The Prevalence of microcystic paramacular changes on optical coherence tomography of the paramacular region in optic nerve atrophy of non-neuritis origin: a prospective study

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Key words: optic atrophy, microcystic macular oedema, optical coherence tomography, scanning laser ophthalmoscopy

Word count (excluding titel, abstract, tables, figures and references): 3027

ABSTRACT

Background: Microcystic macular changes, also called microcystic macular oedema (MMO), have recently been reported in patients with multiple sclerosis (MS), particularly after optic neuritis. But it has since emerged that the finding is not specific for optic neuritis. This study was designed to prospectively investigate the prevalence of microcystic perifoveal changes in patients with optic atrophy not due to optic neuritis.

Methods: A prospective, cross-sectional study including 54 patients with a history of optic atrophy. Spectral domain optical coherence tomography (SD-OCT) was used to scan the macular area and to measure the peripapillar retinal nerve fibre layer thickness. Scanning laser ophthalmoscopy (SLO) was used for imaging of the macular area.

Results: Microcystic macular changes were present in 11/54 patients (20.4%), 17/90 eyes with optic atrophy (18.9%) and absent in the normal eyes of patients with monocular optic atrophy. There was a trend for a higher prevalence of microcystic changes with longer duration of optic atrophy. No correlations were found with the age, or severity of optic atrophy. Besides the known perifoveal (semi) circular abnormal reflexes on SLO imaging, we also noticed a more patchy pattern of low SLO reflections in some patients with optic atrophy.

Conclusion: Microcystic macular changes are a frequent observation in patients with optic atrophy of another cause then optic neuritis. The cause of these abnormalities

remains a matter of debate. It is important for clinicians to recognise these macular changes and to realise that the cause may lie remotely away from the macula.

INTRODUCTION

Recently, a new phenomenon of optical coherence tomography (OCT) imaging of the perifoveal region of the retina has been reported, with microcystic like changes in the inner nuclear layer (INL).[1] The term 'microcystic macular oedema (MMO)' was coined,[1] and subsequently translated to US spelling 'edema' as MME.[2] This new phenomenon drew a lot of attention in the neurological literature. Importantly, the microcystic changes were described in the retina of patients suffering from multiple sclerosis (MS) and were related to clinical and radiological disease activity.[1,3]
The rapid recognition that these microcystic changes were not specific for MS stimulated an extensive exchange of letters.[4-7] Notably, microcystic changes were also seen in patients with non-MS types of optic neuritis, such as relapsing isolated optic neuritis (RION),[4] chronic relapsing optic neuropathy (CRION),[8,9] neuromyelitis optica ON (NMO-ON),[8] as well as aetiologies other then optic neuritis (ON).[5-7,10-14] It has also become apparent that microcystic macular changes occurred in ophthalmological degenerative diseases like age-related macular degeneration, diabetic retinopathy, vascular occlusion and with epiretinal membranes.[14,15] As the etiology of this retinal abnormality remains unknown and evidence for oedema not conclusively been provided, Kisimby et al. (2013) suggested to be careful about the terminology.[11] Therefore Abegg et al proposed to refer to a “retrograde maculopathy”.[13]
Kisimbi *et al. (2013)* were also first to report that infrared imaging (IR) may be a convenient method to demonstrate the localisation of microcystic changes in the retina.[11] This has since been confirmed and scanning laser ophthalmoscopy (SLO) was added to the list more recently.[8,10,12,13] Taken together these imaging modalities consistently describe the microcysts to be distributed in a circular area, or semicircular

area around the fovea.[8,10-13,16] An important limitation of all these observations was the retrospective study design resulting in a large variation of the reported prevalence, ranging from 0.8% to 25%.[3-8,10-15] In addition, there has been an inclusion bias towards ON and a publication bias of the neurological literature with the true clinical spectrum being much broader.[15]

Therefore, the present study was designed to prospectively investigate the prevalence and epidemiology of microcystic paramacular changes in patients who did not suffer from ON and close the gap between the neurological and ophthalmological literature.

