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Non-arteritic anterior ischemic optic neuropathy: cystic change in the inner nuclear layer due to edema and to retrograde maculopathy.

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ABSTRACT

Purpose: Microcystic macular oedema (MMO), also known as Retrograde Maculopathy, is associated with severe optic atrophy due to a range of causes. However, similar changes have also been described in primary retinal pathology and the pathogenesis of MMO is debated.

Design: A retrospective observational case series

Participants: Patients with non-arteritic ischaemic optic neuropathy

Methods: A retrospective observational case series was carried out in the University Hospital of Liège, Belgium. The medical records of patients who were referred to our Neuro-ophthalmology department with a diagnosis of non-arteritic anterior ischaemic optic neuropathy (NA-AION), between 2014 and 2021, were reviewed.

Main outcome measures: ganglion cell complex thickness, acute and chronic inner nuclear change

Results: In the cohort of 34 patients (mean age: 60±12.5 years; 65.6% male) with NA-AION, we identified a transient microcystic change in the inner nuclear layer (INL) associated with optic disc swelling in 19 eyes at presentation. This early change was associated with a transudate of intra- and sub-retinal fluid originating from the optic disc. Among patients who had shown this transient change 3 subsequently developed MMO which remained fixed during the period of observation (range:12-34 months). No MMO was observed in patients without early INL transient change. MMO was observed in patients with severe ganglion cell complex thinning at 6 months: mean (±SD) loss in superior hemi-macula: -28.2±5.2 µm (-33.3%, range: -22.3 to -30.3 µm) and in inferior hemi-macula: -30.7±5.6 µm (-31.0%, range: -24.3 -34.8 µm).

Conclusion: Our study has revealed two causes of INL cystic change in the same patients suffering from NA-AION, one reversible and the other likely permanent. This finding highlights the distinction between genuine oedema related to transudation of fluid (in this case secondary to ischaemic optic disc swelling) and the phenomenon observed in retrograde maculopathy which is related to the degree of RNFL/GCC thinning.

Summary: Cystic change in the INL is associated with severe optic atrophy (MMO). However, similar changes have been described in retinal pathology and the pathogenesis of MMO is debated. We report 3 cases highlighting the distinction between genuine tissue oedema (transudation of fluid secondary to ischaemic optic disc swelling) and the phenomenon observed in retrograde maculopathy related to the degree of RNFL loss.
Keywords: microcystic macular oedema, retrograde maculopathy, ischaemic optic neuropathy, swollen disc, neuro-ophthalmology

Abbreviations:
AMD: age macular degeneration
BCVA: best-corrected visual acuity
ERM: epiretinal membrane
FFA: fundus fluorescein angiography
GCC: ganglion cell complex (inner plexiform layer (IPL) + ganglion cell layer (GCL))
INL: inner nuclear layer
MMO: microcystic macular oedema
MRI: Magnetic resonance imaging
NA-AION: non-arteritic anterior ischaemic optic neuropathy
OCT: optical coherence tomography
pRNFL: peripapillary retinal nerve fibre layer
RGC: retinal ganglion cell
RM: retrograde maculopathy
VF: automated perimetry
**Introduction**

MMO was first described in the context of optical coherence tomography (OCT) findings in Multiple Sclerosis by Gelfand *et al.* [1]. The abnormality was more likely to be seen in patients who had had a previous episode of optic neuritis and in cases with more marked thinning of the retinal nerve fibre and ganglion cell layers. INL cell loss and thinning had previously been reported in a histopathological study of the retina in MS, also correlated with the severity of axonal loss, without mention of the presence of cystic change [2]. The microcysts are located in the INL and show a perifoveal distribution [1,3]. MMO is associated with severe optic atrophy found in: optic neuritis [1,4]; neuromyelitis optica [5,6]; hereditary optic neuropathies [7,8]; toxic and nutritional deficiency neuropathy [9,10]; glaucomatous neuropathy [11,12]; compressive optic neuropathy [13]; and infiltrative optic neuropathy such as glioma [14,15]. Abegg has suggested the term “retrograde maculopathy” (RM) for INL cystic change in this context [14,16]. However, similar changes have also been described in retinal pathology for example in: epiretinal membrane [17]; age related macular degeneration; diabetic retinopathy; and central serous retinopathy [18]. Indeed, the earliest use of the term MMO known to the authors (albeit in Romanian as “edemul macular microchistic”) was published in a description of an “isolated case” of suspected microcystic macular dystrophy in 1988 [19].

