Eye (2011) 25, 596–602

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Pattern of retinal ganglion cell loss in dominant optic atrophy due to *OPA1* mutations

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Release date: 4 March 2011; Expiration date: 4 March 2012

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Learning objectives

Upon completion of this activity, participants will be able to:

1. Describe the clinical features of DOA
2. Identify the extraocular features associated with DOA
3. Identify the peripapillary retinal nerve fibre layer (RNFL) quadrants most affected in patients with *OPA1* mutations
4. Differentiate the pattern of RNFL thinning between patients with pure DOA and DOA + phenotypes

Authors/Editors disclosure information

Andrew J Lotery has disclosed the following relevant financial relationships: Received grants for clinical research from: Novartis Pharmaceuticals Corporation. Served as an advisor or consultant for: Alcon Laboratories, Inc. Served as a speaker or member of the speakers bureau for: Bausch & Lomb Inc.
Patrick Yu-Wai-Man has disclosed no relevant financial relationships.
Maura Bailie has disclosed no relevant financial relationships.
Alaa Atawan has disclosed no relevant financial relationships.
Patrick F Chinnery has disclosed no relevant financial relationships.
Philip G Griffiths has disclosed no relevant financial relationships.

Journal CME author disclosure information

Désirée Lie has disclosed the following relevant financial relationship: Served as a nonproduct speaker for: 'Topics in Health' for Merck Speaker Services.

CLINICAL STUDY

Pattern of retinal ganglion cell loss in dominant optic atrophy due to *OPA1* mutations

P Yu-Wai-Man[1,2,3], M Bailie[2], A Atawan[2], PF Chinnery[1,3] and PG Griffiths[1,2]

Abstract

Purpose **The majority of patients with autosomal dominant optic atrophy (DOA) harbour pathogenic *OPA1* mutations. Although DOA is characterised by the preferential loss of retinal ganglion cells (RGCs), about 20% of patients with *OPA1* mutations will develop a more severe disease variant (DOA+), with additional neuromuscular features. In this prospective, observational case series, optical coherence tomography (OCT) was used to define the pattern of retinal nerve fibre layer (RNFL) loss in patients with both the pure and syndromal forms of DOA.**

Methods **Forty patients with a molecular diagnosis of DOA due to *OPA1* mutations were prospectively recruited from our neuro-ophthalmology clinic: 26 patients with isolated optic atrophy and 14 patients manifesting DOA+ features. Peripapillary RNFL thickness was measured with the Fast RNFL (3.4) acquisition protocol on a Stratus OCT.**

Results **There was a statistically significant reduction in average RNFL thickness in the *OPA1* group compared with normal controls ($P<0.0001$). The percentage decrease was greatest in the temporal quadrant (59.0%), followed by the inferior (49.6%), superior (41.8%), and nasal (25.9%) quadrants. Patients with DOA+ features had worse visual outcomes compared with patients with pure DOA. Except in the temporal quadrant, RNFL measurements were significantly thinner for the DOA+ group. There was an inverse correlation between average RNFL thickness and logarithm of the minimum angle of resolution (LogMAR) visual acuity ($P<0.0001$).**

Conclusions **RGC loss in DOA is characterised by severe involvement of the temporal papillomacular bundle, with relative sparing of the nasal fibres. RNFL thinning is more pronounced in patients with DOA+ phenotypes.**

Eye (2011) **25,** 596–602; doi:10.1038/eye.2011.2; published online 4 March 2011

Keywords: dominant optic atrophy; mitochondrial DNA; *OPA1*; optical coherence tomography; retinal ganglion cells

Introduction

Autosomal dominant optic atrophy (DOA, OMIM 605290) has an insidious onset in early childhood and it classically presents with bilateral, symmetrical, central visual loss and dyschromatopsia.[1,2] About 60% of families harbour mutations in the *OPA1* gene (3q28–q29), and over 200 pathogenic mutations have been reported with mutational hotspots in the GTPase and dynamin central domains.[3,4] DOA is the most common inherited optic nerve disorder seen in the general population,[5,6] and the majority of patients experience significant visual morbidity owing to progressive retinal ganglion cell (RGC) loss.[7,8] Although the primary site of pathology is the RGC layer, up to 20% of patients with *OPA1* mutations will also develop additional neuromuscular deficits, and we recently described the expanding clinical phenotypes associated with these complicated DOA+ variants.[9–11] Sensorineural deafness was the most frequently observed extraocular feature, followed by chronic progressive external ophthalmoplegia, myopathy, ataxia, and peripheral neuropathy.[9]

