

---

**Neurology Publish Ahead of Print**

**DOI: 10.1212/WNL.0000000000207079**

**Peals & Oy-sters: Homozygous Complement Factor I Deficiency Presenting as Fulminant Relapsing Complement-Mediated CNS Vasculitis**

Elle Levit, MD<sup>1</sup>; Janice Leon, MD<sup>2</sup>; Matthew Lincoln, DPhil, MD, FRCP(C)<sup>3,4</sup>

**Corresponding Author:**

Elle Levit, elle.levit@uvmhealth.org

1. Yale University School of Medicine, New Haven, Connecticut
2. Miami VA Healthcare System, Veterans Health Administration, Miami, Florida
3. Division of Neurology, Department of Medicine, University of Toronto, Toronto ON Canada
4. Keenan Research Centre for Biomedical Science, Toronto ON Canada

**Equal Author Contribution:**

**Contributions:**

Elle Levit: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Janice Leon: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

Matthew Lincoln: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data

**Figure Count: 2**

**Table Count:** 0

**Search Terms:**

[ 91 ] All Genetics, [ 134 ] Vasculitis, [ 137 ] Encephalitis

**Acknowledgment:**

**Study Funding:**

The authors report no targeted funding

**Disclosures:**

E.Levit has no disclosures. J. Leon has no disclosures. M.R. Lincoln is supported by a Career Transition Fellowship from the Consortium of MS Centers and the National MS Society and an Early Career Award from the Waugh Foundation.

**Preprint DOI:**

**Received Date:**

2022-05-27

**Accepted Date:**

2023-01-05

**Handling Editor Statement:**

Submitted and externally peer reviewed. The handling editor was Associate Editor Roy Strowd III, MD, Med, MS.

**Abstract:**

A 36-year-old man who presented multiple times with fever, headache, alteration of mental status, and focal neurological deficits. MRI revealed extensive white matter lesions that were partially reversed between episodes. Workup revealed persistently low complement factor C3, low factor B, and absent alternative complement pathway activity. Biopsy revealed neutrophilic

vasculitis. Genetic testing revealed a homozygous mutation in complement factor I (CFI), that was felt to be pathogenic. CFI regulates complement mediated inflammation, and deficiency in this factor leads to unchecked alternative pathway activity and decrease in C3 and factor B through consumption. The patient has remained stable since starting IL-1 $\beta$  inhibition. Complement factor I is a rare disorder that should be considered in patients with atypical relapsing neurological disease associated with neutrophilic pleocytosis.

**Pearls:**

- Complement factor I (CFI) deficiency has variable presentations, and genetic evaluation should be considered in recurrent, severe neurologic inflammation with complement aberrations and neutrophilic pleocytosis.
- Complement cascade interruptions may lead to episodic unchecked neuroinflammation.
- Complement cascade activation induces secretion of IL-1 $\beta$ , which may be selectively inhibited by anakinra or a complement inhibitor such as eculizumab.

**Oy-sters:**

- Genetic workup should not be overlooked early in disease course of severe central nervous system inflammation of unexplained etiology.
- Understanding the pathophysiology of complement mediated disorders allows for targeted treatment selection.

**Case report:**

A 36-year-old man with a past medical history of beta-thalassemia and treated H. pylori infection presented to medical attention with cough, high-grade fever (39.4°C), headache and vomiting. He had emigrated from Afghanistan to the United States 3 years previously, and also reported yearly upper respiratory infection (URI) lasting weeks since childhood. At the time of presentation, he had no recent travel, and apart from his child having a mild URI, there were no significant known infectious exposures.

On examination, there was no meningismus. He had left-beating nystagmus, bilateral limitation of rightward gaze, and dysarthria. MRI brain demonstrated bilateral, asymmetrical, predominantly white matter hyperintensities with vasogenic edema, and patchy parenchymal postcontrast enhancement without restricted diffusion (Figure 1, Panel A). There was no evidence of vascular involvement, including no infarcts or microbleeds, and vessel imaging with MRA was without stenosis. Spinal fluid was notable for 367 white blood cells (normal <5); differential revealed 65% neutrophils and 32% lymphocytes. Protein was 106 mg/dL (normal 15-60mg/dL), and glucose was 83mg/100mL (normal 50-80mg/dL). Gram stain revealed 3+ WBC but no organisms.

