Microcystic Macular Edema

Retrograde Maculopathy Caused by Optic Neuropathy

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Purpose: To investigate retrograde axonal degeneration for its potential to cause microcystic macular edema (MME), a maculopathy that has been previously described in patients with demyelinating disease. To identify risk factors for MME and to expand the anatomic knowledge on MME. Design: Retrospective case series. Participants: We included 117 consecutive patients and 180 eyes with confirmed optic neuropathy of variable etiology. Patients with glaucoma were excluded. Methods: We determined age, sex, visual acuity, etiology of optic neuropathy, and the temporal and spatial characteristics of MME. Eyes with MME were compared with eyes with optic neuropathy alone and to healthy fellow eyes. With retinal layer segmentation we quantitatively measured the intraretinal anatomy. Main Outcome Measures: Demographic data, distribution of MME in the retina, and thickness of retinal layers were analyzed. Results: We found MME in 16 eyes (8.8%) from 9 patients, none of whom had multiple sclerosis or neuromyelitis optica. The MME was restricted to the inner nuclear layer (INL) and had a characteristic perifoveal circular distribution. Compared with healthy controls, MME was associated with significant thinning of the ganglion cell layer and nerve fiber layer, as well as a thickening of the INL and the deeper retinal layers. Youth is a significant risk factor for MME. Conclusions: Microcystic macular edema is not specific for demyelinating disease. It is a sign of optic neuropathy irrespective of its etiology. The distinctive intraretinal anatomy suggests that MME is caused by retrograde degeneration of the inner retinal layers, resulting in impaired fluid resorption in the macula. Ophthalmology 2014;121:142-149 © 2014 by the American Academy of Ophthalmology.

Retinal ganglion cells project axons to the lateral geniculate nucleus, from where visual information is relayed to the visual cortex. Compression, inflammation, hereditary conditions, or ischemia may harm axonal function and result in characteristic visual field defects, decreased visual acuity, or impaired color vision. Irreversible axonal injury induces a retrograde axonal degeneration, which may become evident at the level of the optic disc. In the retina, optic atrophy is associated with thinning of the retinal nerve fiber layer thickness¹ and reduced ganglion cell layer thickness. Histologic analyses showed reduced cell counts in the inner nuclear layer (INL) of eyes with optic neuropathy, but not in thinning of the INL in vivo measurements. In 2012, Gelfand et al described small vacuoles in the INL of the macula in a subset of patients with multiple sclerosis (MS). The presence of this microcystic macular edema (MME), or oedema in the original spelling, was associated with greater disease severity (Multiple Sclerosis Severity Score) and was later demonstrated to predict an increased recurrence rate of MS. With a higher incidence rate than in MS, MME was also found in patients with neuromyelitis optica. The specificity of MME for demyelinating disease has been questioned by reports demonstrating MME in a patient with non–MS-associated relapsing optic neuritis and in a series of patients with Leber’s hereditary optic neuropathy and autosomal-dominant optic atrophy. The mechanism underlying MME is not clear and subject to an active debate: Inflammatory processes, transsynaptic degeneration, and vitreous traction have been suspected to play a role. The association of MME to non–MS-associated optic neuropathy has not been investigated systematically.

We recently reported MME in a 13-year-old boy suffering from neurofibromatosis type 1 and chronic compressive optic neuropathy in both eyes owing to a chiasmal glioma. Our observation raised the possibility that MME may be noninflammatory and result from retrograde possibly transcellular degeneration from a lesion remote to the macula. To investigate the association of optic neuropathy with MME, we retrospectively analyzed retinal layers in consecutive patients with non–MS-associated MME of ischemic, compressive, and hereditary origin.

Methods

Study Design and Patients
All medical records of patients seen at the Department of Ophthalmology, Inselspital, University Hospital, University of Bern, between January 2008 and August 2012 were retrospectively analyzed.
Figure 1. Study design and patient selection. Number of patients included are shown in parentheses. MME = microcystic macular edema; OCT = optical coherence tomography; ON = optic neuropathy.

