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# CNS Inflammation as the First Sign of Complement Factor I Deficiency

## A Severe Myelitis Treated With Intense Immunotherapy and Eculizumab

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## Abstract

### Objectives

Complement factor I (CFI) deficiency is a rare autosomal recessive inborn error of immunity. In this report, we highlight that complete CFI deficiency may present with isolated and severe CNS inflammation without associated systemic features nor prior non-CNS episodes. This inflammation may respond to complement blockade therapy.

### Methods

This is a case description of a young girl with severe longitudinal transverse myelitis treated with aggressive immunotherapy that included eculizumab. Published cases of CFI-associated CNS inflammation were reviewed and discussed.

### Results

A primary immunodeficiency panel revealed 2 germline pathogenic variants in the CFI gene. Further complement testing of the index case and her family confirmed complete CFI deficiency.

### Discussion

We describe a unique case of severe spinal inflammation secondary to complete CFI deficiency. Although rare, isolated CNS inflammation may be the primary manifestation of complete CFI deficiency. To halt the uncontrolled complement-mediated inflammation associated with CFI deficiency, prompt targeted blockade of the complement pathway using eculizumab may be life changing in the acute phase. Long-lasting blockade of the complement pathway is also essential to prevent relapse in this subgroup of patients.

## Introduction

Complement factor I (CFI) deficiency is a rare autosomal recessive inborn error of immunity. CFI is a plasma glycoprotein with serine proteinase activity responsible for cleaving complement factor C3b and C4b in inactivated C3b and C4b. Because the alternative pathway is constitutively activated at a low basal rate, the absence of CFI leads to secondary reduction of C3 because of chronic overconsumption (Figure, A). After activation, lack of CFI results in excessive levels of proinflammatory anaphylatoxins C3a and C5a.

CFI deficiency can present as partial or complete defects.[1] *CFI* pathogenic variant heterozygosity (partial defect) is a known risk factor of atypical hemolytic uremic syndrome (aHUS) and age-related macular degeneration. Complete *CFI* defects are secondary to homozygous or compound heterozygous mutations and lead to absent CFI expression or function. Complete

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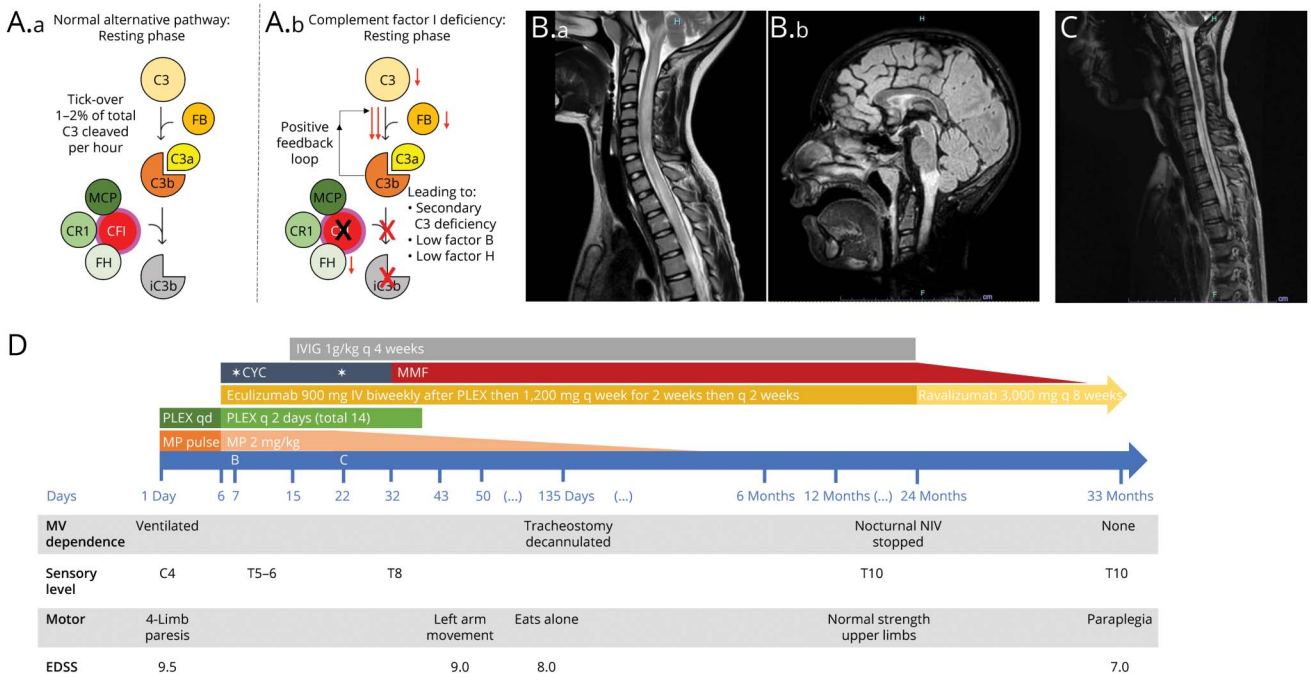
**Figure** Alternative Complement Pathway Activation and Clinical and Radiologic Manifestations of Complete Complement Factor I Deficiency in a Young Girl With Longitudinal Extensive Transverse Myelitis




