



Late-Onset Neuromyelitis Optica Spectrum Disorder Mimicking a Non-Arteritic Anterior Ischemic Optic Neuropathy—Case Report

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Abstract

A 60-year-old white woman presented to the emergency department with painless decrease of visual acuity in the left eye (LE). The diagnosis of a non-arteritic anterior ischemic optic neuropathy in the LE was established based on the clinical picture and the results of static perimetry, fluorescein angiography, visual evoked potential, and magnetic resonance imaging (MRI) of the brain and orbit. Six months later, the patient reported visual impairment in the right eye (RE). Best corrected visual acuity (BCVA) in the RE was 5/10. Gadolinium-enhanced MRI showing inflammation of both optic nerves and the optic chiasm in correlation with positivity for immunoglobulin G antibody against aquaporin-4 led to the diagnosis of late-onset neuromyelitis optica spectrum disorder. High-dose intravenous methylprednisolone therapy followed by oral tapering was administered and oral azathioprine was started to reduce the risk of further relapse. At discharge, BCVA was 5/5 in the RE. The patient remains under the care of neurology and ophthalmology clinics, with no recurrences for two years. The possibility of neuromyelitis optica spectrum disorder with optic neuritis in older patients is important in the differential diagnosis of ischemic optic neuropathy.

Keywords: Neuromyelitis optica spectrum disorder, late-onset NMOSD, optic neuritis, anti-aquaporin 4 antibody, AQP4

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a complex immune-mediated disease in which demyelination and loss of astrocytes constitute the main pathological findings in the central nervous system (CNS). It can affect the optic nerves, brain, brainstem, and spinal cord. The most common presentations are severe, recurrent attacks of optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM), distinct from multiple sclerosis (MS). Serological positivity for immunoglobulin (Ig) G antibody against aquaporin 4 (AQP4) was found to be the pathologic cause as well as a reliable biomarker for NMOSD.^{1,2}

The reported incidence of NMOSD ranges from 0.05 to 0.4 per 100,000 individuals.^{2,3} However, these data are limited, as up to 29% of cases are initially misdiagnosed as MS.³ Typical age at presentation is between 32 to 41 years, with a female predominance (woman constituting 70-90% patients with NMOSD).^{2,3} It is postulated that there is also predilection for the non-white population, mainly people of East Asian and Afro-Caribbean descent.⁴ NMOSD with onset at age ≥ 50 years is known as late-onset NMOSD (LO-NMOSD). It is an exceedingly rare presentation associated with worse final visual outcome, greater susceptibility to disability, and higher mortality rate.^{5,6,7}

Case Report

A 60-year-old white woman presented to the emergency department with complaints of sudden, painless decreased visual acuity in the left eye (LE) for 3 days. There was no history of preceding trauma, eye drop usage, or ocular surgery. Systemic history included well-controlled hypertension and

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hypothyroidism. Best corrected visual acuity (BCVA) was 5/5 in the right eye (RE) and 5/10 in the LE. There was no pain associated with eye movements. Left relative afferent pupillary defect was present. Fundus examination revealed diffuse optic edema in the LE, while the right optic disc appeared normal but with no cup. Intraocular pressure was 18 mmHg in the RE and 19 mmHg in the LE.

The patient was admitted to the ophthalmology department for further work-up. Various tests including full blood count, prothrombin time, activated partial thromboplastin time, serum electrolytes, glucose level, C-reactive protein, serum erythrocyte sedimentation rate, renal, liver, and thyroid function tests, serum vitamin B₁₂ and folate levels, angiotensin-converting enzyme, rheumatoid factor, antinuclear-antibody, anti-neutrophil cytoplasmatic antibody, double-stranded DNA, and anti-cardiolipin antibodies were within normal limits. Serological infective screening including anti-herpes simplex virus, *Borrelia burgdorferi* antibodies, hepatitis B surface antigen, anti-hepatitis C virus, Human Immunodeficiency Virus antibody/antigen combo, and treponemal antibody test for syphilis were all non-reactive. Deviations from the standard included elevated levels of total cholesterol (246 mg/dL, normal: 115-190), low-density lipoprotein cholesterol (164 mg/dL, normal: <115), and a history of cytomegalovirus infection (IgG 376 AU/mL, normal: <6.0; IgM 0.08 AU/mL, normal: <0.85). No abnormalities were detected on neurology and internal medicine consultations. Blood pressure was 110/75 mmHg. Magnetic resonance imaging (MRI) of the brain and orbit showed no abnormalities. However, the patient only agreed to undergo the examination without any contrast agent. She stated that she probably had an anaphylactic reaction to contrast in the past, but she was unable to accurately describe the incident and had no documentation.

