Article type : Short Communications

Uveitis and optic perineuritis in the context of myelin oligodendrocyte glycoprotein antibody seropositivity

Sudarshini Ramanathan^{1,2} FRACP PhD, Clare Fraser³ FRANZCO, Sarah R Curnow⁴ MBBS, Mina Ghaly⁵ MBChB, Richard J Leventer⁶ FRACP PhD, Jeanette Lechner-Scott^{7,8} FRACP PhD, Andrew Henderson^{2,9} FRACP PhD, Stephen Reddel^{10,11} FRACP PhD, Russell C Dale^{1,10,12*} MRCP PhD, Fabienne Brilot^{1,10,13*} PhD

* These senior authors contributed equally

- 1 Brain Autoimmunity Group, Kids Neuroscience Centre at Kids Research, The Children's Hospital at Westmead; Sydney Medical School, University of Sydney, Sydney, Australia
- 2 Department of Neurology, Westmead Hospital, Sydney, Australia
- 3 Save Sight Institute, University of Sydney, Sydney, Australia
- 4 Department of Neurology, Royal Children's Hospital, Melbourne, Australia
- 5 University Hospital Geelong, Geelong, Australia
- 6 Department of Paediatrics, Royal Children's Hospital, Murdoch Children's Research Institute, University of Melbourne, Melbourne, Australia
- 7 Department of Neurology, John Hunter Hospital, Newcastle, Australia
- 8 Hunter Medical Research Institute, Faculty of Medicine and Public Health, University of Newcastle, Newcastle, Australia
- 9 Department of Ophthalmology, Westmead Hospital, Sydney, Australia
- 10 Brain and Mind Centre, University of Sydney, Sydney, Australia
- 11 Department of Neurology, Concord Repatriation General Hospital, Sydney, Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ENE.13932](#)

- 12 TY Nelson Department of Neurology and Neurosurgery, Children's Hospital at Westmead, Sydney, Australia
- 13 Applied Medical Sciences, University of Sydney, Sydney, Australia

Corresponding author:

Associate Professor Fabienne Brilot, Brain Autoimmunity group, Kids Neuroscience Centre at Kids Research, The Children's Hospital at Westmead, Westmead NSW 2145, Australia.

Phone number: +61 2 9845 1456

Email: fabienne.brilot@sydney.edu.au

Running Title: Uveitis and MOG antibody seropositivity

Keywords: Myelin oligodendrocyte glycoprotein antibodies, optic neuritis, uveitis, optic perineuritis, peripheral ulcerative keratitis

Abstract

Background: Antibodies to myelin oligodendrocyte glycoprotein (MOG) have been identified in both children and adults with demyelination, with a strong association with bilateral or recurrent optic neuritis (ON). However, the full clinical spectrum of this newly described condition is unknown. We sought to describe non-ON inflammatory ophthalmological presentations such as uveitis and optic perineuritis in the context of MOG antibody seropositivity.

Methods: Using a live cell-based assay analysed by flow cytometry, we identified seropositive patients referred for MOG antibody testing in Australasia between 2014-2017. We identified four MOG antibody-positive patients with non-ON inflammatory ophthalmological presentations, and present their detailed clinical information in this case series.

Results: Three patients had uveitis either in association with, or remote from, ON. One patient had optic perineuritis and peripheral ulcerative keratitis. We describe the presentation, examination, investigation findings, and clinical course of these four patients.

Conclusions and relevance: Recognition of these novel clinical associations may expand the clinical spectrum of MOG antibody-associated presentations. An expedited diagnosis may guide the management of these complex patients.

INTRODUCTION

Myelin oligodendrocyte glycoprotein (MOG) is a component of myelin expressed in the central nervous system (CNS)[1]. Antibodies to MOG have been recently identified in demyelination, primarily in the context of acute disseminated encephalomyelitis in children, or bilateral or recurrent optic neuritis (ON) and spinal involvement in children and adults[1,2]. MOG antibody-associated ON (MOG-ON) frequently presents with optic disc swelling[3], and perineural enhancement in a third of patients[4].

