

A new association: acute macular neuroretinopathy in acute optic neuritis

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ABSTRACT.

Background: Acute optic neuritis (AON) is a common optic nerve disease leading to retrograde degeneration of optic nerve axons, reflected by thinning of the inner retinal layers on optical coherence tomography. On the contrary, acute macular neuroretinopathy (AMN) type 2 is a rare outer retinal disorder that leads to thinning of the outer nuclear layers and is diagnosed by multimodal imaging. The aim of this study was to report a new association between these two diseases.

Methods: Patients with a first episode of optic neuritis were invited to participate in a study that involved optical coherence tomography evaluation at baseline and the following 1, 3, 6 and 12 months. All the study patients underwent ophthalmologic evaluation that comprised of visual acuity, visual field and multimodal imaging as well as orbital and brain Magnetic Resonance Imaging. A diagnosis of multiple sclerosis was made according to the 2010 McDonald criteria.

Results: Six of the 114 patients with acute optic neuritis also had acute macular neuroretinopathy, of whom three were positive for myelin oligodendrocyte glycoprotein antibodies (MOG-Abs), two had relapsing–remitting multiple sclerosis and one had clinical isolated syndrome.

Conclusion: Our study suggests that it is imperative to check for associated AMN in cases of AON, especially those associated with MOG-Abs.

Key words: acute macular neuroretinopathy – multiple sclerosis – myelin oligodendrocyte glycoprotein – optic neuritis

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Introduction

Acute optic neuritis (AON) is a common optic nerve disease characterized by axonal loss resulting from inflammatory damage to the axons (Jenkins & Toosy 2017). Multiple sclerosis (MS) is the most common cause although AON can also occur with antibodies (Abs)

targeting aquaporin-4 (AQP4) or myelin oligodendrocyte glycoprotein (MOG), or as an isolated disease (Deschamps et al. 2017). Advances in imaging technologies have enabled optical coherence tomography (OCT) to be considered as a main biomarker during

the course of AON through the assessment of axonal loss reflected by thinning of the retinal nerve fibre layer and the combined ganglion cell and inner plexiform layers (Petzold et al. 2017).

Acute macular neuroretinopathy (AMN) is a rare but increasingly diagnosed disorder of the outer retinal layers with characteristic reddish brown and wedge-shaped retinal lesions; the apices of which tend to be directed towards the fovea often in a petalloid or tear-drop configuration (Bhavsar et al. 2016). Clinically, the patient presents with a sudden onset of small paracentral scotoma(s) sparing the fixation point, little or no visual acuity reduction, occasional photopsias and no other visual symptoms. These scotomas may indefinitely persist or partially decrease. The risk factors for AMN are numerous and essentially consist of vascular factors (hypo- or hypertension, sympathomimetic drugs use, anaphylaxis, thrombocytopenia, anaemia, hyperviscosity, hypovolaemia and dehydration) (Bhavsar et al. 2016; Munk et al. 2016).

Since the advent of OCT imaging, two types of AMN have been described: AMN type 1 or PAMM (paracentral acute middle maculopathy) and AMN type 2 (classical AMN) (Sarraf et al. 2013). AMN types 1 and 2 are distinct but may be related. They may have a common pathophysiology of ischaemia, most likely in the deep and/or intermediate retinal capillary plexus (Yu et al. 2014; Rahimy et al. 2015; Nemiroff et al. 2016). Acute macular neuroretinopathy (AMN) is presently

easily diagnosed thanks to the spread of and improvements in multimodal imaging. The fundus usually shows dark red petaloid lesions, and two examinations will confirm the diagnosis: infrared scanning laser ophthalmoscopy (SLO) and spectral domain (SD)-OCT B scanning at the site of the lesions seen on infrared SLO that correspond to the scotomas. On SD-OCT B scan, at the site of the lesions seen on infrared SLO, AMN type 1 shows a hyperreflective white lesion at the level of the inner nuclear layer (INL)-outer plexiform layer (OPL) while AMN type 2 shows a hyperreflective lesion at the level of the OPL-outer nuclear layer (ONL). The ONL contains rod and cone cell bodies, and the OPL the synapses between horizontal cells or bipolar cells from the INL and photoreceptor terminal axons from the ONL. The ellipsoid layer is often disrupted but will slowly reconstitute during the evolution of the disease whereas the ONL will become thinner (Azar et al. 2012; Fawzi et al. 2012).

Our aim was to describe the previously unreported association of AMN with AON. The data presented here are preliminary because the follow-up of our study patients is still ongoing.

