EJCRIM
European Journal
of Case Reports
in Internal Medicine

ISOLATED CYTOMEGALOVIRUS OPTIC NEURITIS IN AN IMMUNOCOMPETENT PATIENT

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Received: 23/04/2026
Accepted: 30/04/2026
Published: 03/06/2026

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: The patient has provided his written informed consent for publication of this case report and any accompanying images.
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How to cite this article: Petrakis V, Aggelopoulou C, Tartanis G, Tsakaldimi S, Panopoulou M, Grapsa A, Periklis P. Isolated cytomegalovirus optic neuritis in an immunocompetent patient. *EJCRIM* 2026;**13**:doi:10.12890/2026_006826

ABSTRACT

Introduction: Cytomegalovirus (CMV) typically causes asymptomatic or mild, self-limiting infections in immunocompetent individuals. Severe end-organ disease, particularly isolated central nervous system or ocular involvement, is associated with significant immunosuppression. Isolated optic neuritis due to CMV in a healthy, immunocompetent host is a rare clinical entity, which can lead to delayed diagnosis and potential vision loss.

Case description: We report a rare case of a previously healthy 25-year-old male who presented with a 3-day history of intermittent right retrobulbar pain and was found to have early bilateral optic disc oedema. Best-corrected visual acuity was 9/10 in the right eye, with normal colour vision and no relative afferent pupillary defect. An extensive neurological, immunological, and infectious disease workup was negative for autoimmune and demyelinating conditions. However, serological testing revealed positive immunoglobulin M and immunoglobulin G titres for CMV. Concurrent polymerase chain reaction (PCR) testing detected CMV viremia in both blood and cerebrospinal fluid (CSF), confirming an active CMV infection with central nervous system involvement. The patient was treated with high-dose intravenous corticosteroids and systemic antiviral therapy with valganciclovir leading to a complete clinical and anatomical recovery and no clinical relapse during the follow-up period.

Conclusion: This case highlights that severe CMV neuroretinal manifestations can occur in strictly immunocompetent patients. Prompt molecular diagnostic testing, specifically CSF and blood PCR, is crucial when atypical optic neuritis is encountered. A combined regimen of antiviral therapy and high-dose corticosteroids represents a highly effective, organ-saving approach for managing CMV-induced optic neuritis.

KEYWORDS

Cytomegalovirus, optic neuritis, immunocompetent, papillitis, neuro-ophthalmology

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

LEARNING POINTS

- Cytomegalovirus must be included in the differential diagnosis of acute optic neuritis and bilateral optic disc oedema, even in young, strictly immunocompetent patients without concurrent retinitis or prior immunosuppression.
- The utilization of polymerase chain reaction to detect viral copies in both blood and cerebrospinal fluid is essential for confirming active systemic and central nervous system viral involvement.
- The management of viral optic neuritis may necessitate a dual pharmacological strategy. High-dose corticosteroids are crucial to rapidly suppress tissue-damaging inflammation behind an intact blood-brain barrier, while systemic antiviral therapy is required to eradicate the underlying viral load and prevent clinical relapse.

INTRODUCTION

Cytomegalovirus (CMV) is a ubiquitous deoxyribonucleic acid virus with a worldwide seroprevalence ranging from approximately 60 to 100%[1]. Following a primary infection, the virus enters a latent phase where it resides inside infected myeloid progenitor cells[1]. Primary CMV infection in immunocompetent patients typically runs an undifferentiated viral syndrome or is manifested by a self-limited mononucleosis-like syndrome[2]. Symptomatic CMV infection in non-immunocompromised hosts has traditionally been considered to have a benign, self-limited course[2]. Conversely, CMV can cause severe, life-threatening disease in immunocompromised patients, either via the reactivation of a latent CMV infection or via the acquisition of a primary CMV infection[2]. The morbidity and mortality associated with CMV infection in immunocompromised patients, such as human immunodeficiency virus-infected patients and transplant recipients, as well as individuals with congenital CMV infection, are well known[2]. Clinical syndromes frequently observed in this clinical setting include encephalitis, pneumonitis, hepatitis, uveitis, retinitis, colitis, and graft rejection[2].

