ORIGINAL ARTICLE

Optical Coherence Tomographic Comparison of Cuban Epidemic and Leber's Hereditary Optic Neuropathy

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ABSTRACT

Following the epidemic of optic and peripheral neuropathy, which occurred in Cuba between 1991 and 1993, a number of patients have been re-evaluated, including testing with optical coherence tomography (OCT) and electrophysiology. At the same time, a number of patients with Leber's hereditary optic neuropathy have also been evaluated. The purpose of this study was to detect residual loss of retinal nerve fibre layer (RNFL) in patients who suffered Cuban epidemic optic neuropathy (CEON), and to compare these findings with those in patients with Leber's hereditary optic neuropathy (LHON). Optical coherence tomography as well as clinical examinations were performed on 11 patients diagnosed with CEON 15 years following the epidemic and 14 patients with LHON. OCT in CEON patients showed thinning of the RNFL in the temporal sector and normal thickness in other quadrants. However, patients with chronic LHON had more diffuse RNFL loss throughout the retina. OCT findings corresponded with clinical findings in CEON and LHON. There was drop out of the papillomacular bundle in both diseases. Two patients in the acute stages of LHON and three LHON carriers showed thinning of the temporal RNFL only. This is the first report of OCT in CEON that shows residual damage in the papillomacular bundle compared with chronic LHON where there is more diffuse and progressive loss of the RNFL. The importance of OCT for the diagnosis and evaluation of similar optic neuropathies is emphasised.

Keywords: Cuban epidemic optic neuropathy, optical coherence tomography, Leber hereditary optic neuropathy

INTRODUCTION

The epidemic of optic and peripheral neuropathy, which affected the Cuban people lasting from the end of 1991 through 1993, occurred when the country fell into a special period of general shortages.¹ The disease affected more than 50,000 people, half of them with damage to the optic nerve and that rest with sensory peripheral neuropathy that also coexisted with the optic form of the illness. Few children were affected. The optic neuropathy tended to be bilateral and symmetrical with impaired colour vision, centrocoecal

scotomas, occasional hyperaemia with mild swelling of the optic disc, or mild temporal pallor of the optic disc similar to tobacco-alcohol amblyopia.² The optic form of the disorder was later named Cuban epidemic optic neuropathy (CEON).² Early on, this type of optic neuropathy was suspected by one of us^{1,2} to be due to toxic-nutritional deficiency after observing loss of the papillomacular bundle (PMB) retinal nerve fibres using red-free light for ophthalmoscopy (originally described by the Cuban ophthalmologist Argilagos in 1862³).

There was a rapid and continuous increase in cases during the first 3 years of the epidemic, with the peak

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incidence occurring in 1993. The incidence of the condition fell rapidly when the Cuban Health Authority gave free oral vitamin supplementation to the entire population. Between 1994 and 1995, only a few cases appeared, and after the year 2000, the disease disappeared completely.¹ During the first 3 years of the epidemic, multiple investigations were carried out in order to determine the cause of this condition.^{1,4–20} Several investigations of other toxic and inherited optic neuropathies have determined that this type of optic neuropathy is an acquired mitochondrial disorder mainly because of predominance of papillomacular bundle involvement.^{1–4,6,18–20}

In 2005, 12 years after the onset of CEON, we began using optical coherence tomography (OCT; Stratus; Allergan, Irvine, California, USA) with the purpose of objectively evaluating the nerve fibre layer to determine residual loss of the retinal nerve fibre layer (RNFL) in affected patients. This was intended to further define the location and extent of the damage and also to see if there was any evolution of the disorder. At the same time, the OCT findings in these patients were compared with those in patients identified during the same period of time with Leber's hereditary optic neuropathy (LHON), which was beginning to be identified more commonly during this period in Cuba.^{4,5,15,16}

METHODS

A reassessment of 11 patients diagnosed with CEON and 14 patients with LHON was conducted. All patients were evaluated for best-corrected visual acuity (BCVA) using a Snellen chart, visual field testing using the Octopus 101 automated perimeter (Haag Streit, Bern, Switzerland) or tangent screen, colour vision (Ishihara), and Pelli-Robson contrast sensitivity. The ocular fundi were examined with both direct and indirect ophthalmoscopy using red-free light. OCT was performed with time-domain OCT (Stratus OCT; Carl Zeiss Meditec, Dublin, California, USA) in order to measure RNFL thickness. The RNFL thickness 3.4 acquisition protocol was used. RNFL thickness mean value (360 degree mean measure) was registered, and the results were segregated by quadrants: temporal (316 to 45 degrees), superior (46 to 135 degrees), nasal (136 to 225 degrees), and inferior (226 to 315 degrees).

All patients with CEON received oral vitamin supplements (A, C, E, and B complex, methionine, and folic acid) immediately after the diagnosis. Initial visual acuities fluctuated between 0.2 and 0.7. Improvement in vision was usually evident within a few weeks after treatment. OCT and clinical examinations were done on these patients approximately 12 years after disease onset.

