

Atypical Optic Neuritis with Brainstem Demyelination: A Diagnostic and Therapeutic Challenge in Seronegative Demyelinating Disease

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ABSTRACT: Optic neuritis is an acute inflammatory disorder of the optic nerve, commonly associated with central nervous system demyelinating diseases such as multiple sclerosis, neuromyelitis optica spectrum disorder (NMOSD), and MOG antibody-associated disease (MOGAD) [1,2,3]. However, atypical and seronegative presentations remain diagnostically challenging. We report a 37-year-old female who presented with progressive unilateral vision loss associated with pain on eye movement. MRI revealed FLAIR hyperintense lesions involving the left optic nerve, optic chiasm, and cervico-medullary junction. Cerebrospinal fluid analysis showed mild lymphocytic pleocytosis, while AQP4-IgG and MOG-IgG antibodies were negative [4,5,6,7]. Following systematic exclusion of infectious, autoimmune, toxic, and nutritional causes, the patient was treated with high-dose intravenous methylprednisolone followed by an oral taper, resulting in significant visual recovery. Given the atypical presentation, brainstem involvement, and seronegative status, maintenance therapy with mycophenolate mofetil was initiated to reduce relapse risk [2,8,9]. This case highlights the diagnostic complexity of seronegative demyelinating disease and underscores the importance of early recognition and timely immunotherapy in atypical optic neuritis. Notably, the coexistence of optic neuritis with cervico-medullary demyelination in a seronegative patient represents an unusual and instructive presentation that challenges conventional diagnostic frameworks across multiple sclerosis, NMOSD, and MOGAD.

KEYWORDS: Optic neuritis; seronegative demyelinating disease; neuromyelitis optica spectrum disorder; MOG antibody-associated disease; brainstem demyelination; cervico-medullary

junction; mycophenolate mofetil; intravenous methylprednisolone.

I. INTRODUCTION

Optic neuritis is an acute inflammatory demyelinating disorder of the optic nerve, typically presenting with subacute monocular vision loss, pain on eye movement, and impaired colour perception [1,2]. It is often an early manifestation of central nervous system demyelinating diseases, particularly multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and MOG antibody-associated disease (MOGAD) [3,10,4].

Although many patients experience a self-limiting course with good visual recovery, certain features such as bilateral involvement, poor recovery, or lesions extending beyond the optic nerve should raise suspicion for atypical demyelinating disease [5,11]. In particular, associated brainstem involvement broadens the diagnostic spectrum and warrants further evaluation.

The diagnostic challenge becomes greater in seronegative cases, where AQP4-IgG and MOG-IgG antibodies are absent [6,7]. In such situations, diagnosis relies on careful clinical assessment, imaging findings, and systematic exclusion of alternative causes including infections, autoimmune disorders, drug-induced toxicity, and nutritional deficiencies [12].

Involvement of the cervico-medullary junction adds further clinical significance, as lesions in this region can disrupt motor pathways and produce upper motor neuron features that may mimic neuromuscular disorders [13,14]. Additionally, shared immune mechanisms such as T-cell activation and antibody-mediated injury link CNS demyelination with other immune-mediated neurological conditions [12].

This case exemplifies the diagnostic and therapeutic challenges posed by atypical, seronegative optic

neuritis and underscores the importance of timely recognition and appropriate immunotherapy in improving clinical outcomes.

II. CASE PRESENTATION

A 37-year-old female presented with a 6–7 day history of progressively worsening vision in her left eye. The visual loss was initially painless but later became associated with pain on eye movement and a frontal headache. There was no history of recent infection, vaccination, drug exposure, or prior neurological episodes, and her family history was unremarkable.

On examination, visual acuity was 6/6 in the right eye and reduced to counting fingers at one metre in the left eye. A relative afferent pupillary defect (RAPD) was present on the left. Fundoscopic examination revealed optic disc pallor with blurred margins, and colour vision was markedly impaired in the affected eye using Ishihara plates. Visual field assessment revealed a central scotoma in the left eye on confrontation testing. Vital signs were stable, with no fever or systemic signs of infection. Neurological examination was otherwise normal, with no motor, sensory, or cerebellar deficits. Muscle tone, power (MRC grade 5/5 throughout), and deep tendon reflexes were symmetrical and normal bilaterally. Plantar responses were flexor. No signs of meningeal irritation were elicited.