(A) Representative schemas of the alternative complement pathway at the resting phase showing very small amounts of C3 being cleaved spontaneously at a low rate (A.a) and complete complement factor I deficiency which results in the spontaneous cleavage of C3 without CFI inhibition, leading to secondary deficiency of C3, factor B, and factor H (A.b) and the increase of anaphylatoxin C3a and C5a (not shown). (B) MRI findings at presentation (sagittal views of the spinal cord (B.a) and brain (B.b)): T2 hyperintense signal in the medulla and cord with an expanded (edematous) appearance of the spinal cord. (C) MRI findings 27 months after initial presentation (sagittal views of the spinal cord): significant atrophy of the spinal cord below the sixth cervical vertebra. (D) Caption of the clinical evolution of the patient after therapy. Duration (in days or in months) of each immunosuppressive therapy is represented by a distinct rectangle. CYC = cyclophosphamide; EDSS = Expanded Disability Status Scale; MMF = mycophenolate mofetil; MP = methylprednisolone; MV = mechanical ventilation; NIV = noninvasive ventilation; PLEX = plasmapheresis; qd = daily.

CFI deficiency remains an extremely rare entity. Only 52 cases have been described to date.[2,3] Most patients present with recurrent infections, but other reported systemic features include systemic lupus erythematosus, vasculitis, glomerulonephritis, and CNS inflammation.[4] In this report, we discuss a patient presenting with fulminant longitudinal extensive transverse myelitis (LETM) associated with complete CFI deficiency successfully treated with aggressive immunotherapy including eculizumab, a blocker of complement activation.

## Case Presentation

A previously healthy 11-year-old febrile girl presented with fulminant hyperacute quadriparesis and respiratory failure that evolved over 12 hours. These symptoms were preceded by a prodromal flu-like illness. Her neurologic examination was compatible with a spinal injury ASIA grade A. She showed a 4-limb areflexic flaccid paresis and a sensory level at the fourth cervical root (C4). MRI showed an extensive hyperintense T2 signal of the whole spine, from the medulla oblongata to the conus, most apparent in its central and posterior portions (Figure, B). Gadolinium enhancement was noted in the medulla and in the central aspect from C3 through C6. There was no optic nerve involvement. CSF analysis showed pleocytosis (1961 WBC $\times 10^6$/L) with neutrophil predominance (94%) and elevated proteins (2.64 g/L). Oligoclonal bands were absent. Serum and CSF anti-Aquaporin 4 and anti-MOG antibodies eventually came back negative. Based on the extensive LETM with bulbar involvement, we considered seronegative NMOSD the most likely diagnosis at the time although she did not completely fulfill the criteria.[5] An extensive immunologic, rheumatologic, hematologic, and infectious workup remained negative, except for complement studies that showed a reduced complement factor C3, normal C4, and elevated sC5b9 levels (Table 1).

The patient was acutely treated with daily high-dose methylprednisolone pulses and plasmapheresis (Figure, D). One week after treatment initiation, there were no signs of improvement. As we identified terminal complement activation, we added eculizumab after each plasmapheresis (900 mg IV initially). She also received cyclophosphamide on days 7 and 22, followed by mycophenolate mofetil (MMF) maintenance therapy. She showed some improvement a few days after the introduction of eculizumab, with a sensory level evolving from the fourth cervical root (C4) to the sixth thoracic root (T6). She started to

**Table 1** Description of the Complement Pathway Analyses in the Index Case and Her Family Members

| | Index case | Sister | Mother | Father |
|---|---|---|---|---|
| **Protein change** | I340T, G162D | I340T, G162D | I340T | G162D |
| **Clinical presentation** | Recurrent infections, longitudinal extensive myelitis | Asymptomatic | Asymptomatic | Asymptomatic |
| **C3** (g/L; N = 0.83–1.52) | 0.53 (↓) | 0.50 (↓) | 0.70 (↓) | 0.93 |
| **C4** (g/L; N = 0.13–0.37) | 0.39 | 0.20 | 0.26 | 0.28 |
| **Classical pathway C100** (U/mL; N = 31.5–57.6) | 31.8 | 44.0, 35.2 | 50.4 | 53.9 |
| **Alternative pathway AH50** (N = 30–113%) | Not tested (on eculizumab) | 0% (↓) | 20% (↓) | 73% |
| **Factor I** (U/mL; N = 0.60–1.40) | 0.62 | 0.80 | 0.78 | 0.81 |
| **Factor B** (mg/L; N = 173-453) | <113 (↓) | <113 (↓) | 250 | 262 |
| **Factor H** (mg/L; N = 441-761) | 339 (↓) | 339 (↓) | 454 | 604 |
| **Sc5b9** (ng/mL; N <300) | 942 (↑) | 244 | — | 194 |