We also evaluated clinical examination findings and OCT results in 14 LHON patients from five

different families. All of them, except two, were diagnosed during the epidemic in the 1990s. Ten patients had the primary 11778 mutation. Eight of these were in the chronic stage and two were evaluated in the acute stage. The four remaining patients were in the chronic stage and had 3460 deletions. They included a family with three affected members and an isolated case of a woman. Additionally, three relatives who were known carriers with 11778 mutation and who were asymptomatic were evaluated. One of them developed clinical disease 2 years later, whereas the others remained asymptomatic.

RESULTS

At the time of performing OCT, none of the patients with CEON had BCVA below 0.7, and they all identified at least 14 of the Ishihara colour plates. Contrast sensitivity was diminished by 0.30 to 0.60 log units. Fundus examination showed temporal pallor of the optic disc and loss of the nerve fibres in the papillomacular bundle in most all cases (Figure 1).

Of the 10 patients with the 11778 Leber mutation, 2 were in the early phase of the illness. Visual acuity was 0.1 or less, they could not identify more than one of the Ishihara colour plates, and all had significantly diminished contrast sensitivity. They all showed thinning of the RNFL in the papillomacular bundle along with normal or thickened RNFL in the nasal quadrant. The superior and inferior quadrants were even thicker.

The eight remaining cases with the 11778 Leber mutation were in the chronic phase when OCT was performed. BCVA was between 0.1 and 0.05. Colour vision and contrast sensitivity were severely diminished. Large centrocoecal scotomas and optic atrophy in all four quadrants was observed. On OCT, all of them showed generalized loss of nerve fibres. The nasal quadrants were most preserved (Figure 2).

Of the two asymptomatic carriers with the 11778 mutation, one developed visual loss and was evaluated in the chronic stage with OCT. The younger, asymptomatic sibling had been treated with oral vitamins for years and remains with normal BCVA but mildly diminished colour and contrast sensitivity. Two OCT examinations done at 3 months showed loss of RNFL thickness in the temporal quadrant of the right eye, less than half of that in the nasal quadrant, which was in the normal range (44 microns temporally versus 103 microns nasally) (see Table 1). The inferior quadrant showed slightly increased thickness. The left eye showed similar findings (temporal nerve fibre layer averaged 50 microns versus 86 microns in the nasal region). Two years later, there was more generalized thinning of the nerve fibre layer throughout, although she continued to have normal BCVA. The other asymptomatic patient from another family

FIGURE 1 Red-free fundus photograph and corresponding optical coherence tomography of the retinal nerve fibre layer from a patient with Cuban epidemic optic neuropathy.

FIGURE 2 Red-free fundus photograph and corresponding optical coherence tomography of the retinal nerve fibre layer from a patient with Leber's hereditary optic neuropathy.

had generalized RNFL thinning. Three months later, the OCT showed further thinning of the temporal quadrant in both eyes (see Table 1).

Four patients with the 3460 mitochondrial mutation were studied in the chronic stage of the disease; BCVA was below 0.05 associated with large scotomas greater than 30 degrees. In these cases, the OCT RNFL measurements were generally decreased throughout the fundus. A third patient, an 11 year-old boy, had BCVA of 0.1 in both eyes at the disease onset. Two years later, BCVA improved to 0.3 on the right and 0.5 on the left. Colour vision, contrast, and visual fields also improved. OCT showed RNFL thinning in both the temporal and inferior sectors in both eyes (see Table 1).

A patient from another family with the 3460 mutation had slowly progressive RNFL loss over a

TABLE 1 OCT RNFL values (microns) in the chronic phase of LHON (11774 mutation) and CEON patients.

OCT RNFL area	LHON		CEON	
	Median	SD	Median	SD
Superior	89	13.6	146	9.0
Inferior	82	12.6	155	13.0
Temporal	43	18.5	44	10.6
Nasal	106	10.0	109	11.2

period of months with an initial BCVA of 0.2, which then improved to 0.5. She was in the chronic phase when studied with OCT but only showed thinning of the RNFL in the papillomacular bundle that corresponded with pallor seen in the temporal part of the optic disc of the fundus (see Table 1).

DISCUSSION

An epidemic similar to the one that affected Cuba in the 1990s also occurred during the time of the country's independence wars in the 19th century. The recent epidemic in Cuba was also similar to other epidemics, including one in Tanzania, that has been continuing for years.^{1,20,24–28} Cuban doctors in the 19th century were probably the first to describe temporal pallor of the optic disc typical of mitochondrial dysfunction that characterizes these epidemics.^{27–32,34}

Clinical and physical examination of patients with CEON showed symmetrical damage of the RNFL at the papillomacular bundle in both eyes as the objective manifestation of the illness, thus avoiding diagnostic confusion with other diseases as we have previously reported.^{1–4,33–36} Now we have been able to prove this by means of OCT in CEON patients studied 12 years after the onset of the illness.