Clinical presentation of fever, headache, and subacute neurologic deficits suggested meningoencephalitis, either infectious or immune-mediated. Spinal fluid with profound neutrophilic pleocytosis raised concern for an infectious etiology and he was treated empirically with broad spectrum antibiotics and acyclovir, without clinical improvement. CSF culture was negative, along with routine viral and autoimmune antibody panel testing.

While in hospital, his mental status declined and he developed progressive dysarthria and cranial nerve VI-VIII palsies prompting ICU transfer. Given lack of response to empiric therapy, atypical inflammatory and viral etiologies were considered. Arboviral infections such as Eastern equine encephalitis virus and Powassan were considered, along with enterovirus and herpesvirus; while lymphocytic pleocytosis is more common in these conditions, neutrophils can predominate early in disease course. Inflammatory conditions presenting with neutrophilic pleocytosis were considered including neuromyelitis optica (NMOSD), Behçet's disease, and less commonly autoimmune encephalitis. CNS vasculitis usually presents with a lymphocytic pleocytosis, as does acute demyelinating encephalomyelitis (ADEM), and were therefore thought to be less likely. He exhibited dramatic clinical improvement following a five-day course of high-dose methylprednisolone (IVMP) 1g daily, followed by five days of intravenous immunoglobulin (IVIg), 0.4g/kg/day. At the time of discharge, examination revealed a residual gaze palsy. Repeat MRI showed dramatic resolution of white matter lesions and contrast enhancement (Figure 1, Panel B).

Six months later, he presented with recurrent fever (38.7°C) and altered mental status. Spinal fluid on this occasion was notable for 733 WBC (75% neutrophils, 21% lymphocytes), elevated protein 194.2 mg/dL and normal glucose 80mg/100dL. Gram stain, culture, and viral testing were negative. MRI brain revealed extensive, confluent T2/FLAIR white matter hyperintensities bilaterally with patchy enhancement. Empiric antimicrobials again produced no clinical response. Given the recurrent fever and neutrophilic pleocytosis, there was concern for an atypical infection, such as *Mycoplasma pneumoniae*, *Mycobacterium*, Q fever or *Listeria monocytogenes*. Tests for these were negative. He received a second course of IVMP followed by IVIg in light of prior response. He again demonstrated significant improvement, returning to work within weeks. Repeat MRI again demonstrated near-complete resolution of white matter lesions.

The rapid improvement of white matter lesions on MRI was thought to be atypical for vasculitis. CNS autoimmune panels were again negative, and CT imaging to look for sources of paraneoplastic disease were negative. Bickerstaff's encephalitis was considered at this point, though this was less likely given extensive supratentorial involvement and negative GQ1b antibodies. Neuro-Sweet syndrome was also unlikely as the patient did not have acute neutrophilic dermatosis<sup>1</sup>. Rheumatologic entities including lupus cerebritis were felt to be less likely given normal ANA. He did not have characteristic skin/genital lesions of Beçhet's disease, there was no cerebral ischemia or cutaneous manifestations of systemic vasculitis or Sneddon syndrome. Periodic fever syndromes such as Familial Mediterranean Fever were strongly considered, but genetic testing was unrevealing. Workup during his second hospitalization did reveal low complement C3 of 59 (normal 88-201mg/dL), with normal C4 at 33 (normal 15-45mg/dL).

Over the next six months, he reported progressive cognitive symptoms and underwent outpatient workup including CSF analysis, which showed 7 WBC (87% lymphocytes, 13% monocytes), protein 38.0mg/dL and glucose 66mg/100dL. IgG index was 0.46mg/dL (normal 0.0-0.7mg/dL), oligoclonal bands (OCBs) were not detected and infectious studies were negative. At time of CSF analysis, he reported a URI. Five days later, he presented with headache and ataxia. MRI revealed a new T2/FLAIR lesion in the left cerebellar hemisphere with associated contrast

enhancement (Figure 1, Panel C). CSF had 1750 WBC (91% neutrophils, 4% lymphocytes, 5% monocytes), protein 248.8mg/dL and glucose 62mg/100dL. IgG index was 1.16mg/dL, with no OCBs. Gram stain, culture and infectious and autoimmune antibody panels were negative. Metagenomic testing later produced no evidence of an atypical infectious organism, and fungal, mycobacterial cultures were negative.