However, there are a considerable number of reports documenting severe clinical manifestations of CMV infection in immunocompetent patients[3-5]. Severe life-threatening complications of CMV infection in immunocompetent patients may not be as rare as previously thought[4,5]. A comprehensive systematic review encompassing 290 immunocompetent adults revealed that the gastrointestinal tract (colitis) and the central nervous system (meningitis, encephalitis, transverse myelitis) were the most frequent sites of severe CMV infection[5]. Less frequent manifestations of severe CMV infections in immunocompetent patients included vascular thrombosis, ocular involvement, and pulmonary disease[5]. Ocular manifestations of CMV infection are a hallmark of the disease in immunosuppressed patients, notably presenting as keratouveitis, retinitis, and retinal branch angiitis[5]. The co-occurrence of papillitis with juxtapapillary retinitis occurs in 4% of immunosuppressed patients with CMV retinitis and significantly worsens the visual prognosis[5]. Isolated optic neuropathy (mostly papillitis) due to CMV is exceedingly rare in immunocompetent patients, with only a few cases reported in the literature[6,7]. Because the reason some immunocompetent patients develop neuroretinal disease remains unknown, it is highly likely that such presentations are underdiagnosed in routine clinical practice.

Herein, we report a remarkably rare case of a previously healthy, immunocompetent adult who presented with acute retrobulbar pain and bilateral optic disc oedema. The patient was diagnosed with presumed isolated CMV optic neuritis based on systemic serology and viremia and was successfully managed with a combination of high-dose corticosteroids and systemic valganciclovir.

CASE DESCRIPTION

A previously healthy 25-year-old male was referred to the Emergency Department by a private ophthalmologist due to a 3-day history of intermittent right retrobulbar pain. Initial ophthalmologic examination revealed early bilateral optic disc oedema *(Fig. 1)*. Upon admission, best-corrected visual acuity (BCVA) was 9/10 in the right eye. There were no disturbances in colour perception, and the relative afferent pupillary defect was negative. The patient exhibited no focal neurological signs. The patient had no past medical history and didn't receive chronic medication. He was not former or current smoker and did not consume alcohol. On admission, his vital signs, cardiopulmonary and lymph node assessment and the physical examination of the abdomen were normal. Initial laboratory tests revealed a normal white blood cell count (leukocytes 4,250 cells/µl), red blood cells (haematocrit 43%) and platelets (182,000 cells/µl), normal liver function tests (alkaline phosphatase 28 U/l, gamma-glutamyl transferase 11 U/l, aspartate aminotransferase 12 U/l, and alanine aminotransferase 11 U/l) and a normal creatinine level (0.65 mg/dl). C-reactive protein (0.5 mg/dl), erythrocyte sedimentation rate (8 mm/hour) and procalcitonin (0.1 ng/ml) were within normal range.

The patient was admitted to the Neurology Department for further evaluation and management of suspected optic neuritis. Computed tomography scan and magnetic resonance imaging of the brain showed no abnormal findings *(Fig. 2)*. A lumbar puncture was performed, revealing a normal intracranial opening pressure of 12 mm Hg, absence of cells (0 cells/µl), cerebrospinal fluid