METHODS

Study design and patient population

Patient and controls were enrolled at two Dutch university medical centres (Groningen, Amsterdam), between May 2013 and April 2014 for this cross-sectional study. The study was approved by the medical ethical committees and the scientific research committee at both centres. Written informed consent was obtained from all patients included. Patients were prospectively recruited either by referral to our tertiary care neuro-ophthalmology service or own follow-ups.

Inclusion criteria: All patients were older then 18 years of age, and had a history of optic nerve atrophy.

Exclusion criteria: optic neuritis due to multiple sclerosis (MSON), isolated optic neuritis (ION), relapsing isolated optic neuritis (RION), chronic relapsing inflammatory optic neuropathy (CRION), optic neuritis due to neuromyelitis optica (NMO-ON) and Harding's disease. An onset of optic atrophy of less then 4 months ago after AION, because of possible presence of subretinal oedema. We also excluded cases with intra-ocular surgery in the past 6 months, previous radiotherapy to the visual pathways, diabetes mellitus, macular degeneration, retinal vein occlusion, retinal dystrophy, uveitis or retinal detachment.

Clinical assessment: Demographic data and the medical history were obtained in all patients. Snellen visual acuities (VA) were recorded using high contrast charts.

Spectral domain optical coherence tomography (SD OCT)

Two SD OCT devices were used, a Canon OCT –HS100 in Groningen and a Heidelberg Spectralis in Amsterdam. Bot devices have a build in scanning laser ophthalmoscopy (SLO) camera and the eye tracking function was enabled as required for accurate quantitative OCT data assessment by maintaining eye alignment during image recording.

In Groningen, multi-cross high resolution scans were made in horizontal and vertical direction through the macular area. In order to include the whole macular area, multi-cross scans were made with a scan size of 3x3 mm and 10x10mm. We used a low averaging mode of 5 scans only, because in our experience these microcysts can be so small that they can be averaged out from the summary image. Furthermore, a macular volume scan was made (10x10 mm), and a 3D scan of the optic disc area (6x6 mm), including an about 3.45 mm ringscan of the peripapillary retinal nerve fibre layer (pRNFL). The multicross scans and the macular volume scans were analysed for the presence of so-called MMO using validated criteria.[14] The quantitative pRNFL data served to grade the degree of optic atrophy seen by funduscopy. The normative database of the Canon OCT-HS100 was used for this purpose. The OCT scan divides the circle into four quadrants (temporal, superior, nasal, inferior) and gives the RNFL thickness for these sectors. For each eye, we calculated the mean value of these four quadrants to get an average RNFL thickness.

Likewise, in Amsterdam, an about 3.4 mm peripapillary ringscan was performed as well as two volume scans with vertically orientated OCT B-scans of a 20x20 degree field (25 sections) for the macular and a 15 x 15 degrees field (73 sections) for the optic nerve head.

Statistical analyses

All statistical analyses were done in SPSS (version 22) and SAS (version 9.2). Normal distribution was checked graphically and using Shapiro-Wilk statistics. Normally distributed data were presented as mean and standard deviation (SD) and non-Gaussian data as median and interquartile range (IQR). Parametric and non-parametric testing was used according to normality. Categorical data were compared using the Fisher exact test.

RESULTS

Fifty-four patients were included with a mean age of 46.5 years (range 18 to 79 years). Twenty-four (44.4%) were female and twenty-eight (55.6%) male. Almost all patient were recruited by one centre (Groningen, n=52). The ethnic background was Caucasian in 52, Asian in one, and Arabic in another patient.

In all patients both eyes were imaged by SLO and OCT. Optic atrophy was binocular in 37/54 (68.5%) patients and monocular in 17/54 (31.5%) patients. In all cases a pale disc on funduscopy corresponded to a pathological degree of pRNFL thinning.

Table 1 summarises the aetiologies of optic atrophy in this study. The number of patients with microcystic macular changes in the different etiologic subgroups is also given.

