

CASE SERIES

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Peripapillary edema in anti-myelin oligodendrocyte glycoprotein-associated optic neuropathy

Michel van Lint, Rob JW de Keizer

ABSTRACT

Introduction: We report the peripapillary location of optic disc edema in four patients with anti-myelin oligodendrocyte glycoprotein (MOG)-associated optic neuropathy.

Case Report: Retrospective case report on four patients. The optic disc edema is initially concentrated in the peripapillary region.

Conclusion: In case of anti-MOG-associated optic neuropathy, our cases demonstrate an optic disc edema that is localized mostly around the edges of the optic nerve. Recognizing this particular feature may aid in a speedy diagnosis and prevent a misdiagnosis of another condition.

Keywords: Anti-MOG, Optic disc edema, Optic neuropathy, Optic perineuritis

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INTRODUCTION

Myelin oligodendrocyte glycoprotein (MOG) is a substance that is found in the myelin layer encapsulating the optic nerve and elsewhere in the central nervous system (CNS). In rare occasions it may be the target of specific antibodies (anti-MOG). When such antibodies occur, they can cause an immune reaction at the optic nerve [1, 2]. In one-third up to half of cases magnetic resonance imaging (MRI) shows inflammation and enhancement of the peri-optic nerve sheath, which can extend into the surrounding orbital fat [3–5]. This pattern of inflammation is not seen in multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD) with neuromyelitis optica (NMO) antibodies [3, 4]. This in turn leads to secondary demyelination. At the optic nerve head this results in an optic disc edema. In this small case series, we assess a more specific pattern of the edema and its localization with regard to the optic nerve head in four patients.

CASE REPORT

Case 1

A 49-year-old male presented to the emergency department in our hospital with complaints of visual loss, headache, and vomiting. His complaints had started a week before and had progressively deteriorated since then. Snellen visual acuity comprised 6/18 for both eyes. Eye fundus demonstrated bilateral optic disc swelling, concentrated around the margins of the optic disc (Figure 1). Visual fields suggested a right homonymous hemianopia, but progressed to a diffuse and near absolute visual field loss the next day [macular degeneration (MD) right eye –32.47/MD left eye –32.60]. The causes of infection could not be demonstrated and intravenous (IV)

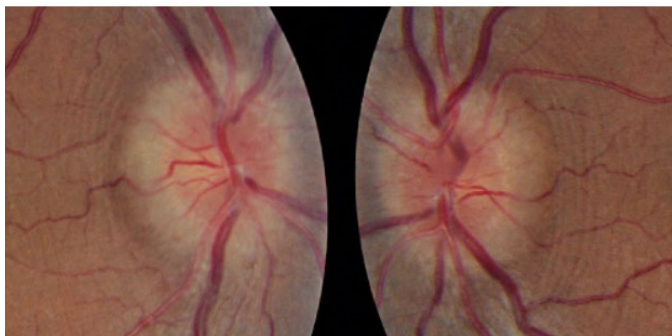


Figure 1: (Case 1) Bilateral papilledema at presentation, mostly peripapillary in nature. Circumferential retinal folds in peripapillary region due to papilledema. Right eye on the left. Left eye on the right.

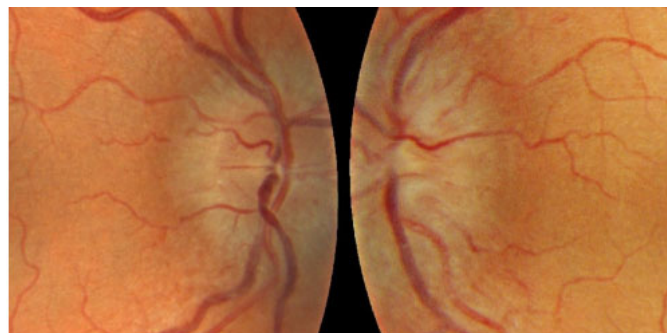


Figure 2: (Case 2) Bilateral papilledema at presentation. Right eye on the left. Left eye on the right.

corticosteroids were started because of the progressive visual loss (IV methylprednisolone 1 g/day for seven days, followed by oral methylprednisolone 64 mg/day and then slowly tapered over the course of three months). In the ensuing days his vision progressively improved to 6/6 in both eyes. Visual fields also gradually returned to normal (MD right eye -1.13 dB/MD left eye 1.85 dB). Finally, further work-up revealed the presence of anti-MOG antibodies after three weeks. At this point, the patient was still on oral methylprednisolone 48 mg/day and azathioprine 3×50 mg/day was then added for long-term treatment by the neurologist.

