Polskie Towarzystwo Okulistyczne
www.pto.com.pl

KLINIKA OCZNA 2023, 125, 2: 75-78
Received: 9.03.2022 Accepted: 28.04.2022

REVIEW ARTICLE

Access this article online

Website:
www.klinikaoczna.pl

DOI:
https://doi.org/10.5114/ko.2023.124696

Myelin oligodendrocyte glycoprotein (MOG)-IgG associated optic neuritis as a new issue in the differential diagnosis of optic neuropathy

Barbara Nowacka, Wojciech Lubiński

2nd Department of Ophthalmology, Pomeranian Medical University, Szczecin, Poland

ABSTRACT

Myelin oligodendrocyte glycoprotein (MOG)-IgG associated optic neuritis has been established as a new subset of optic neuropathy. The recent development of serological diagnostics of MOG-IgG has improved our ability to identify this disease, which differs from multiple sclerosis and aquaporin 4 (AQP4)-IgG positive neuromyelitis optica spectrum disorder in terms of clinical features and treatment outcomes. Based on available literature, we summarize the current knowledge of the clinical presentation, evaluation and management of patients with MOG-IgG associated optic neuritis, with a comparison to the other most common types of optic neuritis.

KEY WORDS: myelin oligodendrocyte glycoprotein, MOG, optic neuritis, multiple sclerosis, aquaporin 4, neuromyelitis optica spectrum disorder.

PATHOPHYSIOLOGY

Optic neuritis (ON) is a cardinal manifestation of inflammatory conditions of the central nervous system (CNS). It can be the first symptom of multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD). Neuromyelitis optica spectrum disorders are inflammatory demyelinating diseases of the CNS that cause optic neuritis, transverse myelitis and some other CNS syndromes. In more than 80% of cases, NMOSD is caused by immunoglobulin G autoantibodies to aquaporin 4 (AQP4), the most frequent water channel protein in the CNS. A subset of AQP4-negative cases may be associated with myelin oligodendrocyte glycoprotein (MOG) antibodies even in 42% of patients [1-4].

Oligodendrocytes are a type of glial cells present in the optic nerves. They form a myelin sheath on their axons (Figure 1). Myelin oligodendrocyte glycoprotein is a surface protein located on the oligodendrocytes; it is involved in maintaining the myelin structure. Unlike AQP4, MOG is closely related to the CNS and does not occur in other tissues of the body [4]. It is known to be highly immunogenic with the potential of causing autoimmune diseases, which confirms its use for the induction of experimental autoimmune encephalitis in laboratory animals [5]. Autoantibodies to MOG can activate the complement system and induce a cytotoxic reaction, leading to primary demyelinating damage, sparing axons and astrocytes in the initial stage of the disease [6, 7]. Meanwhile, AQP4 antibodies at first lead to massive astrocyte destruction, disturbance of the blood-brain barrier function and secondary damage to the myelin sheath [3, 8].

EPIDEMIOLOGY

Myelin oligodendrocyte glycoprotein-IgG-associated disorder (MOGAD) is generally observed more often in younger individuals (compared to AQP4-IgG NMOSD) and affects females and males equally. The overall incidence is estimated at 0.16 per 100,000 per year (0.31 for children and 0.13 for adults) [9].

CLINICAL PRESENTATION

Overall, the most common clinical presentation of MOGAD is ON [10]. MOG-IgG positive ON tends to be more often recurrent (in approximately 50% of patients) and bilateral (72.7% of MOG-IgG patients vs 24% of AQP4-IgG patients) [10, 11]. Significant eye pain is common in the acute phase. It is also more often associated with optic disc oedema than other causes of acute demyelinating ON, which can sometimes be severe and include peripapillary haemorrhages. That is why it may lead to misdiagnosis of papilloedema from elevated intracranial pressure in bilateral cases or nonarteritic anterior optic neuropathy in unilateral ones. Overall, optic disc oedema is reported in up to 86% [12-14]. Optic nerve MRI reveals longitudinal, extensive (involving > 50%

