Macular sensitivity and fixation patterns in patients with autosomal dominant optic atrophy

Cecilia Rönnbäck[1, 2] & Michael Larsen[1, 2]

ABSTRACT

INTRODUCTION: The objective of this study was to test macular sensitivity, fixation stability and fixation location using microperimetry in patients with autosomal dominant optic atrophy (ADOA) and mutation-free relatives.

MATERIAL AND METHODS: This was a cross-sectional study of 43 patients with exon 28 (2826 delT) mutation in *OPA1* (age 11.7-71.5 years, best-corrected visual acuity (BCVA) 20/24-20/13). The patients and 49 mutation-free first-degree relatives (BCVA 20/25-20/10) underwent ophthalmic examination including macular microperimetry out to 12° eccentricity with registration of fixation stability and fixation location.

RESULTS: The average (± standard deviation) sensitivity was significantly reduced in ADOA patients compared with controls, 14.9 (± 4.4) dB versus 19.7 (± 0.4) dB ($p < 0.0001$). In a retinotopic projection, the largest relative sensitivity deficits in ADOA were seen in the nasal macula (13.6 (± 5.7) dB versus 19.7 (± 0.7) dB) and in the central macula (14.2 (± 5.1) dB versus 19.9 (± 0.3) dB). The average sensitivity decreased with decreasing BCVA in ADOA ($p < 0.0001$). Stable fixation was found in 58% of ADOA patients versus 86% of controls, and relatively unstable fixation was observed in 35% of ADOA patients versus 14% of controls. Unstable fixation was found only in ADOA, where its prevalence was 7%.

CONCLUSION: ADOA was associated with unstable fixation and subnormal microperimetric sensitivity, especially in the central and nasal macula where the ganglion cell deficit is most pronounced.

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Autosomal dominant optic atrophy (ADOA), also known as Kjer disease, (OMIM165500) is the most common inherited optic neuropathy [1, 2]. Both retinal nerve fiber layer and ganglion cell/inner plexiform layer thickness are lower than in healthy controls [3-6]. Patients are generally diagnosed with bilateral symmetric subnormal visual acuity during the first two decades of life and often before the age of ten years [7, 8]. Phenotype variation is considerable, both within and between affected families, where best-corrected visual acuity (BCVA) may range from normal to light perception [2, 9]. Patients typically have a central or centrocecal scotoma [2, 9, 10]. Nevertheless, many patients perform well in daily life into their older years [11], which suggests that there are lessons to learn from a close characterisation of visual function and its development with time in ADOA and other degenerative diseases that affect vision.

Microperimetry, which enables retinotopic mapping of fixation and localised fundus sensitivity, can be used to find small visual field defects that escape detection with conventional perimetry [12-15]. Studies of fixation patterns have been made in optic neuropathies other than ADOA. In the somewhat comparable Leber hereditary optic neuropathy, good visual acuity is related to stable fixation [16] and, likewise, severe glaucoma can be accompanied by poor, predominantly eccentric fixation [13].

The present study is part of a cross-sectional study of ADOA that aims to characterise retinal anatomy and visual fields in a homogenous group of patients with c.2826_2836delinsGGATGCTCCA mutation in *OPA1* [6]. The purpose of the present report is to describe microperimetric light sensitivity and fixation patterns in c.2826_2836delinsGGATGCTCCA ADOA and a control group of mutation-free relatives.

MATERIAL AND METHODS

This study was designed as a cross-sectional observational study and included 43 patients with c.2826_2836delinsGGATGCTCCA mutation in *OPA1* and a control group of 49 mutation-free first-degree relatives. The study population and the inclusion and exclusion criteria have been described elsewhere [6].

Patients and mutation-free first-degree relatives were recruited from a national register and examined in the order they volunteered. Written informed consent was obtained from all patients and healthy subjects. For participants under the age of 18 years, informed consent was obtained by their respective guardian. The study was approved by the Medical Ethics Committee of Copenhagen County and followed the tenets of the Declaration of Helsinki.

All subjects underwent an ophthalmologic examination, including refraction, determination of BCVA in Early Treatment Diabetic Retinopathy Study (ETDRS) letters and microperimetry visual field testing. Pupils were dilated using tropicamide 1% and phenylephrine hydro-

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1) Department of Ophthalmology, Glostrup Hospital
2) Faculty of Health Sciences, University of Copenhagen

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TABLE 1

Microperimetric sensitivity in patients with autosomal dominant optic atrophy and healthy controls. The values are dB.