Table 1. Cause of optic atrophy in 54 patients

	n	% of total	Patients with microcystic macular changes
Trauma	3	(5.6%)	2
Compression	28	(51.9%)	3
AION	10	(18.5%)	1
Hereditary optic neuropathy	7	(1.9%)	3
Metabolic/Toxic	1	(13.0%)	
Optic nerve head drusen	1	(1.9%)	
Intracranial hypertension	2	(3.7%)	1
Unknown	2	(3.7%)	1

Microcystic changes were seen in 11/54 patients (20.4%). Considering individual eyes, microcystic changes were present in 17/90 eyes (18.9%) with optic atrophy. In four

patients microcystic changes were monocular, with one having evidence for bilateral optic atrophy. This patient suffered from a chiasmal glioma treated 13 years earlier. The eye showing MMO was the eye with poorer visual function as compared to the other eye (fig 3). The other three patients had a monocular optic atrophy. Importantly, microcystic changes were never seen in absence of optic atrophy. There was one patient with bilateral microcystic changes and only a unilateral AION. A follow-up investigation revealed presence of burried optic disc drusen in the presumed healthy eye. This eye also showed a segmental thinning of the pRNFL on OCT. We rated this patient as having a binocular optic neuropathy.

OCT and SLO images

Examples of OCT scans with microcystic macular changes together with SLO images are shown in figures 1-3. Figure 1 is the OCT and SLO image of the right and left eye of a 24 years old patient who experienced a traumatic optic neuropathy of his left eye 10 month earlier. The OCT image of his right eye (Fig 1A) shows an intact RNFL (filled white arrow) at site of the inferior optic disc (Fig 1B). The OCT of the left eye (Fig 1 C) has no visible RNFL on the cross-section and a thinned ganglion cell layer (GCL) compared to the right eye. The open arrow points to the microcystic changes in the inner nuclear layer (INL). An enlargement of this area is shown in the insert image (Fig 1 D). Interestingly, hyperreflective dots were also seen in the INL far beyond the area of visible microcystic changes. A vertical OCT cross-section through the macular area is shown in the insert (Fig 1 F). The SLO image of the left eye (Fig 1 E) shows a C-shaped dark ring representing the area where the MMO was present on the OCT imaging. Figure 2 shows another two eyes of two patients with microcystic macular changes. The OCT image (Fig 2 A) is of a 62 years old patient with chiasmal compression 26 years ago due to a pituitary tumor, relieved by neurosurgical decompression at the time of

diagnosis. The SLO image shows a circular pattern of abnormal dark reflection. The horizontal OCT scan through the macular area shows microcystic changes on both sides of the fovea, in concordance with the abnormal pattern of the SLO image in Figure 2 B. Again, hyperreflective dots were seen to involve a larger area than the microcysts (Fig 2 A). The OCT image in Fig 2 C is of a 65 years old patient suffering from bilateral optic atrophy following a severe subarachnoid haemorrhage (SAH) with Terson syndrome and complications 10 years earlier. The aneurysmal SAH was Fisher grade IV and complicated by secondary hydrocephalus. Therefore, the bilateral optic atrophy was thought to be due to increased intracranial pressure. We do not know about other possible complications associated with a poor grade SAH.[17] The horizontal OCT cross-section through the macular area shows microcystic cysts on both sides of the fovea. The SLO image shows a more diffuse and patchy pattern of abnormal reflections. When scrolling through the OCT images, these abnormal areas of SLO reflections covered a larger area than the microcystic changes on OCT. As noted before, hyperreflective dots were also present in a larger area than microcystic changes involving several retinal layers.

We made another observation not reported earlier on in relationship to microcystic macular changes. Figure 3 shows an OCT image of the right eye of a 25 years old man, who suffered from a chiasmatic glioma in his first year of life. Visual fixation was not possible because of the very poor vision. Therefore the accidental eccentric scanning permitted to discover more peripheral microcystic changes of the INL. The approximate region of these microcystic changes is shown by the open arrow in the SLO image (Fig 3). There was no abnormal reflection of the SLO image in this region. The INL also showed the typical thickening at the site of microcystic changes. As before, hyperreflective dots were seen adjacent to microcystic changes. Critical revision of the

OCT scans from the darkened area on the SLO image did not reveal any visible microcystic changes.