Clinical neurological examination was unremarkable. No other neurological deficits were present.

Initial MRI scan at presentation did not show any abnormalities, but did not include fluid-attenuated inversion recovery (FLAIR). Additional scanning after 10 days revealed a hyperintense left optic nerve on MRI-FLAIR.

The patient has been followed for four years.

Case 2

A 49-year-old male was referred for bilateral optic disc edema (asymmetric, more on the left) after a flu-like episode two weeks before presentation. For the past week, he had been experiencing a progressive loss of vision, which first started in the left eye and then consecutively also in the right eye. At presentation, visual acuity was counting fingers for the right eye and hand movements for the left eye. Unfortunately, as the patient was seen outside the neuro-ophthalmology clinic, monocular visual fields were not performed. Instead, a binocular Esterman was taken with diffuse loss of sensitivity (60/120 not seen; periphery relatively spared, but diffuse loss of sensitivity otherwise). Optic disc edema was noted in the eye fundus, along with some splinter hemorrhages around the left optic disc. Again, the edema was most pronounced at the border of the optic disc (Figure 2). Work-up for infectious causes remained negative and

empirical treatment with intravenous corticosteroids was instituted (IV methylprednisolone 1 g/day for 5 days). In the following weeks, Snellen visual acuity restored to 6/6 for the right eye and 6/9 for the left eye (eventually 6/6 after five months). Visual fields normalized as well (MD right eye -1.78 dB/MD left eye -1.77 dB). Continued work-up revealed the presence of anti-MOG antibodies.

Clinical neurological examination was unremarkable. No other neurological deficits were present.

Magnetic resonance imaging scan demonstrated the presence of some aspecific, punctate, hyperintense white matter lesions on T2, but did not show any optic nerve abnormalities.

Immunosuppression was started six months after presentation by the neurologist (ledertrexate 2×2.5 mg/week—low dose because of lymphopenia and azathioprine was not tolerated).

The patient was lost to follow-up after four years.

Case 3

A 34-year-old male presented with increasing pain of the left eye and headache. Snellen visual acuity comprised 6/4 and 6/6 for the right and left eye, respectively. Vision of the left eye progressively decreased to 6/36 after four days. The optic nerve head appeared to be more swollen (Figure 3), but the photo was taken several days after presentation. A central cupping could still be recognized and the majority of the edema appeared to be on the outer side of the optic disc. Visual fields demonstrated a possible loss of sensitivity temporally for the right eye (MD -10.87 dB) and slightly for the left eye (MD -3.06 dB). As work-up remained negative and failed to demonstrate an infectious cause, empirical treatment was given using intravenous corticosteroids (methylprednisolone 1 g/day for five days), after which visual acuity of the left eye improved to 6/6. However, after six days he had a recurrent optic neuropathy of the left eye with loss of the temporal hemifield (MD -17.00 dB). The right eye was moderately affected as well (MD -6.42 dB). Oral corticosteroids were started (methylprednisolone 48 mg/day) and tapered over the ensuing two months. Visual

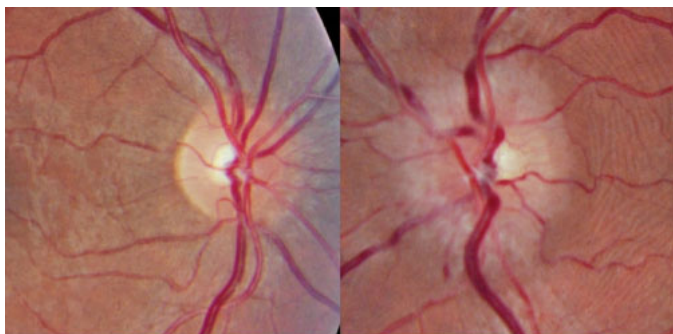


Figure 3: (Case 3) Asymmetric, bilateral papilledema several days after presentation. The edema is mainly centered on the border of the optic disc and peripapillary. Circumferential retinal folds in the peripapillary region in the left eye due to papilledema. Right eye on the left. Left eye on the right.

acuity improved to 6/5 on the left. Visual fields revealed no remaining sensitivity loss (MD right eye -1.15 dB/MD left eye -1.64 dB). Further work-up revealed the presence of anti-MOG antibodies.