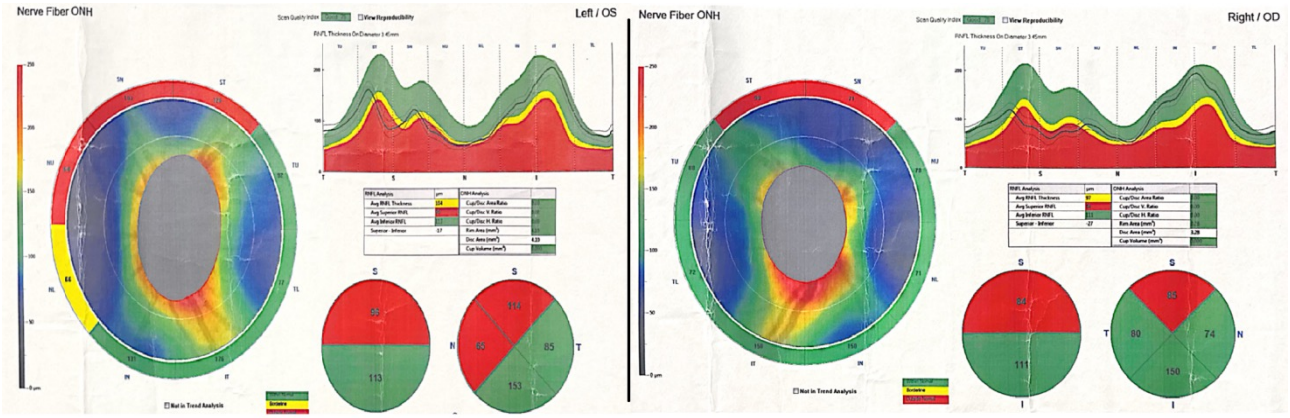


Figure 1. ONH/GCC report from optical coherence tomography scan in both eyes performed at admission day. Bilateral optic disc oedema. Abbreviations: ONH, optic nerve head; GCC, macular ganglion cell complex.

(CSF) glucose 82 mg/dl with normal CSF: serum glucose ratio and normal protein levels (31 mg/dl). Polymerase chain reaction analysis and CSF culture were negative. An extensive serological and virological workup was largely unremarkable. Screening for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, syphilis, tuberculin skin testing, Wright test for Brucella and serological tests for herpes simplex virus-1, herpes simplex virus-2, varicella-zoster virus, *Cryptococcus*, *Toxoplasma*, *Bartonella henselae*, *Borrelia burgdorferi*, West Nile virus and Epstein-Barr virus were all negative. Immunological studies including antinuclear antibodies, rheumatoid factor (RF) and serum complement components C3 and C4 and tumour markers (carcinoembryonic antigen, prostate-specific antigen, CA 19-9, human chorionic gonadotropin and alpha fetoprotein) were normal. No evidence of underlying immunodeficiency was reported. Optic myelitis was excluded due to negative serum testing for anti-aquaporin-4 (AQP4) and anti-myelin oligodendrocyte glycoprotein (MOG). No CSF oligoclonal bands were revealed. Remarkably, serological evaluation revealed positive titres for both immunoglobulin G (IgG) and immunoglobulin M (IgM) against CMV. Concurrently, blood polymerase chain reaction (PCR) testing detected CMV viremia. PCR results for CMV in the CSF were also positive.

Given the acute optic neuritis, the patient was initially treated with high-dose corticosteroids, which yielded significant clinical and laboratory improvement. Due to the serological and molecular evidence pointing toward active CMV infection, a diagnosis of presumed CMV-induced optic neuritis was made, and systemic antiviral therapy with valganciclovir was initiated. Following treatment, subsequent ophthalmologic evaluations demonstrated complete resolution of the clinical findings. The patient's BCVA improved to 10/10 bilaterally, colour vision remained normal, and the optic disc margins returned to sharp, well-defined borders. The patient was discharged in excellent clinical condition with instructions to continue the antiviral regimen. At follow-up visits 2 and 3 months after the completion of antiviral treatment, the patient did not appear to have any clinical or laboratory abnormalities.

DISCUSSION

While the manifestations of CMV infection in immunocompromised hosts have been extensively documented, the severe morbidity that CMV infection may cause in immunocompetent patients has received comparatively little attention[5]. Our case highlights a critical and exceptionally rare manifestation of CMV—bilateral optic disc oedema and optic neuritis—in a strictly immunocompetent individual without concurrent retinitis. The central nervous system (CNS) is not spared in CMV infections observed in immunocompetent patients, as evidenced by literature documenting severe manifestations such as meningitis, encephalitis, myelitis, nerve palsies, and myeloradiculopathy[5]. However, isolated inflammatory involvement of the optic nerve is a rare clinical condition.

