Macular spectral domain optical coherence tomography findings in Tanzanian endemic optic neuropathy

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Bilateral optic neuropathy in Dar es Salaam is now considered endemic and is estimated to affect 0.3–2.4% of young adults. The condition is characterized by a subacute bilateral loss of central vision of unknown aetiology. Findings of spectral domain optical coherence tomography have not previously been reported for these patients. All patients diagnosed with endemic optic neuropathy over a 2-year period at the Muhimbili National Hospital underwent spectral domain optical coherence tomography macular imaging. Scans were graded qualitatively for severity of retinal nerve fibre layer loss as well as the presence of microcystic macular changes, which have not previously been described in this condition. Of the 128 patients included (54.7% male; median age 20 years), severe retinal nerve fibre layer loss was found in 185 eyes (74.0%). There was full concordance in retinal nerve fibre layer thickness between the two eyes in 113 (91.1%) patients. Microcystic macular spaces were found in 16 (12.5%) patients and were bilateral in nine (7.0%) individuals. These changes were typically more prominent in the nasal than the temporal macula, predominantly involving the inner nuclear layer, and often occurred in an annular configuration that was evident on en face infra-red imaging, though not discernible on colour fundus photography or clinically. All patients with microcystic macular changes had severe thinning of the retinal nerve fibre layer (P = 0.02). Four patients in whom cystic spaces were demonstrated had sequential scans, and there was no detectable alteration in the configuration of these changes over a period of up to 16 months. This is the first study to document optical coherence tomography findings in endemic optic neuropathy. We have observed symmetrical severe loss of the caeco-central projection (papillomacular bundle) with otherwise well-preserved macular architecture. Also, we have observed microcystic retinal changes in a significant proportion of patients, which were associated with severe retinal nerve fibre layer loss. Similar changes have recently been reported from optical coherence tomography images of patients with multiple sclerosis, relapsing isolated optic neuritis, dominant optic atrophy, Leber’s hereditary optic neuropathy and a patient with a chronic compressive optic neuropathy, supporting the hypothesis that this may be a non-specific phenomenon secondary to ganglion cell death. The correspondence of the changes to an annulus discernible on infra-red en face imaging, but not using other conventional retinal imaging techniques highlights the potential usefulness of this modality.
Introduction

First described in 1988, bilateral optic neuropathy in Dar es Salaam, Tanzania, is now considered endemic and has been projected to affect 0.3–2.4% of young adults in the city (Johnson et al., 1991; Dolin et al., 1998; Bowman et al., 2010). The condition is characterized by the subacute onset, within days to weeks, of bilateral loss of central vision, with particular involvement of colour vision. In Tanzania, the disorder has primarily affected individuals below the age of 40 years. Examination typically reveals reduced visual acuity and colour vision, as well as temporal disc pallor. The condition was originally thought to be a maculopathy (Johnson et al., 1991) but subsequent investigations including fluorescein angiography, electroretinographic and visually-evoked potential studies confirmed evidence of predominantly optic neuropathy (Plant et al., 1997a). However, it had been recognized that in some patients the foveal reflex appeared abnormal and there was clear electrophysiological evidence of retinal dysfunction in a small proportion of patients (Plant et al., 1997a).

The aetiology of endemic optic neuropathy remains unclear. The condition shows similarities to so called ‘tobacco-alcohol amblyopia’ and Leber’s hereditary optic neuropathy, although in Tanzania affected individuals rarely consume alcohol or tobacco, and none were found to harbour any of the three common pathogenic mitochondrial mutations found in Leber’s hereditary optic neuropathy (Plant et al., 1997a). Some authors have hypothesized the role of cyanide poisoning, either through tobacco or cassava consumption, but this possibility is excluded by the finding of normal serum and urine thiocyanate levels in acute cases (Plant et al., 1997b).

