Current Trends in Immunology
Vol. 24, 2023

Case Report

# Compound heterozygous complement factor I deficiency: a case report

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## ABSTRACT

Complement Factor I (CFI) deficiency, an autosomal recessive immunodeficiency disorder, presents challenges in diagnosis and management due to its rarity and varied clinical manifestations. We report the case of a 44-year-old patient with compound heterozygous CFI deficiency, a rare presentation characterized by impaired complement system regulation. The patient exhibited a history of recurrent respiratory infections and two episodes of meningococcal meningitis. Laboratory analyses revealed low complement levels and genetic testing identified two heterozygous mutations in the CFI gene. Notably, the patient also had a partial deficiency in complement component C2. Despite detectable factor I levels, the patient's immune function remained compromised, emphasizing the complexity of CFI deficiency. Our findings underscore the importance of comprehensive complement studies and genetic analysis in diagnosing rare immunodeficiency diseases. Further research and collaboration are needed to better characterize and develop treatments for CFI deficiency and related disorders.

**KEYWORDS:** Complement Factor I (CFI), autoimmune disorders, immunodeficiency diseases, recurrent infections.

## INTRODUCTION

Complement deficiencies are rare and frequently underdiagnosed [1]. These immunodeficiencies, which account for approximately 6% of all immunodeficiency cases, can result in increased susceptibility to infections but also auto-immune diseases [2]. This complex cascade system can be activated along three different pathways: the classic pathway, the lectin pathway and the alternate pathway. It regulates the alternative pathway by downregulation of the complement cascade.

CFI possesses the capability to break down complement proteins C3b and C4b, aided by a range of cofactors including factor H (fH), complement receptor type 1 (CR1 or CD35), membrane cofactor protein (MCP), C4-binding protein (C4BP), and CD46. CFI's significance lies in its inhibition of the amplification loop within the alternative pathway, which is responsible for producing C3 convertase from C3b [3].

CFI deficiency leads to dysregulation of complement activation, resulting in immunological impairments that can be severe [4]. Individuals with CFI deficiency may experience recurrent encapsulated bacterial infections, auto-immune diseases, and other disorders such as atypical hemolytic uremic syndrome and macular degeneration [5].

In this article, we will discuss a case of compound heterozygote CFI deficiency, with partial C2 deficiency that resulted into lower and upper respiratory infections along with recurrent meningococcal meningitis.

## CASE REPORT

A 44-year-old female patient of Caucasian and French-Canadian origin was referred to the

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immunology clinic for repeated upper and lower respiratory infections since young age. In addition, she has a past history of asthma, eczema and pulmonary bronchiectasis. She also has a past history of cigarette smoking. At age one, she was seen in the emergency room for pneumonia. Thereafter, she consulted multiple times for recurrent otitis. At the age of two, she had meningococcal meningitis. The same year, she presented with another pneumonia complicated with a streptococcal empyema. At age six, she required a myringotomy with adenoidectomy. She had a second episode of meningococcal infection at age fifteen associated with meningococcemia. Over the next years, she suffered from multiple oto-sinopulmonary infections and pulmonary infections that required several antibiotic treatments. She also received prophylactic antibiotics for a few years. Lupus and other auto-immune diseases were ruled out.

According to her family history, her parents and sister were in good health. She has one daughter who regularly suffers from ear infections and was followed by an ear, nose and throat specialist. The patient declined medical investigations for her daughter. She has an aunt, who died at age 26 due to an unknown infection. She has also a cousin who has repeated respiratory infections. There was no consanguinity within the family. The patient was lost to follow-up for almost a decade; however, her infectious course remained favorable without follow-up or antibiotic prophylaxis. She finally accepted to be followed again. Extensive investigation was recently performed (Table 1). She was treated with prophylactic antibiotic therapy. She was vaccinated against *Streptococcus pneumoniae* and *haemophilus influenzae*. She also received the vaccines against diphtheria and tetanus. Family screening was offered but was refused.

## RESULTS

A large immunologic work-up was performed in order to investigate a possible immunodeficiency.