In immunocompetent patients, isolated optic nerve involvement is exceedingly rare[6,7]. Our patient's presentation closely parallels a recent case described by Melancia et al., which reported a CMV optic neuropathy in a young, previously healthy female patient following a

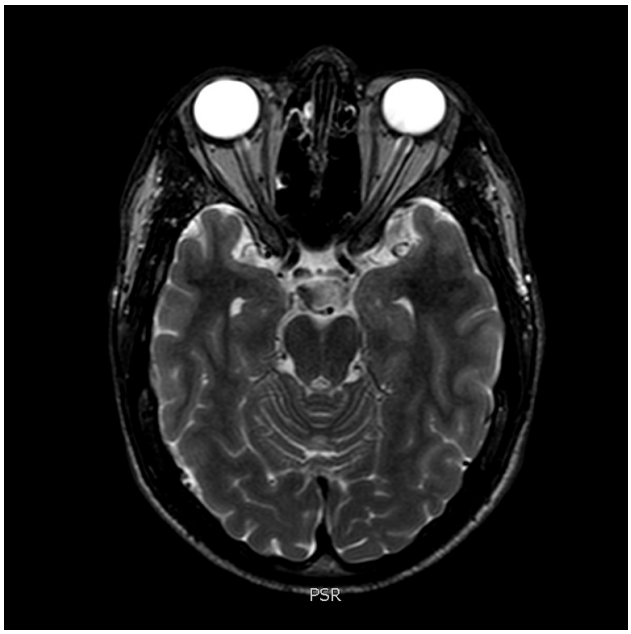


Figure 2. Brain magnetic resonance imaging. No reported abnormal findings.

presumed CMV reinfection[6]. In their report, the diagnosis was established through the detection of viral copies in both the blood and CSF, alongside an elevated IgG titre without IgM[6]. In contrast, our patient exhibited positive titres for both IgG and IgM CMV antibodies, coupled with elevated levels of CMV-RNA copies in blood and CSF, strongly suggesting an active primary infection or a severe acute reactivation phase with systemic hematogenous spread.

The exact pathophysiological mechanism by which CMV infiltrates the optic nerve in a healthy host remains a subject of ongoing scientific debate[7]. Generally, CMV utilizes both monocytic cells and polymorphonuclear cells to disseminate throughout the body[7]. Takahashi et al. recently elucidated a potential mechanism for CMV propagation involving the cerebrospinal fluid[7]. They reported a unique case wherein an immunocompetent patient developed CMV optic neuritis in one eye induced by virus-infected CSF transmission from a CMV retinitis-bearing contralateral eye[7]. In their proposed mechanism, the transmission pathway of CMV may be similar to that of the herpes virus in acute retinal necrosis, where the virus transfers from one eye to the other via the optic nerve and central nervous system[7]. They speculated that local inflammation allowed CMV to infiltrate the CSF and transfer to the optic nerve on the opposite side, causing optic neuritis[7]. In our patient, the bilateral nature of the early optic disc oedema, combined with positive systemic viremia and the total absence of prior localized retinitis, suggests that the virus may have reached the retrobulbar optic nerves haematogenously or via direct CNS tracking, bypassing the retina altogether. Diagnosing severe CMV manifestations in immunocompetent hosts requires a high index of suspicion and rigorous laboratory testing to exclude alternative aetiologies[8]. The diagnostic workup for isolated optic neuritis must aggressively rule out autoimmune and demyelinating conditions before confirming an infectious source[8]. In the Melancia et al. case, cerebrospinal fluid inflammatory panels revealed no oligoclonal bands, and anti-neuromyelitis optica (NMO) antibodies (MOG and AQP4) were negative[6]. Due to a preceding flu-like illness, their thorough investigation included common neurotropic viruses in both blood and CSF[6]. Similarly, in our patient, serum testing for AQP4 and MOG antibodies was sent to an external laboratory to rule out NMO spectrum disorder and MOG antibody-associated disease. The ultimate detection of CMV viremia alongside elevated IgM and IgG in our patient shifted the diagnostic paradigm decisively toward an infectious aetiology.