	Patients with ADOA, mean ± SD (range) (N = 43)	Healthy mutation-free relatives, mean ± SD (range) (N = 49)	p-value[a]
Central field	14.2 ± 5.1 (0-20)	19.9 ± 0.3 (18.2-20)	< 0.0001
Superior field	15.4 ± 4.1 (0-20)	19.5 ± 0.7 (17.0-20)	< 0.0001
Nasal field	13.6 ± 5.7 (0-20)	19.7 ± 0.7 (15.7-20)	< 0.0001
Inferior field	14.8 ± 4.6 (0-20)	19.8 ± 0.4 (18.3-20)	< 0.0001
Temporal field	16.7 ± 4.2 (0-20)	19.8 ± 0.6 (16.8-20)	< 0.0001
Average	14.9 ± 4.4 (0-20)	19.7 ± 0.4 (18.0-20)	< 0.0001

ADOA = autosomal dominant optic atrophy; SD = standard deviation.
a) Mann-Whitney's U test.

chloride 10%. In subjects younger than 15 years old, only tropicamide 0.5% was used.

Microperimetry (MP-1, Nidek Technologies, Padova, Italy) was performed with one eye covered at the time. Before each examination, a short test sequence was used to reduce learning effects. A Goldmann III stimulus of 200 ms duration was projected on a background intensity of 1.27 cd/m^2 and tested using threshold strategy 4-2. Stimulus intensity ranged 0-20 dB and was set to start at 10 dB and titrated to 0.1 log scale accuracy, albeit with a sensitivity ceiling of 20 dB, which is reached by many healthy subjects in the central visual field. Automatic eye-tracking allowed each stimulus to be assigned to a specific location on a photograph of the fundus. The fixation target was a 1° red cross. The background illumination in the examination room was dim light. Before examination start, the instrument focus was adjusted to compensate for spherical refraction error. The blind spot was manually marked on the optic nerve head and automatically tested with a suprathreshold stimulus. The examination pattern was a macula 12° programme with 45 test points. For analysis, the test points were subdivided into five fields; the central, the superior, the nasal, the inferior and the temporal fields. Only fovea-centred fundus monitoring images of good quality were accepted.

Fixation stability was described automatically by a count of the percentage of fixation points located within the macular central 2° and 4°, respectively. The points were then divided into three groups; stable fixation (75% of fixation points within the central two degrees), relatively unstable fixation (less than 75% of fixation points within the central two degrees but 75% or more within the central four degrees) and unstable fixation (less than 75% of fixation points within the central four degrees). Fixation location was divided into three groups; predominantly central (more than 50% of fixation points within the central two degrees diameter circle), poor central (more than 25% of fixation points but less than 50% within the central two degrees diameter circle) and predominantly eccentric (less than 25% of the fixation points within the two degrees diameter circle).

Data from the microperimetry examination were analysed in relation to macular ganglion cell-inner plexiform layer (GC-IPL) thickness and peripapillary retinal nerve fiber layer (RNFL) thickness, which were determined as previously described [6]. The position of the locus of fixation was determined in relation to the bottom of the foveal depression by aligning Cirrus optical coherence tomography (OCT) scans [6] by superimposing these on corresponding microperimetry images using Gimp 2.6.12 software. Retinal vessels were used as markers to ensure a complete match between the images. It was noted whether or not there were fixation points in the six different sectors and in the central field.

Data are presented as means ± standard deviations (SD) and full ranges. There was no statistical difference between the right and left eyes and therefore only right eyes are presented. Data were analysed using Mann-Whitney's U test and the Spearman correlation coefficient (SAS 9.1 Software package, SAS Institute, Inc., Cary, North Carolina, USA).

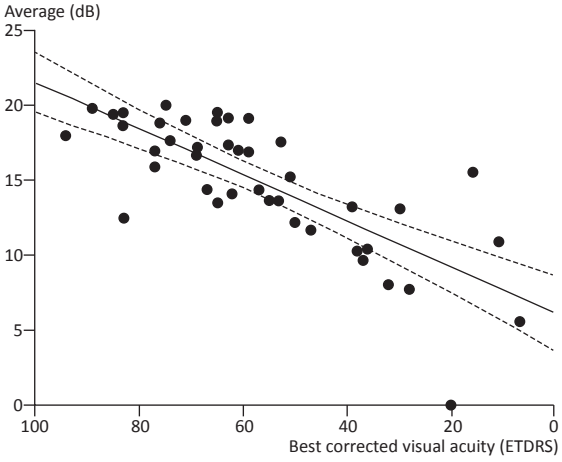
Trial registration: NCT01522638.