CORRESPONDING AUTHOR

Prof. Wojciech Lubiński, 2nd Department of Ophthalmology, Pomeranian Medical University, 72 Powstańców Wlkp. St., 70-111 Szczecin, Poland,
e-mail: okulistyka@spsk2-szczecin.pl; lubinski@pro.onet.pl

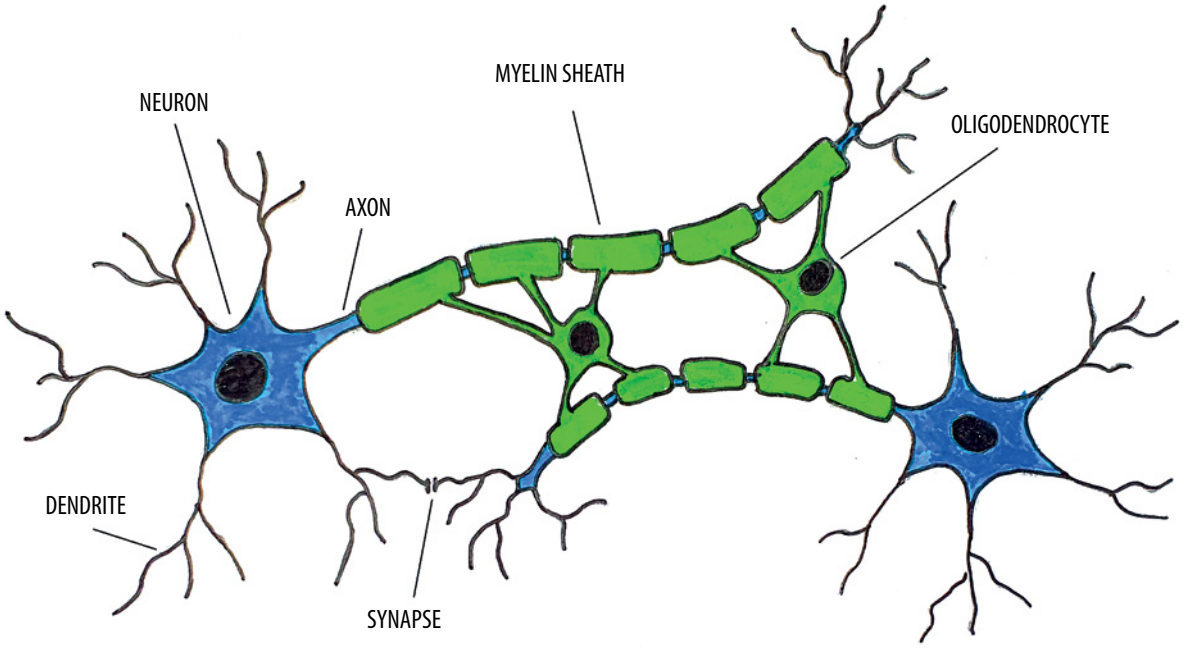

Figure 1. The relationship between neurons and oligodendrocytes in the central nervous system