We consider the following case series concerning three patients with NA-AION to be of particular interest in this context. These patients showed early acute transient microcystic change in the INL associated with disc swelling in parallel with other evidence of retinal oedema. Longstanding, perhaps permanent, MMO was developed subsequently. The pathophysiological basis for these two manifestations of INL cystic change following NA-AION will be discussed.

**Material and Methods**

A retrospective observational case series was carried out at the University Hospital of Liège, Belgium. 23 patients were referred complaining of sudden painless monocular loss of vision to our Neuro-ophthalmology department or to the Emergency Department (9 cases). Recruitment took place between 2014 and 2021. The diagnosis of NA-AION was based on the anamnesis (painless sudden loss of vision involving one eye) and fundus examination. The latter showed a swollen disc in the affected eye and, in the fellow eye, either a crowded disc (typical of the “disc at risk” associated with NA-AION, [20–22]) or sectoral atrophy indicating a previous episode of NA-AION. Spontaneous resolution of the optic disc swelling was noted within 8 weeks and the outcome was sectoral infarction. Giant cell arteritis was excluded by appropriate investigations. The clinical features were not compatible with a diagnosis of optic neuritis. Two patients were excluded because optic nerve head drusen were identified on OCT. Patients were white European, representing the typical local population of the clinic, except one who was Turkish. The mean age of the subjects was 60±12.5 years (range: 22-88 years, median: 60.5) and 65.6% were male. A favourable opinion of the ethics committee at the University of Liège for the study had been received. The study adhered to the tenets of the declaration of Helsinki and a written informed consent was obtained for the three patients described in this case series.

The patients were all followed at baseline and at 1, 3 and 6 months post episode. Fundus fluorescein angiography (FFA) and a macular spectral domain OCT (Heidelberg Engineering, Heidelberg, Germany) were performed in 27 patients at baseline: 6-line radial scans and/or 25-line raster scans
centred on the fovea were obtained. Subsequently, patients were seen annually. Clinical examination included best-corrected visual acuity (BCVA, Snellen scale), slit-lamp examination and fundus biomicroscopy. At follow-up, patients underwent automated perimetry (VF, Humphrey 24-2, Dublin, California), with appropriate refractive correction and OCT (HD-OCT Cirrhus, Carl Zeiss Meditec, Dublin, California), for which manual correction of segmentation was not possible. Thickness of the peripapillary retinal nerve fibre layer (pRNFL) and of the Ganglion Cell Complex (Inner plexiform layer + ganglion cell layer, GCC) were evaluated at each visit along with en face OCT B-scan. Studies demonstrating poor image quality, not allowing adequate visualisation of all retinal layers, were excluded. Scans were analysed for the presence of intraretinal fluid and subretinal fluid by 3 skilled observers who were masked as to the aim of the study. For the 3 patients described in this series, INL thickness was also evaluated initially and at the latest follow-up visit. For INL thickness assessment, adequate segmentation was assessed and adjusted manually in one case with macular spectral domain OCT.

Grading of the acute optic disc swelling was carried out as a function of the mean RNFL thickness and the numbers of quadrant sectors involved (temporal, superior, inferior, nasal). For example, optic disc swelling showing pRNFL thickening in at least one sector to be less than 120 µm was considered moderate. In the three cases described below, the swelling of the disc was considered severe because all sectors were involved (pRNFL thickness of all sectors greater than 120µm) and the mean pRNFL thickness was high (mean (±SD): 257.7 ± 81 µm, range: 189-347µm).