The development of optical coherence tomography (OCT) has made it possible to quantify accurately the thickness of the retinal nerve fibre layer (RNFL) around the optic

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Received: 24 June 2010
Accepted in revised form: 5 November 2010;
published online 4 March 2011

disc.[12,13] This technology is currently being investigated in the management of glaucoma[14,15] and other neuro-ophthalmological disorders such as multiple sclerosis[16–18] and idiopathic intracranial hypertension.[19] In this study, OCT imaging was used to compare the pattern of RGC loss in *OPA1* patients with both the pure and syndromal forms of DOA, and to document the progression of RNFL thickness with disease duration.

Patients and methods

DOA cohort

We prospectively recruited 40 patients with confirmed pathogenic *OPA1* mutations from our neuro-ophthalmology clinic: 26 patients with isolated optic atrophy and 14 patients manifesting DOA+ features (Table 1). The clinical and molecular descriptions of these patients have been detailed previously.[5,9] Best-corrected visual acuity was measured using the Snellen chart and converted to logarithm of the minimum angle of resolution (LogMAR) decimal values for the purpose of statistical analysis.[20] The peripapillary RNFL profile in our DOA cohort was compared with age-matched normal controls recruited among members of staff of our eye unit ($N=15$), and the normative database ($N=328$) included in the Stratus OCT operating software (Carl Zeiss Meditec, Dublin, CA, USA; http://www.zeiss.de/C12568E80025517D/EmbedTitelIntern/References_normatives/$File/czm_ndb_paper.pdf, accessed 18 September 2010). This study had the relevant institutional ethical approval and complied with the Declaration of Helsinki.

Table 1 Molecular genetic profile of our DOA cohort

OPA1 *mutation*	*Location*	*Consequence*	N = [a]
Exons 1–5b deletion	—	p.M1fsX208	3
c.32+1g>a	Intron 1	Splicing defect	4
c.636_637 del (AG)	Exon 6	p.K214fsX2	1
c.794_797 del (TTGA)	Exon 8	p.I265fsX42	1
c.870+5g>a	Intron 8	Splicing defect	2
c.876–878 del (TGT)	Exon 9	p.V294fsX667	6
c.889C>T	Exon 9	p.Q297X	3
c.1212+3a>t	Intron 12	Splicing defect	1
c.1294A>G	Exon 13	p.I432V	2
c.1334G>A	Exon 14	p.R445H	1
c.1516+1g>t	Intron 15	Splicing defect	2
c.1635C>G	Exon 17	p.S545R	3
c.2613+1g>a	Intron 25	Splicing defect	3
c.2708_2711 del (TTAG)	Exon 27	p.V903fsX3	1
c.2713C>T	Exon 27	p.R905X	4
c.2818+5g>a	Intron 27	Splicing defect	3

[a]Number of patients.

Optical coherence tomography

Peripapillary RNFL thickness was measured with the Fast RNFL (3.4) acquisition protocol on a Stratus OCT (Carl Zeiss Meditec), as described previously.[21,22] Scans were repeated for each eye until proper centration of the optic disc was achieved within the 3.4 mm ring, with a signal strength ≥ 7. The analysis software automatically compares the measurements obtained with the appropriate normative range: (i) $\leq$29 years; (ii) 30–39 years; (iii) 40–49 years; (iv) 50–59 years; (v) 60–69 years; and (vi) $\geq$70 years. The RNFL parameters are colour-coded according to the normal distribution indices: (i) red $<1\%$; (ii) yellow 1–5%; (iii) green 5–95%; and (iv) white $>95\%$ (Supplementary Figure 1).

Statistical analysis

Statistical analysis was performed using GraphPad v.4 statistical software (San Diego, CA, USA). The χ^2-test and the independent sample *t*-test were used for group comparisons, as required. The relationship between RNFL thickness and LogMAR visual acuity were assessed with Spearman's rank correlation coefficient.