Correlation with age and disease duration

There was no significant difference in the mean age between the patients without (46.7 years, SD ±17.2 years) and with microcystic macular changes (46.3 years, SD ±15.3 years) (T-test, p=0.095). Patients with microcystic macular changes had a longer duration of optic atrophy (median 155 months, interquartile range 246 months) as compared to patients without microcystic macular changes (median 66 months, interquartile range 211 months), but this difference failed to reach statistical significance (Kruskal-Wallis test, p = 0.29). If we divide our study group in two equal groups of 27 patients according to the duration of optic atrophy, the first group with a duration of optic atrophy of 8 years or shorter had a microcystic macular changes prevalence of 11.1 % (3/27). In the second group of patients with a duration of optic atrophy of longer then 8 years the prevalence of MMO was 29.6% (8/27). This difference was not significant (Fisher exact test).

Correlation with RNFL measurement

Figure 4 shows box plot of the mean pRNFL thickness in the normal eyes of patients with monocular optic atrophy, the eyes with optic atrophy, but without microcystic macular changes and the eyes with microcystic macular changes. The groups were unbalanced and the data not Gaussian. General linear models showed a significant difference between groups ($F_{2,89}$=46.01, p<0.0001) with a significant degree of atrophy in both groups (p<0.0001 for both, Fig 4) but no difference between those with and without microcystic changes.

DISCUSSION

The main outcome of this prospective study was that microcystic macular changes were present in 20.4% of the patients with optic atrophy not due to optic neuritis. At first sight this appears to be substantially more compared to the pooled prevalence of 7.7% reported by Abegg et al. (2014).[6] Of note, the averaged disease duration was shorter in the Abegg study with 6.5 years compared to the 16 years in the present study. It is possible that the prevalence of microcystic changes might be higher with longstanding otpic atrophy, but prospective longitudinal data will be required to test this. The presence of microcystic changes in the context of hydrocephalus as described in one of our patients is consistent with another recent report on bilateral microcystic changes in a child with bilateral optic atrophy due to hydrocephalus (see Figure 5 in Tawse et al. (2014)).[18]

From a clinical practice point of view it is relevant that microcystic macular changes are much more frequent with compressive aetiologies as compared to a recent episode of multiple sclerosis associated optic neuritis (MSON) 4.7- 6.3%.[1,8] The literature on other conditions is only emerging, but it might be prudent to consider neuroimaging if metabolic and heriditary conditions have been excluded and there is no other obvious ophthalmogical explanation. [5,11,14,15]

There is clearly a need for future studies to longitudinally investigate the temporal and spatial profile of microcystic changes. Do microcystic changes appear earlier than for example the two to three months it takes for optic atrophy to develop after optic neuritis? Does the longitudinal profile help with the differential diagnosis of inflammatory and compressive pathologies? Does their spatial distribution change over time? There are no data at present to answer any of these pertinent questions.

In the present study there was no difference in the mean age of patients with and without microcystic changes. This is in contrast with the study of Abegg et al. (2014) where they found that younger patients had a significant higher chance of having microcystic changes then older patients.[13] In our view it is difficult to attribute this to age alone and future prospective studies addressing this question will need to be careful to avoid an inclusion bias due to the age distribution of various aetiologies.

It has been reported by several studies that the areas with microcystic changes in the macular area can also be detected by infrared or SLO fundus imaging. These areas of hyporeflection form a complete or incomplete ring around the parafoveolar area.[8,10-13] A finding not previously reported in studies on microcystic changes is the patchy pattern of SLO abnormalities we found in the posterior pole of the retina in some patients with optic atrophy. In this context it might be relevant to follow-up on the observation made on hyperreflective dots adjacent to microcystic changes.[19] In all cases seen by us so far the area with microcystic changes was smaller compared to the area with hyperreflective dots. Scoles et al. (2014) made the important point that the Rayleigh resolution limits visibility. It may be possible that very small microcystic changes are just not visible on an individual OCT B-scan.[19] This argument led the John Hopkins group to develop an automated algorithm which possibly more accurately describes the spatial resolution of these microcystic changes.[20] It is therefore intriguing to note that microcystic changes were also not necessarily visible on all OCT B-scans were the focally darkened SLO image suggested their possible spatial distribution.