Units and normal values are indicated.

mobilize her upper limbs 5 weeks after eculizumab initiation. Mechanical ventilation was progressively weaned off over a period of 6 months. During the following year, she continued to regain significant motor function of her upper limbs and trunk, but remained with a permanent paresis of her lower limbs and sphincter dysfunction. A contemporary spinal MRI showed significant spinal atrophy (Figure, C). Her relapse prevention regimen consisted of eculizumab (1,200 mg every 2 weeks), monthly high-dose immunoglobulins (1 g/kg), and MMF for 2 years. As she remained relapse-free, IVIG and MMF were weaned and stopped while eculizumab (and then ravalizumab) remained her only long-term prevention therapy.

## Results

An immunodeficiency gene panel (Blueprint Genetics) revealed 2 heterozygous pathogenic missense variants in *CFI*: c.1019T>C (p.I340T) and c.485G>A (p.G162D). Further familial segregation studies showed that both the index case and her asymptomatic sister were compound heterozygous for these 2 pathogenic variants. Like the index case, the sister showed a low C3 level, undetectable factor B level, and absent alternative pathway function (Table 1). CFI plasma level was in the normal range for all tested family members and at the lower limit of normal for the index case.

Pathogenic variants in the *CFI* gene have been classified as type 1, preventing secretion, or type 2, altering CFI function. The I340T variant is a type 2 mutation and has already been described in other cases of complete functional CFI deficiency.[6,7] Functional analysis of this allelic variant has confirmed pathogenicity.[8] The G162D variant is a type 1 mutation and has been described at the homozygous state.[9] As previously reported in other cases of complete CFI deficiency, the relatives of our patient are heterozygous for the allelic variants and completely asymptomatic, although theoretically at risk of aHUS. At present, her 18-year-old sister remains healthy, highlighting the variable clinical expression of CFI deficiency.

## Discussion

Complete CFI deficiency is extremely rare and usually presents with recurrent pyogenic infections. We identified 8 additional cases of CFI deficiency that manifested with CNS inflammation (Table 2). In Table 2, we retrospectively applied the modified Rankin Scale to cases reported. Presentations ranged from mild recurrent episodes of aseptic encephalomeningitis to catastrophic neurologic inflammation. Cases 3 and 6 had other signs of CFI deficiency (skin vasculitis and meningococcal sepsis, respectively) before presenting with an isolated episode of CNS inflammation. All other reported patients presented with de novo isolated CNS disease. Attacks started in the second or third decade of life, and significant CSF pleocytosis with neutrophilic predominance was noted in all cases. Excess of anaphylatoxin C5a, a potent chemoattractant of neutrophils, could explain this finding.[10] Brain biopsies revealed perivascular hemorrhagic necrosis, demyelination, neutrophilic infiltration, and evidence of vasculitis in 1 case.[3] Neuronal membrane attack complex and C3 deposition was observed in 2 patients.[6,11] These findings are suggestive of complement-mediated damage. It remains to be deciphered why this uncontrolled complement inflammation targets the CNS in some CFI-deficient patients. An infectious trigger with neurologic chemotaxis or mimicry is to be considered.

Because we evidenced uncontrolled complement activation, we opted to rapidly target the complement pathway using eculizumab. Since multiple immunomodulatory therapies were

