

# Seminars in Ophthalmology



Date: 31 July 2016, At: 16:00

ISSN: 0882-0538 (Print) 1744-5205 (Online) Journal homepage: http://www.tandfonline.com/loi/isio20

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**To cite this article:** Mehmet Talay Koylu, Gokhan Ozge, Murat Kucukevcilioglu, Fatih Mehmet Mutlu, Osman Melih Ceylan, Dorukcan Akıncıoglu & Onder Ayyıldız (2016): Fixation Characteristics of Severe Amblyopia Subtypes: Which One is Worse?, Seminars in Ophthalmology, DOI: 10.3109/08820538.2015.1123739

To link to this article: <a href="http://dx.doi.org/10.3109/08820538.2015.1123739">http://dx.doi.org/10.3109/08820538.2015.1123739</a>

|           | Published online: 18 May 2016.                           |
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ISSN: 0882-0538 print / 1744-5205 online DOI: 10.3109/08820538.2015.1123739



## ORIGINAL ARTICLE

# Fixation Characteristics of Severe Amblyopia **Subtypes: Which One is Worse?**

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# **ABSTRACT**

Purpose: To determine differences in macular sensitivity and fixation patterns in different subtypes of severe amblyopia. Methods: This case-control study enrolled a total of 73 male adults, including 18 with pure strabismic severe amblyopia, 19 with pure anisometropic severe amblyopia, 18 with mixed (strabismic plus anizometropic) severe amblyopia, and 18 healthy controls. MP-1 microperimetry was used to evaluate macular sensitivity, location of fixation, and stability of fixation. Results: Mean macular sensitivity, stability of fixation, and location of fixation were significantly worse in all amblyopia subtypes when compared with healthy controls. Intergroup comparisons between amblyopia subtypes revealed that mean macular sensitivity, stability of fixation, and location of fixation were significantly worse in pure strabismic and mixed amblyopic eyes when compared with pure anisometropic amblyopic eyes. Conclusions: Strabismus seems to be a worse prognostic factor in severe amblyopia than anisometropia in terms of fixation characteristics and retinal sensitivity.

Keywords: Amblyopia, anisometropia, fixation, microperimeter-1, strabismus

# INTRODUCTION

Amblyopia is unilateral or rarely bilateral reduced visual acuity caused by vision deprivation and/or abnormal binocular interaction during the first years of life; an organic cause cannot be detected. The most common causes of amblyopia are strabismus and anisometropia, respectively; ametropic (high refractive error in both eyes) and deprivational amblyopia are other infrequent factors.<sup>2</sup> Amblyopia is the most common cause of monocular visual loss in children and affects up to 3.6%<sup>3</sup> of them. Diagnosis of amblyopia is mainly based on testing the best-corrected visual acuity (BCVA).4 However, measuring visual acuity alone does not totally reflect the function of the macula and the entire visual system.<sup>5</sup> However, with the same visual acuities, the entire visual function of amblyopic eyes may be different in many ways among different subtypes.

New technologies present new opportunities to investigate fundamental processes

conditions. The advent of MP-1 microperimetry has recently made possible an automatic, accurate, repeatable fast topography examination of the retina and has gained increasing clinical interest in the evaluation of visual functional impairment, especially in retinal diseases. 6-10 The clinical use of MP-1 microperimeter in amblyopia practice is not established, but it may be beneficial in monitoring residual visual functions in severe amblyopia. Even for patients with unsteady or non-foveal fixation in amblyopia, the quantification of retinal sensitivity and fixation patterns by microperimetry may offer new data about the functional characteristics of the different subtypes of severe amblyopia.

The aim of this study was to determine fixational differences in severe amblyopia subtypes by assessing mean macular sensitivity, location of fixation, and stability of fixation with the use of an MP-1 microperimeter.

# **MATERIALS AND METHODS**

This case-control study enrolled medical records of a total of 73 young adults who participated in military recruitment examinations, including 55 unilateral severe amblyopia (BCVA logMAR < 1.0 logMAR) associated with pure strabismus (n = 18), pure anisometropia (n = 19), mixed strabismus and anisometropia (n = 18), and healthy controls (n = 18). The study was performed at a tertiary referral center, and the ethics approval was approved by the Institutional Review Board. The research followed the tenets of the Declaration of Helsinki.