Materials and Methods

This study was approved by the local Ethics Committee, registered in ClinicalTrials.gov (NCT02573792) and conducted in compliance with the principles of the Declaration of Helsinki; all study participants gave informed consent. All consecutive patients who presented at our institution from October 2015 until June 2018 with a first episode of AON were invited to participate in this study. The main objective was to evaluate the sensitivity of SD-OCT for aetiological diagnosis of optic neuritis in 120 patients.

The inclusion criteria were (1) age ≥ 18 years, (2) a first AON event and (3) a diagnosis of AON within 3 months. Subjects without a diagnosis of demyelinating ON (i.e. with optic neuropathy secondary to other inflammatory causes, e.g. systemic diseases or with noninflammatory optic neuropathies) or with prior ON in the currently affected eye were excluded. All the subjects underwent the following examinations: 1. visual acuity evaluation, 2. visual fields, 3. SD-OCT at baseline and at follow-up months 1, 3, 6 and 12, and 4. multimodal imaging with

colour fundus photography, infrared SLO, as well as SD-OCT B and OCT C-scan, at study baseline and during follow-up at months 1, 3, 6 and 12.

For AMN diagnosis, the infrared SLO images had to clearly show a dark petaloid lesion more or less pointing towards the macula and, on SD-OCT B scan, at the site of the lesions seen on infrared SLO, hyperreflective lesion at the level of the INL-OPL (AMN type 1) or at the level of the OPL-ONL (AMN type 2). The SD-OCT (Spectralis OCT-II; Heidelberg Engineering GmbH, Germany) parameters were for 1. RNFL: Circle, #ART Mean 100, High resolution; 2. Posterior pole – for volume: $30^\circ \times 25^\circ$, 61 scans, $120 \mu\text{m}$ between sections, #ART Mean 9, resolution HS and 3. Posterior pole – for horizontal and vertical central lines: #ART Mean 100 in High resolution. The parameters for SD-OCT angiography (OCT-A) were: volume $15^\circ \times 15^\circ$, $11 \mu\text{m}$ between sections, #ART Mean 7.

All patients underwent orbital and brain MRI (Magnetic Resonance Imaging) prior to the initiation of steroid treatment. The diagnosis of MS and clinical isolated syndrome (CIS) were made according to the 2010 McDonald criteria (Polman et al. 2011). AQP4 and MOG-Abs were determined by cell-based assay. Patients who did not fulfil the diagnostic criteria for MS or CIS, and who were negative for AQP4-Ab and MOG-Ab, were classified as idiopathic AON. General information such as blood pressure, oral contraceptive use, smoker status, history of infection, recent vaccination and drug use was obtained for all patients with AMN.

Results

There were 114 patients with a first episode of AON in our study, 6 (5.3%) of whom were identified as also having AMN (all type 2; Fig. 1). There were five females with a mean age of 38.4 (range: 26–56) years and one male (Table 1). It was the first episode of AON in all our patients; no one had been previously diagnosed or treated for multiple sclerosis (MS) or clinical isolated syndrome (CIS). The symptoms of decreased vision experienced by our study patients were all attributable to AON which induced visual field defects in the territory of the AMN involvement and so AMN symptoms could not be perceived by the

patients. Thus, the diagnosis of AMN in all our patients was made only because of the detection of areas of petaloid infrared hyporeflectivity corresponding to the hyperreflective lesion at the level of the OPL-ONL on SD-OCT B scans (Fig. 1).

The mean time between symptoms onset and study inclusion was 16.8 (range: 9–30) days. None had photopsias. Two patients had bilateral AON and one patient had bilateral AMN. Regarding their recent medical history, one patient had gastroenteritis one week prior to presentation at our clinic while another had a tooth abscess 2 months before. Their past medical history revealed smoking (10 pack-years smoked), treated high blood pressure, oral contraceptive use and pollen allergy – all in one patient each. The aetiology of AON in the six AMN patients was anti-MOG-Abs in three patients, MS in two and CIS in one patient.

There were 108 patients without AMN, of whom 71 (65.7%) were female, and the overall mean age was 35 (19–60) years. The aetiology of AON in these patients was MS (45 cases), CIS (26), idiopathic (20), MOG-Ab positive (12) and AQP4-Ab positive (5).

Discussion

Acute macular neuroretinopathy and AON are currently considered as separate entities that do not appear to be related to or associated with each other. AON is relatively common with an annual incidence in population-based studies of 1–5 per 100 000, while AMN is very rare (Bhavsar et al. 2016; Jenkins & Toosy 2017). It is highly unlikely that this association, seen in 6 (5.3%) of our 114 patients, could be purely coincidental.