**Results**

**Summary of findings**

In the cohort of 34 patients (45 affected eyes and 23 healthy fellow eyes), we identified a transient microcystic change in the INL associated with optic disc swelling in 19 eyes at presentation. In these cases, the vacuoles were localised to the INL and were associated with transudation of intra- and sub-retinal fluid originating from the optic disc (see Figure 1 for one example). The microcystic change in these cases was transient and had resolved in all cases at 1 month (Figure 1). In cases with moderate optic disc swelling assessed in the global cohort, cystic changes were visible only in the peripapillary region (e.g., Figure 1). Four patients, who had shown this transient change subsequently developed MMO which remained fixed during the period of observation (range:12-34 months). The other cases (n=30) did not show MMO during the follow-up period.

At baseline, mean INL thickness in these three cases was 48.9 ± 17.03 µm in the affected eyes compared to 45.3 ± 1.7µm in the unaffected eyes (p=0.77). INL thickening was greatest in case 2 associated with the greatest microcystic change (mean INL thickness: 68.4 and maximal INL thickness 137µm). At the final follow-up visit (range: 2 to 3 years post episode), no significant INL thinning was observed between the affected and unaffected eyes (40.7 ± 5.3 µm and 39.4 ± 2.0 µm, respectively). However, we observed an upward trend in affected eyes possibly related to the continuing presence of microcystic change. Significant GCC thinning was observed at 6 months in all patients compared to the unaffected eye in the superior hemi-maculae (mean loss of GCC thickness: -28.2 ± 5.2 µm (-33.3%, range: -22.3 -30.3 µm) and in the inferior hemi-maculae (mean loss of GCC thickness: -30.7 ± 5.6 µm (-31.0%, range: -24.3 -34.8 µm) (Figure 2). We observe a significant GCC thinning in both hemi-maculae in patients with MMO compared to the entire cohort, where greater involvement of the superior hemi-macula is shown (mean superior hemi-macula thinning: -23.01 ± 9.33, -27.9%, range: 1 to 40.7μm, mean inferior hemi-macula thinning: -19.14 ± 12.1µm, -28.51%, range: 5 to -39µm; Figure 2). In two patients with similar lesion of GCC, only one had also MMO(Figure 2). This
additional patient of the cohort who had significant thinning of both the superior and inferior hemi-maculae at 6 months had also significant MMO observed (yellow dot). The other case without MMO had a better fovea threshold (25dB), suggesting a better residual function than the other (mean ±SD: 16±2.6). Finally, in these three patients we observed significant thinning of the RNFL at 6 months (mean pRNFL: 57.7 ± 2.5µm; temporal RNFL: 48.7± 1.5; nasal pRNFL: 56 ± 6.2; inferior pRNFL: 62 ± 2.6µm and superior pRNFL: 63.7±3.5). Mean pRNFL was especially thin compared to the overall cohort (mean pRNFL: 62.3 ± 9.7 µm; median: 61µm; temporal pRNFL: 51.7± 15.5 µm; median: 49.5µm , nasal pRNFL: 60.1 ± 11.8 µm; median: 49.5µm; inferior pRNFL: 74.9±24.4µm; median:66µm and superior pRNFL: 62.78 ± 13 µm; median: 62µm).

Case Histories

CASE 1

A 42-year-old gentleman was referred because of sudden painless loss of vision in his right eye which developed 4 days previously. At presentation, the best corrected visual acuity (BCVA) was 1/20 in the right eye and 10/10 in the left eye. Funduscopy showed an optic disc swelling and haemorrhages in the right eye. In the left eye, a crowded disc was noted. A diffuse visual field defect with central involvement was observed in the affected eye (Figure 3). OCT showed a significant thickening of mean pRNFL (363µm) and a normal thickness of GCC (85µm). Peripapillary microcystic oedema in the INL was also observed on the macular OCT. FFA showed a superior hypoperfusion of the optic disc and a late leakage around it. No choroidal filling defect was observed.

Full blood count and inflammatory biomarkers (ESR or CRP) were within normal limits. However, hypercholesterolemia (LDL 121 mg/dL, reference range <100mg/dL) was noted. Severe obstructive sleep apnoea (OSA) was diagnosed following polysomnography and pre-existing hypertension was shown to have been inadequately treated. Magnetic resonance imaging (MRI) with and without gadolinium enhancement of the brain demonstrated evidence of small vessel disease. A diagnosis of NA-AION was made.