Magnetic resonance imaging (MRI) of the brain and orbits with gadolinium contrast demonstrated FLAIR hyperintensity and enhancement involving the left optic nerve and optic chiasm. In addition, a T2-hyperintense lesion was identified at the cervico-medullary junction. Notably, a prior non-contrast MRI had been unremarkable, highlighting the importance of contrast-enhanced imaging in suspected demyelinating disease.

Cerebrospinal fluid (CSF) analysis revealed mild lymphocytic pleocytosis (10 cells/ μ L,

predominantly lymphocytes), with normal protein and glucose levels. Oligoclonal bands were absent, and microbiological studies for bacterial, mycobacterial, and fungal pathogens were negative.

Serological testing for aquaporin-4 IgG (AQP4-IgG) and myelin oligodendrocyte glycoprotein IgG (MOG-IgG) was negative. A comprehensive diagnostic workup excluded infectious, autoimmune, drug-induced, and nutritional causes. Haematological, biochemical, and CSF findings are summarised in Table 1 and Table 2, and MRI findings are described in Table 3.

Based on the clinical, radiological, and laboratory findings, a diagnosis of atypical seronegative optic neuritis with associated brainstem demyelination was made.

The patient was treated with intravenous methylprednisolone (one gram per day for five consecutive days), followed by a tapering course of oral prednisolone (1 mg/kg/day, tapered over four weeks). Visual evoked potentials (VEP) performed prior to treatment initiation demonstrated prolonged P100 latency in the left eye, corroborating optic nerve dysfunction. Significant improvement in visual acuity was observed, improving to 6/24 by day 10 and 6/9 by day 30 in the affected eye. Pain on eye movement resolved within the first week of therapy. Consistent with established management strategies for acute optic neuritis, this approach resulted in rapid clinical recovery [2].

Given the atypical presentation, brainstem involvement, and seronegative status — factors associated with an increased risk of relapse — maintenance immunosuppression with mycophenolate mofetil (500 mg twice daily) was initiated, with close follow-up planned [8,9].

The chronological progression of clinical events from symptom onset through maintenance therapy is illustrated in Figure 1.