Given the recurrent nature of his condition, he underwent diagnostic brain parenchymal biopsy. Pathology revealed an acute vasculitic process, with multifocal neutrophils within vessel walls, and brain parenchyma with scattered perivascular CD68-positive macrophages (Figure 2, Panel B). There was no evidence of demyelination and few T cells. Serum analysis showed persistently low complement C3, normal complement C4, and low Factor B (11.0; normal 13.3-31.5mg/dL). Additionally, factor H within normal limits (55.2; reference 37.0-68.0mg/dL) and factor H autoantibody was negative (<22.0; reference <22.0 unit/mL). Factor I was on the low end of normal (2.6; reference 2.4-4.9 mg/dL). There was absent alternative complement pathway (AH50) (0; normal 77-159 U/mL) and persistently low classical complement pathway (CH50) (33.5; normal >41 U/mL). He underwent genetic analysis, revealing a homozygous mutation affecting the initiator codon (c.1A>G) of the complement factor I gene of unknown significance. Given the serum complement abnormalities, and abnormalities in the alternative and direct complement pathway, this mutation was thought to be disease-causing. During a period of disease quiescence CFI was low-normal; he was therefore felt to have a partial deficiency of CFI resulting in recurrent bouts of autoinflammation.

After his most recent relapse, our patient was started on anakinra, an interleukin-1 receptor antagonist that blocks the activity of IL-1 $\beta$  and IL-1 $\alpha$ <sup>2</sup>. Complement induces IL-1 $\beta$  secretion via the NLRP-1 inflammasome<sup>3</sup>, and inhibition of IL-1 $\beta$  ameliorates the pro-inflammatory effects of this cytokine. Additionally, IL-1 $\beta$  inhibition may slow complement production as well as membrane attack complex (MAC) formation, limiting further complement induced inflammation<sup>4</sup>. Since starting anakinra, he has been clinically and radiographically relapse free for twenty months. Sequential MRI brain imaging demonstrates atrophy, likely a consequence of recurrent inflammation (Figure 1, Panels A-D). Other therapeutic considerations include complement inhibition with eculizumab.

## **Discussion:**

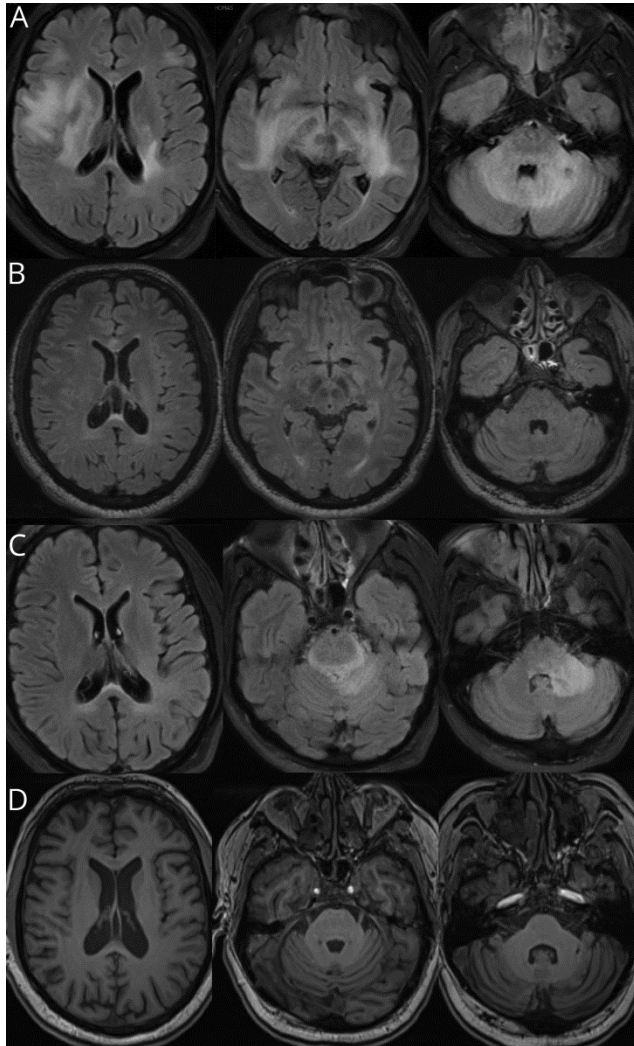
CFI is a plasma phase serine protease which negatively regulates the alternative and classical complement pathways by deactivating C3b and C4, so that C3 convertase is not formed<sup>5</sup>. This prevents progression to C5 convertases in both pathways, preventing further amplification of the complement cascade. The activation of the alternative pathway involves formation of C3 convertase, which requires C3b, Factor B, and Factor D (Figure 2, Panel A).

