Changes in binocular function in anisometropic nonstrabismic children with optical correction and occlusion therapy

Ahmed Awadein, MD, FRCS(Glas), and Mohamed A. Fakhry, MD, FRCS(Ed)

PURPOSE
To identify factors that influence binocular function in anisometropic, nonstrabismic children before and after optical correction and amblyopia therapy.

METHODS
This was a prospective observational study of consecutive patients with nonstrabismic anisometropia. Visual acuity and responses to the 4\(^\circ\) base-out prism test, the Worth 4-dot test, and the TNO test were recorded after spectacle correction and every 3 months for 1 year. Factors affecting visual acuity and binocular function were analyzed using univariate and multiple stepwise regression analysis.

RESULTS
A total of 118 subjects were enrolled. At the end of the first year, the mean improvement in visual acuity was 2.6 ± 2.3 lines. The percentage of patients showing a positive response to the 4\(^\circ\) base-out prism test increased from 47% to 79%; fusion in the Worth 4-dot test, from 37% to 66%; and measurable stereopsis on TNO testing, from 59% to 80%. Better initial visual acuity and better final visual acuity were associated with better binocular function. Interocular refractive error difference was a predictor of poor binocular function in multiple regression analysis if the difference in spherical error exceeded 4 D. Patients with amblyopia showed significantly worse binocular function compared to those with no amblyopia.

CONCLUSIONS
Binocular function of anisometropic children can be improved with refractive correction and amblyopia therapy. (J AAPOS 2011;15:545-550)

...
reliable visual acuity or sensory data could not be obtained on account of poor cooperation.

Patients were divided into the following groups: spherical hypermetropic anisometropia, spherical myopic anisometropia, cylindrical anisometropia, and combined spherical and cylindrical anisometropia. Two peculiar groups of anisometropia were excluded from the study because of their small number and their lack of uniformity for statistical analysis; the first consisted of patients with mixed anisometropia (hypermetropia in one eye and myopia in the other eye); the second group consisted of patients with significant difference in cylindrical axis symmetry.

All included patients received a complete initial ophthalmological examination, including unaided visual acuity in each eye, cycloplegic refraction, and slit-lamp and dilated fundus examination. Ductions and versions were evaluated in all patients. A cover-uncover test was performed for both distant and near accommodative targets to detect heterotropia in primary position. Sensory evaluation was not done at the initial visit.

Distance visual acuity was measured by single-surround HOTV using a standard commercial chart projector. Best-corrected visual acuity was recorded after instillation of cycloplegic eye drops (1% cyclopentolate, three times at 10-minute intervals, the last drop 30–45 minutes before refraction); refraction was done using both objective streak retinoscopy and subjective refinement. All patients were prescribed spectacles based on the cycloplegic refraction performed on the initial visit. Astigmatism and myopia were fully corrected. Hypermetropia was symmetrically undercorrected by 1 D in both eyes. Patching or penalization was deferred until measurement of visual acuity in subsequent visits.

Patients were reevaluated 2–4 weeks after the screening visit and were instructed to wear glasses until they were reevaluated. Spectacles were checked first to ensure that the prescription was correct. Visual acuity was measured in each eye separately. For the purpose of analysis, amblyopia was defined as a difference of $\geq 3$ lines expressed as the logarithm of the minimum angle of resolution (logMAR).

The $4^4$ base-out prism test was used for assessment of the presence of bifoveal fixation and to exclude monofixation syndrome. Patients were asked to look at a distant target. A $4^4$ base-out prism was inserted rapidly before one eye and then quickly removed. The test was repeated on the other eye. A fast movement in the direction of the prism’s apex (inward) was considered as a positive sign for foveal fixation. The Worth 4-dot test was used to test for fusion at distance (6 m) and near (33 cm); however, only the results for distance were analyzed statistically. The Netherlands Organization for Applied Scientific Research (TNO) test was used to determine stereoaucuity. The test was performed at a distance of 40 cm while the patient is wearing red-green goggles. (The TNO test contains three screening plates [retinal disparity, 1980 arcsec] and three quantitative plates [retinal disparities ranging from 15 to 480 arcsec], as well as a suppression test.) For statistical analysis, patients with no measurable stereopsis were assigned to the worst measurable value of 3,000 arcsec.

Patients were categorized into one of three groups according to the results of sensory testing: those with normal or near-normal stereopsis ($\leq 60$ arcsec), fusion on Worth 4-dot testing, and positive response to 4 D base-out prism test; those with suppression on Worth 4-dot test and subnormal stereopsis (240–60 arcsec) (monofixation pattern); and those with frank unilateral suppression (unilateral suppression on Worth 4-dot testing and negative response to the 4$^4$ base-out prism test) and markedly diminished stereopsis (>240 arcsec).