Clinical neurological examination was unremarkable. No other neurological deficits were present.

Magnetic resonance imaging scan revealed perioptic edema of the left optic nerve and a slight hyperintensity of the optic nerve itself. The right optic nerve did not reveal any abnormalities.

Immunosuppression was started two months after presentation by the neurologist for two years (stopped after anti-MOG antibodies were no longer detectable).

This patient was lost to follow-up after 1.5 years with the advent of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

Case 4

A 40-year-old male presented with recurrent transient visual loss of the left eye, which was considered to be a transient visual loss elsewhere due to cardiovascular risk factors. Two weeks later he presented again with progressive loss of vision in the right eye and headaches. At the acute stage there was no apparent optic disc edema, which only appeared several days later. Regardless, a diagnosis of anterior ischemic optic neuropathy (AION) was made. Because of continued loss of vision to hand movements in the right eye and associated loss of the peripheral visual field, he consulted us for a second opinion. History revealed a syphilis that had been successfully treated five years before presentation and was no longer active. There was no history of human immunodeficiency virus (HIV). Examination of the fundus revealed a swelling mainly of the peripapillary retinal nerve fiber layer, instead of a true optic disc edema (Figure 4). Snellen visual acuity of the left eye was 6/6. Visual field demonstrated a dense and diffuse loss of sensitivity in the right eye (MD -20.04 dB) and was considered normal for the left eye, but unreliable (MD

$+1.30$ dB, 30% false positive). An additional blood sample was taken to check for the presence of anti-MOG antibodies and which returned positive. Treatment was started with intravenous corticosteroids (methylprednisolone 500 mg/day for three days), followed by oral corticosteroids (methylprednisolone 64 mg/day, tapered over the course of four months). Snellen visual acuity for the right eye restored to 6/12, initially, but further recuperated to 6/6, eventually. The visual fields improved globally (MD right eye -0.70 dB/MD left eye $+1.37$ dB, 23% false positive).

Clinical neurological examination was unremarkable. No other neurological deficits were present.

Initial MRI scan did not reveal optic nerve abnormalities, but follow-up MRI after one year revealed right optic nerve atrophy and an increased signal on MRI-FLAIR.

Aside from corticosteroids, no further immunosuppression was given.

As a precaution to starting corticosteroids, the authors always ask for a Quantiferon test. This test returned positive, which is why a lower dose of intravenous corticosteroids were used. Pneumological examination diagnosed latent tuberculosis and additional treatment was given for nine months (isoniazid 1×300 mg/day, pyridoxine 1×250 mg/week, folic acid 1×4 mg/week).

This patient has been in follow-up for two years.

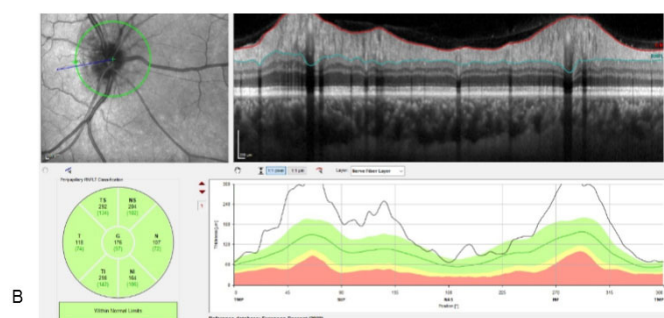
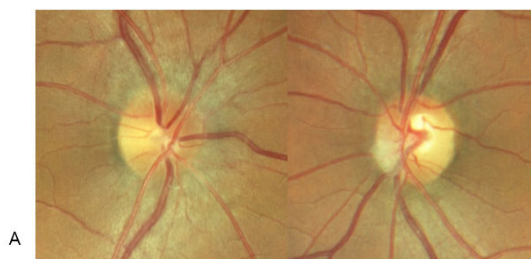


Figure 4: (Case 4) (A) Mostly peripapillary edema of only the right eye at presentation. Right eye on the left. Left eye on the right. (B) Optical coherence tomography (OCT) scan of the peripapillary retinal nerve fiber layer of the right eye.