Hereditary deficiency of CFI has autosomal recessive inheritance<sup>5</sup>. Loss of functionality of CFI can thereby lead to unchecked complement activation via C3, leading to an increase in anaphylatoxin C3a and opsonin C3b production, a decrease in circulating C3 and factor B through consumption, and absent AH50<sup>4,6,7</sup>. Homozygous partial CFI deficiency has been associated with autoinflammatory processes, which are a group of disorders often characterized by episodic inflammation driven by the innate immune system in the absence of pathogens, autoantibodies, or antigen specific T cells<sup>8</sup>. The relapsing nature of this patient's disease process is curious, and perhaps explained by the speculation that chronic alternative pathway activation caused by CFI deficiency is limited by depletion of C3<sup>10,11</sup>. A surge of C3 can be induced by a stressor, such as viral illness. With this surge, the alternative pathway is no longer substrate limited, and can mount a fulminant unchecked inflammatory response. While tissue was not stained for complement deposition, it is possible our patient's vasculitis was mediated by deposition of immune complexes and initiation of a local inflammatory response which was responsible for the changes seen on brain biopsy<sup>7,12</sup>.

This case highlights both an unusual presentation of a rare disorder as well as a unique opportunity to blend knowledge of pathophysiology with patient specific biomarkers to guide disease management. While this case does not directly provide evidence that anakinra will benefit patients with CFI deficiency, it raises this possibility and suggests the need for further study.

**Figure 1. Sequential MRI brain T2/FLAIR sequences during relapse and recovery.**

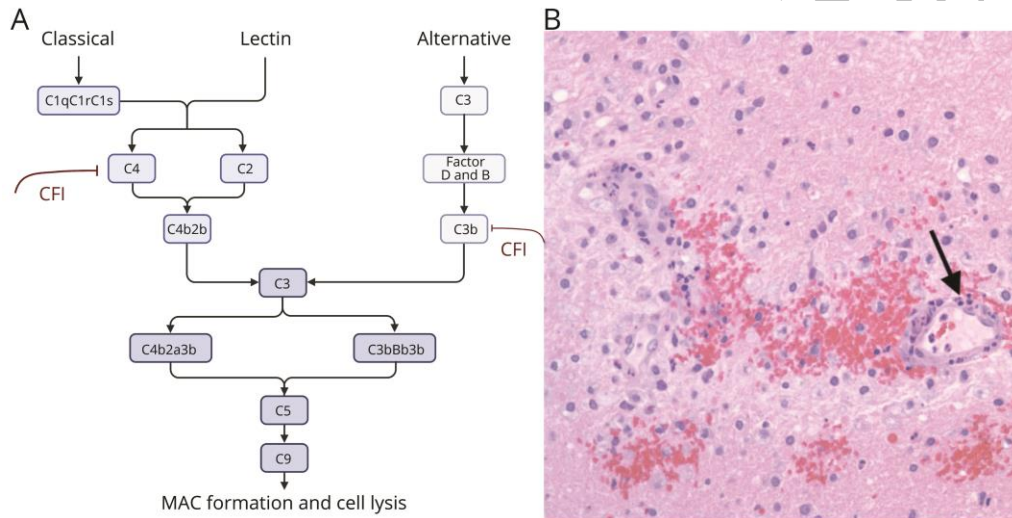
Panel A exhibiting extensive supratentorial and infratentorial white matter involvement on MRI brain T2/FLAIR sequence of patient's initial relapse. Panel C shows the most recent relapse and recovery three months later in Panel D. Also apparent is the brain atrophy that developed over time from image A – D.