A nutritional cause is suggested by studies that have shown the condition to be more prevalent in poorer individuals (Bowman et al., 2010), as well as those with low serum folate (Hodson et al., 2011). Furthermore, a similar epidemic of optic neuropathy in Cuba in the early 1990s ended following the mass distribution of multivitamins to the population (Román, 1994; The Cuba Neuropathy Field Investigation Team, 1995; Thomas et al., 1995). Both the Tanzanian and Cuban epidemics have been associated with a mixed large and small fibre peripheral neuropathy, hearing loss, stomatitis and other features likely also to be due to an unidentified nutritional deficiency (Román, 1994; The Cuba Neuropathy Field Investigation Team, 1995; Thomas et al., 1995). There is evidence that the condition is prevalent in Somalia (Dalmar et al., 2011), but has a much lower prevalence in the Gambia, an East African nation in which nutritional deficiencies are also not prevalent (Dalmar et al., 2013).

Optical coherence tomography (OCT) has revolutionized clinical practice in ophthalmology, and is increasingly used in neurological research (Jindahra et al., 2010; Mendoza-Santiesteban et al., 2010; Cohen et al., 2012). The instrument is based on the principle of interferometry, in which an infra-red beam is directed at the anatomical tissue in question, commonly the peripapillary retina or macula. The reflected beam is then used to generate striking histological-quality real-time images in a fast, non-invasive manner. The most up-to-date spectral domain instruments are able to provide images of resolution as fine as 1 μm (Wolff-Schnurrbusch et al., 2009).

The optic disc and retina are anatomical structures highly relevant and accessible in the study of CNS disease. They are readily visible, and can be imaged by OCT without pupillary dilatation in most patients. Furthermore, as retinal ganglion cell axons lack myelin in the retina, the study of axonal loss is not complicated by the presence of this supporting tissue. The retinal nerve fibre layer (RNFL) has been shown to be thinned in migraine (Gipponi et al., 2013), Alzheimer’s disease (He et al., 2012; Kirbas et al., 2013), Parkinson’s disease (Garcia-Martin et al., 2012) and neuromyelitis optica (Monteiro et al., 2012). Optic neuritis in multiple sclerosis is known to lead to RNFL loss, but many recent studies have shown significant thinning in patients with multiple sclerosis without a history of optic neuritis (Petzold et al., 2010).

Recently, Gelfand et al. (2012) described macular oedema in patients with multiple sclerosis and showed this to be associated with disease severity. Similar findings were documented in relapsing isolated optic neuritis (Balk et al., 2012), dominant optic atrophy and Leber’s hereditary optic neuropathy (Barboni et al., 2013), compressive optic atrophy from a chiasmal glioma (Abegg et al., 2012), neuromyelitis optica (Gelfand et al., 2013) and in chronic relapsing inflammatory optic neuropathy (Petzold and Plant, 2013). We noted similar OCT findings in endemic optic neuropathy in Dar es Salaam and conducted a study to investigate the prevalence of these changes in this disorder.

Materials and methods

As part of a co-operative assistance arrangement known as the VISION 2020 Link Programme, a spectral domain OCT imaging device (Topcon 3D OCT-1000, Topcon Medical Systems) was installed in October 2010 at the Ophthalmology Department of the Muhimbili National Hospital. Spectral, or Fourier, domain OCT allows for higher resolution scanning in comparison with earlier technology, time domain OCT. As well as being used for general clinical service, all patients seen at the unit with a diagnosis of endemic optic neuropathy were investigated with OCT imaging in the form of a macular cube FastMap scan without averaging, which provides histological-quality imaging in the form of 512 A-scans × 128 B-scans across a 6 × 6 mm square centred on the fovea. Patients also underwent 3.4 mm diameter circle OCT scans centred on the optic disc to quantify peripapillary RNFL thickness. The device features TrueMap software alignment to mitigate the effects of natural axial eye movements, together with PinPoint registration to indicate the location of OCT scanning on a fundus or infrared image. Mydriasis was used in all examinations.

