosis, and thus may contribute to *Mycobacterium tuberculosis* bacteria elimination [30, 31]. The role of this protein in the body's defense against infections induced by *Cryptosporidium parvum* in AIDS patients is also stressed [32].

Scientific research carried out mainly in the last decade has also shown that complement proteins could participate in infectious kidney diseases. One example is acute glomerulonephritis (aGN), a disease of sudden onset and in most cases self-limiting course. This disease can be caused in the kidneys by immune complex-induced complement activation during beta-hemolytic streptococci infection. aGN usually occurs in children and can lead to kidney failure [33–35]. In this disease, complement is activated mainly by the alternative pathway, with a simultaneous inhibition of the classical route. Decreased levels of proteins C3, C5 and properdin were observed in aGN patients, concomitant with normal concentration of component C4 [36]. There are several hypotheses of aGN development. One of them implies the binding of a bacterial antigen to the nephritis glomeruli membrane. This probably leads to the antigen-antibody inflammatory reaction and complement activation resulting in the damage of the glomeruli membrane [37]. According to another approach, bacterial proteins transform glomerular molecules, which are recognized as "foreign" antigens and became the target of complement proteins [38]. Therefore, it seems very important to promote prevention, making it possible to avoid urinary tract infections, especially in childhood when the development of the immune system is not completed.

Genetically Determined Complement System Disorders in Non-Infectious Diseases

In addition to bacterial infections, deficiencies of complement proteins underlie many non-infectious disorders.

In humans, genetically determined MBL deficiencies are observed in autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [39, 40]. Observation of the low concentrations of MBL and other complement proteins (e.g. C1q, C1r, C4) and poor activation of the complement system are also characteristic findings in active SLE [41]. It has become more and more obvious that the pathogenesis of SLE is very complex, connected with multiple gene modifications and additionally dependent on environmental factors [40].

Reduced levels of H and B factors are associated with age-related macular degeneration (AMD) [42]. Recently conducted studies [43–45] have shown that mutations in *HTRA1* and *CFH* genes, encoding the complement regulatory factors H and B, can significantly increase the risk of AMD. Under normal, physiological conditions, factor H inhibits the inflammatory response, converting C3b to an inactive iC3b form, and also weakens the binding of C3b with factor B. The point mutation in the *CFH* gene weakens the affinity of its product – factor H to CRP (C-reactive protein). This probably reduces the complement activity regulation in the eye fundus and leads to pathological inflammation in the macula.

It is worth noting that the participation of complement components in the atypical form of hemolytic-uremic syndrome (aHUS) has also been confirmed [46, 47]. aHUS is a disorder caused by excessive complement activation, caused by defects in genes encoding proteins of this system and the presence of autoantibodies against regulatory proteins indispensable for proper complement functioning [47]. aHUS is mainly induced by the defects in genes encoding mainly factors H and I, deficiencies of which cause severe disorders in the activation of complement resulting in kidney failure. A somewhat less frequent cause of aHUS is mutations in the gene of thrombomodulin – a glycoprotein with anticoagulant properties, playing a role in the inactivation of C3a and C5a anaphylotoxins [48].

Inherited C1q deficiency is noted in patients with systemic lupus erythematosus and provides the proof for the complement components' participation in the pathogenesis of autoimmune processes [40, 49].

It has been also observed that the genetically determined deficiency of the C1 inhibitor (C1-INH, C1-esterase inhibitor) occurs in hereditary angioedema (HAE). This is a rare, life-threatening disease of the skin and mucous membranes, manifesting as intermittent, recurrent swelling of the face, genitalia, digestive tract and larynx. C1-INH is one of the key regulators of the complement system, coagulation and kallikrein-kinin cascade [50]. C1-INH inhibits the activity of C1s and C1r, thus preventing the uncontrolled integration of the C2 and C4 components, and excessive complement activation through the classical pathway. Its deficiency causes continuous stimulation of this complement route, which is the result of increased self-activation of the C1 protein. In patients with HAE, this activation is persistent and independent of the appearance of clinical symptoms. C1-INH also inhibits active coagulation factor XII and kallikrein resulting in the release of bradykinin, responsible for the formation of edema and pain [50, 51].