Figure 2. Anatomic characteristics of microcystic macular edema (MME). A, A 30° infrared image of the left eye of a patient with MME. The microcysts cause a diffraction of the infrared reflex originating from layers below the edema, thereby leading to a dark appearance of the MME in infrared images. The location of the optical coherence tomography (OCT) section is indicated with a white horizontal line and arrows. B, The OCT section shows that microcystic inclusions are located in the inner nuclear layer (INL) but not in the other layers. The presence of microcysts corresponds well with the dark area in the infrared image (white vertical arrows). C, Cumulative probability of MME location (16 eyes). The scale bar indicates the percentage of patients with MME in a given area. White areas indicate that all patients had MME in that area; black indicates that MME was present in none of the patients in the MME group. The MME shows a characteristic perifoveal distribution in all patients. Asterisk indicates location of the temporal raphe. D, Magnified and contrast-enhanced infrared example of MME. The speckled area shows that microcysts can be detected in the infrared image, illustrating the use of infrared imaging for detecting MME.
Figure 3.
screened for the keyword optic neuropathy. Patients who had (1) confirmed optic neuropathy and (2) had undergone a macular optical coherence tomography (OCT) were identified (Fig 1). The indication for OCT imaging was made in the clinical routine usually to complement a peripapillary nerve fiber analysis. This resulted in a heterogenous sampling rate and follow-up time. To better match patients with MS in whom MME had been first described, patients with glaucoma were excluded. Optic neuropathy was defined as the presence of either reduced peripapillary retinal nerve fiber layer thickness or presence of an apparent pupillary defect, and an associated loss of function, with either reduced visual acuity, reduced color vision (measured with Ishihara plates), or visual field defects. The study was conducted with the approval of the local ethics committee.

Demographics and Clinical Characteristics

For each patient, we determined age, sex, visual acuity, and the underlying cause of the optic neuropathy. The latter was categorized as compressive, ischemic, hereditary, inflammatory, or traumatic. Visual acuity was converted from Snellen values into the logarithm of the minimum angle of resolution (logMAR). Visual acuity for counting fingers (logMAR = 1.85), hand motion (logMAR = 2.3), light perception (logMAR = 2.7), and no light perception (logMAR = 3.0) were converted using a previously published conversion table.13 We determined the duration of presumed disease onset to the first demonstration of MME and the follow-up period from the first to the last macular OCT scan.

Imaging and Image Analysis

A combined spectral domain, high-resolution OCT with a scanning laser ophthalmoscope (Spectralis HRA+; OCT; Heidelberg Engineering, Heidelberg, Germany) was used for imaging. The system allows for simultaneous OCT scans with infrared imaging. For infrared images, we averaged 36 images acquired with a scan angle of 30°. The OCT scans included 6 mm in cross-hair scans centered on the fovea (horizontal and vertical) as well as a volume scan (20’ × 20’) using 49 line scans. For single scans, 25 OCT scans were averaged and for each of the volume scans 9 OCT scans were averaged. Macular line scans were screened manually by 2 of the authors for the presence of vacuoles in the INL. To map the probability of the MME location, we colored the area containing microcysts for each eye in Photoshop (Adobe Systems Inc., San Jose, CA) with a grey value of 256/n. These 8-bit grayscale images were added mathematically in ImageJ (National Institutes of Health, Bethesda, MD).14 Images of the right eye were mirrored vertically to match the left eye (Fig 2).

For the analysis of retinal layers, we used a custom-built segmentation software.15,16 The local thickness was determined for each B scan of the volume scan. The automatic segmentation was verified by an experienced examiner and, when necessary, manually adapted. The segmentation algorithm determined the border between (1) the internal limiting membrane, (2) ganglion cell layer, (3) INL, (4) outer nuclear layer (ONL), (5) junction of the inner and the outer segments, (5) outer segment of photoreceptors/pigment epithelium complex, and (6) Bruch’s membrane. For quantitative analysis of the layers, we exported a thickness value for each layer and each sector of a superimposed grid, which was initially defined in the Early Treatment Diabetic Retinopathy Study. Because patients with acute ischemic optic neuropathy showed swelling of the disc and the adjacent retinal layers, only scans obtained 2 months after disease onset were included in the segmentation analysis. We assumed that by this time nerve fiber atrophy had reached the macula and disc swelling had regressed. Both eyes of each patient were included in the analysis. If optic neuropathy was unilateral, we used the contralateral eye as healthy control. This resulted in 3 groups: optic neuropathy with MME, optic neuropathy without MME, and healthy control eyes. To simplify the analysis, the mean of all sectors of the Early Treatment Diabetic Retinopathy Study grid for each layer, except for the central foveal area, for each patient was calculated and used for further analysis, resulting in a single thickness value per layer per eye.