Patients were diagnosed with endemic optic neuropathy if they gave a history of bilateral symmetrical central visual loss (with Snellen visual
acuity of 6/9 or worse) and reduced colour vision (at least one Ishihara pseudoisochromatic plate not seen) occurring over a period of days to weeks. Some also gave a history of a peripheral sensory neuropathy or hearing loss, although this was not necessary to make the diagnosis. All patients had a thorough slit-lamp biomicroscopic examination, and were excluded if anterior segment or dilated fundus examination revealed abnormalities suggestive of other ocular pathologies such as cataract or glaucoma. Most patients with endemic optic neuropathy were seen with bilateral temporal optic disc pallor. In some patients, the foveal reflex was abnormal.

In June 2012, we undertook a retrospective review of the OCT images for all patients with endemic optic neuropathy seen in the period October 2010 to June 2012. Although all patients had had circle scans, these were rejected from the analysis for two primary reasons: firstly, poor fixation meant that many scans failed to capture a full uninterrupted circle around the optic disc; secondly, the OCT analysis software frequently failed to delineate appropriately the boundary between the nerve fibre layer and the underlying ganglion cell and inner plexiform layers.

Macular FastMap 6 × 6 mm square scans were analysed as follows: firstly, nerve fibre layer thickness was graded qualitatively as normal or mildly, moderately or severely thinned based on the standard images outlined in Fig. 1A–D. This was done qualitatively as automated layer delineation frequently proved unreliable, commonly including the inner plexiform layer as part of the RNFL in cases of severe RNFL thinning. Secondly, presence or absence of microcystic macular changes, defined as cystic, lacunar areas of hyporeflectivity with clear boundaries (Gelfand et al., 2012), was noted. In addition the infra-red en face images were viewed to assess whether they might yield more information than the colour fundus photographs.

Statistical analysis was performed with SPSS Statistics 17.0 (IBM Corporation). Statistical significance was defined as $P < 0.05$. It is routine practice at Muhimbili to offer vitamin supplementation to all patients with suspected endemic optic neuropathy. As this was a retrospective study of OCT imaging performed as part of routine clinical care, an institutional review board confirmed formal ethical committee approval was not required.

### Results

In total, 128 patients with endemic optic neuropathy had OCT scans available for analysis. Of these, 70 (54.7%) were male. The majority (89.8%) of affected individuals were between the ages of 10 and 40 years (Fig. 2). The median age was 20 years (range, 10–67 years).

Of the 128 patients, 118 had OCT imaging at a single time point only, with 10 having scans at two or more clinic visits.

#### Retinal nerve fibre layer thinning

In two patients, both macular scans were excluded from RNFL analysis as the images were deemed to be of insufficient quality to permit adequate analysis. In a further two patients, one macular scan from one eye was excluded for the same reason.

Of the 250 scans deemed to be of sufficient quality for analysis, severe RNFL loss was found in 185 cases (74.0%) (Table 1). In the 124 patients with two high quality macular scans, there was full concordance in the grading of RNFL loss between the two eyes in 113 (91.1%) patients. Five (4.0%) patients had mild disparity (e.g. a normal RNFL thickness in one eye and mild thinning in the other). Six (4.8%) had more considerable disparity (e.g. mild nerve fibre layer thinning in one eye but severe thinning in the contralateral eye).

In all patients, the RNFL thinning was localized specifically to the centro-caecal projection (papillomacular bundle) (Plant and Perry, 1990), with marked sparing of other regions.