None of the CEON patients showed decreased thickness in other quadrants aside from the temporal regions, suggesting that the damage is solely limited to maculopapillary fibres and not the rest of the optic nerve, at least in those patients who were treated with vitamins immediately. Some investigations have suggested exclusive impairment of retinal parvocellular neurons in CEON.^{19,20} Mild reduction of electroretinographic (ERG) amplitude that resolved after vitamin treatment also has been reported.^{1,4} This suggests reversal of damage to the external layers of the retina independent of optic nerve damage. In most patients with CEON, improvement in vision after treatment was the rule, and most of the sequelae were mild, as demonstrated by the national annual follow-up carried out over 12 years by the country's health authorities (C. Serano, Estadísticas Nacionales, MINSAP, personal communication). This was also documented by Santiesteban in which CEON and LHON incidences followed the same curve of increased incidence during 1991–1993 and diminished together from 1993 to 2000.³⁹ In the 11 patients studied after vision improved, OCT demonstrated residual loss of ganglion cell fibres, including four subjects who recovered visual acuity to normal. Thus, the severity of damage to the PMB was not in agreement with clinical tests that showed relative conservation of visual function with slight decrease in the ability to perceive colour and contrast. This indicates that maintaining good vision can occur after significant RNFL loss.

CEON is similar in its ophthalmologic manifestations to toxic-nutritional optic neuropathy such as tobacco alcohol amblyopia and hereditary optic neuropathy such as LHON and other hereditary optic neuropathies, in which loss of the RNFL in the PMB occurs.^{1–4,15,16,21,22,26,35–37,39} These diseases appear to be due to acquired or inherited mitochondrial failure.

We have previously shown differences between the clinical and epidemiologic picture of CEON and LHON patients in Cuba during the epidemic.^{15,16,37} The number of people who consumed tobacco and alcohol was less than half for the patients with LHON, but it was greater than the general population. The mean age of visual loss was at least 20 years less for the LHON patients than CEON patients. The majority of LHON patients knew about affected relatives, and this was not seen in CEON. The visual loss appeared at the same time in both eyes in all patients with CEON but not always in LHON. The LHON group had greater loss of visual acuity, colour, contrast, and central visual field, which extended outside 20 degrees from the centre in these cases. In CEON, the central scotomas were less than 10 degrees, with a small and more dense area of no more than 3 to 5 degrees from the centre. Funduscopic studies showed severe optic atrophy in the majority of LHON patients, whereas only mild pallor in the temporal portion of the optic disc occurred in CEON patients. Visual improvement was observed during the first weeks of treatment in the majority of CEON patients, but recovery was unusual in LHON patients.

In eight chronic LHON cases with the 11778 mutation, in whom an OCT was performed, loss of RNFL fibres was mainly in the temporal sector but also affected other areas of the NFL with a tendency towards a flat OCT. These results coincided with worse vision and severe pallor of the optic disc. In two acute cases of LHON, another pattern was observed on OCT. There was temporal thinning of the RNFL and thickening of the superior and inferior quadrants. When these cases were studied in the chronic phase of the optic neuropathy, their OCT was similar to those previously described in the chronic phase of other LHON patients with nearly flattened OCT curves.

The characteristics of the chronic stage in LHON, described by others,^{15,16,38–46} were also seen by us in eight patients with the 11778 mutation. On the other hand, CEON patients who received vitamin therapy displayed a very different pattern wherein loss of RNFL in chronic stages was limited to the temporal area. An OCT obtained in the chronic stages of the only child with the LHON with the 11778 mutation who had improved vision showed that the loss of the RNFL also extended to other quadrants as well as the temporal region in both eyes.

Barboni *et al.* showed RNFL thickening acutely but diffuse loss in both children and adults in the chronic stages of 11778 LHON.⁴¹ The same group showed this in a more recent longitudinal study,⁴² as we found with all our patients with 11778 mutation. Savini *et al.* showed more focal maculopapillary loss in patients with LHON who recovered as we also found in our patients who recovered.⁴¹ In our cases patients with LHON who had improved vision, OCT done years later showed loss only in the temporal and inferior

quadrants that was less in other acute-onset patients whom we have seen in the chronic stage. The patients we studied with the 3460 mutation in the chronic phase of LHON had different patterns of impairment that corresponded with the intensity of the functional sequelae. However, they also had loss of RNFL in other quadrants, especially in those with worse vision.

Our study using OCT shows differences between CEON and LHON in the chronic phase of both illnesses. The main difference being that CEON selectively affected the maculopapillary bundle, whereas LHON caused more diffuse loss of the RNFL. It was not possible to study acute patients with CEON by means of OCT because the epidemic resolved. Notwithstanding, we hypothesise, taking into account the fundus findings, which include hyperaemia and oedema in the early phases of CEON, and the OCT findings of acute or subacute LHON, that OCT could show accentuated peaks in the RNFL and possibly mild thinning of the fibres in the temporal quadrants before symptom onset. Epidemic optic neuropathy occurred in Cuba once before during the War of Independence, and similar epidemics have and are occurring elsewhere, including Tanzania. During such outbreaks, it is possible that patients with Leber mutations may be more susceptible to losing vision due to mitochondrial stress. OCT may be useful in such situations to identify such individuals, especially if treatment for mitochondrial optic neuropathies becomes available in the future.

Declaration of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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