The pathophysiology of AMN is yet to be clearly determined. However, a mostly vascular mechanism is suspected because AMN is associated with vascular risk factors and there is often no improvement. AMN probably results from the ischaemia of retinal capillaries, most likely in the deep capillary plexus that vascularizes the outer retinal layers. However, vascular risk factors are not always present, and AMN often occurs in young patients (over 80% of patients are women, and over half are in the third decade of life) (Bhavsar et al. 2016). Moreover, AMN can also occur after

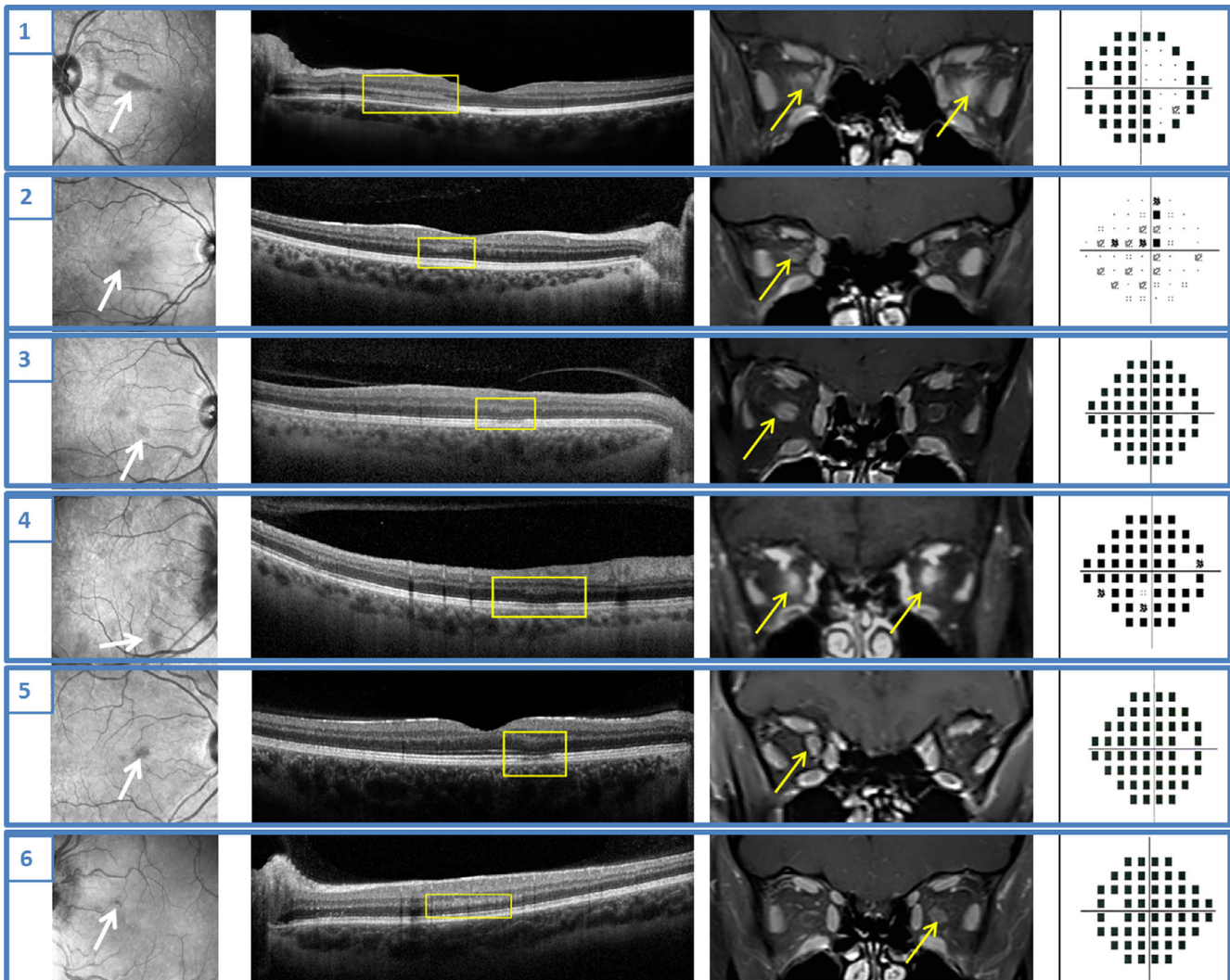


Fig. 1. In all patients (1–6), near-infrared reflectance imaging demonstrates well-demarcated hyporeflective macular lesions (white arrows, first column) and spectral domain optical coherence tomography imaging shows hyper-reflectivity of the outer nuclear-outer plexiform layer (yellow framed, second column) corresponding to acute macular neuroretinopathy location. The Coronal T1-weighted after gadolinium injection and fat suppression showing unilateral or bilateral enhancement of optic nerve (yellow arrows, third column), associated to the visual field defect (Mean deviation, fourth column) confirm the diagnosis of acute optic neuritis.

non-specific infection or vaccination or in association with autoimmune disorders (Bhavsar et al. 2016; Lee et al. 2016; Liu et al. 2018). AMN is bilateral in over 50% of the affected patients and is rarely associated with disc oedema (Bhavsar et al. 2016). This was not apparent in our study population because AON had significant disc oedema in many affected eyes. This unusual AMN population may indicate an alternative pathophysiologic mechanism.