#### Microcystic macular changes

All patients had macular FastMap imaging that permitted the determination of presence of macular changes. Microcystic macular changes were found in 16 patients (12.5%), and were bilateral in nine patients (7.0%). These cysts were typically more prominent in the nasal than the temporal macula, and occurred in an annular configuration that was evident on en face infra-red imaging, but not clinically or on colour fundus photographs. When severe and widespread, they formed a full circle around the macula. The cysts predominantly involved the inner nuclear layer of the retina.
The presence of macular changes was not related to patient age (Mann-Whitney U Test, \( P = 0.788 \)) or gender (55.4% of patients without macular oedema male, 50.0% of those with macular oedema male). All patients with microcystic macular changes had severe RNFL thinning (Chi-square statistic 9.57, two-tailed \( P = 0.02 \)). No such cystic changes were seen in patients with absent, mild or moderate RNFL thinning. Microcystic macular spaces varied between and within individuals, being mild in some and severe in others (Fig. 5).

Four of the 16 patients with microcystic macular changes had OCT imaging at more than one time point, with scans separated by 5 to 16 months. In all cases the cysts remained present throughout the follow-up period (Fig. 6).

Other than the discussed thinning of the caeco-central projection and associated ganglion cell layer, macular OCT images failed to reveal any other gross qualitative abnormalities. All cellular layers appeared otherwise continuous and well preserved. The trilaminar band of the retinal pigment epithelium, inner segment-outer segment junction and outer limiting membrane appeared conserved in all subjects.

### Table 1 Severity of RNFL thinning in 250 macular OCT images surveyed

<table>
<thead>
<tr>
<th>RNFL thinning</th>
<th>Number of eyes</th>
<th>Percentage of eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>27</td>
<td>10.8</td>
</tr>
<tr>
<td>Mild</td>
<td>14</td>
<td>5.6</td>
</tr>
<tr>
<td>Moderate</td>
<td>24</td>
<td>9.6</td>
</tr>
<tr>
<td>Severe</td>
<td>185</td>
<td>74.0</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Figure 2  Age distribution of patients with endemic optic neuropathy (median 20 years). Bars distinguish between patients with severe RNFL loss in at least one eye and those with non-severe loss. The number of patients (n) with microcystic macular changes in each age-group is displayed below the chart.

Discussion

This is the first study to document OCT findings in endemic optic neuropathy in Dar es Salaam. We have shown that these patients typically have a symmetrical severe loss of the caeco-central projection with well-preserved macular architecture. Furthermore, we have demonstrated a pattern of microcystic macular changes in 12.5% of affected patients, often occurring in an annular or part-annular configuration that is more discernible on infra-red imaging than on clinical examination or colour fundus photographs. Furthermore, these changes were present only in those with severe RNFL thinning.

Although first described over two decades ago, the pathophysiology of endemic optic neuropathy remains poorly understood. Plant et al. (1997a) studied 38 young Africans at Muhimbili with endemic optic neuropathy to characterize the visual and associated neurological disorder. They found affected individuals had bilateral temporal disc pallor with loss of the caeco-central nerve fibre layer, observations confirmed in our study. Interestingly, although the disorder was thought to be primarily one of the optic nerve, some patients showed macular ‘oedema’, ‘mottling’ or ‘stippling’ on dilated fundal examination. It is possible these findings represent the microcystic changes observed in the current study. The disorder had originally been described as a maculopathy based on the finding of central scotomas and abnormal appearance of the macula. The pattern electroretinogram studies did confirm evidence of retinal dysfunction in some cases although the predominant findings were indicative of optic neuropathy.

The aetiology of endemic optic neuropathy remains elusive. Although initially suspected, cyanide toxicity (in the form of heavy tobacco smoking or cassava consumption) has been excluded and patients have been found to be negative for the common mutations causing Leber’s hereditary optic neuropathy.
Affected individuals have been shown to have low folate with greater exposure to indoor pollution, yet with normal serum vitamin B12 levels (Hodson et al., 2011). The condition seems to be more common in low income households (Bowman et al., 2010).

Endemic optic neuropathy clearly presents a significant public health concern. This study observed 128 individuals with bilateral visual impairment from a single hospital. Bourne et al. (1998) estimated the condition to affect 1.0% of primary school students in Dar es Salaam, whereas other investigators found a prevalence of 0.3% of secondary school students (Bowman et al., 2010). A community survey using stratified simple random sampling estimated prevalence as high as 2.4% (Dolin et al., 1998). All three statistics are of concern, given the true prevalence is likely to be higher as children with poor vision and hearing are pulled out of the educational system altogether.