Results

Peripapillary RNFL profile among patients with OPA1 *mutations*

The majority of eyes from patients with *OPA1* mutations had an average RNFL thickness $<1\%$ of the normal range (73/80, 91.3%), and this was also observed independently for the temporal (70/80, 87.5%), inferior (69/80, 86.3%), and superior (53/80, 66.3%) quadrants. For the nasal quadrant, only 13/80 (16.2%) eyes had an RNFL thickness $<1\%$, compared with 44/80 (55.0%) eyes in the 5–95% range (Table 2). There was a significant difference in the distribution of RNFL thickness between quadrants (Supplementary Table 1), except for the comparison between the temporal and inferior quadrants ($P=0.5868$). To confirm these findings, peripapillary RNFL thickness in the *OPA1* group (mean age = 42.7 years, standard deviation (SD) = 14.9 years, range = 7.0–69.0 years) was compared with the measurements obtained from an independent cohort of 15 age-matched normal controls (mean age = 40.3 years, SD = 12.3 years, range = 22.0–66.0 years, $P=0.5745$). *OPA1* patients had a statistically significant reduction in mean RNFL thickness for all measurement parameters (Supplementary Figure 2, Table 3), and the percentage decrease was greater in the temporal quadrant (59.0%), followed by the inferior (49.6%), superior (41.8%), and nasal (25.9%) quadrants.

Table 2 Distribution of RNFL indices for our *OPA1* cohort

Normal indices (%)	*Quadrants*				*Average*
	Temporal	*Inferior*	*Superior*	*Nasal*	
<1	70 (87.5%)	69 (86.3%)	53 (66.3%)	13 (16.2%)	73 (91.3%)
1–5	9 (11.3%)	8 (10.0%)	12 (15.0%)	23 (28.8%)	5 (6.2%)
5–95	1 (1.2%)	3 (3.7%)	15 (18.7%)	44 (55.0%)	2 (2.5%)

Table 3 RNFL thickness data for *OPA1* patients and normal controls

Quadrant	*Mean RNFL thickness (SD) (μm)*				P-*value*[b]
	OPA1 *(N = 80)*	*Controls (N = 30)*	*Percentage decrease*[a]	*95% CI*	
Average	54.11 (11.98)	98.77 (10.86)	45.2	40.2–50.2	<0.0001
Temporal	33.44 (8.31)	81.60 (14.31)	59.0	53.7–64.4	<0.0001
Inferior	61.84 (18.72)	122.70 (20.14)	49.6	43.0–56.2	<0.0001
Superior	71.00 (21.58)	122.00 (14.86)	41.8	34.9–48.8	<0.0001
Nasal	49.99 (12.76)	67.43 (17.59)	25.9	16.9–34.8	<0.0001

[a]In RNFL thickness for the *OPA1* group compared with our Newcastle control data.
[b]Independent sample *t*-test analysis.

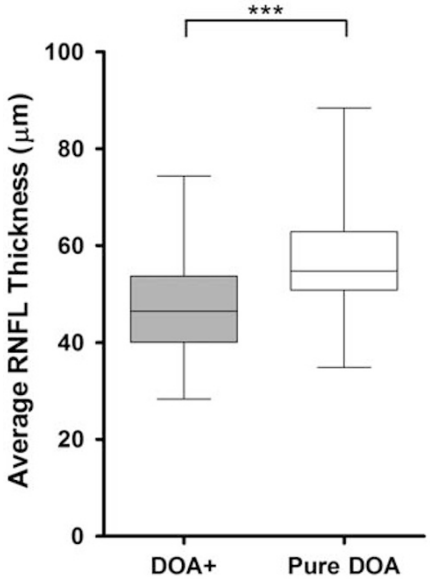

Figure 1 Comparison of average RNFL thickness between patients with pure DOA and DOA+ phenotypes. ***P-value = 0.0006.