Strabismus is defined as any misalignment of eyes at a distance and/or near fixation >10 prism diopters. Anisometropia is defined as the difference in refractive error between two eyes ≥ 1 diopter of spherical equivalent. Severe amblyopia is defined as BCVA < 1.0 log MAR in the amblyopic eye. For non-amblyopic healthy participants, those with a BCVA of 0.1 log MAR or better in each eye were included as a control group. Patients with organic eye disease, a history or evidence of strabismus surgery, cataract, glaucoma, retinal disorders, or laser treatment were excluded from the study.

All subjects underwent detailed ophthalmic examination. Refraction was evaluated half an hour after conducting cyclopentolate 1% two times. Subjects presumed to be malingering were examined with fogging, dissociation fogging, polarizing lenses, and distance test. Pattern visual evoked potentials were performed to confirm severe amblyopia, as BCVA < 1.0 log MAR.<sup>11</sup> MP-1 microperimetry was performed as described in the following.

# Microperimetry

Microperimetry was performed with the use of an MP-1 microperimeter (Nidek Technologies, Japan). Refractions of the subjects were corrected for recordings categorized as "near before." Patients were asked to fixate on a target and to respond to a number of stimuli that were projected in real time onto the retina by a liquid crystal color monitor completely controlled by dedicated software. The infrared light was used for imaging, and the internal liquid crystal display was used for stimulus presentation. At the beginning of the examination, an infrared camera (resolution, 1 pixel [equivalent to 0.1°]) tracked a reference frame, and an area of interest was defined, placing a cursor on a retinal landmark on the frozen image. During the examination, any eye movement was detected by image acquisition of 25 frames per second. The computer then calculated the shift between the reference image and the real-time fundus images with the stimulus position on the display, corrected according to the actual location of the fundus. Results were displayed with color fundus photography obtained with an MP1 color fundus camera at the end of the examination. For assessment of fixation, the fundus movements were tracked during examination while the patient gazed at the fixation target. The auto tracking system calculated horizontal and vertical shifts relative to a reference frame and returned a map of the patient's eye movements during the examination. At the conclusion of testing, a scatter graph depiction of fixation was displayed. This was used to quantify the fixation pattern. Our MP-1 microperimetry protocol consisted of a normal test type, including a red circle fixation target 1° in diameter, a white background at 4 asb, 33 stimuli on the average covering the central 20°, Goldmann III stimulus size, 200 ms projection time, and a 4-2 threshold strategy. Mean differences of light sensitivity of all the locations were analyzed for the study. The MP-1 fixation pattern was graded according to two variables: the location of fixation (defined as the position of fixation with respect to the center of foveal avascular zone) and stability of fixation (defined as the ability of the eye to maintain fixation in the PRL). The fixation characteristics were calculated according to the classification of Fuji et al. 12 To assess fixation location, a standard, circular, central fixation area two degrees in diameter (approximately 700 µm) centered on the fovea was defined. Eyes with more than 50% of the preferred fixation points located within the central fixation were classified as having predominantly central fixation. Eyes with more than 25% but less than 50% of the preferred fixation points located within the central fixation were classified as having poor central fixation. Eyes with less than 25% of the preferred fixation points located within central fixation were classified as having predominantly eccentric fixation (Figure 1 a, b, c). Eyes with more than 75% of the fixation points located within a twodegree diameter circle positioned with respect to the gravitational center of all fixation points were classified as stable. If less than 75% of the fixation points were located within a two-degree diameter circle but more than 75% of the fixation points were located within a four-degree diameter circle positioned with respect to the gravitational center of all fixation points, patients were classified as having relatively unstable fixation. If less than 75% of the fixation points were located within a four-degree diameter circle positioned with respect to the gravitational center of all fixation points, the pattern was described as being unstable fixation (Figure 1 d, e, f). The stability of fixation was classified separately from the location of fixation because some eyes may present with predominantly eccentric relatively unstable fixation.