We provide the first description of four retrospectively diagnosed MOG antibody-positive patients who manifest inflammatory ophthalmological phenotypes including uveitis, optic perineuritis (OPN), and peripheral ulcerative keratitis (PUK), in association with or remote from ON. MOG antibody testing should be considered in these diagnostically challenging patients in addition to exploring infectious and inflammatory aetiologies.

METHODS

We test serum for MOG antibodies using a live cell-based assay analysed by flow cytometry, with high specificity [99%, 95% CI 93.7%-99.8%][2,5]. We identified four seropositive patients (Table 1) with non-ON ophthalmological presentations including uveitis, OPN, or PUK tested between 2014-2017. Ethics and research protocol approval (NEAF 12/SCHN/395) has been granted, and informed consent was obtained.

RESULTS

The clinical characterisation of these four patients is outlined in Table 1 and Figure 1, and detailed in the Supplementary Text. Three patients had five episodes of uveitis (recurrent in one patient with three episodes and monophasic in two patients). Uveitis was bilateral at onset in all three patients; and associated with bilateral ON at first presentation in two patients, but not in the third. The first presentation of uveitis was anterior and intermediate in two patients, and intermediate and posterior in one patient. All three patients had severe visual impairment at onset and mild to moderate visual acuity loss, two had visual field deficits, and one had retinal nerve fibre layer atrophy at follow-up. The patient with recurrent uveitis developed additional neurological symptoms and dynamic and enhancing white matter MRI lesions. All three patients had uveitis refractory to treatment with topical steroids and progression of visual impairment prior to the identification of MOG antibodies. A fourth patient presented with OPN followed four months later by PUK.

DISCUSSION

We describe the novel clinical association of inflammatory ophthalmological presentations such as uveitis and PUK with MOG antibodies, in both adults and children. In 1450 patients with uveitis, concomitant neurological conditions which were thought to be causally related were identified in 7.9%; with Vogt-Koyanagi-Harada disease (1.1%), primary CNS lymphoma (1.1%), MS (1%), herpes virus infections (0.7%), and ON (0.5%), accounting for the majority[6]. The association of clinically definite MS and uveitis is uncommon. The prevalence of MS among patients with uveitis, and conversely of uveitis in MS, is 1%[7,8]. MS patients with intermediate uveitis[7,9] do not differ in clinical course and disability compared to those with MS alone[10]. There is no literature regarding AQP4 or MOG antibodies being associated with uveitis. This case series highlights that some MOG antibody-positive patients may have anterior, intermediate, or posterior uveitis. Further follow-up is required to determine the outcomes in these patients

Case 2's ophthalmological presentation was attributed to, and treated as, ocular syphilis. The majority of patients with syphilitic uveitis who are treated accordingly have a good visual prognosis[11]. In contrast, Case 2 has severe visual impairment despite treatment for syphilis, raising questions regarding the contribution of the MOG antibodies. We could alternatively hypothesise that a primary infection (ocular syphilis), may have triggered an autoimmune pathology

(MOG-ON). A recent description of a patient with MOG-ON in the setting of acute cytomegalovirus infection lends weight to this hypothesis[12].

OPN, in which the primary target is the optic nerve sheath is often idiopathic, but uncommonly attributed to systemic inflammatory disorders[13]. MRI may show characteristic “tram-track” and circumferential enhancement of the optic nerve sheath and orbital fat[13,14]. Kim et al[4] described a third of MOG-ON patients had perineural enhancement extending to soft tissue, as in Case 4. Many OPN patients treated with corticosteroids experience rapid pain relief, and relapse on steroid cessation[13]. We have similarly reported rapid symptomatic improvement with steroids and propensity to relapse on cessation, with MOG-ON[2,5]. It is interesting to speculate that a subgroup of patients classified as idiopathic OPN may be MOG antibody-positive. It is essential to distinguish ON from OPN, as patients with a typical ON are at increased risk for MS, but corticosteroids are not shown to influence the visual outcomes[13]. In contrast, patients with OPN may continue to lose vision unless treated adequately with corticosteroids[13]. PUK can be associated with systemic autoimmune conditions such as rheumatoid arthritis and lupus[15], but has not previously been described with MOG antibodies.