To address the association of MME with optic atrophy we compared the ganglion cell layer thickness and nerve fiber layer thickness of areas with MME to retinal locations without MME within the same subjects (Fig 2). Mirror locations were defined as squares of the Early Treatment Diabetic Retinopathy Study grid mirrored along the horizontal or vertical axis. Thus, a superonasal region could be compared with either a supertemporal or inferonasal retinal location. Only data from 5 eyes were included for this analysis because the OCT images of 3 eyes were insufficient to perform segmentation. A circular pattern of MME was found in both eyes of 4 patients, thus not allowing identification of a control region within the same subject.

Statistical Analysis

For analyzing risk factors we statistically compared the eyes with MME to eyes without MME 2 months after disease onset. For this we used either the Student’s t-test or Pearson chi-square test. For the segmentation analysis, we compared 3 groups (healthy, MME, and optic neuropathy without MME) using a 1-way analysis of variance. Pairwise contrasts were explored with the Tukey’s honest significant difference test. P<0.05 was considered significant.

Results

Characteristics of Patients

A total of 180 eyes from 117 patients were identified. In 33% of the eyes, optic neuropathy resulted from ischemia, in 39% from compression; 9% were classified as hereditary, and 9% were of inflammatory origin. Toxic, traumatic, and “not determined” each accounted for <5% of the eyes. From this dataset we identified 16 eyes from 9 patients, namely, 7.7% of all patients or 8.8% of eyes, with MME. One patient with bilateral MME had a vitrectomy procedure for bilateral macula-on retinal detachment before. No other confounding macular diseases such as epiretinal membranes or diabetic retinopathy were present in the MME patient group. All patients of the MME group with bilateral optic neuropathy also showed bilateral MME. None of the patients showing MME had MS.

Figure 3. The correlation of optic atrophy and microcystic macular edema (MME). A, B, T1-weighted magnetic resonance images of a patient with a right optic tract lesion causing a complete homonymous hemianopia to the left. The causal ganglioglioma is enhanced by gadolinium. C, D, Infrared fundus photographs show the corresponding location of MME in the same patient. The distribution of MME (outlined in white) illustrates the distribution of nerve fibers in the fundus. E, G, Nerve fiber layer (NFL) thickness in areas with MME compared with areas without MME within patients in the MME group. F, H, Scatter plots show a correlation of inner nuclear layer (INL) thickness with ganglion cell layer (GCL) thickness, but not NFL thickness in eyes with MME.
Anatomic Characteristics and the Use of Infrared Imaging

The location of the microcysts showed a characteristic perifoveal circular distribution (Fig 2). In 14 of 16 eyes, the distribution of MME could be readily visualized in the infrared images. Pairwise comparison of retinal areas with MME to retinal areas without MME showed that the ganglion cell layer was significantly thinner in regions with MME compared with regions without MME (P = 0.007, paired Student t test). In keeping with the loss of ganglion cell bodies, the retinal nerve fiber layer was significantly thinner in areas with MME compared with areas without MME (P = 0.017, paired Student t test). A correlation of nerve fiber layer thickness and ganglion cell thickness with INL thickness showed a significant correlation of ganglion cell layer thickness with INL thickness (r = 0.59; P = 0.035; Fig 2). The correlation of nerve fiber layer thickness with INL thickness did not reach significance (r = 0.11; P = 0.712; Fig 2).

Time Course of MME

MME was detected 6.5±6.8 years after the first diagnosis of optic neuropathy. In 1 patient, we observed a decrease of the MME in the course of the observation period of 7.4 months. In 1 patient with acute-onset neuropathy, we found that MME appeared in a control visit 4 months after disease onset. In all other patients MME remained unchanged during the observation period of 5.3±8.0 months.

Risk Factors

To analyze risk factors we included only the patients who had imaging 2 months after disease onset. We found that patients with MME were significantly younger than patients without MME (P = 0.0003, Student t test). Sex (44% females in the MME group and 50% females in the no MME group), visual acuity (0.5±0.9 logMAR in the MME group and 0.5±0.7 logMAR in the no MME group), and temporal nerve fiber layer thickness (65±18 µm in the MME group and 75±25 µm in the no MME group) were comparable; no statistical significant differences were found (P>0.1 for all comparisons). The etiology of optic neuropathy was not significantly different between the MME group and the no MME group. In the latter, we found 53 compressive, 36 vascular, 13 inflammatory, 12 hereditary, 7 toxic, and 6 not determined cases. In the MME group we had 9 compressive, 3 vascular, 2 hereditary, and 2 not determined cases (P = 0.37, Pearson’s test).