RESULTS

The 43 patients with ADOA (22 males and 21 females) had a mean age of 39.3 (range: 11.7-71.5) years, BCVA ranged 7-94 (mean 56.9 ± standard deviation 21.5) ETDRS letters and mean axial length 24.3 ± 1.3 mm. A control group of 49 mutation-free first-degree relatives (25

FIGURE 1

Average sensitivity correlated with best-corrected visual acuity in Early Treatment Diabetic Retinopathy Study (ETDRS) letters in patients with autosomal dominant optic atrophy (r = 0.74; p < 0.0001; regression line and 95% confidence intervals).



males and 24 females) had a mean age of 32.8 (range: 8.9-68.7) years (p = 0.01), a mean BCVA of 88.8 ± 4.4 ETDRS letters (p < 0.0001) and a mean axial length of 23.5 ± 1.1 mm (p = 0.02).

In ADOA patients, the average sensitivity of the central 0-12° eccentricity visual field was subnormal compared with controls (p < 0.0001, **Table 1**), as were each of the five subfields (p < 0.0001, Table 1). Seen from the centre of the fovea, the fields with the lowest relative sensitivity in ADOA patients were the nasal subfield (13.6 ± 5.7 dB versus 19.7 ± 0.7 dB) followed by the central subfield (14.2 ± 5.1 dB versus 19.9 ± 0.3 dB) and the inferior subfield (14.8 ± 4.6 dB versus 19.8 ± 0.4 dB). The relative deficits amounted to 16-31%.

In ADOA, BCVA decreased with decreasing average sensitivity (r = 0.74, p < 0.0001, **Figure 1**). In three of the macular fields, sensitivity decreased with increasing age: superior (r = –0.49, p = 0.0009), inferior (r = –0.31, p = 0.04) and temporal (r = –0.35, p = 0.02). A borderline significant correlation was seen between average sensitivity and age (r = –0.30, p = 0.05). In the control group, average sensitivity decreased with age (r = –0.30, p = 0.04), but there was no correlation with BCVA (r = –0.19, p = 0.20). There was no effect of sex in any of the two groups.

In ADOA, average sensitivity increased with increasing GC-IPL thickness (r = 0.38, p = 0.012). There was no relationship between average sensitivity and the average RNFL thickness (r = 0.29, p = 0.06).

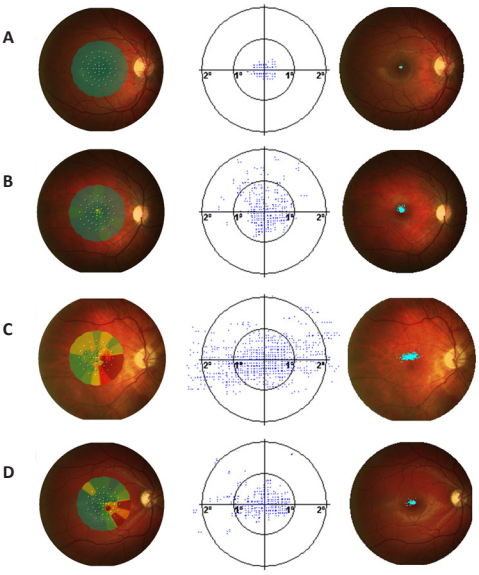
Stable fixation was found in 58% (25/43) of ADOA patients and 86% (42/49) of controls, relatively unstable fixation in 35% (15/43) of ADOA patients and 14% (7/49) of controls, whereas unstable fixation was found only in ADOA, where the prevalence was 7% (3/43) (**Figure 2**).

Predominantly macular central fixation location was found in 49% (21/43) of ADOA patients and 84% (41/49) of controls, poor central fixation location in 14% (6/43) of ADOA patients and 10% (5/49) of controls, whereas predominantly eccentric fixation location was found in 37% (16/43) of ADOA and 6% (3/49) of controls. The majority of patients, 53% (23/43) had a fixation pattern that covered the four superotemporal sectors and the central part. The same was true for 27% (13/49) of the healthy subjects. Fixation points that only covered the central field were seen in 7% (3/43) of ADOA patients and in 39% (19/49) of healthy controls. Only 2% (1/43) of the patients and 6% (3/49) of the controls had fixation points that covered the two inferonasal sectors and the central field. The remaining patients and controls had a more diffuse fixation pattern. No correlation was seen between fixation location and age, BCVA and average sensitivity in ADOA (Figure 2).

In 44% of the ADOA patients, fixation was both stable and predominantly macular central. In 26%, fixation was relatively unstablewand predominantly eccentric (**Table 2**). The majority of control subjects, 76%, had stable and predominantly central fixation (Table 2).