Patients were reexamined every 3 months for 1 year. During each visit visual acuity was tested in each eye, sensory functions were retested, and cycloplegic refraction was repeated. If a difference of 0.5 D or more was found between the old prescription and the new refraction, a new spectacle prescription was given to the patient, who was then reevaluated 2–4 weeks later with the new prescription.

Patients who failed to achieve improvement in visual acuity at the end of the first 3 months and satisfied the definition of amblyopia were started on amblyopia therapy using standard guidelines (2 hours of daily patching for moderate amblyopia and 6 hours of daily patching for severe amblyopia). Amblyopia therapy was continued until the difference of visual acuity between both eyes was $\leq 1$ line.

Analysis of variance was used to quantify changes in visual acuity and sensory function over the course of the study period. The factors associated with improvement of visual acuity and binocular function were analyzed statistically using simple regression analysis. These factors were then analyzed using stepwise multiple regression analysis to identify predictors of better outcome.

Results

Of the 136 patients initially enrolled, 18 did not complete the required follow-up and were excluded from analysis. The mean age of the remaining 118 patients was 6.9 ± 1.6 years (range, 4–11 years) at the time of enrollment (e-Supplement 1, available at jaapos.org). The male-to-female ratio was 48:52.

The visual acuity in both eyes, measured after 2–4 weeks of spectacle therapy, is given in Table 1. The mean initial visual acuity in the more ametropic eye was 0.45 logMAR, approximately 20/70 (e-Supplements 2 and 3, available at jaapos.org). At the end of the 1-year follow-up period, the mean visual acuity improved by 2.6 ± 2.3 lines to 0.20 logMAR, approximately 20/34. The greatest improvement of visual acuity was at the end of the first 3 months (1.3 lines); however, improvement continued until the last visit (Figure 1A).

The definition of amblyopia was met by 63 of the 118 patients (53%) during the initial visit. Of these, 29 had severe amblyopia and 34 had moderate amblyopia. This decreased to 45 patients (38%) after 3 months and 21 patients (18%) after 1 year. No patient had severe amblyopia at the end of the study.

Factors associated with improvement in visual acuity were better baseline best-corrected visual acuity ($P < 0.01$), smaller interocular acuity difference ($P < 0.01$), and smaller difference in refractive error ($P = 0.01$). These factors remained statistically significant in multiple regression analysis (adjusted $r^2 = 0.28$). Improvement of

Journal of AAPOS
At the initial visit, the 4<sup>th</sup> base-out prism test was positive on both sides in 55 patients (47%). On multiple regression analysis, only poor initial visual acuity was a predictive factor for negative initial response (adjusted $r^2 = 0.46, P < 0.001$). At the end of the 1-year follow-up period, the 4<sup>th</sup> base-out test became positive on both sides in another 38 patients so that a total of 93 patients (79%) showed positive response (Figure 1B). In logistic regression analysis, only poor initial visual acuity and poor final visual acuity remained as predictive factors for residual negative response (adjusted $r^2 = 0.49, P < 0.001$).

At the initial visit, the Worth 4-dot test showed fusion for distance in 44 patients (37%) and suppression of the more ametropic eye in the remaining patients. On multiple regression analysis, only poor initial visual acuity remained as a predictive factor for unilateral suppression (adjusted $r^2 = 0.44, P < 0.001$). At the end of the 1-year follow-up period (Figure 1C), the Worth 4-dot test showed fusion in 78 patients (66%). Using multiple regression analysis, only poor initial visual acuity and poor final visual acuity remained as predictive factors for unilateral suppression (adjusted $r^2 = 0.47, P < 0.001$).

At the initial visit, 70 patients (59%) showed measurable stereopsis on TNO testing, with a mean of 1.671 arcsec. On multiple regression analysis, only poor initial visual acuity remained as a predictive factor for poor stereopsis (adjusted $r^2 = 0.47, P < 0.001$). At the end of the 1-year follow-up period (Figure 1C), the number of patients with measurable stereopsis increased to 94 patients (80%), with a mean of 959 arcsec. Using multiple regression analysis, only poor final visual acuity and poor initial visual acuity in the ametropic eye remained as predictive factors (Figure 2) for poor outcome (adjusted $r^2 = 0.47, P < 0.001$).

At the beginning of the study, 29% of patients had normal or near-normal binocular function, with about 16% of patients having monofixation response and 55% having frank unilateral suppression. At the end of the study, the number of patients with near normal response increased to 67%; another 13% showed monofixation response (Figure 3).