of the length of the optic nerve) and anterior (usually seen in the orbital and intracranial region of the optic nerve) enhancement, while AQP4-IgG positive ON tends to have more posterior, often optic chiasm involvement. Another common finding is optic perineuritis with optic nerve sheath enhancement, in contrast to MS-related ON, where parenchymal optic nerve enhancement is usually seen [13, 15]. Brain MRI in MOGAD reveals non-specific white matter lesions in the brainstem, adjacent to the fourth ventricle or a normal appearance, but not the ovoid, periventricular (adjacent to the lateral ventricles), white matter lesions typical of MS. However, MRI of the spinal cord may present swelling and contrast enhancement that can resemble the transverse myelitis of NMOSD [10]. MOG-IgG positive ON typically causes severe vision loss at the onset in the form of central scotomas to complete visual loss in up to 95% of patients [16]. Despite that, as many as 75-80% of cases show a complete or significant visual recovery [10]. By comparison, over one-third of AQP4-IgG positive ON cases lead to the final visual acuity of Snellen 0.1 or worse [17]. Optical coherence tomography (OCT) studies reported greater peripapillary retinal nerve fibre layer (RNFL) and ganglion cell complex (GCC) thickness in MOG-IgG positive ON compared to AQP4-IgG positive ON [18, 19]. Subsequently, optic nerve injury results in thinning of the RNFL and GCC after the acute phase, whose severity is generally similar and more pronounced in both mentioned types of ON than in MS-related ON [20, 21]. However, despite a similar seriousness of RNFL and GCC thinning in MOG-IgG and AQP4-IgG positive ON, visual outcomes clearly diverged, with relatively preserved visual acuity in the first case and markedly worse visual outcomes in the latter [21]. Pattern visual evoked potentials (PVEPs) were employed to separate MS from inflammatory and demyelinating CNS diseases, including NMOSD. The studies indicate that P100 latency is more delayed in MS than NMOSD, with a greater proportion of absent responses and less frequent subclinical alterations in the latter group [22]. Prolongation of P100 latency persists after the acute phase, even when visual acuity returns to normal [23]. The characteristics of MOG-IgG positive ON in comparison to AQP4-IgG positive ON and MS-related ON are presented in Table I. Other manifestations of MOGAD are acute disseminating encephalomyelitis (ADEM) and transverse myelitis (TM), less frequently isolated brainstem syndromes (e.g. eye movement disorder, hearing loss, trigeminal neuralgia, dysphagia, hemiparesis, dizziness, breathing problems), rarely encephalitis or seizures. The clinical presentation of MOGAD varies based on age at onset. A recent study suggested that ADEM is the most common clinical presentation in younger children, followed by ON and ON with TM [9]. In adults, the most common presentation was ON, followed by TM and simultaneously ON and TM. Acute disseminating encephalomyelitis, especially accompanied with ON, strongly suggests MOGAD, as it is not common in MS and AQP4-IgG positive NMOSD. Transverse myelitis can appear similar to AQP4-IgG positive NMOSD but more commonly affects the *conus medullaris* [15, 24].

DIAGNOSTICS

The gold standard in MOGAD suspected cases is serological diagnostics of MOG-IgG. Characteristics of cerebrospinal fluid are neither sensitive nor specific. Very few patients were found to have oligoclonal bands seen with MS. Usually, analyses yield normal results or show a pleocytosis with a range of white blood cell counts [10, 11]. Cases of ON with bilat-

Table I. Characteristics of optic neuritis associated with MOG-IgG, AQP4-IgG and multiple sclerosis (MS)

	MOG-IgG ON	AQP4-IgG ON	MS ON
Epidemiology/aetiology			
Mean age	Children, 30s	40s	20s
Sex	Female = male	Female >> male	Female > male
Histopathology	Inflammation + demyelination	Astrocytes destruction, secondary demyelination	Severe demyelination, decreased axonal and oligodendrocyte numbers, and glial scarring
ON – main clinical features			
Eye pain	Very frequent	Less frequent	Frequent
Bilateral	Frequent	Frequent	Rare
Severe visual loss at onset	Very frequent	Very frequent	Frequent
Optic papillitis	Frequent	Rare	30%
Risk of recurrence	Very frequent	Very frequent	Frequent
Risk of severe visual loss	Infrequent	Very frequent	Infrequent
Additional ophthalmological examinations			
VEP	↑ P100 peak time + normal or mildly ↓ amplitude	↑ P100 peak time + mildly ↓ amplitude, ↓ amplitude with normal latency absent response	↑ P100 peak time + normal or mildly ↓ amplitude
Visual field	Central scotomas to complete visual loss	Total loss, central, quadrant, altitudinal	Diffuse field loss, central scotoma
OCT	Acute peripapillary RNFL and GCC thickening, followed by thinning, worsens with recurrence	Severe peripapillary RNFL thinning	Acute peripapillary RNFL and GCC thickening, followed by thinning
Optic nerve MRI findings			
Length and location	Enhancement of > 50%, orbital portion involved (lesions extend from anterior portion to whole length)	Lesions often extend from posterior portion to whole length	Short
Perineural enhancement	Frequent	Rare	Rare (usually parenchymal optic nerve enhancement)
Optic chiasm involvement	Rare	Frequent	Rare
Steroid treatment:	Steroids i.v. Followed by prednisolone p.o.	Frequently resistant to steroid therapy	Faster recovery without influence on final visual acuity