**Table 1.** Immunological investigations.

| **Analysis** | **Result** | **Reference value** |
|---|---|---|
| *Immunoglobulin levels (g/L)* | | |
| IgG | 8,63 | 6,81-14,47 |
| IgA | 2,06 | 0,67-3,75 |
| IgM | 2,30 | 0,47-1,88 |
| *Specific antibody levels* | | |
| Pneumococcal antigens (mg/L) | 60,93 | > 11 |
| Diphteria (UI/L) | 70 | > 1 |
| Tetanus toxin (UI/L) | 0,8 | > 0,1 |
| Haemophilus influenzae (mg/L) | 1,12 | > 1 |
| *Lymphocyte counts (absolute)* (µL) | | |
| CD3+ | 1075 | 700-2100 |
| CD4+ | 832 | 300-1400 |
| CD8+ | 233 | 200-900 |
| CD19+ | 117 | 100-500 |
| CD16CD56+ | 164 | 90-600 |
| *Complement component levels* | | |
| C2 (KU/L) | 1373 | 8000-16000 |
| C3 (g/L) | 0,24 | 0,90-2,04 |
| C4 (g/L) | 0,15 | 0,14-0,50 |
| C5 (g/L) | 0,26 | 0,67-1,33 |
| C6 (g/L) | 0,87 | 0,67-1,33 |

Table 1 continued..

| | | |
|---|---|---|
| C7 (g/L) | 0,57 | 0,67-1,33 |
| C8 (g/L) | 0,67 | 0,75-1,25 |
| C9 (g/L) | 1,24 | 0,66-1,33 |
| Factor I (mcg/mL) | 4,3 | 29,3-56,5 |
| Factor B (mcg/mL) | 62,7 | 127,6-276,5 |
| Factor D (mcg/mL) | 0,95 | 1,69-3,08 |
| Factor H (mg/L) | 317 | 441-761 |
| Properdin (mg/L) | 3,80 | 10-33 |
| CH50 (KU/L) | 140 | 340-580 |
| Alternative pathway (L) | 0 | 30-113 |
| MBL pathway (%) | 18 | 0-125 |

The complete blood count was normal with a normal differential. On flow cytometry, T, B, and NK lymphocyte counts were normal. The immune response after vaccination for *Streptococcus pneumoniae*, *haemophilus influenzae*, tetanus and diphtheria were adequate. In addition, to this investigation, the HIV serology was non-reactive and the sweat test done twice was negative. These tests had been carried out with the aim of eliminating cystic fibrosis and HIV immune deficiency. The extended immunological evaluation is summarized in Table 1.

A genetic analysis was also carried out for complement components (Blueprint, Complement system disorder – 80 genes). Sequence and copy number analysis by next generation sequencing of the Factor I gene (CFI) was performed. It identified a heterozygous splice donor variant, c.1429G> C/p.Y354, and a heterozygous missense mutation, c.1624G>A, p. (Gly542Ser). Sanger sequencing was used as a secondary confirmation for c.1429+1G> C. A heterozygous C2 c.841_849+19del was also detected in the patient.

## DISCUSSION

Complement factor I (CFI) is a serine protease that plays a crucial role in regulating the alternate pathway. It is essential for initiating the cleavage and inactivation of C3b and C4b with the help of cofactor proteins such as MCP (CD46), CR1 (CD35), C4BP and complement factor H [6].

C3b and C4b are complement proteins that are essential for the initiation of the complement cascade, leading to various immune responses, including the formation of the membrane attack complex (MAC). Alternative pathway (C3bBb) and classical pathway (C4b2a) C3 convertase promote the complement cascade activation [7]. Several studies have shown that the alternate pathway is more compromised than the classical pathway, requiring lower concentrations of its components to function [8].

Hereditary factor I deficiency is a rare autosomal recessive disease. Less than 50 cases have been reported in the medical literature [9]. Factor I deficiency results in a constant activation of the alternate pathway consuming therefore C3, factor B and H as well as properdin [10]. Decreased CFI levels, elevated C3b and C4b fragments, and decreased complement activity are typical findings in affected individuals [11].

Clinical manifestations of CFI deficiency can vary widely, making the diagnosis challenging [12]. Amongst the genetically confirmed cases, a mild prevalence is noticeable in females (2.2:1), with onset occurring in childhood [13]. Patients with CFI deficiency are prone to recurrent and severe infections, particularly those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. This susceptibility to infections is due to the secondary deficiency in C3 and ineffective bacterial opsonization [14]. Meningitis, septicemia, and respiratory tract infections are common complications. This dysregulated complement system increases risk of life-threatening infections

such as sepsis. More than 81% of individuals afflicted with a CFI deficiency will exhibits symptoms of invasive bacterial infections [15]. Additionally, individuals with CFI deficiency may experience immune complex-mediated disorders, including systemic lupus erythematosus (SLE) and glomerulonephritis, due to the deposition of immune complexes and complement activation [16]. Inflammatory encephalitis has also been described [17].