At the initial postspectacle visit (Table 2), binocular function was significantly lower in amblyopic children than in those with no amblyopia ($P < 0.01$). At the end of the follow-up period, binocular function of amblyopic children improved, but was still significantly lower than in those with no amblyopia ($P < 0.01$). Although binocular function appeared to be lower in the subset of amblyopic patients whose vision improved than in patients who never had amblyopia, the trend was not statistically significant (Table 3).

Myopic and hypermetropic anisometropia patient groups were further subdivided into those with interocular refractive error difference less than 4 D and those with interocular refractive error difference 4 D or more. Patients of the spherocylindrical group were merged with those of the corresponding spherical group according the spherical equivalent. The number of patients in the cylindrical group with interocular refractive error difference of 4 D or more was too small to allow for meaningful analysis. For each subtype, multiple stepwise regression analysis was performed to identify the factors affecting the binocular function in those with small degrees of anisometropia and those with high degrees of anisometropia. With both myopic and hypermetropic anisometropia, an interocular refractive error difference of >4 D was associated with reduced binocular function after treatment (e-Supplements 4-6, available at jaapos.org).

### Table 1. Baseline demographic and clinical characteristics (n = 118)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males–female ratio: n (%)</td>
<td>56:62 (48:53)</td>
</tr>
<tr>
<td>Age (yr): mean ± SD (range)</td>
<td>6.9 ± 1.6 (4-11)</td>
</tr>
<tr>
<td>BCVA (logMAR): mean ± SD, Snellen equivalent</td>
<td>In the more ametropic eye</td>
</tr>
<tr>
<td></td>
<td>In the less ametropic eye</td>
</tr>
<tr>
<td>Interocular acuity differences (lines): mean ± SD</td>
<td>4.1 ± 2.8</td>
</tr>
<tr>
<td>IRED (D): mean ± SD, range</td>
<td>Myopic group (n = 38)</td>
</tr>
<tr>
<td></td>
<td>Hypermetropic group (n = 39)</td>
</tr>
<tr>
<td></td>
<td>Cylindrical group (n = 22)</td>
</tr>
<tr>
<td></td>
<td>Spherocylindrical group (n = 19)</td>
</tr>
</tbody>
</table>

**BCVA**, best-corrected visual acuity; **IRED**, interocular refractive error difference; **logMAR**, logarithm of the minimum angle of resolution; **SD**, standard deviation.

Discussion

Anisometropia is associated with amblyopia, reduced binocular function, and impaired stereopsis.<sup>1-11</sup> Although it is well known that treatment can improve visual acuity, it is now recognized that motor fusion may also improve at a later age than previously believed.<sup>29</sup> This raises the question of whether improvement of visual acuity is associated with a parallel improvement in binocular function.

Although many studies have investigated binocular function of anisometropic patients, most of these were cross-sectional studies lacking adequate longitudinal follow-up. Weekley,<sup>11</sup> for example, examined 411 patients with anisometropia. These patients were prescribed spectacle correction at the time of the initial visit and were allowed time to wear the correction for an average of 14.8 weeks, allowing for adjustment to the glasses. Binocular function with correction was examined only during the second visit; these patients were not reevaluated later to determine whether binocular function had improved. Lee and Isenberg<sup>17</sup> studied binocular function in anisometropic children before and after amblyopia therapy; however, this was a retrospective study that included patients with microtropia and intermittent exotropia. In addition, they used the Titmus test, which has monocular clues that may reduce the accuracy of the results. Cleary and colleagues<sup>15</sup> reported improvement of binocular function in a prospective study, which, however, was mainly
FIG 1. A, Degree of improvement of best-corrected visual acuity in the more ametropic eye among the studied children along the 1-year follow-up period. B, Percentage of patients with positive response to 4⁰ base-out test in the more ametropic eye along the follow-up period. C, Percentage of patients with distance sensory fusion in Worth 4-dot test along the follow-up period. D, Mean near stereoacuity measured with TNO stereo test along the follow-up period.

FIG 2. Correlation between the final near stereoacuity at the end of the first year as measured with TNO stereotest, on one hand, and both the initial and the final best-corrected visual acuity (VA) in the more ametropic eye, on the other.

FIG 3. Grades of binocular function achieved during the follow-up period.
IRED, interocular refractive error difference; logMAR, logarithm of the minimum angle of resolution; PD, prism diopters.