RNFL – retinal nerve fibre layer; GCC – ganglion cell complex; i.v. – intravenous; p.o. – per os.

eral ON, recurrent ON or optic disc swelling on fundoscopy should be primarily considered for cell-based assays. The differential diagnosis includes MS, NMOSD (caused by AQP4-IgG), nonarteritic anterior optic neuropathy, sarcoidosis, Lyme disease and granulomatosis with polyangiitis (Wegener's granulomatosis) [25].

TREATMENT

Randomized, controlled treatment trials are limited for MOG-IgG positive ON, but based on available results, it is recommended to use 1 g per day of intravenous methylprednisolone for 3-5 days for treatment of acute MOG-positive ON. Patients usually show rapid and significant improvement. However, the recovery increase after intravenous steroids is rated at 10-20% compared to no treatment [15, 26]. In patients who do not respond to steroid treatment, intravenous immunoglobulin or plasma exchange can be used [10, 15]. There are no prospective trials to guide the maintenance therapy for MOG-positive ON, but observational open-label work suggests its role in preventing recurrent attacks. Notably, the majority of individuals in all studies had a recurrence within the first year of attack [13, 15]. In one study, 95% of patients receiving doses of at least 20 mg of prednisone for 6 months following an acute phase treatment had no recurrent ON episodes at follow-up of over a year [14]. High dose and longer length of treatment were strongly associated with remittance, and patients who were given a tapered dose or discontinued therapy earlier had relapse rates comparable to those with no treatment [14, 15]. There are also data pointing to the role of immunosuppressive drugs, such as azathioprine, mycophenolate mofetil, rituximab and intravenous immunoglobulin, in reducing the relapse rate of MOGAD [14, 15]. These drugs should be considered in the absence of the therapeutic effect of steroids, the necessity of their limitation or the most severe

cases [27]. As the pathophysiology of MOGAD is better explained, target therapies are expected to be developed.

CONCLUSIONS

In conclusion, MOG-IgG positive optic neuritis is a new subset of optic neuropathy. It usually responds well to steroid therapy, and visual acuity outcomes are favourable. However, significant visual field defects, damage of the retinal ganglion cells, reduction of the peripapillary retinal nerve fibre layer thickness and prolonged PVEPs may remain. The risk of recurrence is high during the first year, and subsequent attacks are associated with an increased risk of permanent neurologic deficit. Further research is needed to determine the optimal management and therapy for MOGAD.

DISCLOSURE

The authors declare no conflict of interest.