Comparison of RNFL thickness between pure DOA and DOA+ subgroups

There was no statistically significant difference in age between the pure DOA (mean = 40.1 years, SD = 15.7 years, range = 7.0–69.0 years, $N = 26$) and DOA+ subgroups (mean = 47.6 years, SD = 12.1 years, range = 21.0–64.0 years, $N = 14$, $P = 0.1295$) (Supplementary Figure 3A). Patients with DOA+ features had significantly worse LogMAR visual acuities (mean = 1.26, SD = 0.85) compared with patients with pure DOA (mean = 0.76, SD = 0.54, $P = 0.0018$)

Table 4 Comparison of RNFL thickness between pure DOA and DOA+ subgroups

Quadrant	*Mean RNFL thickness (SD) (μm)*			P-*value*[b]
	Pure DOA (N = 52)	*DOA+ (N = 28)*	*Ratio*[a]	
Average	57.37 (11.39)	48.05 (10.80)	0.838	0.0006
Temporal	32.81 (8.32)	34.61 (8.30)	1.055	0.3587
Inferior	64.92 (17.75)	56.11 (19.44)	0.864	0.0438
Superior	78.60 (19.67)	56.89 (17.72)	0.724	< 0.0001
Nasal	52.92 (11.73)	44.54 (12.99)	0.842	0.0043

[a]DOA+/pure DOA.
[b]Independent sample *t*-test analysis.

(Supplementary Figure 3B). Except for the temporal quadrant, RNFL measurements were significantly thinner in the DOA+ group (Figure 1, Table 4). There was a statistically significant inverse correlation between average RNFL thickness and LogMAR visual acuity (Figure 2), and this relationship was also significant for the inferior, superior, and nasal quadrants on subgroup analysis (Supplementary Table 2).

Discussion

The results of our study have confirmed the marked loss of RGC axons previously documented in post-mortem histopathological studies of two patients with DOA.[23,24] OCT imaging performed on 40 patients with molecularly confirmed *OPA1* mutations revealed a generalised decrease in peripapillary RNFL thickness, and a regional pattern was apparent, with the temporal quadrant being more severely affected and the nasal quadrant relatively spared. This preferential involvement of the

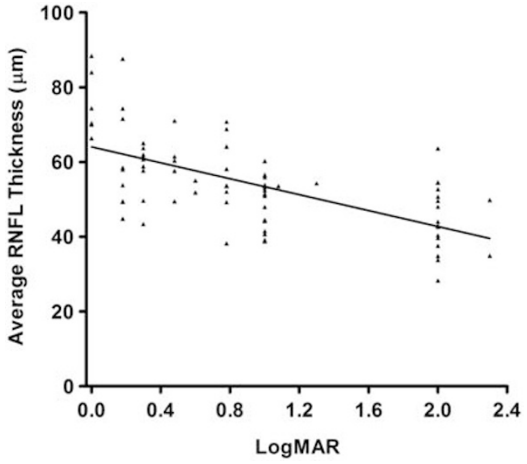

Figure 2 Correlation of average RNFL thickness with LogMAR visual acuity. Spearman's rank correlation coefficient = −0.6355, $P < 0.0001$.

papillomacular bundle is consistent with the characteristic wedge of temporal disc pallor observed clinically in DOA.[5,25] It also supports earlier OCT reports of RGC loss in patients with *OPA1* mutations.[26–28] These studies, which only included patients with isolated optic atrophy, revealed a similar pattern of peripapillary RNFL thinning, with the temporal and nasal quadrants being the worst and least affected, respectively. Macular OCT measurements centred at the fovea showed no degeneration of the outer retina, and both the photoreceptor outer and inner segments were of normal thickness.[27,28] Our larger case series included patients with both pure DOA and DOA + phenotypes, allowing a more comprehensive subgroup analysis based on disease severity. Patients with DOA + features had significantly worse visual acuities, and except for the temporal quadrant, RNFL thinning was more pronounced in this group compared with patients with only optic nerve involvement. There was also a strong correlation between RNFL thickness and LogMAR visual acuity. The greater deleterious consequences of some *OPA1* mutations on RGC survival is therefore clearly linked to the development of multi-system organ involvement in DOA + . Further studies are warranted to define the pathophysiological pathways involved.[9]

It is important to stress that time-domain OCT has a minimum axial resolution of 30–40 μm,[29] and it is entirely possible that RNFL thickness in the temporal quadrant was actually much lower than the values recorded. This could explain the lack of any significant difference in temporal RNFL thickness between patients with pure DOA and DOA + , and the absence of any significant correlation with LogMAR visual acuity for temporal quadrant measurements. Having already suffered the 'greatest hit' early in the disease process, the papillomacular bundle rapidly falls below the OCT detection threshold, but progression of RNFL thinning in the other quadrants is in keeping with the worsening of visual function and the development of DOA + features.