DISCUSSION

Anti-MOG-associated optic neuropathy has recently been recognized as a separate entity [1–4] and is presumed to be an optic perineuritis [6]. It is caused by antibodies

that attack MOG in the myelin sheath around the optic nerve, causing secondary demyelination. Clinically, this manifests as an acute or progressive loss of vision in one or both eyes. Eye fundus often reveals optic disc edema that may be pronounced. Optic disc edema and pain both occur in 86% of patients [5]. Visual fields show marked loss of sensitivity. With treatment, the prognosis is rather favorable with Snellen visual acuity restoring to around 6/9 [5].

We are unaware of visual prognosis without treatment. Without proper treatment, however, the prognosis might not be good. Recovery of vision may be incomplete [4, 7]. We hypothesize this is most likely secondary to the loss of axons and the development of optic atrophy. Chen et al. report a final visual acuity of 20/200 or worse in 6% of patients [5]. Jarius et al. find “severe visual impairment or functional blindness” in 36% of patients [4].

This is in stark contrast to optic neuritis due to multiple sclerosis that often heals spontaneously after 7–14 days. Therefore, it is important to recognize the presence of anti-MOG-associated optic neuropathy in order to be able to start corticosteroids within a timely fashion. Of interest, optic disc edema is only present in up to one-third of cases of multiple sclerosis related optic neuritis [8]. Papillitis is more common in children less than 14 years old and some ethnic populations [9, 10].

Optic disc edema is an unspecific sign and can be attributed to many causes, e.g., anterior ischemic optic neuropathy (AION), intracranial hypertension, central retinal vein occlusion, infectious causes, and alternative inflammatory causes (autoimmune disorders like sarcoidosis and so on).

Frequent causes of optic neuropathy are optic neuritis in multiple sclerosis (MS) and AION. Often, one concludes to one of these as a diagnosis. Since only one-third of MS-related optic neuritis presents with optic disc edema, the presence of edema may falsely lead to the diagnosis of AION. In case of AION, most practitioners will assume that treatment is futile. In the case of anti-MOG-associated optic neuropathy being the cause, a small group of patients may be left with partial loss of vision that could have been prevented.

When suspecting MS-related optic neuritis or AION, it is crucial to check the history taking and clinical findings for red flags. For example, a typical AION presents with a Snellen visual acuity of at least a few tenths and an altitudinal visual field loss. In our cases visual acuity loss was more pronounced and none had an altitudinal loss of visual field that is considered typical for AION. The eye fundus will demonstrate an optic disc edema. Typically, the clinical picture remains constant after the acute event.

None of our patients had a history of MS, nor was the MRI suggestive of MS.

In addition to MS and AION, we also considered alternative diagnoses, but the results came back negative [anti-aquaporin-4, antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), sarcoidosis, and infectious serology]. Anti-aquaporin-4

is the antibody that is associated with neuromyelitis optica (NMO), but is less typically associated with optic disc edema, since the optic nerve inflammation is more posterior to the eye. Antinuclear antibody is associated with autoimmune disease and may be present in multiple conditions, e.g., systemic lupus erythematosus, scleroderma, Sjögren disease, and mixed connective tissue disease. Antineutrophil cytoplasmic antibodies are also associated with autoimmune disease and manifests as vasculitis of the small blood vessels due to autoantibodies.

In case of anti-MOG-associated optic neuropathy, however, one may find more pronounced and diffuse loss of visual field that is progressive in nature over the course of several days and also progressive loss of vision to as low as finger counting. These findings also apply to our cases: visual loss progressed over the course of days and was severe with the entire visual field implicated. All patients had dense and central visual field deficits. Visual acuity may decrease rapidly to counting fingers or hand movements at its nadir, as is demonstrated in our cases as well. Along with the visual complaints, headache may be a pronounced feature as in our cases. None of our patients had other associated neurological deficits.