Different diseases and pathological syndromes with excessive complement activation are shown in Fig. 3. These disturbances were recorded in a wide range of medical disorders including patients with Huntington's chorea, Alzheimer's disease, schizophrenia, etc. [3, 5, 7, 33]. In patients with Alzheimer's syndrome, deposition of beta-amyloid plaques in the brain stimulates microglia not only to cytokines secretion, free radicals and nitric oxide production, but also activates the complement system proteins, including the C1 component, CR3 and CR4 receptors. This leads to dysfunction of neurons, their degeneration and eventually the patient's death [52]. On the other hand, it is worth noting that the data collected in recent years suggests neuroprotective properties of some complement components [7].

The attempts to link Crohn's disease with the presence of MBL2 gene polymorphism and low MBL level have also been undertaken [53]. Certainly, there should be research continuously carried out that will allow us to better understand the molecular cause of this very serious disease.

To date, it has been established that early complement proteins (C1q, C1r, C1S, C3, C4) and MBL play a key role in the clearance of apoptotic debris, and their genetically determined deficiencies can be associated with the development of glomerulonephritis and vasculitis [2, 5, 33, 34, 54, 55]. This phenomenon is also observed in multiple sclerosis (MS), a very complex and still poorly known disease of the central nervous system [33, 55].

Therapeutic Strategies in Disorders of Complement System Functioning

Both deficiency and excessive activation of complement system proteins require therapy. However, it is not easy to find appropriate and long-term effective methods of treatment and elimination of the clinical consequences of complement system activity disorders. Newer and better therapeutic strategies are being developed all the time. An example is the treatment of HAE. In 2009, C1-INH replacement therapy and kallikrein inhibitors became available for the treatment of acute HAE attacks [56]. Prior to this treatment, fresh-frozen plasma transfusion was administered for acute HAE attacks [57].

One of the possibilities of treatment of MBL deficiency is replacement therapy, or intravenous injection of purified MBL preparations. Research

carried out in this field shows that the use of MBL preparations in children brings several years' lasting improvement in their health, without any unwanted side effects [58]. Some hope is also associated with the use of recombinant MBL preparations, free from the risk carried by the administration of blood-derivative products. In the future, it is planned to use them on a larger scale in the treatment of the autoimmune diseases, cystic fibrosis and hepatitis C, as well as in women with recurrent miscarriages and patients with infective endocarditis [27, 59].

Difficulties in removal of the blocking autoantibodies and excessively activated complement components make it necessary for partial or complete replacement of the plasma to be used as the first-line therapy for patients with aHUS. Kidney transplants are also performed, but in both cases, therapy is frequently inefficient and relapses are often observed. In the currently proposed treatment strategies, in parallel with kidney and liver transplantation, the elimination of the effects of factors H and I gene mutations have been proposed. One of the tested medications is usage of eculizumab – a monoclonal anti-C5 antibody, an inhibitor of the final complement activation stage. It acts by binding to C5 and inhibiting its breakdown into C5a and C5b, thereby preventing the formation of MAC complexes [48]. This compound, approved by the European Medicines Agency has been successfully used since 2007 in the treatment of paroxysmal nocturnal hemoglobinuria (PNH) [60], in which, in addition to reduced levels of cholinesterase, deficiencies of membrane inhibitor CD59 and factor DAF (CD55) have been observed. Such a situation greatly facilitates the binding of the component C3 to erythrocyte membranes and their lysis [60]. Currently, a lot of expectations are associated with the use of eculizumab in aHUS treatment [47, 48]. Anti-C5 antibodies have also been found to reduce tissue damage in complement-dependent myocardial infarction and stroke [61] and are proposed as therapeutic agents in chronic inflammation in, for instance, RA and nephritis [62].

Now, after more than 100 years since the complement system was described, new ways of its activation are still being discovered. Research carried out in this area constantly leads to new and often surprising results. As illustrated by examples described above, of the pathologies caused by reduced as well as excessive complement activation, this complicated protein system requires constant and very precise control. Therefore, it is important to conduct further research and clinical trials, and search for new treatment strategies which will allow us to integrate even better with the dangerous consequences of these disorders.

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