● Symptom onset ● Diagnosis / workup ● Acute treatment ● Follow-up ● Maintenance

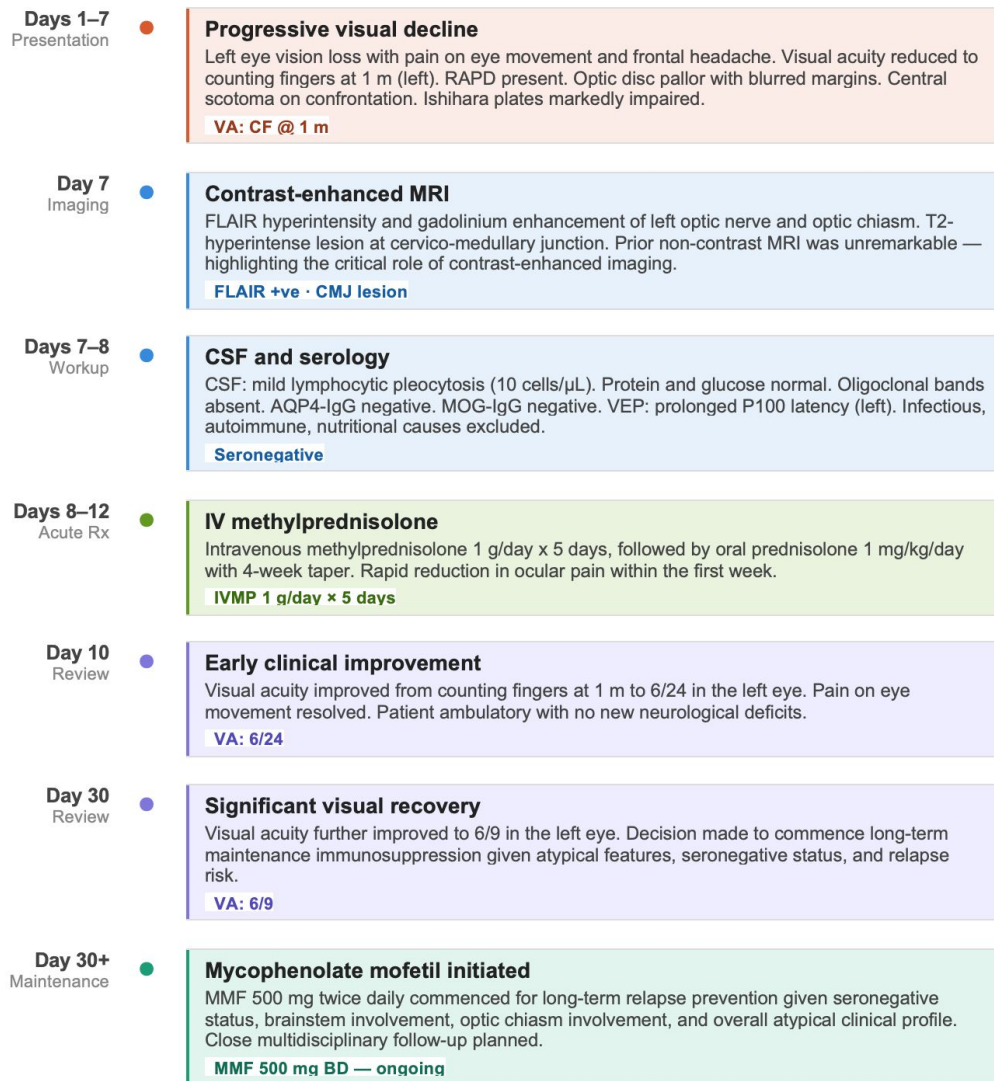


Figure 1. Clinical timeline — atypical seronegative optic neuritis with brainstem demyelination. Chronological case milestones from symptom onset through maintenance therapy. VA: visual acuity; RAPD: relative afferent pupillary defect; FLAIR: fluid-attenuated inversion recovery; CMJ: cervico-medullary junction; CSF: cerebrospinal fluid; AQP4-IgG: aquaporin-4 immunoglobulin G; MOG-IgG: myelin oligodendrocyte glycoprotein immunoglobulin G; VEP: visual evoked potentials; CF: counting fingers; IVMP: intravenous methylprednisolone; MMF: mycophenolate mofetil; BD: twice daily.

III. DISCUSSION

This case illustrates the diagnostic and therapeutic challenges of atypical optic neuritis, particularly when associated with brainstem involvement and negative antibody markers. To our knowledge, the combination of unilateral optic neuritis, optic chiasm involvement, and a concomitant cervico-medullary demyelinating lesion in a seronegative patient is an unusual presentation that does not fit neatly within established diagnostic

criteria for MS, NMOSD, or MOGAD — underscoring the value of systematic, criteria-based evaluation. While classical optic neuritis is typically confined to the optic nerve, the presence of additional central nervous system lesions broadens the differential diagnosis and raises suspicion for a more extensive demyelinating process [1,3,8].

Seronegative variants of neuromyelitis optica spectrum disorder (NMOSD) and MOG antibody-associated disease (MOGAD) are increasingly

recognised. A subset of patients fulfilling clinical criteria may lack detectable AQP4-IgG or MOG-IgG antibodies, making diagnosis heavily reliant on clinical presentation and radiological findings [15]. The key differentiating features across the three major demyelinating conditions are summarised in Table 4 [3,4,5,11,6,7,8,15,16]. In seronegative cases such as this, a structured and systematic diagnostic approach becomes essential.

The involvement of the cervico-medullary junction in this patient adds further clinical significance. Demyelination in this region can disrupt descending motor pathways, potentially producing upper motor neuron features that may overlap with neuromuscular disorders [13,14]. Additionally, shared immunological mechanisms such as antibody-mediated injury and T-cell dysregulation highlight the overlap between CNS demyelination and other immune-mediated neurological conditions [12].

A major strength of this case lies in the systematic exclusion of alternative diagnoses. Infectious causes, including tuberculosis, syphilis, and viral infections, were ruled out through appropriate investigations, while drug-induced and nutritional causes were excluded based on clinical history and laboratory findings [12,16,17,18]. This approach is particularly important in seronegative cases, where diagnosis is often one of exclusion.

High-dose intravenous corticosteroids remain the cornerstone of acute optic neuritis management. Evidence from the Optic Neuritis Treatment Trial demonstrates that intravenous methylprednisolone accelerates visual recovery, although long-term visual outcomes remain comparable [1,2]. The clinical response observed in this patient is consistent with these findings [8,19].

For long-term management, mycophenolate mofetil was selected as maintenance immunosuppressive therapy. It inhibits lymphocyte proliferation and has shown efficacy in reducing relapse rates in NMOSD and related demyelinating disorders, particularly in settings where alternative therapies may not be feasible [9,20].

