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Review

Classical pathway deficiencies – A short analytical review

Lennart Truedsson*

Department of Laboratory Medicine, Section of Microbiology, Immunology and Glycobiology, Lund University, University Hospital of Skåne, 22185 Lund, Sweden

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ABSTRACT

Deficiencies in the classical pathway of complement activation have some common features but show also great differences. Deficiencies of each of the components (C1q, C1s, C1r, C4 and C2) imply increased susceptibility to bacterial infections. They are also associated with increased risk to develop systemic lupus erythematosus where deficiency of C1q is strongly associated to the disease while C4 less and C2 much less. Deficiency of C1q affects only activation of the classical pathway while deficiency of C4 and C2 also prevent activation of the lectin pathway. Bypass mechanisms may result in complement activation also in absence of C2 but not in absence of C1q or C4. The genes for C2 and C4 isotypes are closely located within the MHC class III region on chromosome 6p and the genes for the 3 C1q chains are on chromosome 1p. Deficiencies of C1q and of C4 show genetic heterogeneity while deficiency of C2 in the great majority of cases is caused by a specific deletion. The production of C4 and C2 is mainly by the hepatocytes in the liver while C1q is produced by monocytic bone marrow derived cells. This has implications for the possibility to treat the deficiency and hematopoietic stem cell transplantation has been tried in C1q deficiency.

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1. Introduction

Complement deficiency states are primary immunodeficiency states which predispose to infections, immune dysregulation with autoimmune disease and also malignancy. The deficiency states affecting the complement system can be either primary (hereditary) or secondary (acquired). Secondary deficiency can be caused by complement consumption, induced by inflammation for instance caused by immune complexes and auto-antibodies (*e.g.* against C1q or C1 inhibitor), reduced synthesis or increased catabolism of complement components (Agnello, 1986; Botto et al., 2009). In these situations there is usually not a low level of only one single component but several components are affected, and in this review secondary deficiencies are not discussed. In general, primary complement deficiencies are rare. For some components only a very few cases are reported.

Deficiency of components within all the three major activation pathways, the classical pathway (CP), the alternative pathway (AP) and the lectin pathway (LP) confer increased infection susceptibility, but the severity and type of infection may be different (for review, see Skattum et al., 2011). Deficiency in the LP caused by low concentration of functional mannan binding lectin (MBL) is common in Caucasians (prevalence 10–15%). Low concentrations of MBL in serum are usually asymptomatic but also associated with bacterial infections. In combination with other immunodeficiency, MBL deficiency has been shown to be a risk factor particularly for respiratory tract infections caused by a broad spectrum of microorganisms. A few cases of other LP deficiencies involving MASP-2 and Ficolin 3 both associated with respiratory infections are reported (Grumach and Kirschfink, 2014). Deficiency of components in the AP (properdin, factor B and factor D) is associated mainly with increased risk for meningococcal disease. The same is true for deficiencies in the terminal sequence (C5, C6, C7, C8 and C9) although the association in C9 deficiency is very weak. A recent finding is that properdin deficiency also may aggravate the kidney disease C3 glomerulopathy caused by deficiency of the complement regulator factor H as was recently commented by Daha (2013). Activation through all the pathways leads to C3 activation and C3 concentration is low or absent both in inherited deficiency of C3 and of complement inhibitors factor H and factor I. Infections in

Abbreviations: AP, alternative pathway; C1qD, C1q deficiency; C2D, C2 deficiency; C4D, C4 deficiency; CP, classical pathway; HSCT, human hematopoietic stem cell transplantation; LP, lectin pathway; MBL, mannan-binding lectin; SLE, systemic lupus erythematosus.

* Tel.: +46 46173294.
E-mail address: lennart.truedsson@med.lu.se

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C3 deficiency are typically caused by encapsulated bacteria due to insufficient opsonization with C3 fragments. Immune-complex mediated disorders like vasculitis and nephritis are also frequent in this deficiency.

Of the CP deficiencies C2 deficiency (C2D) is least rare and in Caucasian population it has been estimated to occur in about 1 in 20,000 individuals (Pickering et al., 2000). Already in 1960 the first case of selective C2D was reported when Silverstein described a clinically healthy adult male with no C2 in his blood (Silverstein, 1960). Now is known that C2D is associated with disease although apparently healthy individuals with C2D also are seen, which is further discussed here. In 1977 a case of complete selective C1q deficiency (C1qD) in a 10-year-old Turkish boy with recurrent skin lesions and chronic infections was reported (Berkel et al., 1979). The same year complete deficiency of C4 (C4D) was reported in a boy having severe systemic lupus erythematosus (SLE) with nephritis by Schaller et al. (1977). The inheritance of these CP deficiencies is usually autosomal recessive. To date more than 60 cases of C1qD are described (Schejbel et al., 2011), while less than 30 cases of complete C4D are reported (Grumach and Kirschfink, 2014). Thus, several cases with these deficiencies have then been reported allowing a comparison and description of typical features characterizing the different CP deficiencies. Around 1970 cases of mostly combined deficiencies of C1r/C1s were reported, but so far less than 20 cases are known (Grumach and Kirschfink, 2014). Around 60% develop SLE or similar disease, and infections mainly due to encapsulated bacteria are frequent (Pettigrew et al., 2009). Thus, like other CP deficiencies these are associated with SLE and infection proneness, but not further discussed here.