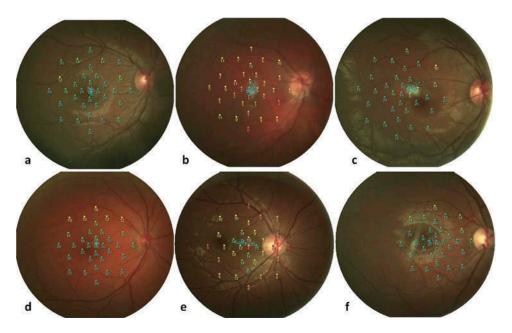


FIGURE 1. Classification of location of fixation: predominantly central (a), poor central (b), and predominantly eccentric (c). Classification of the stability of fixation: stable (d), relatively unstable (e), and unstable (f).

# Statistical Analyses

The findings of amblyopic eyes were compared with the right eye of healthy controls. Intergroup comparisons between amblyopia subtypes were performed among pure strabismic, pure anisometropic, and mixed (strabismic plus anisometropic) amblyopic eyes. The SPSS 16.0 software package was used in data analysis. For the descriptive statistics, discontinuous variables were shown as numbers and percentages (%); continuous variables were shown as mean ± standard deviation. Normality of the data was evaluated with the Kolmogorov Smirnov test. A chi square test was used for categorical values. Student's t-test was used for continuous variables that distributed normally. The Mann-Whitney U-test was used for continuous variables that did not distribute normally. A P value of 0.05 or less was considered significant.

# **RESULTS**

Baseline characteristics (age, BCVA, refractive error, and angle of deviation) of the study groups are shown in Table 1. The mean BCVA of amblyopic eyes were similar among different severe amblyopia subtypes (p = 0.336).

Table 2 summarizes the MP-1 microperimeter results. Mean macular sensitivity was significantly worse in strabismic (p<0.001), anisometropic (p = 0.001), and mixed amblyopic (p<0.001) subtypes when compared with the healthy group. Intergroup comparisons between different amblyopia subtypes revealed that mean macular sensitivity of strabismic amblyopic eyes (p<0.001) and mixed amblyopic eyes (p = 0.008) was significantly worse than in anisometropic amblyopic eyes. The mean macular sensitivity difference between strabismic and mixed amblyopic eyes was not significant (p = 0.247).

The stability of fixation was significantly worse (more relatively unstable or unstable, less stable) in strabismic (within 2 and 4 degrees, p = <0.001), mixed amblyopic (within 2 degree < 0.001; within 4 degree, p = 0.001) when compared with the healthy group. Anisometropic amblyopic eyes showed significantly worse stability of fixation within 2 degrees (p = 0.011), whereas the difference was not significant within 4 degrees (0.20) when compared with healthy group. Intergroup comparisons between different amblyopia subtypes revealed that

TABLE 1. Baseline characteristics (BCVA, age, refractive error, and angle of deviation) of the study groups are shown. The mean age in all groups and the mean BCVA among the ambliyopic groups were similar.

| Group                    | Strabismic<br>Amblyopia<br>(n = 18) | Anisometropic<br>Amblyopia<br>(n = 19) | Mixed<br>Amblyopia<br>(n = 18) | Healthy<br>Controls<br>(n = 18) |
|--------------------------|-------------------------------------|----------------------------------------|--------------------------------|---------------------------------|
| BCVA (log MAR)           | 1.11 ± 0.11                         | $1.11 \pm 0.13$                        | $1.04 \pm 0.12$                | 0.0                             |
| Age (years)              | $21.3 \pm 2.3$                      | $22 \pm 2.7$                           | $22.6 \pm 2.6$                 | $22 \pm 2.2$                    |
| Spherical equivalent (D) | $0.32 \pm 0.09$                     | $3.30 \pm 1.27$                        | $2.43 \pm 0.86$                | $0.27 \pm 0.1$                  |
| Angle of deviation (PD)  | $17.8 \pm 5.3$                      | 0                                      | $15.0 \pm 6.6$                 | 0                               |

BCVA: best-corrected visual acuity; D: diopter; PD: prism diopter; log MAR: logarithm of the minimal angle of resolution.