Static perimetry in the LE demonstrated an inferior altitudinal defect in the visual field (VF) (Figure 1A). Fluorescein

angiography (FA) in the LE showed increasing hyperfluorescence of the temporal part of the optic disc, with contrast leakage indicative of edema. Visual evoked potential (VEP) was normal in the RE, while the LE exhibited increased P100 latency (prolonged to 120%), an amplitude of 25% after 1° stimulation, and residual response after 15 minutes (Figure 2A, B). It was considered that these results may correspond to a non-arteritic anterior ischemic optic neuropathy (NAION) in the LE.

During hospitalization, the patient received topical brinzolamide 3 times a day to the LE and intravenous methylprednisolone (IVMP) 1 g daily for 3 days and pentoxifylline 100 mg twice daily. BCVA at discharge was 5/5 in the RE and 5/8 in the LE. The patient was referred to the cardiology, vascular, and pulmonology clinics for further testing. Two weeks later, the patient presented to the ophthalmology outpatient clinic for post-hospitalization follow-up. BCVA in the LE was only light perception. VEP showed no response, indicating atrophy of the left optic nerve. The patient was referred for another neurological consultation, where no abnormalities were found.

Six months later, the woman returned to the ophthalmology department due to deterioration of vision, this time in the RE. BCVA was 5/10 in the RE and light perception in the LE. Fundoscopic examination of the RE showed a normal optic disc, while the left optic disc was pale. Arterial attenuation was also observed in the LE. Her general physical and systemic examination as well as laboratory tests were normal. Static perimetry in the RE revealed a superior altitudinal VF defect (Figure 1B). FA was unremarkable in both eyes. VEP pattern was normal in the RE, while the LE showed optic disc atrophy (Figure 2C).

Although the patient initially refused to undergo MRI of the brain and orbit with contrast agents, the next day she consented to the examination. Gadolinium-enhanced MRI (Gd-MRI) showed that the right and left optic nerves were the same width.

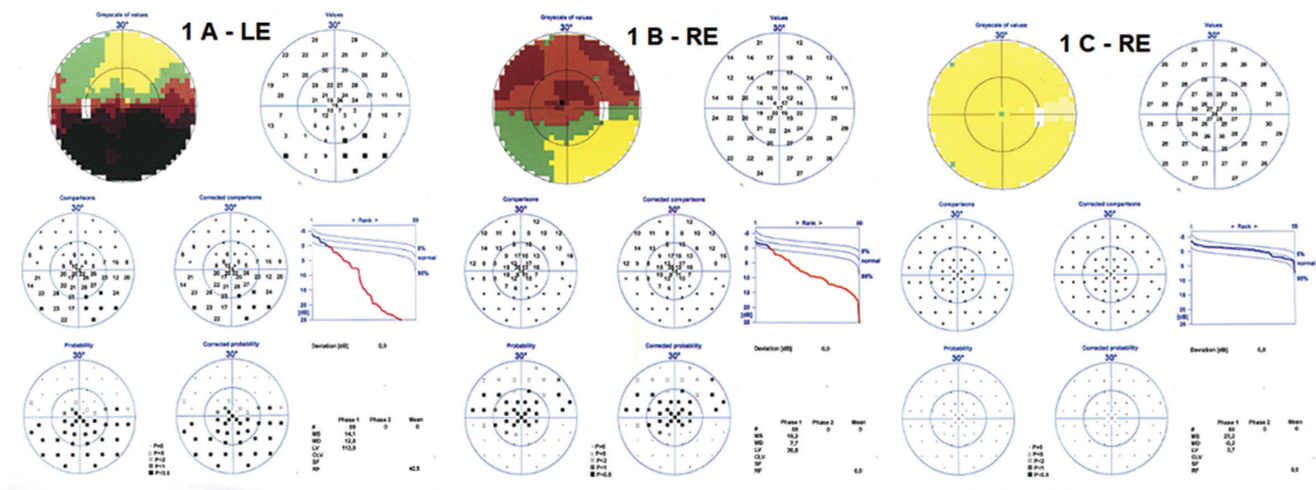


Figure 1. Static perimetry showed inferior altitudinal defect in the left eye (A) and in the right eye revealed superior altitudinal VF defect during the second hospitalization (B) and normal VF two years after discharge (C)
VF: Visual field