The significance of contrast-enhanced MRI in this case cannot be overstated. The initial non-contrast MRI was unremarkable, and the demyelinating lesions were only detected following gadolinium administration — a finding that underscores the critical role of contrast-enhanced sequences in the evaluation of suspected inflammatory optic neuropathy. Enhancement patterns on MRI not only confirm active inflammation but also help delineate the extent of involvement, as seen here with both optic nerve and

chiasmatal enhancement, as well as the cervico-medullary junction lesion [8]. This has important implications for clinical practice, as non-contrast MRI alone may significantly underestimate disease burden in seronegative demyelinating presentations.

The CSF findings in this case, while non-specific, provided important supportive information. Mild lymphocytic pleocytosis is reported in a proportion of patients with both NMOSD and atypical optic neuritis, and the absence of oligoclonal bands and normal IgG index helped reduce the likelihood of classical multiple sclerosis [6,7]. The negative infectious panel further substantiated an inflammatory rather than infective aetiology. These findings collectively reinforce the diagnostic value of comprehensive CSF analysis in seronegative presentations, where a single definitive biomarker is unavailable.

Prognostically, seronegative atypical optic neuritis with brainstem involvement carries a meaningful relapse risk, though the natural history is less well-defined than in seropositive NMOSD. Studies suggest that the absence of detectable antibodies does not necessarily confer a more benign prognosis, and that relapse rates remain significant in patients with atypical features [17,9]. Early initiation of maintenance immunosuppression — as employed in this case with mycophenolate mofetil — is therefore a clinically sound strategy, particularly given the involvement of the optic chiasm and cervico-medullary junction, both of which represent high-risk anatomical locations.

From a clinical practice perspective, this case also highlights the important role of clinical pharmacists in optimising immunosuppressive therapy, monitoring for adverse drug reactions, and ensuring adherence to long-term treatment, thereby contributing to improved patient outcomes.

IV. CONCLUSION

Early recognition and prompt initiation of high-dose intravenous corticosteroid therapy are crucial in the management of optic neuritis associated with demyelinating disease. This case underscores the importance of a comprehensive diagnostic approach — including systematic exclusion of infectious, autoimmune, drug-induced, and nutritional causes — particularly in atypical presentations with brainstem involvement and seronegative antibody status, where differentiation from NMOSD, MOGAD, and multiple sclerosis remains challenging. The use of maintenance immunosuppression with mycophenolate mofetil may reduce relapse risk in seronegative

demyelinating conditions, and the involvement of clinical pharmacists in optimising therapy, monitoring adverse effects, and supporting long-term adherence further reinforces the value of a multidisciplinary approach in managing such complex demyelinating disorders.

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Author Contributions: Prince Mehta and Isha Patel conceptualised the case report and drafted the manuscript. Shivam Patel and Dhruvit Jariwala contributed to data collection and literature review. Dr. Bhavin Vyas reviewed and revised the manuscript critically. All authors approved the final version for submission.

Table 1. Haematological and Biochemical Investigations

Investigation	Result	Reference Range
Haemoglobin	12.6 g/dL	12.0–16.0 g/dL
Total WBC Count	7680 / μ L	4000–11000 / μ L
Platelet Count	231000 / μ L	150000–450000 / μ L
ESR (one hour)	12 mm/hr	0–21 mm/hr
MCV	79.8 fL	83–101 fL
Serum Creatinine	0.57 mg/dL	0.5–1.4 mg/dL
ALT (SGPT)	10.5 U/L	0–37 U/L
C-Reactive Protein (CRP)	0.60 mg/L	0–5 mg/L
Prothrombin Time / INR	15.8 s / INR 1.14	12.2–16.0 s
Anti-Nuclear Antibody (ANA)	Negative	Negative
C-ANCA / P-ANCA (by ELISA)	Negative	Negative
HIV I & II	Non-Reactive	Non-Reactive
Malarial Parasite	Not detected	Not detected
Urine Routine Examination	Within normal limits	—

Abbreviations: WBC – white blood cells; ESR – erythrocyte sedimentation rate; MCV – mean corpuscular volume; ALT – alanine aminotransferase; CRP – C-reactive protein; INR – international normalized ratio; ANA – antinuclear antibody; ANCA – antineutrophil cytoplasmic antibody; HIV – human immunodeficiency virus.