Layer Analysis

Layer analysis revealed that the INL was significantly thicker in MME patients compared with healthy control eyes and compared with patients with optic neuropathy (analysis of variance; Tukey’s honest significant difference test; P<0.05). No difference of INL thickness was found between eyes with optic neuropathy without MME and healthy eyes. For both nerve fiber layer thickness and ganglion cell layer thickness, we found that the MME group and the optic neuropathy group had significant thinning of both layers compared with healthy controls (Tukey’s honest significant difference test; P<0.05). No difference was found between MME and optic neuropathy without MME. The analysis of other retinal layers showed that eyes with MME had a significant increase in thickness in the ONL compared with healthy eyes, but not with eyes with optic neuropathy (Tukey’s honest significant difference test; P<0.05).

Discussion

We found that 8.8% of all eyes with optic neuropathy showed vacuolar inclusions in the INL. This MME has identical features to the one described in patients with MS and neuromyelitis optica and it shares striking similarities with the macular changes described recently by Wolff et al17 in patients with optic neuropathy. Presence of MME is restricted to retinal areas with nerve fiber loss and is associated with reduced ganglion cell layer thickness. Young age is a significant risk factor for the development of MME. The presence of MME does not depend on the site of the optic nerve damage, which may be at the level of the disc or even retrochiasmal, or on the cause of optic neuropathy.

The particular anatomic location of MME distinguishes it from other types of edema in the retina. In keeping with previous reports, it is restricted to the INL—outer plexiform layer complex of the retina. As recently pointed out by Lujan et al,18 the axons of photoreceptor somas, which are located in Henle’s fiber layer between the INL and ONL, show variable reflectivity patterns depending on the entry position of the OCT beam through the pupil. Neither our imaging parameters nor our segmentation algorithm were determined to detect the Henle’s layer. Thus, we cannot exclude that microcysts are located also in Henle’s layer. Using infrared imaging we were able to show that MME does not involve the fovea, but is rather located in a characteristic perifoveal circle (Fig 2). The distribution resembles the location of the cell bodies of midget cells in the retina, which project to the parvocellular layers of the lateral geniculate nucleus. Midget cells do not have cell bodies in the fovea and represent the majority of ganglion cells in a perifoveal ring with a decreasing cell density toward the retinal periphery.19

Similar changes in the INL have been previously described in enucleated human eyes with lesions of the optic nerve20 and in optic nerve crush experiments in nonhuman primates.21 These reports showed histologic evidence that retrograde transsynaptic degeneration from optic neuropathy results in a significant loss of cells in the INL, which is detected ≥2 years after the lesion. These reports also show cystic lesions at the level of the INL in histologic sections. Several salient features in our patients support the proposition that MME is caused by retrograde transcellular degeneration as well. In the first instance, the prolonged time course from optic nerve damage to the appearance of MME suggests a degenerative process rather than inflammation as the underlying cause. Furthermore, the finding of reduced thickness of the nerve fiber layer and ganglion cell layer in areas affected by MME as well as the finding that MME respected the topographic distribution of optic tract fibers in the retina (Fig 3) corroborate the theory of retrograde degeneration as a cause of MME. Although in 14 of 16 eyes the causal pathology is clearly distant from the macula, we cannot exclude that 1 patient with prior macula-on retinal detachment and subsequent vitrectomy had an additional intraretinal pathology causing edema. Macular edema after intraocular surgery, however, has other OCT features and does not spare the fovea.
We can only speculate about the pathomechanisms of MME. However, the microvacuolar aspect, the sparing of the fovea, and the limitation of the edema to the INL distinguish MME from other commonly encountered macular edemas, which are usually caused by vascular leakage. Because the microvacuolar spaces are exquisitely confined to areas of nerve fiber loss, we hypothesize that MME may not be of vascular origin. Unfortunately, none of our patients with MME had fluorescein angiography to underline that point. The recent report by Wolff et al. shows no vascular leakage in their patients with probable MME. In addition, the slow natural history of MME with persistent MME despite inactive optic neuropathy for years would be consistent with a nonvascular origin. If MME is caused by retrograde degeneration, it may be argued that the microvacuolar changes do not represent true edema but rather fluid-filled empty spaces replacing degenerated cells. Our segmentation analysis shows that MME in our patients was associated with increased INL thickness compared with normal eyes and with other eyes with optic neuropathy. This is in keeping with a recent report of INL thickening in MME in MS patients. This finding indicates that the vacuoles truly represent an increase of tissue volume in that layer. Because breakdown of the blood retina is not likely in our patients, we argue that the swelling results from impaired fluid clearance of the inner retina rather than from exudation from retinal vessels. Müller cells have been