A specific feature of SLO is the high degree of spatial sensitivity which makes it a good tool to identify areas with possible MMO. In addition, the spread areas of abnormal reflections on SLO imaging suggests that the degenerative changes might not be limited to the perifoveolar area. This is supported by another observation made in this study and shown in figure 3 where microcystic changes were detected just outside the perifoveolar area because of a serendipitous eccentric OCT scan in a patient who was not able to fixate. This is an area which is not routinely included in macular OCT imaging.

The precise nature of the microcystic changes remains unknown. There have been no studies correlating OCT findings with histology. There are, however earlier histological observations which clearly demonstrate retinal vacuoles in the inner nuclear layer of the retina. [21,22] Retrograde axonal degeneration was the most probable mechanism in the macaccae model. An alternative mechanism, inflammation, was proposed with the recent OCT driven rediscovery of these microcystic changes in patients with MS.[1-3] But several studies have shown that there was no dye leakage on fluorescein angiography.[5,10] The data of the present study are more in keeping with the neurodegenerative hypothesis because inflammation was excluded and the long disease duration of 16 years. We and others have therefore drawn an analogy to the appearance of lesions on magnetic resonance imaging, appearing either as a T1 black hole representing neurodegeneration or a T2 lesion representing inflammation.[23]

It has also been suggested that retrograde axonal degeneration influences the integrity of the retinal organisation and that loss of retinal Müller cell function may play a role in microcyst formation.[4,10,13,14,24] Finally, vitreo-retinal traction can lead to the formation of microcystic changes,[5,7] but certainly does not represent an unifying mechanism because it has conclusively shown to be absent in a number of cases.[25]

Taken together, the present study is the first prospective report on the prevalence of microcystic changes in patients with optic atrophy. The data show that microcystic changes are a frequent phenomena, particularly in the context of optic atrophy. It is important for ophthalmologists to recognise these macular changes because they can be the result by pathology remotely located from the macula. Presence of microcystic macular changes should trigger pertinent questions and in absence of a history for optic neuritis or another evident aetiology one should consider imaging of the brain and orbits.

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microcysts independent of vitreous traction changes. *Neurology* 2014;**83**:1–5.

FIGURE LEGENDS

Figure 1: A 24 years old patient with traumatic atrophy of his left eye. (A) Horizontal OCT scan through macular area. The white filled arrow points to the intact nerve fibre layer. (B) SLO image of right eye. The striped line shows the approximate location of OCT scan in A. (C) Horizontal OCT scan of the eye with optic atrophy. Note the absence of visible retinal nerve fibre layer. The open arrow points to microcystic changes in the inner nuclear layer (INL). An enlargement of the area with changes is given in (D). (E) SLO image of left eye. Note the dark C-shaped ring around fovea. This represents the area where microcystic chages were found on horizontal scans and vertical scans (F) through the macular area. The white line in SLO image represents the approximate location of the vertical scan.

Figure 2: (A) Horizontal OCT scan of the left eye of a 62 year old patient with chiasmal compression 26 years ago due to a pituitary tumor. The scan shows microcystic changes on both sides of the fovea. (B) SLO image of same eye showing a complete circle of abnormal reflection around the fovea (C) Horizontal OCT scan of the right eye of a 65 year old patient who had optic atrophy due to increased intracranial pressure after a Fisher grade 4 subarachnoidal haemorrhage 10 years ago. (D) SLO image of the same eye, showing a patchy pattern of abnormal reflex in the macular area.

Figure 3: (A) OCT image of the right eye of a man who was treated for a chiasmatic glioma at the age of 12 years. Microcystic changes (open arrow) were found in a more peripheral region then normally reported. The approximate location of the horizontal

OCT scan is given by the striped line in the SLO fundus image (B). The area with microcystic changes is given by the open arrow.

Figure 4: Box plot of the mean pRNFL thickness in the normal eyes of patients with monocular optic atrophy, the eyes with optic atrophy but without microcystic macular changes and the eyes with optic atrophy and with microcystic changes.