The occurrence of AMN in AON could be explained by inflammatory oedema compressing and reducing retinal arterial blood flow, particularly in the deep capillary plexus. Chen et al. (2017) demonstrated that the peripapillary choroidal thickness became thinner in eyes with AON and disc swelling

while no obvious change was seen in retrobulbar neuritis. Also, vascular hypoperfusion in the peripapillary area was correlated with the severity of nerve swelling. They advocated the hypotheses that in AON with disc swelling, reactive astrocytes around the optic nerve head might release endothelin-1 to further compromise the surrounding perfusion. As all the lesions in our patients were located in the outer retina (AMN type 2), this hypothesis could explain the outer retinal oxygen deprivation in such patients since the choroid supplies oxygen to the outer retina (Chen et al. 2017). Interestingly, in our study, MOG pathology was overrepresented since three of the six (50%) patients with AMN had anti-MOG-Abs while

only 12 of the 108 (11%) AON without AMN patients had anti-MOG-Abs. This recently described entity is usually far less frequent than MS AON and is often accompanied by optic nerve head swelling (Biotti et al. 2017).

Not all of our study patients with AMN had optic disc swelling; the two patients with MS had unremarkable fundus examination possibly suggesting different pathophysiologic mechanisms. Recently, Feucht et al. (2018) reported that early MS or CIS patients with a history of AON showed reduced vessel densities in the superficial and deep vascular plexuses as measured by retinal OCT-A. One possible explanation is that rarefaction of retinal vessel structures could be the result of a direct inflammatory process affecting retinal

Table 1. Summary of the characteristics of the patients with acute macular neuroretinopathy and acute optic neuritis.

Patient	1	2	3	4	5	6
Gender/Age	M/34	F/28	F/55	F/56	F/27	F/26
AMN	OS	OD	OD	OD	OU	OS
Initial VA OD/OS	1/0.1	1/1	CF/1	0.4/0.6	LP/1	1/CF
Orbital pain	Yes	Yes	Yes	Yes	No	Yes
Optic nerve head Swelling	OU	None	OD	OU	None	OS
Acute optic nerve enhancement on MRI	OU	OD	OD	OU	OD	OS
Visual Field defect OD/OS	DD/CS	PCS	CS	PCS/PCS	CS	PCS
Initial RNFL in AE (µm)	154/245	92	130	194/176	96	198
GCIPL Volume in AE (mm ³)	0.98/0.87	0.98	0.86	0.83/0.83	1.01	1.15
Final VA OD/OS	1/1	1/1	1/1	1/1	1/1	1/1
Follow-up period (months)	3	1	12	22	8	12
Diagnosis	MOG+	MS	MOG+	MOG+	MS	CIS

AE, affected eye; AMN, acute macular neuro retinopathy; CF, counting fingers; CIS, clinically isolated syndrome; CS, central scotoma; DD, diffuse deficit; F, female; GCIPL, combined ganglion cell and inner plexiform layers; LP, light perception; M, male; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; OD, right eye; OS, left eye; OU, both eyes; PCS, paracentral scotoma; pRNFL, peripapillary retinal nerve fibers layer; VA, visual acuity in decimal.

vessels during AON. AON is occasionally associated with peripheral retinal perivascular inflammation (periphlebitis) that can evolve into occlusive vasculitis; in such cases, AMN could be the representation of this phenomenon at the posterior pole (Green et al. 2010; Feucht et al. 2018).

In the past, the diagnosis of AMN and AON has been occasionally confused (Jiang et al. 2013; Cebeci et al. 2015). In our study, four patients with AMN type 2 mostly complained of large scotomas that were different from the usual small AMN type 2 scotomas and this symptomatology raised the diagnosis of AON, not AMN. The diagnosis of AMN in these patients was only made thanks to multimodal imaging with infrared SLO and SD-OCT B scan visualization. So, it is likely that AMN associated with AON has been significantly under-diagnosed even in the recent past. The diagnosis of AMN can be easily missed without conscious evaluation using infrared fundus SLO and SD-OCT B scanning.

Conclusion

Our study suggests that it is imperative to check for associated AMN in cases of AON, especially those associated with MOG-Abs. Conversely, in the case of AMN it is important to rule out the possibility of AON. This study also raises the possible involvement of the outer retinal layers in AON. Further studies are required to confirm our observations.

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