Our patient was diagnosed with CFI deficiency, based on the genetic analysis. The CFI is thought to be partial defect since factor I was detectable in serum of the patient. Interestingly, the patient also had moderate decreased levels of C3, factor B, factor D, factor H and properdin. This finding might reflect how CFI deficiency leads to amplification of C3 cleavage and uncontrolled consumption of other complement components of the alternative pathway [18].

Our patient had two different mutations on each of the alleles of the CFI gene coding for factor I, making it a compound heterozygous mutation. Since the factor I levels were detectable, it is assumed that impaired function of factor I is partial and not complete. It is known that some CFI mutations may result in partial production of factor I over time [19].

Alba-Dominguez and Lopez-Lera described five Spanish families in which seven people had a homozygous mutation in factor I, ten were heterozygous and two were normal [9]. Homozygous patients presented at hospital with pyogenic infections (*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*) and sometimes glomerulonephritis or autoimmune and vasculitic diseases. Heterozygous mutations were associated with hemolytic uremic syndrome and hemolytic anemia problems [20]. Currently, there is no clear relationship between mutations in CFI and the resulting clinical phenotype of complete CFI deficiency [15]. However, environmental and genetic factors seem necessary for an individual to develop these diseases. Studies report that respiratory infections, meningitis, and arthritis are the usual clinical consequences of Factor I deficiency [2]. Another publication showed that all individuals with CFI deficiency had an undetectable alternative pathway and reduced levels of factor H and properdin [3]. Also, in all descriptions of affected families, immunoglobulins were normal.

At present, the approach to treating individuals with CFI deficiencies involves administering periodic vaccinations against encapsulated bacteria along with prophylactic antibiotics. The efficacy of penicillin in managing infections has been demonstrated [2].

The particularity of our case is the presence of two different mutations in the CFI gene. The first mutation, heterozygous for CFI c.1429+1G>C, was also described in eight other individuals. This p.Gly542Ser variant is located in the serine proteinase domain of the protein, which includes the catalytic site of CFI [15]. Compared to our patient, two of these patients had hemolytic uremic syndrome, one patient also had a CFH/CFHR1 hybrid mutation and another 40-year-old individual had severe renal failure. Macular degeneration is also associated with factor I deficiency [21].

The second mutation, in our patient, CFI c.1624G>A, is much less known. Close monitoring for autoimmune complications is crucial to initiate timely and appropriate interventions. These non-infectious clinical manifestations may appear over time.

We also observed a partial deficiency in C2, a component of the classical pathway. This deficiency is much more common in the general population and is associated with an increased risk of autoimmune diseases and higher risk of encapsulated bacterial infections. More than half of individuals with homozygous C2 deficiency have rheumatological disorders such as systemic lupus erythematosus, Henoch-Schonlein purpura, or polymyosis [22]. However, C2 deficiency is inherited in recessive manner and no other variant was found in this gene.

## CONCLUSION

Complement Factor I deficiency is an extremely rare and complex immunological disorder that challenges our comprehension of the delicate immune balance maintained by the complement system. So far, 130 mutations have been identified in CFI [23]. This diagnosis should be suspected in

patients with a history of recurrent infections caused by encapsulated organisms or in those experiencing recurrent sino-pulmonary infections [24]. In this case study, we describe a rare and unique case of compound heterozygous mutation in factor I. Alike other similar cases described in the literature, our patient suffers from repeated encapsulated bacterial infections since a young age. Interestingly, our patient has not developed auto-immune diseases and vasculitis.

Knowing the clinical manifestations associated with the various deficiencies of the complement system is helpful to prevent related infections by offering prophylactic antibiotic therapy and adequate vaccination. It seems relevant to screen family members to improve research in this field and to offer a better treatment and follow-up of affected individuals. Following this clinical case, one might wonder whether the combination of a CFI deficiency involving two distinct mutations on the two alleles, along with heterozygous deficiency in factor C2, renders the patient even more susceptible to infections caused by encapsulated pathogens. Further research and collaboration are needed to advance our knowledge, improve our management and to explore potential targeted therapies for this rare immunodeficiency disorder.

## CONFLICT OF INTEREST STATEMENT

Authors have no conflict of interest to declare.

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