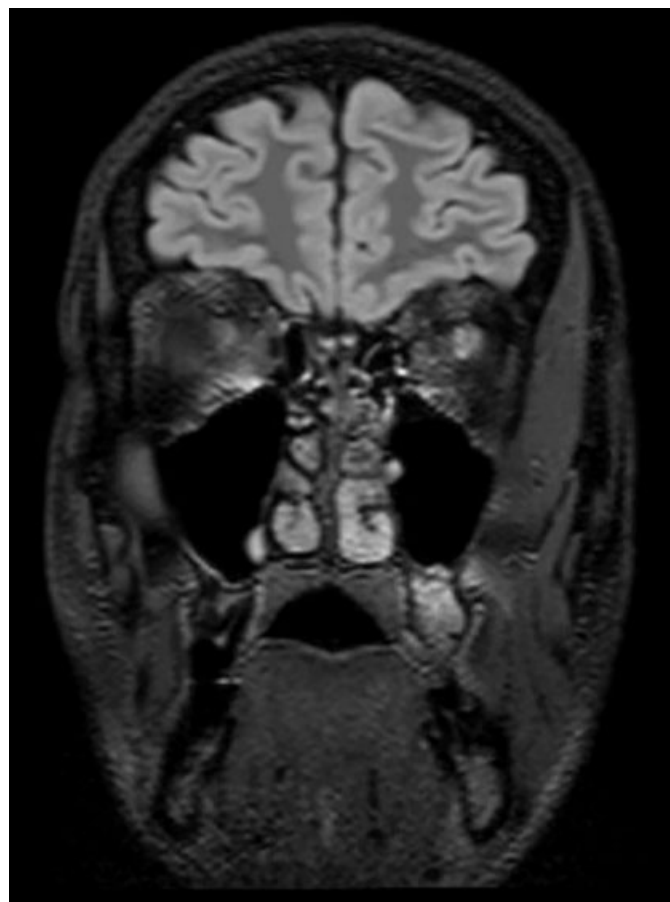


Figure 5: MRI FLAIR of case 3: Edematous alterations in the perioptic fat tissue around the retrobulbar left optic nerve. Increased FLAIR-signal of the left optic nerve.

In our cases, we noted an additional sign that may help in differentiating anti-MOG-associated optic neuropathy from other causes, which is readily apparent upon inspection. All of our four cases had an optic disc edema that was concentrated around the edges of the optic nerve, leaving the center of the optic disc relatively untouched. This may be explained by the fact that anti-MOG-associated optic neuropathy is a perioptic inflammation, which is also revealed by MRI demonstrating the presence of inflammation in the surrounding fat tissue [3–5]. This is exemplified in Figure 5.

This fact may help explain why prognosis for visual acuity is favorable in general. Since the macular fibers are located deep in the center of the optic nerve at its retrolaminar part, these fibers might be spared from inflammation initially.

In addition to the edema, there is also an apparent disc hyperemia that appears to be more diffuse in nature. We assume this can be attributed to the inflammation.

CONCLUSION

In case of anti-MOG-associated optic neuropathy, our cases demonstrate an optic disc edema that is localized mostly around the edges of the optic nerve. Recognizing this particular feature may aid in a speedy diagnosis and prevent a misdiagnosis of another condition. To the best of our ability, we are unaware of previous publications reporting this feature. We assume its pathophysiological explanation is found in the fact that anti-MOG-associated optic neuritis is believed to be an optic perineuritis. Therefore, other causes of optic perineuritis should still be considered as well.

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Author Contributions

Michel van Lint – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Rob JW de Keizer – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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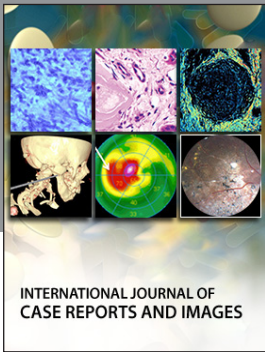
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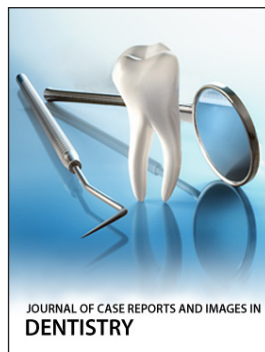
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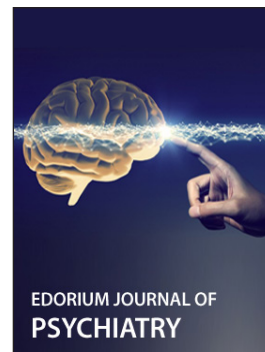
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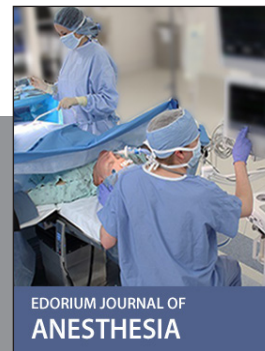
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