Previous investigators have generally recognized endemic optic neuropathy as a condition of those below the age of 40 years. We did not specify age as an inclusion criterion and so our study may give a more reliable age demographic. We found that although the overwhelming majority (89.8%) of patients were aged 10 to 40 years, some were as old as 67 years. Nevertheless, as seen in previous studies, there is no obvious sex predilection (54.7% male). In the Cuban epidemic the age range affected was much older with few teenage individuals being affected (Román, 1994; The Cuba Neuropathy Field Investigation Team, 1995; Thomas et al., 1995). This may reflect the pattern of food distribution during the Cuban epidemic with the system of rationing favouring school age children.

OCT has transformed clinical care and research into retinal disease. The most common causes of blindness in developed nations (diabetic retinopathy, age-related macular degeneration, retinal vein occlusion and glaucoma) rely heavily on OCT for diagnosis and disease monitoring. Increasingly, OCT is being employed in neurological research, as the retina, being readily accessible even without pupillary dilatation, provides a window to the CNS.
Multiple sclerosis and endemic optic neuropathy is the diffuse nature in the former, which leads to a generalized loss of colour vision and contrast sensitivity, with focal loss of the caeco-central projection in the latter, leading to a severe reduction in visual acuity.

This study found microcystic macular changes in 12.5% of patients with endemic optic neuropathy. All affected patients had severe nerve fibre layer loss. In an important study published recently, Gelfand et al. (2012) described microcystic macular oedema in 4.7% of a cohort of 318 patients with multiple sclerosis, and showed the finding was predictive of greater disability on the Expanded Disability Score Scale, as well as poorer prognosis on the Multiple Sclerosis Severity Score. Interestingly, the authors observed that microcystic macular oedema was more common in eyes with a history of optic neuritis, and consistent with the findings of our current study, in eyes with greater nerve fibre layer loss. In response, Abegg et al. (2012) described similar OCT findings in a patient with chronic compressive optic neuropathy secondary to a chiasmal glioma in neurofibromatosis type 1. Microcystic macular oedema has also been observed in relapsing isolated optic neuritis (Balk et al., 2012), and in a subset of patients with Leber’s hereditary optic neuropathy and dominant optic atrophy (Barboni et al., 2013), neuromyelitis optica (Gelfand et al., 2013) and in chronic relapsing inflammatory optic neuropathy (Petzold and Plant, 2013). Other investigators have gone on to show increased inner nuclear layer thickness, a quantitative indicator of microcystic macular oedema, is associated with disease activity in multiple sclerosis (Saidha et al., 2012), potentially providing a useful prognostic biomarker (Petzold, 2012). Although some authors have described dynamic appearance and disappearance of microcystic changes (Saidha et al., 2012), our small cohort of four patients with microcystic changes who underwent serial OCT imaging showed preserved cysts over a follow-up period of 5–16 months.

The retina is a highly regulated tissue. It is protected by the blood–retinal barrier through two distinct sets of tight junctions—those between retinal capillary endothelial cells, and those between retinal pigment epithelial cells. It is hypothesized that microcystic macular changes represent a breakdown of the blood–retinal barrier in multiple sclerosis and endemic optic neuropathy. The reason for its appearance, however, is not well understood, nor is its predilection for the inner nuclear layer. One possibility is that neuronal and axonal injury leads to the upregulation of local pro-inflammatory cytokines that lead to increased vascular permeability (Gelfand et al., 2012). Another possibility may be loss of inner nuclear cells secondary to retrograde trans-synaptic degeneration (Van Buren, 1963).