**Table 2** Review of Complete CFI Deficiency Cases Associated With CNS Inflammation

| N | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| **Protein change** | **G71V/C196S** | **G71V het[a]** | **I340T/D524V** | **I340T/D519N** | **NA** | **C247G/C247G** | **P64L/Q88K** | **M1V/M1V** | **I340T/G162D[$]** |
| **Initial presentation** | CNS | CNS | Skin vasculitis | CNS | CNS | Meningococcal sepsis | CNS | CNS | CNS |
| **CNS presentation** | AHLE | AHLE | Aseptic encephalomeningitis | ADEM-like | Aseptic meningitis | Aseptic and bacterial meningitis | AHLE | CNS vasculitis | LETM |
| **Sex** | F | M | F | F | F | F | F | M | F |
| **Age symptoms** | 10 | 10 | 16 | 11 | 28 | 16 | 10 | 36 | 11 |
| **Attempted tx** | CCS, IVIG, anakinra | CCS, IVIG, anakinra | CCS, PLEX, CYC, AZA, MMF | CCS, PLEX, rituximab | Antibiotic ppx, NSAIDs | CCS, IVIG, triptorelin | CCS | CCS, IVIG, anakinra | CCS, PLEX, IVIG, CYC, MMF, eculizumab |
| **C3 level (g/L)** | 0.41 (↓) | <0.40 (↓) | 0.57 (↓) | 0.72 (↓) | 0.07–0.34 (↓) | 0.24 (↓) | 0.43 (↓) | 0.59 (↓) | 0.53 (↓) |
| **CSF analysis** | | | | | | | | | |
| **WBC (×10$^6$/L)** | 392 | 607 | 1,500 | N | 0.2–56 | 1,550 | 322 | 367–1750 | 1961 |
| **Neutrophils (%)** | 73 | 91 | 85 | NA | 85–100 | 85 | 55 | 65–91 | 94 |
| **Protein (g/L)** | NA | NA | 1.13 | 0.81 | 0.99–5.7 | ↑ | NA | 1.06–2.49 | 2.64 |
| **AH50** | <10% | 29% (↓) | <10% | <10% | NA | <10% | ↓ | <10% | Not tested |
| **Factor I (mg/L)** | 4.6 (↓) | 6 (↓) | 44 (N) | 29 (N) | ND | ND (↓) | ND (↓) | 26 (N) | N |
| **Evolution** | Full recovery to the basal state | Improved with anakinra, relapse on weaning, restarted | 10 relapses, then stabilization on MMF (2 y), no relapses after MMF weaning | Significant residual neurologic deficit, tetraplegia | Lost to F/U, full recovery each episode | Recurrent episodes with menses, no sequelae | Slow recovery, mild deficit | Great response to CCS and IVIG but relapse, no relapse since anakinra (20 mo) | Persistent paraplegia, recovery of upper limbs function |
| **MRS at d/c** | 1 | NA | 0 | 5 | 0 | 0 | 1 | 0–1 | 4 |
| **Long-term tx** | No | Anakinra | No | No | No | IVIG | No | Anakinra | Eculizumab |
| **Episodes** | 2 | 1 | 10 | 1 | 11 | 20 | 4 | 3 | 1 |
| **Trigger** | No | Flu-like | No | Flu-like | No | Menstruation | URTI | URTI once | Flu-like |
| **Family** | Asx het parents and brother; Asx compound het sister | Asx het father | Asx het parents | NA | NA | Asx het parents and brother; compound het sister meningitis; brother died of meningococcal meningitis | Asx het mother; sister died of fulminant AHLE aged 16 years | NA | Asx het parents; Asx compound het sister |
| **Reference** | 11 | 11 | 7 | 6 | 12 | 13 | 2 | 3 | Current report |

Abbreviations: ADEM = acute disseminated encephalomyelitis; AHLE = acute hemorrhagic leukoencephalitis; Asx = asymptomatic; AZA = azathioprine; CCS = corticosteroid; CYC = cyclophosphamide; d/c = discharge; het = heterozygous; IVIG = IV immunoglobulin; MMF = mycophenolate mofetil; MRS = modified Rankin Scale; N = normal; NA = not available; ND = not detectable; PLEX = plasmapheresis; ppx = prophylaxis; tx = treatment; URTI = upper respiratory tract infection.
[a] Second mutation not found, $: index case.

initiated at once in this extremely sick patient, it is difficult to delineate the clinical benefits directly attributed to eculizumab per se. The physiopathology of complete CFI deficiency supports the notion that complement pathway activation needs to be interrupted in this disease. However, it is possible that corticosteroids, IVIG, and PLEX contributed to the improvement, as they were reported to have some benefits in other reported cases. Notably, MMF and anakinra (not used in our case) seem to be beneficial to reduce relapses.[3,11] It is interesting that under eculizumab therapy, our patient improved, did not present any side effects, and remained relapse-free for at least 33 months. We propose eculizumab as a treatment of choice in complete CFI deficiency–associated neurologic inflammation. This monoclonal antibody links C5 and prevents C5a production and membrane attack complex formation, thus interrupting untoward complement activation consequences. It is approved for the treatment of several neurologic disease entities, notably for adults with AQP4-IgG–positive NMOSD and generalized autoimmune myasthenia gravis.

Above all, this case emphasizes that severe demyelinating disease can be a presenting feature of primary immune deficiency and that blockage of the complement cascade should be considered in patients with biological signs of complement pathway activation. Complement testing (C3, C4) is widely available and any abnormalities should prompt further complement investigation (sC5b9 levels, classical and alternative pathways) to timely exclude complement-mediated neuroinflammation.

## Ethics Statement

Informed consent for publication was obtained from affected individuals or parents before the publication of this report.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