

# Recurrent aseptic meningitis associated with a rare heterozygous complement regulatory factor (CFI) I gene mutation (case report) | 1

The complement regulatory factor I (CFI) is a two-chain serine protease and an endogenous inhibitor of the classical and alternative complement pathways by cleaving C3b and C4b in the presence of cofactor proteins. The CFI gene mutations result in the inability to control the complement cascade appropriately. A complete deficiency of the CFI gene is inherited in an autosomal recessive manner, and results in a C3 deficiency and a predisposition to severe infections caused by encapsulated microorganisms. The authors from the United States and Australia presented a patient with a rare heterozygous CFI mutation and neurological manifestations that have not been previously reported.



#### About the case

An 18-year-old man was referred to the emergency department with new-onset headaches, photophobia, and nausea. In his medical history, he had recurrent painful gum and hard palate ulcers that started at the age of ten, allergic rhinitis, and asthma. His monozygotic twin brother was diagnosed with ulcerative colitis, oral ulcers, and one episode of presumed aseptic meningitis, which was never confirmed by the cerebrospinal fluid (CSF) analysis.

The patient's general and neurologic examinations were normal except for a temperature of 38.4 °C and neck stiffness, which prompted a lumbar puncture. The CSF was cloudy and colorless, with a total white blood cell count of 2,201/μL (reference range 0-5/μL). 68% of cells were polymorphonuclear leukocytes and 31% lymphocytes. Protein concentration was 142 mg/dL (reference range 15-45 mg/dL). The bacterial and fungal cultures, herpes



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simplex virus (HSV) type 1 and 2, and enterovirus were negative.

Presumed bacterial meningitis was treated with methylprednisolone, vancomycin, and meropenem, but this treatment was discontinued after blood cultures showed negative results.

After three months, the patient experienced a low-grade fever of 38 °C and headaches again, but a lumbar puncture was not performed. He received supportive care.

After two years, he presented similar symptoms that responded well to prednisone. He continued to have attacks of headaches and low-grade fevers for the next two years. Repeated lumbar punctures showed aseptic neutrophilic meningitis. Other tests, like the CSF next-generation sequencing, rheumatologic testing, and autoimmune testing with autoimmune encephalopathy panel and aquaporin-4 antibodies, didn't show anything.

After four years, the patient had his first generalized tonic-clonic seizure. Magnetic resonance imaging (MRI) scan showed symmetric T2 signal abnormalities in the hippocampus. Several previous brain MRI findings were normal. He experienced temporal lobe seizures that decreased in frequency with the initiation of valproic acid and lamotrigine. Neuropsychological testing demonstrated new deficits in verbal discrimination, attention, and working memory.

The patient also got painful oral and scrotal ulcers. The HSV types 1 and 2 were negative, and biopsies showed benign results. Considering the neuro-Behçet disease, treatment was initiated with colchicine and azathioprine, which improved the ulcers but did not prevent the meningitis flares. During flares, he was treated with oral pulse prednisone. Due to persistent attacks, he was switched from azathioprine to infliximab for 5 months, but without any improvement.

Whole-exome sequencing revealed a rare variant in the CFI gene (c.859G>A, p.Gly287Arg). Genetic testing confirmed the presence of the same variant in his monozygotic twin brother. Complement analysis demonstrated normal results, but the authors noted that these analyses were done when the patient was treated with immunosuppressive therapy, which may have affected the results.

In this situation, treatment with anakinra, a recombinant IL-1 receptor antagonist was started with gradual withdrawal of prednisone. After that, he switched to canakinumab and successfully weaned off prednisone. He continued to take 150 mg of canakinumab monthly and had no recurrence of ulcers or meningitis in more than 20 months.



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#### Conclusion

This case report presented an association between a rare heterozygous CFI mutation and neurological manifestations with more than 15 episodes of aseptic neutrophilic meningitis, seizures, and persistent cognitive impairments. The patient also had concurrent mouth and genital ulcers.

This case supports the role of CFI gene mutations in neuroinflammation that may resemble infectious meningitis. The authors underscored the importance of genetic testing in patients with uncertain diagnoses. They concluded that future research should investigate the underlying mechanisms by which dysfunction of the CFI gene can result in central nervous system inflammation.

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#### Journal Reference

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