TABLE 2. Comparison for mean macular sensitivity, stability of fixation, and location of fixation by MP-1 microperimetry in severe amblyopia subtypes.

|                                                               | Strabismic (a)                         | Strabismic (a) Anisometropic (b)       | Mixed (c)                              | Control (d)                           | P value          | a-b              | а-с            | a-d              | b-c             | p-q           | p-ɔ    |
|---------------------------------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|---------------------------------------|------------------|------------------|----------------|------------------|-----------------|---------------|--------|
| Mean macular sensitivity (decibel)                            | $6.80 \pm 4.35$                        | 12.73 ± 3.40                           | $8.9 \pm 4.01$                         | 17.38 ± 0.99                          | <0.001           | <0.001           | 0.247          | <0.001           | 0.008           | 0.001         | <0.001 |
| Stability of invation<br>Within 2 degrees<br>Within 4 degrees | $19.61 \pm 12.62$<br>$50.83 \pm 23.49$ | $56.89 \pm 28.52$<br>$83.68 \pm 18.54$ | $35.66 \pm 21.43$<br>$69.77 \pm 28.56$ | $85.88 \pm 13.16$<br>$96.88 \pm 4.63$ | <0.001<br><0.001 | <0.001<br><0.001 | 0.089<br>0.031 | <0.001<br><0.001 | <0.001<br>0.163 | 0.011<br>0.20 | <0.001 |
| Location of fixation<br>Within 2 degrees                      | $3.38 \pm 7.75$                        | $44.78 \pm 34.08$                      | $9.61 \pm 12.7$                        | $81.44 \pm 11.87$                     | <0.001           | <0.001           | 0.782          | <0.001           | <0.001          | <0.001        | <0.001 |

Note: All values computed using ANOVA test.

Mean macular sensitivity, stability of fixation, and location of fixation were worse in all amblyopia subtypes when compared with healthy controls. Intergroup comparisons between amblyopic subtypes revealed that strabismic amblyopic eyes had significantly worse mean macular sensitivity, stability of fixation, and location of fixation compared with anisometropic amblyopic eyes.

TABLE 3. Stability and location of fixation measured with an MP-1 microperimeter.

|                         | Strabismic,<br>n (%) | Anisometropic, n (%) | Mixed,<br>n (%) | P value* |
|-------------------------|----------------------|----------------------|-----------------|----------|
| Stability of fixation   |                      |                      |                 |          |
| Stable                  | 0                    | 7 (36.8)             | 0               |          |
| Relatively unstable     | 4 (22.2)             | 6 (31.6)             | 10 (55.6)       |          |
| Unstable                | 14 (77.8)            | 6 (31.6)             | 8 (44.4)        |          |
| Total                   | 18 (100)             | 19 (100)             | 18 (100)        | < 0.001  |
| Location of fixation    |                      |                      |                 |          |
| Predominantly central   | 0                    | 8 (42.1)             | 0               |          |
| Poor central            | 1 (5.6)              | 5 (26.3)             | 3 (16.7)        |          |
| Predominantly eccentric | 17 (94.4)            | 6 (31.6)             | 15 (83.3)       |          |
| Total                   | 18 (100)             | 19 (100)             | 18 (100)        | < 0.001  |

<sup>\*</sup>Chi-square.

stability of fixation of strabismic amblyopic eyes within 2 and 4 degrees (p<0.001) and stability of fixation of mixed amblyopic eyes within 2 degrees (p<0.001) were significantly worse than in anisometropic amblyopic eyes, whereas stability of fixation of mixed amblyopic eyes within 4 degrees was not significantly different (p = 0.163) from anisometropic amblyopic eyes. The stability of fixation difference between strabismic and mixed amblyopic eyes was not significant (within 2 degrees, p = 0.089; within 4 degrees, p = 0.031).

The location of fixation was significantly worse (more poor central or predominantly eccentric, less central) in all severe amblyopic subtypes when compared to the healthy group (p<0.001). Intergroup comparisons between different amblyopia subtypes revealed that the location of fixation of strabismic amblyopic eyes (p<0.001) and mixed amblyopic eyes (p<0.001) was significantly worse than in anisometropic amblyopic eyes. The location of fixation difference between strabismic and anisometropic eyes was not significant (p = 0.782).