References

1. Hamid SHM, Whittam D, Mutch K, et al. What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients. J Neurol 2017; 264: 2088-2094.
2. Hyun JW, Woodhall MR, Kim SH, et al. Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases. J Neurol Neurosurg Psychiatry 2017; 88: 811-817.
3. Jarius S, Ruprecht K, Kleiter I, et al.; in cooperation with the Neuromyelitis Optica Study Group (NEMOS). MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J Neuroinflammation 2016; 13: 279.
4. Narayan R, Simpson A, Fritsche K, et al. MOG antibody disease: A review of MOG antibody seropositive neuromyelitis optica spectrum disorder. Mult Scler Relat Disord 2018; 25: 66-72.
5. Kezuka T, Usui Y, Goto H. Analysis of the pathogenesis of experimental autoimmune optic neuritis. J Biomed Biotechnol 2011; 2011: 294046.
6. Mader S, Gredler V, Schanda K, et al. Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. J Neuroinflammation 2011; 8: 184.
7. Brilot F, Dale RC, Selter RC, et al. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. Ann Neurol 2009; 66: 833-842.
8. Franciotta D, Gastaldi M, Sala A, et al. Diagnostics of the neuromyelitis optica spectrum disorders (NMOSD). Neurol Sci 2017; 38: 231-236.
9. de Mol CL, Wong Y, van Pelt ED, et al. The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults. Mult Scler 2020; 26: 806-814.
10. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. Brain 2017; 140: 3128-3138.
11. Tajfirouz DA, Bhatti MT, Chen JJ. Clinical Characteristics and Treatment of MOG-IgG-Associated Optic Neuritis. Curr Neurol Neurosci Rep 2019; 19: 100.
12. Jarius S, Paul F, Aktas O, et al. MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. J Neuroinflammation 2018; 15: 134.
13. Chen JJ, Flanagan EP, Jitprapaikulsan J, et al. Myelin Oligodendrocyte Glycoprotein Antibody-Positive Optic Neuritis: Clinical Characteristics, Radiologic Clues, and Outcome. Am J Ophthalmol 2018; 195: 8-15.
14. Ramanathan S, Mohammad S, Tantsis E, et al; Australasian and New Zealand MOG Study Group. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. J Neurol Neurosurg Psychiatry 2018; 89: 127-137.
15. Jarius S, Ruprecht K, Kleiter I, et al; in cooperation with the Neuromyelitis Optica Study Group (NEMOS). MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation 2016; 13: 280.
16. Ishikawa H, Kezuka T, Shikishima K, et al; Working Group on Diagnostic Criteria for Refractory Optic Neuritis Based on Neuroimmunological Perspective. Epidemiologic and Clinical Characteristics of Optic Neuritis in Japan. Ophthalmology 2019; 126: 1385-1398.
17. Zhao Y, Tan S, Chan TCY, et al. Clinical features of demyelinating optic neuritis with seropositive myelin oligodendrocyte glycoprotein antibody in Chinese patients. Br J Ophthalmol 2018; 102: 1372-1377.
18. Akaishi T, Sato DK, Nakashima I, et al. MRI and retinal abnormalities in isolated optic neuritis with myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies: a comparative study. J Neurol Neurosurg Psychiatry 2016; 87: 446-448.
19. Martinez-Lapiscina EH, Sepulveda M, Torres-Torres R, et al. Usefulness of optical coherence tomography to distinguish optic neuritis associated with AQP4 or MOG in neuromyelitis optica spectrum disorders. Ther Adv Neurol Disord 2016; 9: 436-440.
20. Toosy AT, Mason DF, Miller DH. Optic neuritis. Lancet Neurol 2014; 13: 83-99.
21. Sotirchos ES, Filippatou A, Fitzgerald KC, et al. Aquaporin-4 IgG seropositivity is associated with worse visual outcomes after optic neuritis than MOG-IgG seropositivity and multiple sclerosis, independent of macular ganglion cell layer thinning. Mult Scler 2020; 26: 1360-1371.
22. Neto S, Alvarenga R, Vasconcelos C, et al. Evaluation of pattern-reversal visual evoked potential in patients with neuromyelitis optica. Mult Scler 2013; 19: 173-178.
23. Takano S, Hanabusa A, Yoshikawa Y, et al. Pattern Visually Evoked Potentials in Japanese Girl With Optic Neuritis and Seropositive to Anti-myelin Oligodendrocyte Glycoprotein (MOG) Antibody. Front Neurol 2019; 10: 1339.
24. Jurynczyk M, Geraldes R, Probert F, et al. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. Brain 2017; 140: 617-627.
25. Reindl M, Waters P. Myelin oligodendrocyte glycoprotein antibodies in neurological disease. Nat Rev Neurol. 2019; 15: 89-102.
26. Chen JJ, Bhatti MT. Clinical phenotype, radiological features, and treatment of myelin oligodendrocyte glycoprotein-immunoglobulin G (MOG-IgG) optic neuritis. Curr Opin Neurol 2020; 33: 47-54.
27. Dos Passos GR, Oliveira LM, da Costa BK, et al. MOG-IgG-Associated Optic Neuritis, Encephalitis, and Myelitis: Lessons Learned From Neuromyelitis Optica Spectrum Disorder. Front Neurol 2018; 9: 217.