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Figure 4. Retinal layer thickness in patients with microcystic macular edema (MME), optic neuropathy (ON) without MME, and healthy eyes. A, Optical coherence tomography (OCT) sections and the layers as determined with a semiautomatic segmentation software. Panels on the right show relative layer thickness for the nerve fiber layer (NFL), ganglion cell layer (GCL), inner nuclear layer (INL), and the entire retina. The NFL, GCL, and INL share the same grayscale, with greater thickness represented in brighter gray tones. B–G, Boxplots for individual retinal layer thickness of NFL, GCL, INL, outer nuclear layer (ONL), outer segment/retinal pigment epithelium (OS/RPE), and complete retina. Pairs of significant difference in the Tukey’s honest significant difference test are indicated with a line above the graphs.
implicated in fluid absorption from the retinal tissue,\textsuperscript{21} which is mediated by transcellular water transport coupled to currents through potassium channels and aquaporine channels.\textsuperscript{22} We speculate that retrograde transcellular Müller cell degeneration impairs fluid absorption from the retina and thereby may cause MME. Müller cell pathology as a pathomechanism in MME was proposed earlier by Balk et al.\textsuperscript{10} This hypothesis finds support from the fact that layer thickening in MME eyes is not restricted to INL but is also present in deeper layers, thus suggesting that noncystoid fluid accumulation also affects deeper retinal layers (Fig 4). As pointed out before, our imaging technique and segmentation does not allow clear separation of Henle’s fiber layer from the underlying ONL. Thus, INL thickening may be explained by artefactual inclusion of Henle’s layer in the INL thickness measurement. However, the increased thickness of the layers below the INL clearly indicate a true thickening of retinal layers below the ganglion cell layer.

With this background, our interpretation of MME in 4 series of MS and neuromyelitis optica patients is that these patients had an associated optic neuropathy, and MME developed secondarily. This view is supported by the fact that all reports showing MME did also show evidence for an associated optic atrophy.\textsuperscript{6–9} We believe that optic neuropathy is a condition sine qua non for the development of MME. However, our results do not allow us to comment on whether the presence of MME is an independent prognostic factor, as suggested by Gelfand et al\textsuperscript{8} and Saidha et al\textsuperscript{9}: independent of severity of optic neuropathy, MME may still predict a higher MS relapse rate. We speculate that patients with MS and neuromyelitis optica suffered a “double hit”: First, they had optic neuropathy and a retrograde loss of Müller cell function. The second hit might have been from anti-aquaporine antibodies or anti-KIR4.1 antibodies, which caused a further impairment of transcellular water transport. Both channels are expressed on Müller cells\textsuperscript{23} and both are involved in retinal fluid clearance.\textsuperscript{21} The greater incidence rate of MME in patients with neuromyelitis optica\textsuperscript{6–8} may thus be caused by either more severe optic atrophy or possibly because aquaporine antibodies are more potent inhibitors of water resorption. In light of this, it would be interesting to learn whether KIR4.1 antibodies were positive in the patients described by Gelfand et al and Saidha et al.

In conclusion, we find MME in patients with non-demyelinating optic neuropathy, which may be caused by retrograde transcellular degeneration of the retinal water pumps. The fluid inclusion in the INL is accompanied by thinning of the ganglion cell layer and the nerve fiber layer, as well as by a thickening of the deeper retinal layers, leaving the overall retinal thickness unchanged compared with the normal retina. This complex retinal alteration induced by optic neuropathy may be summarized as retrograde maculopathy.

References


Footnotes and Financial Disclosures

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