FIGURE 2

Microperimetry examination (left), fixation stability (middle) and fixation location (right). **A.** Mutation-free control subject with normal microperimetric sensitivity (mean sensitivity 20 decibel), best-corrected visual acuity (BCVA) 99 Early Treatment Diabetic Retinopathy Study (ETDRS) letters and stable and predominantly central fixation. **B.** Patient with autosomal dominant optic atrophy (ADOA). The patient has a small central sensitivity reduction (mean sensitivity 19.3 dB), BCVA 85 ETDRS letters and stable and predominantly central fixation. **C.** ADOA patient with reduced sensitivity on microperimetry examination (mean sensitivity 10.4 decibel), BCVA 36 ETDRS letters and relatively unstable and predominantly eccentric fixation centred immediately above the fovea. **D.** ADOA patient with localised reduced sensitivity (mean sensitivity 15.5 db), BCVA 16 ETDRS letters and stable and predominantly central fixation.



DISCUSSION

This study mapped fixation characteristics and macular visual field sensitivity in a large cohort of ADOA patients with one and the same *OPA1* mutation. Superimposed upon a generally subnormal sensitivity in the central 12° radius visual field, a localised sensitivity reduction was seen in the central and nasal macula, corresponding to the prototype centrocecal scotoma in ADOA. While stable fixation, as defined by a standard developed elsewhere, was found in more than half of the ADOA patients and a predominantly central fixation location in 49%, these rates were clearly lower than in the controls. The direction of the fixation location was localised to the central and superotemporal parts of the macula in ADOA patients. There was no correlation between age, BCVA or average sensitivity and fixation stability or fixation location.

Average sensitivity over the entire 12° radius field was subnormal in most ADOA patients and BCVA de-

TABLE 2

Fixation stability and fixation location in patients with autosomal dominant optic atrophy (ADOA) and healthy controls.

Fixation stability[a]	Fixation location[b]	Patients with ADOA, n (%) (N = 43)	Healthy mutation-free relatives, n (%) (N = 49)
Stable fixation	Predominantly central	19 (44)	37 (76)
	Poor central	3 (7)	2 (4)
	Predominantly eccentric	3 (7)	3 (6)
Relatively unstable fixation	Predominantly central	2 (5)	4 (8)
	Poor central	2 (5)	3 (6)
	Predominantly eccentric	11 (26)	0 (0)
Unstable fixation	Predominantly central	0 (0)	0 (0)
	Poor central	1 (2)	0 (0)
	Predominantly eccentric	2 (5)	0 (0)

a) Stable fixation (75% of fixation points within the macular central 2°), relatively unstable fixation (< 75% of fixation points within the macular central 2° but ≥ 75% within the macular central 4°) and unstable fixation (< 75% of fixation points within the macular central 4°).
b) Predominantly central fixation location (> 50% of fixation points within the macular central 2° diameter circle), poor central fixation location (> 25% of fixation points but < 50% within the 2°) and predominantly eccentric fixation location (< 25% of the fixation points within the 2° diameter circle).

creased with average sensitivity. A comparable finding has been made in glaucoma, where a ganglion cell loss of 50% in the central 12° of the visual field was associated with a 5-dB decrease in sensitivity in the same area [17]. Histological studies have shown a reduction in ganglion cell numbers in ADOA patients [18, 19], and studies of ganglion cell layer thickness on high-definition optical coherence tomography support this finding [6]. In the present study, the average sensitivity decreased with decreasing ganglion cell layer thickness. The average sensitivity deficit in the central 12° between ADOA patients and controls was 4.8 dB suggesting that the ganglion cell deficit in our ADOA patients may, on average, also be approximately 50%.

A relation between good visual acuity and stable fixation has previously been found in Leber hereditary optic neuropathy [16]. In glaucoma fixation, instability is present in early stages of the disease [20] although fixation stability is uncorrelated with visual acuity [13].

Our observations show that subnormal macular visual field sensitivity and a crude pattern of fixation are characteristic of many patients with ADOA, particularly those with poor vision. It remains to be determined whether monocular eccentric fixation, as found in some of our ADOA patients who had comparable visual acuity in both eyes, is associated with bilateral simultaneous eccentric fixation, anomalous correspondence and pseudostrabismus. In our relatively large and uniform population, there was only a moderate decrease in function with age in this cross-sectional study, which is in agreement with structural analyses of the retinal ganglion cell layer in the same study population [6]. The study shows that microperimetry enables characterisation of central vision characteristics that are not revealed by a routine ophthalmic examination.

CORRESPONDENCE: *Cecilia Rönnbäck*, Øjenafdelingen, Glostrup Hospital, Nordre Ringvej 57, 2600 Glostrup, Denmark.
E-mail elisabeth.cecilia.roennbaeck@regionh.dk.

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