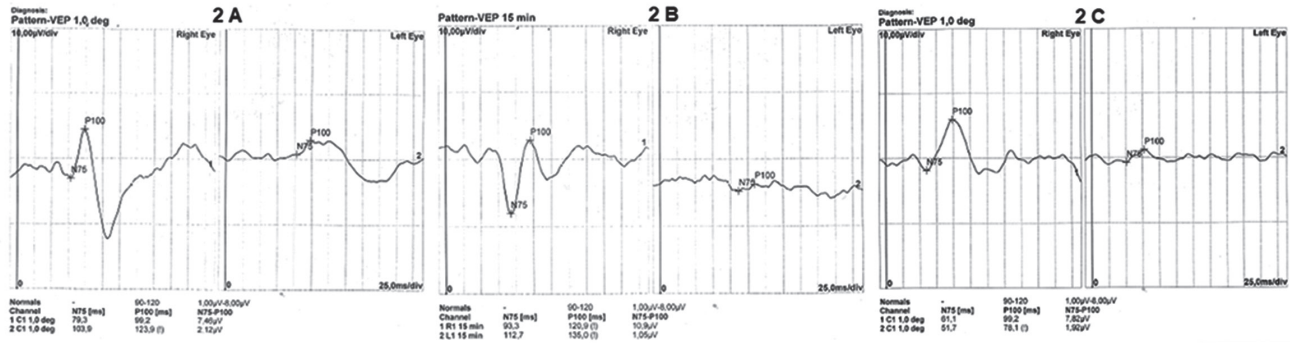


Figure 2. Visual evoked potential was normal for the right eye, while in the left eye, P100 latency was prolonged to 120%, the amplitude after 1° stimulation was 25% (A), response was residual after 15'' (B), and the results indicated optic nerve atrophy (C)

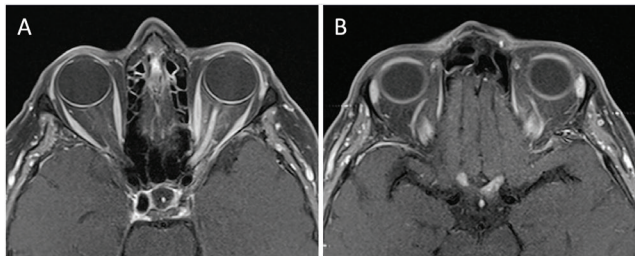


Figure 3. Gadolinium-enhanced magnetic resonance imaging of the brain (A, B) revealed the extended outline of the left part of the optic chiasm and the distal segment of the optic nerve with the cystic lesion. Visible abnormal enhancement after intravenous administration of contrast agent indicating the presence of inflammatory lesions in the left optic nerve, optic chiasm, and the right optic nerve near the optic chiasm

However, the left optic nerve was moderately enhanced after contrast in intraorbital, extraorbital, and optic chiasm sections, indicating active inflammation. The image of the right optic nerve also showed contrast enhancement but only near the optic chiasm (Figure 3A, B).

As the patient had two episodes of acute vision loss within a year, AQP4-IgG antibody testing was done by indirect immunofluorescence and was positive at 1:100 sample dilution, while myelin oligodendrocyte glycoprotein (MOG) IgG was negative. NMOSD was diagnosed and the standard steroid therapy was administered, with a 3-day regimen of daily 1 g IVMP followed by oral tapering over a period of 10 weeks. Gd-MRI showed no signs of longitudinally extensive myelitis in the thoracic or lumbar spinal cord. In addition, the patient was started on oral azathioprine to reduce the risk of further relapse. BCVA at discharge was 5/5 in the RE and light perception in the LE. The patient remains under the care of neurology and ophthalmology clinics, with no recurrences for 2 years (Figure 1C).

Discussion

In 2015, the International Panel for NMO Diagnosis outlined the diagnostic criteria for NMOSD, which consisted of 1) at least one core clinical characteristic (ON, acute myelitis, area postrema syndrome, symptomatic narcolepsy or

acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, symptomatic cerebral syndrome with NMOSD-typical brain lesions); 2) positive AQP4-IgG test; and 3) exclusion of alternative diagnoses.⁸ The key characteristic of NMOSD is the presence of AQP4 antibodies that can penetrate the blood-brain barrier. AQP4 is the main water channel protein predominantly expressed in the cell membrane of astrocytic foot processes, and antibodies against it initiate an immune response, which mediates inflammatory cell infiltration and demyelinating lesions.²

The most common manifestation of NMOSD at onset is ON (37-54%; bilateral in 20% of cases), followed by LETM (30-47%).⁹ ON in NMOSD, although clinically similar to the attacks seen in MS or isolated ON, is characterized by more severe visual loss associated with more profound neuro-axonal damage. The hallmark of NMOSD is a relapsing course, and the time between relapses is shorter as compared to MS. Relapse occurs in up to 90% of patients and in half of all patients occurs within 1 year of the initial attack,¹⁰ as in the present case.