Table 2. Cerebrospinal Fluid Analysis and Antibody Profile

Parameter	Result	Reference Range
Appearance	Clear, colourless	—
pH	7.0	7.28–7.32
Total Nucleated Cell Count	10 / μ L	0–5 / μ L
Neutrophils	10%	—
Lymphocytes	90%	—
Total Protein	28.9 mg/dL	15–45 mg/dL

Glucose	57 mg/dL	~50–60% of plasma glucose
LDH	17 mg/dL	—
Adenosine Deaminase (ADA)	< 1.0 U/L	0–9 U/L
Gram's Stain	No organism seen	—
Ziehl–Neelsen Stain	No acid-fast bacilli detected	—
AQP4-IgG (cell-based assay, CSF)	Negative (<1:10)	Negative
MOG-IgG (cell-based assay, CSF)	Negative (<1:10)	Negative

Abbreviations: CSF – cerebrospinal fluid; ADA – adenosine deaminase; LDH – lactate dehydrogenase; AQP4-IgG – aquaporin-4 immunoglobulin G; MOG-IgG – myelin oligodendrocyte glycoprotein immunoglobulin G.

Table 3. MRI Brain, Orbit, and Spine Findings

Region	Key Findings
Brainstem / Cervico-medullary Junction	FLAIR hyperintense lesion involving posterior medulla extending to cervico-medullary junction (22 × 7.7 mm); no diffusion restriction; no post-contrast enhancement
Left Optic Nerve and Chiasm	T2/FLAIR hyperintensity in pre- and retro-chiasmatic segments with involvement of left optic chiasm; mild patchy post-contrast enhancement of left optic nerve
Brain Parenchyma	No focal abnormal signal; white matter, basal ganglia, internal capsule, and thalami appear normal; no haemorrhage; ventricular system normal
Whole Spine Screening	T2 hyperintense lesion at cervico-medullary junction only; no other spinal cord abnormality
Incidental Finding	Small right parasagittal fronto-parietal extra-axial lesion (~7 × 7 mm), suggestive of meningioma; no mass effect
MRI Impression	Findings suggest inflammatory demyelinating aetiology; differentials include NMOSD and MOGAD; multiple sclerosis considered less likely

Abbreviations: MRI – magnetic resonance imaging; FLAIR – fluid-attenuated inversion recovery; NMOSD – neuromyelitis optica spectrum disorder; MOGAD – myelin oligodendrocyte glycoprotein antibody-associated disease; MS – multiple sclerosis.

Table 4. Comparative Features of Multiple Sclerosis, NMOSD, and MOGAD

Feature	Multiple Sclerosis (MS)	NMOSD	MOGAD
Typical Biomarker	None specific (oligoclonal bands ~90%)	AQP4-IgG (+ve ~70–80%)	MOG-IgG (defining marker)
Optic Nerve Involvement	Unilateral; retrobulbar; good recovery	Often bilateral; severe; poor recovery	Unilateral or bilateral; disc oedema; good recovery
Spinal Cord Lesions	Short segment (<3 vertebrae); peripheral	Longitudinally extensive (≥3 vertebrae); central cord	Short or extensive; conus involvement common
Brainstem Involvement	Periventricular; juxtacortical; common	Area postrema; cervico-medullary junction	Brainstem; cortical/subcortical lesions possible

CSF Findings	Oligoclonal bands common; mild pleocytosis	Pleocytosis; raised protein; OCBs rare	Mild pleocytosis; OCBs rare
Relapse Pattern	Relapsing-remitting or progressive	Relapsing; severe disability accumulation	Relapsing; generally better recovery than NMOSD
Preferred Maintenance Therapy	DMTs (interferons, natalizumab, ocrelizumab)	Rituximab, azathioprine, MMF, inebilizumab	Oral steroids, MMF, rituximab
Present Case	Less likely (no periventricular lesions; no OCBs)	Possible seronegative; radiological criteria partially met	Possible; disc pallor and chiasm involvement consistent; seronegative

Abbreviations: MS – multiple sclerosis; NMOSD – neuromyelitis optica spectrum disorder; MOGAD – myelin oligodendrocyte glycoprotein antibody-associated disease; AQP4-IgG – aquaporin-4 immunoglobulin G; MOG-IgG – myelin oligodendrocyte glycoprotein immunoglobulin G; MMF – mycophenolate mofetil; CSF – cerebrospinal fluid; OCBs – oligoclonal bands; DMTs – disease-modifying therapies.

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