2. Diagnostic procedures

When recurrent bacterial infections or symptoms suggesting SLE are present analyses of complement should be performed and the initial analyses should include screening for deficiencies. Classically this was done by hemolytic methods, such as CH50 for the CP of complement activation and AP50 for the AP. Absence of activity in CH50 indicates a CP deficiency and then further analyses of individual components are needed to determine which factor is missing. Other similar methods to screen for complement deficiency are hemolysis in gel (HIG) assays which are described and in use for both the classical and the alternative pathways (Truedsson et al., 1981; Mollnes et al., 2007).

Another approach in the screening for complement deficiencies is to use ELISAs for complement function. These more recently developed assays are available for the CP, AP and also the LP (Seelen et al., 2005). The increased use of complement deficiency screening assays appears to increase the number of identified deficiency cases. The first case of complete Factor B deficiency was recently found by the use of these ELISA assays (Slade et al., 2013). In the case of C1qD only the CP is affected in contrast to both C2D and C4D when also the LP is affected. Thus, the use of such screening assays is a very effective way to find which components that may be missing and guide further analyses.

When results in screening assays give reason to suspect a deficiency, analyses of the individual components have also to be done. Serum or plasma concentration can be measured by various immunochemical methods such as by for example electroimmunoassay or ELISA. In rare cases when this type of assay gives normal results a non-functional complement molecule may be expected and then the further analyses using functional assays for individual components have to be performed. This can be done for example by adding the component expected to be missing in purified functionally active form to the sample under investigation and then check for functional activity in an assay for complement activation (Mollnes et al., 2007).

Table 1
Some molecular characteristics of the classical pathway molecules C1q, C4 and C2.

Molecule	Subunits	Isotypes	Allotypes	Major synthesis
C1q	6 A, B, and C chains	–	–	Monocytic cells
C4	–	C4A, C4B	>40 variants	Liver hepatocytes
C2	–	–	~10 variants	Liver hepatocytes

3. The classical pathway components C1q, C4 and C2

The CP molecules have different molecular characteristics and some of these are summarized in Table 1. The C1q molecule has a molecular weight of 460,000 kDa and is composed of 18 subunits, 6 C1qA, 6 C1qB and 6 C1qC chains. Each chain of the C1q molecule consists of an N-terminal region involved in disulphide bond formation, a collagen region involved in C1r activation and a globular domain with ligand-binding specificities, distinct for each chain. The C1qA and C1qB chains form heterodimers where two heterodimers join a C1qC chain homodimer to form the final C1q structure. The 6 trimers of globular heads have affinity for IgG Fc regions which is the basis for CP activation through C1–immune complex interactions. The consequence of a mutation in any of the C1q genes may therefore affect the formation of functional C1q leading to complete C1qD. The C1q molecule does not show allotypic variation, but single nucleotide polymorphisms in the C1q genes that are correlated with C1q levels and potential risk factors for the development of rheumatoid arthritis are reported (Trouw et al., 2013). In peripheral blood C1q is in complex with $C1r_2$ and $C1s_2$ forming C1. The concentration in plasma is around 80 mg/L. Interestingly, C1q is not produced in the liver hepatocytes but in monocytic cells derived from the bone marrow as first was shown in mice (Petry et al., 2001) and later in humans (Castellano et al., 2004). Through interactions with soluble and cellular molecules C1q modulates a range of macrophage interactions with microbial pathogens (Lu et al., 2008). In addition several other possible functions have been attributed to C1q, such as clearance of apoptotic cells, dendritic cell maturation and T cell modulation (Nayak et al., 2010). Also a role in neuronal synapse modification has been reported (Stevens et al., 2007).

The C4 protein molecules are in the population present in an average concentration of 0.25 g/L. The C4 molecules are synthesized as a large precursor molecule with a molecular weight of approximately 200,000 kDa (Blanchong et al., 2001). The molecule is then processed intracellularly into a three-chain molecule composed of one alpha, one beta and one gamma polypeptide chain, linked together by disulphide bridges. C4 exits as two isotypes C4A and C4B, both very polymorphic with a nearly identical (>99%) amino acid sequence. More than 40 alleles including null alleles (C4A*Q0 or C4B*Q0), defined by the absence of C4 protein in plasma are reported. The polymorphism can be defined by electrophoretic mobility, by serology of Rodgers and Chido determinants and by DNA sequence (Schneider et al., 1996). Usually C4A variants carry Rodgers antigenic determinants whereas C4B in most cases carry Chido antigenic determinants, but rare reversed associations are found.

An internal thioester group present in the alpha-chain allows binding of the larger C4 fragment, C4b formed after C4 cleavage during CP activation, to other molecules through an ester or amid bond. The C4 protein present in the blood circulation is mainly produced in the liver. This has been shown in cases of liver transplantation where the C4 polymorphic variants in the blood follow the donor (Koskimies et al., 1991). C4 protein can also be produced locally by other cell types, for example monocytes (Whaley, 1980).

The C2 protein is present in a relatively low concentration in the blood circulation, approximately 25 mg/L. The molecule is

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