The pathophysiological basis of MOG antibodies resulting in both ON and other ocular manifestations such as uveitis is of interest but not understood. MOG is a minor component of CNS myelin[1], but is not present in unmyelinated ophthalmological structures. Interestingly MOG, which induces demyelinating disease in rodent models of experimental autoimmune encephalomyelitis, has been shown to simultaneously induce uveitis[16]. Specifically, adoptive transfer of MOG-specific T cells were capable of inducing encephalomyelitis and chronic anterior uveitis, demonstrating that an immune response to MOG can be uveitogenic[16]. At present it is unclear whether MOG antibodies in the cases we describe are pathogenic or an epiphenomenon. Further studies demonstrating the pathogenic mechanisms of action of these antibodies are required.

This case series highlights the novel association of MOG antibodies with uveitis and PUK, in addition to previously described ON and OPN, thereby expanding the clinical spectrum of MOG antibody-associated CNS and ophthalmological presentations. Although the incidence of these inflammatory ophthalmological presentations in association with MOG antibodies is likely to be less frequent than ON and further international corroboration is required to confirm this association, awareness of these syndromes may expedite diagnosis. Early recognition may reduce relapses and potentially guide management.

References for online only E-extra publication

1. Ramanathan S, Dale RC, Brilot F. Anti-MOG antibody: The history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. *Autoimmunity Reviews* 2016;**15**:307-324.
2. Ramanathan S, Mohammad S, Tantsis E, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. *Journal of Neurology Neurosurgery and Psychiatry* 2018; **89**:127-137.
3. Ramanathan S, Prelog K, Barnes EH, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. *Multiple Sclerosis* 2016; **22**: 470-482.
4. Kim SM, Woodhall MR, Kim JS, et al. Antibodies to MOG in adults with inflammatory demyelinating disease of the CNS. *Neurology Neuroimmunology and Neuroinflammation* 2015; **2**: e163.
5. Ramanathan S, Reddel SW, Henderson A, et al. Antibodies to myelin oligodendrocyte glycoprotein in bilateral and recurrent optic neuritis. *Neurology Neuroimmunology and Neuroinflammation* 2014;**1**:e40.
6. Smith JR, Rosenbaum JT. Neurological concomitants of uveitis. *British Journal of Ophthalmology* 2004; **88**: 1498-1499.
7. Biouesse V, Trichet C, Bloch-Michel E, Roullet E. Multiple sclerosis associated with uveitis in two large clinic-based series. *Neurology* 1999; **52**: 179-181.
8. Olsen TG, Frederiksen J. The association between multiple sclerosis and uveitis. *Survey of Ophthalmology* 2017; **62**: 89-95.
9. Messenger W, Hildebrandt L, Mackensen F, et al. Characterisation of uveitis in association with multiple sclerosis. *British Journal of Ophthalmology* 2015;**99**:205-209.
10. Le Scanff J, Seve P, Renoux C, et al. Uveitis associated with multiple sclerosis. *Multiple Sclerosis* 2008; **14**: 415-417.
11. Zhang T, Zhu Y, Xu G. Clinical Features and Treatments of Syphilitic Uveitis: A Systematic Review and Meta-Analysis. *Journal of Ophthalmology*; 2017:6594849.
12. Rusescu BV, Diederich NJ, Tsobo C, et al. MOG antibody-associated optic neuritis in the setting of acute CMV infection. *Journal of the Neurological Sciences* 2017; **382**: 44-46.
13. Purvin V, Kawasaki A, Jacobson DM. Optic perineuritis: clinical and radiographic features. *Archives of Ophthalmology* 2001; **119**: 1299-1306.
14. Hickman SJ. Optic Perineuritis. *Current Neurology and Neurosciences Reports* 2016; **16**: 16.

15. Cao Y, Zhang W, Wu J, et al. Peripheral Ulcerative Keratitis Associated with Autoimmune Disease: Pathogenesis and Treatment. *Journal of Ophthalmology*; 2017:7298026.
16. Shao H, Sun SL, Kaplan HJ, Sun D. Induction of autoimmune encephalomyelitis and uveitis in B6 and (B6 x SJL) mice by peptides derived from myelin/oligodendrocyte glycoprotein. *Journal of Neuroimmunology* 2002; **132**: 117-122.