**Figure 2. Schematic of the complement pathway and Complement Factor I (CFI) inhibitory role and Brain pathology H&E stain.**

Panel A) Brief schematic of the complement pathway and Complement Factor I (CFI) inhibitory role. CFI negatively regulates the activation of the alternative, and to a lesser extent the classical complement pathway by deactivating C3b and C4, so that C3 convertase is not formed<sup>5</sup>. This in turn prevents progression to C5 convertases in both the alternative and classical pathways, and prevents further amplification of the complement cascade. Panel B) Pathology from brain biopsy hematoxylin & eosin stain showing multifocal neutrophils within vessel walls, consistent with vasculitis (arrow), 400x magnification. Created with BioRender.com.



## References:

1. Yuan K, Musiek AC, Schaffer A, Bucelli RC. Neuro-Sweet disease: A case of recurrent encephalitis and febrile neutrophilic dermatosis. *Neurol Clin Pract* 2016;6:e20-e23.
2. Gran JT, Midtvedt Ø, Haug S, Aukrust P. Treatment of Schnitzler's syndrome with anakinra: report of three cases and review of the literature. *Scand J Rheumatol* 2011;40:74-79.
3. Laudisi F, Spreafico R, Evrard M, et al. Cutting edge: the NLRP3 inflammasome links complement-mediated inflammation and IL-1 $\beta$  release. *J Immunol* 2013;191:1006-1010.
4. Broderick L, Gandhi C, Mueller JL, et al. Mutations of complement factor I and potential mechanisms of neuroinflammation in acute hemorrhagic leukoencephalitis. *J Clin Immunol* 2013;33:162-171.
5. Vyse TJ, Morley BJ, Bartok I, et al. The molecular basis of hereditary complement factor I deficiency. *J Clin Invest* 1996;97:925-933.
6. Haerynck F, Stordeur P, Vandewalle J, et al. Complete factor I deficiency due to dysfunctional factor I with recurrent aseptic meningo-encephalitis. *J Clin Immunol* 2013;33:1293-1301.
7. Moiseev S, Lee JM, Zykova A, et al. The alternative complement pathway in ANCA-associated vasculitis: further evidence and a meta-analysis. *Clinical and Experimental Immunology* 2020;202:394-402.
8. Zeft AS, Spalding SJ. Autoinflammatory syndromes: fever is not always a sign of infection. *Cleve Clin J Med* 2012;79:569-581.
9. Shields AM, Pagnamenta AT, Pollard AJ, et al. Classical and Non-classical Presentations of Complement Factor I Deficiency: Two Contrasting Cases Diagnosed via Genetic and Genomic Methods. *Front Immunol* 2019;10:1150.
10. Altmann T, Torvell M, Owens S, et al. Complement factor I deficiency: A potentially treatable cause of fulminant cerebral inflammation. *Neurol Neuroimmunol Neuroinflamm* 2020;7.
11. Thurman JM, Holers VM. The central role of the alternative complement pathway in human disease. *J Immunol* 2006;176:1305-1310.
12. Genel F, Sjöholm AG, Skattum L, Truedsson L. Complement factor I deficiency associated with recurrent infections, vasculitis and immune complex glomerulonephritis. *Scandinavian journal of infectious diseases* 2005;37:615-618.

# Neurology<sup>®</sup>

## **Peals & Oy-sters: Homozygous Complement Factor I Deficiency Presenting as Fulminant Relapsing Complement-Mediated CNS Vasculitis**

Elle Levit, Janice Leon and Matthew Lincoln

*Neurology* published online March 20, 2023

DOI 10.1212/WNL.0000000000207079

**This information is current as of March 20, 2023**

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://n.neurology.org/content/early/2023/03/20/WNL.0000000000207079.full">http://n.neurology.org/content/early/2023/03/20/WNL.0000000000207079.full</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>All Genetics</b> <a href="http://n.neurology.org/cgi/collection/all_genetics">http://n.neurology.org/cgi/collection/all_genetics</a> <b>Encephalitis</b> <a href="http://n.neurology.org/cgi/collection/encephalitis">http://n.neurology.org/cgi/collection/encephalitis</a> <b>Vasculitis</b> <a href="http://n.neurology.org/cgi/collection/vasculitis">http://n.neurology.org/cgi/collection/vasculitis</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.neurology.org/about/about_the_journal#permissions">http://www.neurology.org/about/about_the_journal#permissions</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://n.neurology.org/subscribers/advertise">http://n.neurology.org/subscribers/advertise</a>

*Neurology*® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2023 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