The Opa1 protein is located within the mitochondrial inner membrane and it regulates several critical cellular functions related to the stability of the mitochondrial network, mitochondrial DNA (mtDNA) replication, and the activity of the respiratory chain complexes.[30] Similar to Leber hereditary optic neuropathy (LHON), which is caused by primary mtDNA point mutations, RGC loss in DOA is ultimately due to disturbed mitochondrial oxidative function and apoptosis.[1,2] It is therefore not surprising that both these mitochondrial optic neuropathies share striking similarities in RNFL abnormalities, with LHON carriers showing pathological thickening of the papillomacular bundle in the asymptomatic phase,[21] and marked temporal thinning with relative nasal sparing in the atrophic phase of the disease.[22]

The assessment of peripapillary RNFL thickness with OCT is a useful tool now routinely available to clinicians when investigating optic nerve function. It is a practical, non-invasive procedure that can provide important structural information in borderline DOA cases and help direct subsequent investigations (Supplementary Figure 4). RNFL thinning in patients with *OPA1* mutations is also a dynamic process and this provides an objective outcome measure for documenting disease progression in future treatment trials. Finally, the pattern of RGC loss observed in DOA reflects the intrinsic susceptibilities of different RGC populations to disturbed mitochondrial function. Understanding the key factors involved will be crucial in the development of novel neuroprotective strategies and in defining the therapeutic window for potential intervention.

Summary

What was known before

- Pathogenic *OPA1* mutations cause autosomal dominant optic atrophy (DOA), and in about 20% of affected carriers, additional neuromuscular features develop in addition to optic nerve dysfunction (DOA +). Previous studies have shown thinning of the peripapillary retinal nerve fibre layer (RNFL) among patients with pure DOA, indicating marked loss of retinal ganglion cell axons, especially along the temporal papillomacular bundle.

What this study adds

- The peripapillary RNFL is significantly thinner among *OPA1* carriers with DOA + phenotypes compared with those who only have isolated optic nerve involvement. This finding is consistent with the worse visual prognosis associated with the more severe, syndromal forms of DOA.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

PYWM is a Medical Research Council (MRC, UK) Clinical Research Fellow in Neuro-Ophthalmology and PFC is a Wellcome Trust Senior Fellow in Clinical Science. PFC also receives funding from the Parkinson's Disease Society (UK), the MRC Translational Muscle Centre, and the UK NIHR Biomedical Research Centre in Ageing and Age Related Disease.

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1. Which of the following best describes the classic presentation of autosomal dominant optic atrophy (DOA)?

- A Rapid adult onset with unilateral central visual loss
- B Insidious adult onset with bilateral peripheral visual loss
- C Insidious childhood onset with bilateral central visual loss
- D Rapid childhood onset with unilateral central visual loss

2. A 20-year-old patient with *OPA1* mutation has developed chronic progressive external ophthalmoplegia, myopathy, sensorineural deafness, ataxia, and peripheral neuropathy. Which of these is considered the most commonly encountered extraocular feature in DOA+?

- A Peripheral neuropathy
- B Sensorineural deafness
- C Ataxia
- D Chronic progressive external ophthalmoplegia

3. Which one of the following peripapillary retinal nerve fibre layer (RNFL) quadrants shows the greatest percentage decrease among patients with *OPA1* mutations?

- A Temporal
- B Inferior
- C Superior
- D Nasal

4. Which of the following best describes the difference between patients with pure DOA and DOA+ phenotypes?

- A Worse visual acuity
- B More pronounced RNFL thinning
- C Both worse visual acuity and more pronounced RNFL thinning
- D No difference

Activity evaluation

1. The activity supported the learning objectives

Strongly disagree				Strongly agree
1	2	3	4	5

2. The material was organized clearly for learning to occur

Strongly disagree				Strongly agree
1	2	3	4	5

3. The content learned from this activity will impact my practice

Strongly disagree				Strongly agree
1	2	3	4	5

4. The activity was presented objectively and free of commercial boas

Strongly disagree				Strongly agree
1	2	3	4	5