Figure Legends

Figure 1: Uveitis, optic perineuritis, and peripheral ulcerative keratitis associated with MOG antibodies. Case 3 had bilateral optic disc swelling on examination (A). Case 4 had unilateral right optic disc swelling associated with retinal folds and Paton's lines (arrows) (B). Visual field testing on his initial presentation revealed dense peripheral constriction with relative central sparing, in a pattern characteristic of optic perineuritis (C). His MRI demonstrated perineural gadolinium enhancement (arrow) surrounding the optic nerve (D) (Coronal T1 fat suppressed post gadolinium image), as well as involvement of the full length of the right optic nerve and enhancement of the perineural sheath and intraconal fat (arrow) (E) (Axial T1 fat suppressed post gadolinium image). He represented with unilateral left eye conjunctival injection during an episode of peripheral ulcerative keratitis (F).

Table 1: Summary of cases with novel inflammatory ophthalmological presentations associated with myelin oligodendrocyte glycoprotein antibodies

	Case 1	Case 2	Case 3	Case 4
Age and gender	45 yo F	62 yo M	5 yo F	32 yo M
Number of ophthalmological presentations	3	1	1	2
Laterality of presentation	Bilateral with first two episodes, unilateral with third episode	Bilateral	Bilateral	Unilateral (but alternate eyes on each episode)

Clinical Syndrome	<p>Episodes 1: Bilateral optic neuritis associated with anterior and intermediate uveitis</p> <p>Episode 2: Bilateral anterior and intermediate uveitis</p> <p>Episode 3: Right anterior and intermediate uveitis</p>	<p>Episode 1: Bilateral optic neuritis associated with anterior and intermediate uveitis</p>	Bilateral intermediate and posterior uveitis	<p>Episode 1: Right perineuritis with associated optic neuritis</p> <p>Episode 2: Left peripheral ulcerative keratitis</p>
Visual acuity at initial presentation	Counting fingers OD 6/9 OS	Counting fingers OD 6/24 OS	3/9.5 bilaterally	6/6 bilaterally
Visual field deficits at initial presentation	Right central scotoma	Right inferonasal and central scotoma	Subjective testing performed only	Dense peripheral constriction with relative central sparing
Optic disc swelling	Present bilaterally with first episode only, not present at second or third presentations	Present bilaterally	Present bilaterally	Present on right with first episode only, not present at second episode
Uveitis	Present with all three episodes; anterior and intermediate uveitis (inclusive of vitritis) in first two episodes,	Anterior and intermediate uveitis (inclusive of vitritis)	Bilateral intermediate (inclusive of vitritis) and posterior uveitis	-

	anterior uveitis in third episode			
Optic perineuritis	-	-	-	Present with first episode
Peripheral ulcerative keratitis	-	-	-	Present with second episode
Duration of follow up	46 months	14 months	25 months	28 months
Visual acuity at final clinical follow up	6/18 OD 6/9 OS	6/120 OD 6/12 OS	3/6 -1 OD 3/7.5+1 OS	Normal visual acuity bilaterally
Visual field deficits at final clinical follow up	Normal	Right inferonasal scotoma	Mild peripheral restriction	Normal visual fields
Retinal nerve fibre layer thinning at final follow up	Present	Not present	OCT not performed	Not present

F female; M male; OCT optical coherence tomography; OD oculus dexter (right eye); OS oculus sinister (left eye)

A

B

C

D

E

F

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Ramanathan, S;Fraser, C;Curnow, SR;Ghaly, M;Leventer, RJ;Lechner-Scott, J;Henderson, A;Reddel, S;Dale, RC;Brilot, F

Title:

Uveitis and optic perineuritis in the context of myelin oligodendrocyte glycoprotein antibody seropositivity.

Date:

2019-08

Citation:

Ramanathan, S., Fraser, C., Curnow, S. R., Ghaly, M., Leventer, R. J., Lechner-Scott, J., Henderson, A., Reddel, S., Dale, R. C. & Brilot, F. (2019). Uveitis and optic perineuritis in the context of myelin oligodendrocyte glycoprotein antibody seropositivity.. *Eur J Neurol*, 26 (8), pp.1137-1e75. <https://doi.org/10.1111/ene.13932>.

Persistent Link:

<http://hdl.handle.net/11343/285555>