At follow-up visits, OCT showed a diffuse thinning of the GCC (55 µm at 3 and 6 months) and a significant thinning of mean pRNFL (64µm at 3 months and 55 µm at 6 months). Microcysts were observed in the INL in a perifoveal circular distribution. The cysts appeared similar to those seen at presentation apart from the location (Figure 4). The microcysts were first seen four months post episode in the superior hemi-macula, corresponding to the greater involvement of the inferior visual field. At 6 months cystic change in the inferior and central regions of the macula was observed and persisted unchanged at the most recent assessment (34 months; Figure 4).

CASE 2

A 67-year-old man was seen for the first time in 2019 complaining of sudden loss of vision associated with a superior visual field defect in his left eye (Figure 3). He had a past history of treated hypertension and had had a pacemaker implanted. He was borderline overweight (body mass index: 24.3). Polysomnography was within normal limits.

At presentation, BCVA was 10/10 in the right eye and 1.5/10 in the left eye. Examination showed left optic disc swelling. Perimetry revealed a superior visual field defect with a nasal step and central
involvement. Early phases of FFA showed a superior sectoral delayed filling of the optic disc, confirming the diagnosis of NA-AION [23]. Late leakage at the macula was not observed excluding local vasculopathy. Macular OCT showed sub-foveal fluid and microcysts in the INL which resolved within one month as did the pRNFL thickening. GCC analyses were difficult to interpret because of segmentation failure (mean GCC: 70µm) and pRNFL was thickened (mean pRNFL: 189µm)

Ophthalmic and Neurologic examination were otherwise normal. Full blood count, blood chemistry and inflammatory biomarkers were within the respective reference ranges. MRI with and without gadolinium enhancement of the brain and orbits was normal.

Six months post episode, pRNFL was reduced at 58µm and GCC was thinned (mean GCC: 68µm). At one year follow-up, MMO was observed limited to the inferior hemi-macula (Figure 3) matching the area of greater GCC loss.

CASE 3

A 52-year-old truck driver presented with blurred vision in his left eye. He suffered previously from an episode of NA-AION in the fellow eye. BCVA was 1/20 in the right eye and 8/10 in the left eye. A swollen optic disc in the affected eye and diffuse pallor in the fellow eye were observed. Visual field showed an inferior altitudinal defect (Figure 3). Mean pRNFL and GCC were 237µm and 67µm, respectively. Macular OCT scans revealed traction of the retina induced by the disc swelling associated with fluid between the retinal pigmentary epithelium and the outer nuclear layer together with cystic change in the INL. FFA was not carried out at presentation.

Hypercholesterolemia (total cholesterol:220 mg/dL, reference range <190mg/dL; LDL 143mg/dL, reference range <100mg/dL) and a slightly elevated glycosylated haemoglobin (43mmol/mol, reference range: 20 -42 mmol/mol) were noted although his full blood count and inflammatory biomarkers (erythrocyte sedimentation rate or C reactive protein) were within the reference ranges. Polysomnography was performed because of a history of snoring and mild OSA was diagnosed. Magnetic resonance imaging (MRI) with and without gadolinium enhancement of the brain was within normal limits.

Thinning of the GCC was observed (55 µm and 52µm at 3 and 6 months respectively) and the pRNFL (79µm at 3 months and 60 µm at 6 months). Microcysts were observed in the superior hemi-maculae 6 months post episode and were persistent at the latest follow-up (24 months post episode; Figure 4).

Discussion

A degenerative change in the INL following ganglion cell loss was first reported in 1963 [24] in post-mortem studies of primates following chiasmal transection; and shown a few years later in post-mortem studies of human cases of optic neuropathy [25]. In the primate study, the cystic degeneration was distributed in an annular perifoveal distribution from around 500µm outwith the foveal margin extending over a further 1 mm, where the ratio of Müller cells to cone bipolar cells is low (1:4 rising to 1:1 at 3 mm eccentricity) although Müller cell to total bipolar cell ratio remains more constant [26]. Histological examination in the primate study showed debris and tissue in the larger cysts [24] -confirming that is not oedema- and some authors have suggested that degeneration of the Müller cells plays a key role because the MMO is localized in the poorly perivascularized rim [1,27,28] .Müller cells are glial cells which provide metabolic and structural support to retinal
neurons [29]. The microcystic appearance observed in the INL may correlate with the vertical orientation of Muller cells [30].

