












# Inherited defects in the complement system

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## Abstract

The complement system plays an essential role in both innate and adaptive immune responses. Any dysregulation in this system can disturb normal host defense and alter inflammatory response leading to both infections and autoimmune diseases. The complement system can be activated through three different pathways. Inherited complement deficiencies have been described for all complement components and their regulators. Despite being rare diseases, complement deficiencies are often severe, with a frequent onset during childhood. We provide an overview of clinical disorders related to these disorders and describe current diagnostic strategies required for their comprehensive characterization and management.

## KEYWORDS

alternative, classical, complement, deficiency, inherited, lectin, pathways, system

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## 1 | INTRODUCTION

The complement system (CS) is a highly conserved part of the innate immune system comprising multiple membrane-bound and soluble components crucially interconnected with the adaptive immune system. CS is involved in adaptive immune response priming and many host defense processes, including chemotaxis, opsonization, induction of inflammatory response, and lysis of microorganisms, apoptotic cells, and immune complexes.<sup>1</sup> CS can be activated via the classical, alternative, and lectin pathways. Despite activated through different mechanisms, these three distinct enzymatic cascade pathways all converge toward the cleavage of the key proteins C3 and C5 that lead to the activation of the membrane attack complex (MAC) responsible for the lysis of target cells. Noteworthy, these molecular cascades require efficient control by a range of regulatory proteins that counteract potential complement-mediated damage to the host.<sup>2</sup> Inherited defects of the complement system (IDCS) have been reported for almost all complement components or complement regulators with a combined estimated prevalence of 0.03% in the general population, accounting for almost 5% of inborn errors of immunity.<sup>1,3</sup> Most IDCS are expressed in an autosomal recessive pattern. IDCS highlights the homeostatic roles of complement by predisposing primarily to recurrent, invasive infections by bacteria and autoimmune manifestations.

Moreover, specific disorders due to CS hyperactivation can result from the complement regulator deficiencies, while C1-INH deficiency leads to hereditary angioedema (HAE) (Figure S1).<sup>1,4</sup> Warning signs for IDCS have been proposed.<sup>3</sup> However, since a deficiency in any complement components can result in a similar clinical presentation, diagnosing the specific deficiency may be difficult. Nevertheless, modern functional and molecular analyses can detect the activity of different complement pathways, the functional activity of single components, and the total amount of each component, allowing most of IDCS diagnosis. CH50 and AH50 are screening assays able to reveal the integrity of complement pathways. Abnormal results will help direct further testing (Figure S2).<sup>5</sup> A summary of IDCS is reported in Table S1. Special consideration to IDCS presenting in pediatric age is given in the following paragraphs.

## 2 | CLASSICAL PATHWAY DEFICIENCIES (C1q, C1r, C1s, C2, C4)

Deficiency of any component of the classical pathway leads to failure in clearing immune complexes, apoptotic cells, and debris from damaged tissues, resulting in immune complexes deposits in capillary vessels and subsequent tissue inflammation. C1 subunits (C1q, C1r, or C1s) deficiencies invariably cause severe disease with typical SLE features that manifest early in childhood. Increased incidence of SLE-like disease is also described in partial C4 deficiency and Type I C2 deficiency, the commonest IDCS in Caucasians.<sup>6</sup>

### Key Message

Inherited complement deficiencies are associated with increased susceptibility to recurrent, severe infections and autoimmune diseases. Functional and molecular analysis can detect defects in all complement system pathways. Early diagnosis of complement deficiencies can be lifesaving, though no specific treatments are currently available for most of these disorders.

## 3 | C3 DEFICIENCY

C3 is a cornerstone component of the CS, crucial for activation of all pathways and for MAC assembly. C3 deficiency is characterized by early onset, severe and recurrent infections by encapsulated bacteria, while SLE is rarely reported. Untreated subjects usually die before adulthood.

A clinical picture identical to that seen in C3 deficiency is observed in deficiency of early complement components in any activation pathways and secondary loss of C3 due to deficiencies in alternative pathway regulators (fH or fI).<sup>7</sup> Rare C3 gain of function mutations may lead to atypical hemolytic uremic syndrome (aHUS).

## 4 | TERMINAL PATHWAY DEFICIENCIES (C5-C9)

Recurrent, systemic neisserial infections are clinical hallmarks for deficiencies of the terminal complement components (C5-C9) shared by the classical, lectin, and alternative pathways and ultimately responsible for the formation of the MAC.