Historically, the rather moderate accuracy of routinely available diagnostic methods, such as standard serological tests, may have led to the underreporting of severe CMV infections[5]. Currently, molecular diagnostic methods, such as PCR assays, are deemed more rapid and highly sensitive compared to traditional serological or virus isolation tests[8]. When binocular CMV neuroretinal manifestations develop asynchronously or atypically in an immunocompetent patient, CSF PCR can be particularly helpful to confirm the presence of CMV[8]. Prompt diagnosis is crucial for early and proper treatment, as recognizing CMV illustrates the propensity of the virus to track along axons[1,6].

Therapeutic management of severe CMV infections in immunocompetent patients presents a significant clinical dilemma[9]. An issue that has not been comprehensively resolved is the potential role of specific antiviral treatment for these patients[9]. Although current opinion often suggests that CMV infection in immunocompetent patients does not require treatment, the specific risks and benefits of specific antiviral treatment for severely ill patients are not adequately addressed[9]. Consequently, there are no current recommendations or formalized guidelines for the use of antiviral agents against CMV in immunocompetent patients[9]. The data regarding the need for specific antiviral treatment are rather conflicting, and no definitive conclusions can be drawn about the potential benefit of antiviral therapy for severe CMV disease based solely on uncontrolled reports[9]. The presumed benefit of specific antiviral treatment must always be carefully weighed against the potential toxicity of the therapy[9]. The clinical practice reported in the literature demonstrates that physicians generally tend to prescribe antiviral treatment for the most severe manifestations, such as monophasic meningoencephalitis, severe lung involvement, and severe ocular involvement due to CMV[5,9].

Another vital layer of complexity in managing CMV optic neuritis is the controversial role of corticosteroids[10]. In the case documented by Melancia et al., the patient was managed with a 14-day course of intravenous ganciclovir alongside high-dose intravenous corticosteroids (1 g methylprednisolone for 3 days), resulting in the complete resolution of visual complaints[6]. The authors noted that while this suggests a possible benefit of antiviral treatment, the argument is weakened by the concomitant use of high-dose corticosteroids[6]. Similarly, our patient received high-dose corticosteroids initially, which yielded significant clinical improvement, followed by oral valganciclovir to eradicate the viral load. Takahashi et al. observed that while CMV retinitis resolved rapidly with antiviral drugs, CMV optic neuritis required an extended regimen of antiviral drugs and high-dose steroids[7]. They speculated that this discrepancy is due to differences in the integrity of the local blood-retinal barrier (BRB) and blood-brain barrier (BBB) [7]. In localized retinitis, the collapsed BRB allows antiviral drugs to rapidly infiltrate the affected tissue[7]. Conversely, if the BRB and BBB around the optic nerve remain intact, localized inflammation is prolonged and necessitates high-dose steroids to mitigate irreversible tissue damage[7]. Therefore, while steroids are generally effective in idiopathic optic neuritis where the BBB is broken, viral optic neuritis presenting with an incomplete collapse of the BBB might be exceptionally resistant to standard antiviral drugs acting alone [7].

CONCLUSION

In conclusion, severe CMV infection in immunocompetent individuals is an evolving clinical entity that warrants heightened awareness among neurologists and ophthalmologists. Due to the relapsing nature of the disease, close monitoring during the first 3 months is essential to avoid clinical deterioration. The rapid institution of antiviral therapy, combined strategically with corticosteroids to manage severe inflammation behind an intact BBB, appears to be a viable, safe, and organ-saving approach. As suggested by recent literature, we strongly advocate for adding CMV screening to the diagnostic workup in cases of suspected optic neuritis, even in patients with no discernible immune defects.

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