Following the use of OCT, it has become possible to identify acute and chronic cystic change in the INL in daily practice and the clinical spectrum of appearances designated MMO has widened in recent years [18]. Indeed, it has been described not only in retinal pathology but also in severe optic neuropathy with no known associated retinal pathology and this aetiological diversity has led to some confusion among clinicians. There is no consensus regarding the pathogenesis of MMO, some authors have suggested that it may be related to retrograde transsynaptic degeneration of bipolar cells [14,25] others to Müller cell dysfunction [28,31].

Initially the three patients described above had transient reversible microcystic change affecting the INL. We propose that this is related to transudation of fluid from the ischaemic optic nerve head sectors extending within and under the retina. This finding recovered spontaneously after one month. These microcystic changes were observed in the peripapillary region and were associated with fluid localised between the ellipsoid zone and the outer plexiform layer in the parafoveal region (Figure 1). Because we are describing this microcystic change in the peripapillary region, and as it is likely to be genuine interstitial oedema a better term could be “microcystic peripapillary oedema” within the INL although it can extend into the macula (Figure 5). Subsequently, these three patients developed the now “classical” MMO in the perifoveal region, which we have shown may be very long-standing perhaps, permanent.

Acute microcystic change associated with disc swelling is probably caused by a disruption of the blood-retinal barrier as proposed by Gelfand [5], leading to an overwhelming of Müller cell function. Over the past five years, various authors have described the presence of a paravascular transport system in the retina and around the optic nerve similar to the glymphatic system existing in the brain [31–33]. In a human post-mortem study assessing a cross-section of the optic nerve, Wostyn et al found an accumulation of India ink in paravascular spaces around the central retina vein and artery, which could correspond to an optic nerve glymphatic system [33]. It has also been suggested that a hyporeflective area around the vessel walls observed on OCT provide evidence for such a system [32]. In NA-AION, the glymphatic system could be compromised along with the venous drainage by some common mechanisms observed in ischaemia of the optic nerve. Müller cells and the superficial and deep vascular plexuses under normal conditions have a role in the reabsorption of fluid [28,31] but following arterial hypoperfusion and extensive extravasation of fluid from capillaries and venules Müller cells and other mechanisms of tissue homeostasis are saturated. This explains why we observe the OCT microcysts in the INL, similar to what has been observed in MMO [1], although the retinal distribution differs. Another factor may be that the transudate forming subretinal fluid might induce traction on the Müller footplates explaining the cystic appearance observed [7,15]. Once the disc swelling had resolved, we observe a complete resolution of the cystic change.

In contrast MMO appeared a few months post episode – after 4 months in the first case - and persisted over time (at least 34 months). Burgraff et al have described that MMO was transient in 84% of their series but most of the cases were AMD and ERM traction, where the pathogenesis may be quite different. In our cases, we observed the persistence of MMO, indicating a likely permanent change as also observed by Abegg et al [14]. Therefore, retinal ganglion cell (RGC) loss inducing vitreoretinal traction on the Müller cells is a less likely pathogenesis than a metabolic change related to retrograde transsynaptic degeneration [8,16]; either dysfunction of existing Müller cells [3] or empty space following Müller cell degeneration now fluid filled [13]. Indeed, the stationary nature of the cysts over a long follow-up period (3 years), suggesting a fixed change very unlikely to be interstitial oedema (Figure 4).
In NA-AION, patients present with an altitudinal defect corresponding to the loss of ganglion cells induced by hypoperfusion (infarction) of one or more optic disc sectors. We observed a strong relation between the location of MMO and the thinning of ganglion cells, corresponding to the visual field defect. Indeed, MMO seems to respect the horizontal meridian in case 2 and 3, compatible with an effect of retrograde degeneration. Moreover, greater RNFL and GCC thinning are observed in these patients compared to the entire cohort (Figure 2). Contrary to the conclusions of Lee DH et al [17], in NA-AION, a poorer overall visual outcome is not necessary to observe MMO but rather a significant localised loss of RGCs is key. MMO was indeed observed by us in two patients who had poor vision (case 1 and case 2) but also in a patient with good overall vision because central vision was spared (case 3). The question arises as to the impact of the INL change on visual function. Clearly, it signifies greater RGC loss but whether any additional impairment of function occurs is unknown. To investigate this question in NA-AION would require detailed visual function analysis and possibly electroretinography concentrating on the macula, comparing cases with comparable visual field loss with and without MMO.