Retinal microcystic changes in the context of optic nerve damage were in fact first noted by Van Buren (1963). He transected the optic chiasm in two Macaque monkeys and examined the retina of the right eye 20 months later, finding complete loss of ganglion cells in the nasal half of the retina. He also described ‘cystic degeneration’ in the inner nuclear layer of both primates that look remarkably similar to those seen in both endemic optic neuropathy and multiple sclerosis.

Gills and Wadsworth (1966) studied 11 patients with lesions of the optic nerve or chiasm for whom autopsy reports on ocular
Figure 6  Serial right and left nasal macular optical coherence tomography imaging in a 28-year-old female with endemic optic neuropathy. Notice the severe RNFL loss and microcystic changes in both eyes at baseline. These findings are unchanged 6 and 12 months later.

Figure 5  Microcystic macular changes in three patients with endemic optic neuropathy. (A) A 12-year-old male with bilateral widespread cystic spaces. (B) A 38-year-old female with bilateral moderate microcystic changes, more so in the left than the right eye. (C) Bilateral symmetrical mild microcystic cavitations in a 14-year-old female. Note the severe loss of the RNFL in all eyes and the annular area of low intensity on the infra-red image that corresponds to the area of microcystic changes (in the lower panels, only a partial annulus is evident as a crescent nasal to the fovea).
tissues were available. They found loss of ganglion cells in all affected eyes, as well as decreased cellularity in the inner nuclear layer in nine eyes. Interestingly, two patients were found to have cystic changes similar to those seen in our cohort. The first was a 12-year-old male with a craniopharyngioma, whereas the second was a 3-year-old female with spongioblastoma of the optic nerve. The investigators suggested the cystic degeneration seen in the inner nuclear layer of these patients was a result of degeneration of Muller cells.

In view of the previous histological findings, Abegg et al. (2012) suggest the term microcystic macular ‘degeneration’ may be more appropriate than ‘oedema’. We have consequently avoided both terms as the aetiology remains unclear.

Our study has strengths and limitations. It is the first study of OCT findings in endemic optic neuropathy, and represents the largest cohort of the condition to date. Primarily, the study adds to previous reports of bilateral severe loss of the caeco-central nerve fibre layer in affected individuals, and reports the new finding of microcystic changes in 12.5% of the most severely affected patients. As OCT imaging was performed without averaging, microcystic changes were observed with clarity whereas averaged scans may have overlooked such fine pathology. By providing the OCT characteristics of Tanzanian endemic optic neuropathy, the work is relevant clinically as it makes the diagnosis of the condition based on OCT imaging feasible. The work is also relevant in the field as it offers the potential to track responses to health interventions, by considering RNFL thickness, for example.

Nevertheless, conducting research trials in Tanzania has significant challenges due to the poverty of the mostly rural population, as well as the long distances patients are required to travel on a poor transport network to reach a tertiary referral centre such as Muhimbili. Furthermore, poor community eye care facilities mean visual acuity measurements are rarely reliable due to uncorrected refractive error, and limited hospital resources make access of patient hospital records difficult, even for routine clinical care. Consequently, there was a lack of some clinical information, such as visual acuity, visual fields, symptom duration, or any possible recovery once vitamin supplementation was commenced. Furthermore, due to difficulties in the automated segmentation OCT software as well as poor fixation leading to poorly-centred macular scans, our study lacks quantitative markers of RNFL thickness or macular volume. Also, although most patients showed symmetrical loss of the caeco-central projection, six (4.8%) individuals showed a significant disparity in RNFL thinning between eyes. Although these patients may represent an unusual or developing form of the condition, it is possible they represent a group with another pathology altogether.

This study has shown that microcystic changes observed in endemic optic neuropathy are indicative of severe nerve fibre layer loss. Further work is clearly needed to characterize the aetiology and pathophysiology of this condition. Correlating OCT imaging with clinical findings in these patients could be a fruitful avenue of investigation which may shed light on the nature of retinal changes in a wide range of optic neuropathies.

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References


