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.

FUNDING: The study was supported by Øjenfonden, Øjenforeningen, and Synoptikfonden.

TRIAL REGISTRATION: NCT01522638.
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/m² 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).

**TABLE 1**

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

<table>
<thead>
<tr>
<th></th>
<th>Patients with ADOA, mean ± SD (range) (N = 43)</th>
<th>Healthy mutation-free relatives, mean ± SD (range) (N = 49)</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central field</td>
<td>14.2 ± 5.1 (0-20)</td>
<td>19.9 ± 0.3 (18.2-20)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Superior field</td>
<td>15.4 ± 4.1 (0-20)</td>
<td>19.5 ± 0.7 (17.0-20)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Nasal field</td>
<td>13.6 ± 5.7 (0-20)</td>
<td>19.7 ± 0.7 (15.7-20)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Inferior field</td>
<td>14.8 ± 4.6 (0-20)</td>
<td>19.8 ± 0.4 (18.3-20)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Temporal field</td>
<td>16.7 ± 4.2 (0-20)</td>
<td>19.8 ± 0.6 (16.8-20)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Average</td>
<td>14.9 ± 4.4 (0-20)</td>
<td>19.7 ± 0.4 (18.0-20)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

ADOA = autosomal dominant optic atrophy; SD = standard deviation.

a) Mann-Whitney’s U test.

**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](image-url)

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 88.4 ± 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 = 0.009), 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 unstable and predominantly eccentric (Table 2). The majority of control subjects, 76%, had stable and predominantly central fixation (Table 2).

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

<table>
<thead>
<tr>
<th>Fixation stability</th>
<th>Fixation location</th>
<th>Patients with ADOA, n (%) (N = 43)</th>
<th>Healthy mutation-free relatives, n (%) (N = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable fixation</td>
<td>Predominantly central</td>
<td>19 (44)</td>
<td>37 (76)</td>
</tr>
<tr>
<td></td>
<td>Poor central</td>
<td>3 (7)</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td>Predominantly eccentric</td>
<td>3 (7)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Relatively unstable fixation</td>
<td>Predominantly central</td>
<td>2 (5)</td>
<td>4 (8)</td>
</tr>
<tr>
<td></td>
<td>Poor central</td>
<td>2 (5)</td>
<td>3 (6)</td>
</tr>
<tr>
<td></td>
<td>Predominantly eccentric</td>
<td>11 (26)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unstable fixation</td>
<td>Predominantly central</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Poor central</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Predominantly eccentric</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

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 97, 2600 Glostrup, Denmark. E-mail elisabeth.cecilia.roenbaeck@regionh.dk.

ACCEPTED: 23 May 2014.

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

LITERATURE