Disease onset is usually in pediatric age; however, milder disease and a higher median age for meningococcal infection than the general population are observed. Personal or family history of meningococcal infections, mostly involving serotype less frequent in healthy subjects (W-135, X, Y, or Z), is reported. C5-C9 deficiencies are likely underestimated in most affected subjects.<sup>7</sup>

Early diagnosis can be lifesaving by allowing prompt meningococcal vaccination and antibiotic prophylaxis but it is also pivotal in identifying potentially affected relatives before disease onset.

## 5 | LECTIN PATHWAY DEFICIENCIES (MBL, M-FICOLIN, L-FICOLIN, H-FICOLIN, CL-11, MASPs)

Both the lectin pathway and classical pathway share C4 and C2 during downstream activation.

Five lectins, including Mannose Binding Lectin (MBL), the ficolins, and collectin11, can initiate the lectin pathway associated with the MBL-Associated Serine Proteases (MASPs).

While deficiencies in the ficolins and collectin11 are rare, MBL deficiency (MBLd) is described in at least 10% of the general population.<sup>8</sup>

MBLd is of little clinical significance in adults (unless associated with other conditions characterized by immunosuppression), primarily associated with several autoimmune diseases. However, in infants, MBLd leads to increased susceptibility to bacterial and viral infections, particularly in children 6 to 17 months of age.<sup>9</sup>

## 6 | ALTERNATIVE PATHWAY DEFICIENCIES (FACTORS D, B, PROPERDIN)

Deficiencies of either fB or fD prevent complement amplification through the alternative pathway with a significant reduction of opsonization efficiency affected subjects present with severe, recurrent pyogenic infections that makes it imperative to identify affected families to allow prompt administration of the meningococcal vaccine and antibiotic prophylaxis.

Properdin is the only positive regulator in the complement system. Severe meningococcal meningitis, often with septicemia characterize properdin deficiency that is the only X-linked inherited IDCS. The first meningococcal invasive infection is often fatal, while recurrent infections are usually not described in survivors because anti-meningococcal antibodies production enables a response via the classical pathway on the subsequent encounter.

## 7 | C1 INHIBITOR (C1-INH) DEFICIENCY

Intrinsic control mechanisms counteracting excessive activation are present in each pathway.

C1-INH is the primary inhibitor of both classical and lectin pathways and controls activation in the kinin pathway (coagulation cascade) that leads to the generation of active kinins.

C1-INH deficiency is responsible for the autosomal dominant syndrome hereditary angioedema (HAE). HAE may not be regarded as a real IDCS since it depends on the increased production of bradykinin. Absent synthesis of C1-INH is reported in most cases of HAE (type I-HAE), while 15% of patients (type II-HAE) produce functionally defective protein.<sup>10</sup>

Angioedema generally manifests around puberty, often triggered by physical or emotional stress, and rapidly ensues as the kinin's unregulated activation occurs in the affected area inducing vascular leakiness. Swelling might be potentially life-threatening if the upper airway is involved, while gut mucosa, when involved, leads to intestinal obstruction. Prophylactic treatment and emergency treatment for life-threatening attacks are available.

## 8 | CONCLUSION

In conclusion, recurrent bacterial may, suggest a defect of the complement system: CH50 and AH50 assay are the most

appropriate investigations. A timely diagnosis of IDCS can be lifesaving, though currently, no specific treatments are available. Therapeutic approaches are limited to general disease management, including education, vaccinations, antibiotics, and emergency planning, except for C1-INH deficiency and uncontrolled complement activation.

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**Lucia Leonardi:** Writing-original draft (equal). **Francesco La Torre:** Writing-original draft (equal). **Annarosa Soresina:** Writing-review & editing (equal). **Silvia Federici:** Writing-review & editing (equal). **Caterina Cancrini:** Writing-review & editing (equal). **Riccardo Castagnoli:** Writing-review & editing (equal). **Bianca Laura Cinicola:** Writing-review & editing (equal). **Stefania Corrente:** Writing-review & editing (equal). **Giuliana Giardino:** Writing-review & editing (equal). **Vassilios Lougaris:** Writing-review & editing (equal). **Stefano Volpi:** Writing-review & editing (equal). **Gian Luigi Marseglia:** Supervision (lead); Writing-review & editing (equal). **Fabio Cardinale:** Conceptualization (equal); Supervision (lead); Writing-review & editing (equal).

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