In conclusion, our study indicates two causes of MMO in the same patients suffering from NA-AION, one reversible and the other likely permanent. Müller cell dysfunction seems to play a key role in this finding and offer a potential explanation for both conditions. This finding highlights the distinction between genuine oedema related to transudation of fluid (here associated with optic disc swelling) and the phenomenon observed in RM related to the degree of RNFL loss. We consider that MMO might be considered a misnomer if there is no tissue oedema and, until the exact pathology is identified, would recommend the use of the term “retrograde maculopathy” [13,16]. The distribution of the change corresponded in our cases to both the more significant visual field loss and the greater GCC thinning. It appeared after a time interval of some weeks and may persist for many months or years. These are not the characteristics that would be expected if tissue oedema were the underlying mechanism giving rise to the INL cystic change. NA-AION is also a useful model because of the localised retinal change corresponding to localised axonal loss, as has also been found in the nasal hemi-macula in chiasmal compression [34].
Figure legend

Figure 1: SD-OCT (Heidelberg Engineering, Heidelberg, Germany) imaging. A. Microcystic change visible in the peripapillary region in moderate swelling of the disc (Cohort case; blue arrows) B. Transudation of fluid through the retina at presentation and (C)23 days later in one case selected from the 19 out 34 cases showing disc change without subsequent retrograde maculopathy (Cohort case)

Figure 2:. Log ratio of GCC thickness in the superior and inferior hemi-maculae between 6 months and baseline. Patients with MMO had significant thinning of both the superior and inferior hemi-maculae (case 1: blue dot, case 2: green dot, case 3: red point). One additional patient of the cohort who had significant thinning of both the superior and inferior hemi-maculae at 6 months had also significant MMO observed (yellow dot).

Figure 3: CASE 1. (A) Visual field showing central involvement (B) illustration of Δ GCL thickness (C) Cirrhus HD-OCT fundoscopic images showing a hypointense circular distribution of the inner nuclear layer cystic change (D) En face Cirrhus OCT showing microcystic macular change (Case 1). CASE 2. (A) Visual field showing a superior altitudinal defect (B) illustration of corresponding ΔGCL (µm) thinning between the affected eye at 6 months and the unaffected eye (C) En face HRA OCT (Heidelberg Engineering, Heidelberg, Germany) showing microcystic macular change located in the inferior hemimacula (D) HRA infrared imaging and Cirrhus HD-OCT funduscopical imaging showing an inferior hypointense distribution of the vacuoles. CASE 3. (A) Illustration of corresponding ΔGCL (µm) thinning between the eye before the event and 6 months post episode (B) Visual field showing a superior altitudinal defect (C) HD-OCT funduscopy images showing hypointense lesion corresponding to location of microcyst (D) HRA en face OCT (Heidelberg Engineering, Heidelberg, Germany) showing inner nuclear layer microcysts in the inferior hemimacula. This cystic change develops over time, is longstanding, possibly permanent and corresponds with the GCC thinning and visual field loss. For each patient, the distribution of cystic change was confirmed by inspection of the horizontal scans.

Figure 4: evolution of the microcysts in the inner nuclear layer which persist over time (Case 1) with SD-OCT B-scans (HD-OCT Cirrhus, Carl Zeiss Meditec, Dublin, California).

Figure 5: SD-OCT (Heidelberg Engineering, Heidelberg, Germany) imaging. Extension of microcystic change in the INL close to the fovea in A one case from the cohort (Cohort case) and B Case 3. These changes correspond to the degree of optic disc swelling and are reversible with resolution of the retinal oedema.
References


Precis: We identified three cases with non-arteritic anterior ischaemic optic neuropathy demonstrating acute transient microcystic change in the INL. This was associated with retinal oedema associated with optic disc swelling. The cases later developed retrograde maculopathy.