Screening for AQP4-IgG and MOG-IgG may not be necessary for patients presenting with typical ON. However, the presence of atypical features such as severely impaired visual acuity, rapid progression, recurrent episodes, poor visual recovery, bilateral involvement, non-responsiveness to corticosteroids or corticosteroid dependency, prominent disc edema, perineural optic nerve enhancement, and coexisting extra-optic CNS demyelinating lesions should alert the ophthalmologist to consider alternative causes.¹¹ Moreover, granulomatous inflammatory conditions, vasculitis, infections, intracranial lesions, and various autoimmune conditions can mimic NMOSD and need to be excluded if the presentation is not typical.¹²

ON represents the most common cause of acute optic neuropathy among patients under 50 years of age.¹³ This case report illustrates the diverse clinical manifestation of NMOSD-ON, which can make diagnosis challenging at onset in older patients. The typical age range at NMOSD onset is 32 to 41 years. However, it has been encountered among children and older adults as well.⁶ Interestingly, in the majority of LO-NMOSD, the initial presentation is concomitant with findings of myelitis rather than ON.¹⁴ Fundus examination

in NMOSD is usually unremarkable. Only 5-33% of subjects exhibit optic disc edema, whereas optic disc edema with splinter hemorrhage and no cup or small optic disc cup in the fellow eye (referred to as a “disc at risk”) are characteristic of NAION.^{15,16} Our patient presented “disc at risk” in the second eye at initial presentation. However, no splinter hemorrhage was detected in the first affected eye. The ON Treatment Trial identified diffuse VF loss in two-thirds of affected eyes and central field loss in one-third. Altitudinal VF abnormality, which is considered characteristic of NAION, was present in 8% of participants (in the superior as well as inferior half of the VF).¹⁷ Therefore, the presence of altitudinal VF defect should warrant consideration of ON besides the vascular and compressive causes among the differential diagnoses. Furthermore, normal non-contrast MRI scans as well as the results of VEP and FA in correlation with low BP in our patient mimicked NAION as the most likely etiology in her age group. On the other hand, the dramatic deterioration of vision to LP in our patient after stopping steroids during follow-up is highly uncharacteristic for NAION and should alert the clinician to consider other diagnoses. It is worth noting that also in the case of another ON episode in the other eye, VEP and FA records were unremarkable, which indicates their low usefulness in the differential diagnosis of optic disc edema and that Gd-MRI remains the key examination. The findings of longitudinally extensive optic nerve enhancement with a predilection for the posterior optic pathway and the optic chiasm and/or bilateral optic nerve involvement are atypical and should raise suspicion for NMOSD-ON.¹⁸ However, around 40% of patients with NMOSD may also present with a normal orbital MRI.¹⁹ It should be emphasized that awareness of NMOSD-ON in older patients is crucial in the differential diagnosis of ischemic optic neuropathy.

The gold standard treatment for acute attacks of ON includes high-dose corticosteroids, typically IVMP 1 g/day for 3-5 days, followed by oral steroids to avoid early relapse.²⁰ In patients not responding to IVMP, plasma exchange (4-9 cycles) should be commenced.²¹ Although there is no consensus about the duration of preventive treatment, many experts believe that maintenance therapy should be continued for life.¹ The most commonly used are mycophenolate mofetil, azathioprine, rituximab, methotrexate, and tocilizumab. Most patients achieve remission with one of the first two drugs they try. Importantly, treatment modalities for NMOSD and MS are significantly different. MS disease-modifying treatment (e.g., interferon β , fingolimod, and natalizumab) have been associated with nonresponse or exacerbation in NMOSD,²² highlighting the importance of early and accurate diagnosis.

NMOSD has a poor prognosis, with a median survival of 8 years from time of diagnosis and overall 10-year mortality of 20-25%.¹⁰ Furthermore, Papathanasiou et al.⁵ found that older age at the onset of NMOSD is a predictor of poor outcome, and patients with LO-NMOSD were expected to reach higher Expanded Disability Status Scale score during follow-up compared to those with early onset NMOSD (EO-NMOSD). Thongmee et al.⁶ indicated that patients with LO-NMOSD-ON

had significantly worse nadir VA at ON onset as well as worse final VA compared to patients with EO-NMOSD-ON. There is no evidence that there is an arbitrary cut-off age at onset, rather clinical phenotypes and disability gradually change with time.⁵ Poorer recovery from the attack may be caused by the negative relationship between retinal nerve fiber layer thickness and age, as well as reduced repair mechanisms, impaired immune tolerance, and comorbidities.^{7,23}

Early diagnosis and prompt treatment preserve better visual outcomes and prevent the accumulation of severe neurologic disability in patients with NMOSD. Therefore, it is strongly recommended to include LO-NMOSD-ON in the differential diagnosis of acute to subacute optic neuropathy in addition to ischemic optic neuropathy among the middle-aged and older populations.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: D.W-P, L.S., Concept: L.S., M.Š., D.W-P, Design: M.Š., L.S., Data Collection or Processing: M.Š., L.S., Analysis or Interpretation: L.S., M.Š., D.W-P, Literature Search: M.Š., L.S., Writing: M.Š., L.S.

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