# **DISCUSSION**

The basic mechanisms in different subtypes of amblyopia are similar, but differences exist in terms of severity, psychophysical characteristics, and reversibility.<sup>13</sup> The presence of eccentric fixation may be an important prognostic factor in the assessment and treatment of different amblyopia subtypes. Therefore, the ability of diagnosing and measuring quantitative values for fixation in amblyopia may be clinically important. Eccentric fixation contributes to visual impairment in amblyopia, and it has been described in up to 80% of amblyopia cases.<sup>14</sup> Menon et al.<sup>15</sup> investigated the fixation pattern of amblyopic eyes based on the Linkz Star configuration of the standard Heine's direct ophthalmoscope, and 75.49% of anisometropic amblyopic eyes had central fixation as compared to 69.6% of mixed amblyopic eyes and 67.15% of strabismic amblyopic eyes.

Our MP-1 findings revealed that all amblyopia subtypes exhibited worse stability of fixation, location of

fixation, and retinal sensitivity characteristics than healthy controls. Severe amblyopic eyes (all amblyopic eyes had BCVAs of  $\leq 1.0 \log MAR$ ) certainly would be expected to have reduced mean macular sensitivity, location, and fixation stability. However, for the first time, we showed that pure strabismic and mixed amblyopic eyes exhibited significantly worse mean macular sensitivity, stability of fixation, and location of fixation characteristics than anisometropic amblyopic eyes (Table 3).

There is scarce information about fixation and retinal threshold characteristics of amblyopia assessed with MP-1 microperimetry in the current literature; moreover, the differences of fixational characteristics between amblyopia subtypes have not been investigated. Carpineto et al. 16 showed that both the centrality and stability of fixation measured by MP-1 microperimetry were significantly impaired in the microstrabismic eyes of children when compared to fellow eyes. Dickmann et al. 17 showed that macular sensitivity significantly decreased in both strabismic and anisometropic amblyopic eyes when compared to fellow eyes, whereas, contrary to our findings, fixation did not change significantly between amblyopic and fellow eyes. Dickmann et al. 17 also found no significant difference between strabismic and refractive amblyopia in terms of location and stability of fixation. Subramanian et al. 18 found greater fixation instability in amblyopic eyes than normal controls, and fixation instability was not associated with the subtypes of amblyopia (strabismic, anisometropic, or combined mechanism). That was probably due to differences between the studies: mean BCVA of amblyopic eyes were 0.25 log MAR in Dickmann et al.'s study, mean BCVA of amblyopic eyes were ≥ 0.2 logMAR in Subramanian et al.'s study, whereas all amblyopic eyes in our study had a BCVA of ≤ 1.0 log MAR (severe amblyopia).

The current study may show us that strabismic amblyopia has worse fixation characteristics and retinal sensitivities than anisometropic amblyopia, and strabismus may have a more resistant pathology for different amblyopia treatment modalities. Our results support the findings of Woodruff et al.,19 who analyzed the outcome of amblyopia treatment in a cohort of 961 children. The outcome was best for pure anisometropic amblyopia, intermediate for pure strabismic amblyopia, and poorest for mixed amblyopia. The optimal timing of when to perform strabismus surgery in children with amblyopia, before versus after completion of amblyopia therapy, is controversial.<sup>20</sup> Lam et al.<sup>21</sup> showed that performing corrective surgery in children with esotropia before the full resolution of amblyopia is safe and efficient if the amblyopia therapy is continued after surgery, and in light of our results, we agree with Lam et al. in terms of the appropriateness of an earlier and more aggressive approach for strabismic amblyopia. On the other hand, as fixation is more stable and central in severe anisometropic amblyopia, late treatment options, such as keratorefractive procedures, may be helpful in restoring vision. Our results may also support Cağil et al.,<sup>22</sup> who showed that, after photorefractive keratectomy to eliminate and correct refractive errors in anisometropic amblyopia, visual acuity improved significantly in 70% of adult patients with no previous occlusion or chemical penalization treatment.

In conclusion, MP-1 microperimetry provides quantitative data for fixation and central retinal sensitivity characteristics, and the device can be used as an adjunctive tool in amblyopia diagnosis, treatment, follow-up, and research. Interestingly, it showed worse fixation and retinal sensitivity characteristics in strabismic amblyopic eyes when compared to anisometropic amblyopic eyes with the same level of visual acuity.

# **ACKNOWLEDGMENT**

This study was performed at Gulhane Military Medical Academy, Department of Ophthalmology, Ankara, Turkey.

## **DECLARATION OF INTEREST**

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

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