Table 2. Characteristics of children with anisometropic amblyopia and children with anisometropia but not amblyopia at the start of the study

<table>
<thead>
<tr>
<th>Group</th>
<th>No amblyopia (n = 55)</th>
<th>Amblyopia (n = 63)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA with spectacles in the more ametropic eye (logMAR; mean [Snellen equivalent])</td>
<td>0.15 (20/28)</td>
<td>0.69 (20/100)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean IRED (D)</td>
<td>2.2</td>
<td>3.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bifoveal fixation in 4 PD base-out test</td>
<td>64%</td>
<td>32%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Distance fusion in Worth 4-dot test</td>
<td>44%</td>
<td>32%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Near stereopsis (arcsec)</td>
<td>776</td>
<td>2452</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 3. Characteristics of children with anisometropic amblyopia and children with anisometropia but not amblyopia at the end of the study

<table>
<thead>
<tr>
<th>Group</th>
<th>No amblyopia before or after therapy (n = 55)</th>
<th>Amblyopia at inclusion but resolved at end of study (n = 42)</th>
<th>Amblyopia both at inclusion and at end of study (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA with spectacles in the more ametropic eye (logMAR; mean [Snellen equivalent])</td>
<td>0.13 (20/27)</td>
<td>0.17 (20/30)</td>
<td>0.39 (20/56)</td>
</tr>
<tr>
<td>Mean IRED (D)</td>
<td>2.2</td>
<td>3.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Bifoveal fixation in 4 PD base-out test</td>
<td>84%</td>
<td>83%</td>
<td>57%</td>
</tr>
<tr>
<td>Distance fusion (Worth 4-dot test)</td>
<td>73%</td>
<td>71%</td>
<td>38%</td>
</tr>
<tr>
<td>Near stereopsis (arcsec)</td>
<td>645</td>
<td>692</td>
<td>2315</td>
</tr>
</tbody>
</table>

Near stereopsis (arcsec): 776 2452
Distance fusion in Worth 4-dot test: 44% 32%
Bifoveal fixation in 4 PD base-out test: 64% 32%
Mean IRED (D): 2.2 3.8

We found that anisometropic children improved over the first year of treatment; however, it remained lower than normal by the end of the study. Binocular function was significantly lower among amblyopic children. Our findings are in agreement with those of Loudon and colleagues, who found that binocularity was significantly worse in anisometropic amblyopic children compared to anisometropic children with no amblyopia. In the same study, the authors reported that binocularity improved to normal levels in anisometropic amblyopic subjects who improved with treatment, whereas it did not improve in patients who were unresponsive to treatment. We observed similar results in our patients, again highlighting the importance of visual acuity in the more ametropic eye as an important determinant factor of binocular function.

Reduction of binocular function in anisometropic nonstrabismic children can be due to both subnormal visual acuity and retinal image size disparity. In our study, poor visual acuity was the only factor in multivariate analysis associated with lower binocular function in patients with small amounts of anisometropia (<4 D). Although a higher interocular refractive error difference was also associated with poor outcome in univariate analysis, its effect disappeared in multiple regression analysis. A large difference in refractive error possibly reduces binocular function through reduction of visual acuity in the more ametropic eye rather than through a direct effect on retinal image size. Stepwise multiple analysis showed that a large difference in refractive errors starts to become a predictive factor for poor binocular function if the difference exceeded 4 D anisometropia. For cylindrical anisometropia, the magnitude of difference in refractive error was not associated with poor binocular function up to 4 D. The number of patients above 4 D difference in cylindrical anisometropia was too small to allow valuable information from stepwise regression analysis.

Our study was limited by temporal parameters associated with cycloplegic refraction and by the nature of tests we used to evaluate sensory function. We allowed approximately 2 weeks between the prescription of spectacles and the performance of initial sensory tests. This time was allotted to allow the effect of cycloplegic eye drops to wear off and to give some time for the parents to acquire spectacles and have the prescriptions adjusted if necessary. Such time may have allowed some improvement of the binocular function and the actual initial sensory functions may be slightly worse than what we reported. Assessment of sensory function in children may be subject to observer bias and patients’ suggestion in addition to performance variability. The sensitivity and specificity of the Worth 4-dot test in the detection of suppression have been reported to be 90% and 94%, respectively. Stereoacuity testing also shows performance variability. In general, stereoacuity test scores improve with age, whereas performance variability decreases with age. Normal adult findings are usually achieved by age 7. We used a variety of objective and subjective tests to minimize this problem; however, some improvement in sensory tests in children can be attributed to the children’s aging.

It is important to note that the 4 D threshold for high anisometropia was an arbitrary selection. It may be difficult to identify the exact threshold, which may differ depending...
on the sensory test used, visual acuity, age, and type of refractive error. One might speculate—although it is not proved from this study—that higher refractive errors reduce binocular function by altering retinal image sizes. Exploring this hypothesis would require a control group treated with a modality (such as contact lenses or refractive surgery) that would cause minimal change in retinal image size.

**Literature Search**

PubMed was searched, without date restrictions, using the following terms and combinations: *binocular AND anisometropia; stereopsis AND anisometropia; TNO AND anisometropia; Worth 4-dot AND anisometropia; depth perception AND anisometropia; and sensory AND anisometropia.*

**References**