Author's response to reviews

Title: Comparison of Localized Retinal Nerve Fiber Layer Defects in Highly Myopic, Myopic, and Non-myopic Patients with Normal Tension Glaucoma

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Version: 3  Date: 2 July 2013

Author's response to reviews: see over
Reviewer's report

Title: Comparison of Localized Retinal Nerve Fiber Layer Defects in Highly Myopic, Myopic, and Non-myopic Patients with Normal Tension Glaucoma

Version: 2 Date: 29 January 2013

Reviewer: Iwona Grabska-Liberek

Reviewer's report:

No revisions required.

1. Is the question posed by the authors well defined?
Yes. The authors developed a quantitative method for analyzing localized RNFL defects with RNFL photography. The method might improve diagnosis and monitoring of glaucoma in high myopic eye.

2. Are the methods appropriate and well described?
The methods used are appropriate. Exclusion criteria for patients involved in the study were well defined. The study well planned and executed. The evaluation of RNFL was partially blinded.

3. Are the data sound?
Yes. Statistical methods were used properly. The results are discussed in a clear and explanatory way.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Manuscript is in line with the reporting and data management standards. Paper includes conflict of interest.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Yes. The discussion is sound and clear. It is well supported by the data obtained
during the study.

6. Are limitations of the work clearly stated?

The authors indicate some limitations of the study. Because of the retrospective nature of the study the bias can’t be excluded. Angel was not adjusted for axial length and refractive error. The results might be affected by diffuse atrophy in high myopic eyes.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

Citations are well selected and clearly acknowledge previous developments in related areas of research.

8. Do the title and abstract accurately convey what has been found?

Yes. No comments.

9. Is the writing acceptable?

The paper is easily readable. Writing acceptable.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'

Thank you very much for your kind support.
Reviewer's report

Title: Comparison of Localized Retinal Nerve Fiber Layer Defects in Highly Myopic, Myopic, and Non-myopic Patients with Normal Tension Glaucoma

Version: 2 Date: 7 March 2013

Reviewer: Jean-Claude Mwanza

Reviewer's report:

We thank the reviewers for their insightful comments and have clarified or modified content that was ambiguous. We hope you will find this revised manuscript acceptable for publication.

MAJOR COMPULSORY REVISIONS

1)

2) The definition of "localized RNFL defects" is not clearly provided.

It is a form of encroaching upon Optic disc, which is consistent with driving direction of RNFL. Basically, RNFL defects can be observed clearly in Red free photo and they are not included in exclusion criteria. We added as below at method section. We defined the localized RNFL defect as a form of encroaching upon Optic disc, which is consistent with driving direction of RNFL. It is the cases that RNFL defects can be observed clearly in Red free photo and not included in exclusion criteria.

3) The authors stated that patients included in the study had no neuroradiological evidence of optic nerve damage. Clarification is needed. Does it mean that every patient underwent neuroradiological testing? What type of testing did the patients go through and what was the
We routinely recommended the neuro-imaging such as Brain MRI or CT to the patients who showed glaucomatous optic neuropathy under 40 years old. In this study, the patients with neurological problems and all patients showing abnormal findings in neuroimaging are excluded and there was no patient who indicates neurological problems through history taking. We added as below at method section. The patients with neurological problems and all patients showing abnormal findings in neuroimaging are excluded and there was no patient who indicates neurological problems through history taking.

4) The lower cutoff of emmetropia and myopia is -0.5 D. This should be corrected.

The original intention of using the definition was to set a range of emmetropia from +0.5 to -0.5. We will change the definition of ‘Low to moderate myopia’ as -1.0D ~ -6.0. In our data, all ‘Low to moderate myopia’ is over -1.0D, therefore, they will not affect our results.

5) The comparison was made between 3 groups (emmetropic, low to moderate myopic, and high myopic individuals). For a proper comparison, low to moderate and high myopic subjects should have been matched for both age and visual field mean deviation. Also emmetropic and myopic subjects should have been matched for age. Not doing so constitutes a significant weakness of the study and the paper.

As you mentioned, this study will be better if we analysis the results with matching both age and MD values, but it is not easy to do this practically. Considering that glaucoma occurs in a rather younger age in case of myopia patients than that of non-myopia patients and it is
already more developed than emmetropia at the time of glaucoma detection, and many glaucomatous damage progress as time goes by, it is difficult to match the values. In this study, we tried to reduce selection bias with selecting all visiting patients for a year and represent the characteristics of the patients in the real clinic. I believe that this may explain what needs to be understood.

6) Some subjects had both superior and inferior RNFL defects. But it is unclear from the text what defect was entered in the analysis and how it was chosen.

Sorry, our statements might be insufficient. All defects in both hemifields were included in the analysis. In Angle 1, the smaller angle of the two was included in the analysis, and angle 2 was analyzed by combining the widths of the two defects. We change the Figure 1 to help understanding as below.
7) Statistically, the study is also weakened by studying the correlation with only t-test and chi-square. The proper analysis is a multivariate regression adjusting for age, axial length, and IOP, refraction, looking for an association with degree of RNFL defects (as a multivariable regression) or more versus less damaged eye (as logistic regression).

Multiple regression analysis was added as Table 2.

Table 2 Comparison of Angle I and Angle II between the groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Mean ± S.D</th>
<th>Overall p value</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle I</td>
<td>H / M</td>
<td>31.6 ± 11.9° / 40.8 ± 14.7°</td>
<td>.028*</td>
<td>.028*</td>
</tr>
<tr>
<td>Angle I</td>
<td>H / E</td>
<td>31.6 ± 11.9° / 42.2 ± 14.2°</td>
<td>.044*</td>
<td>.044*</td>
</tr>
<tr>
<td>Angle I</td>
<td>M / E</td>
<td>40.8 ± 14.7° / 42.2 ± 14.2°</td>
<td>1.000*</td>
<td>1.000*</td>
</tr>
<tr>
<td>Angle II</td>
<td>H / M</td>
<td>66.6 ± 35.9° / 34.2 ± 18.4°</td>
<td>&lt;.001*</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Angle II</td>
<td>H / E</td>
<td>66.6 ± 35.9° / 30.4 ± 17.1°</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Angle II</td>
<td>M / E</td>
<td>34.2 ± 18.4° / 30.4 ± 17.1°</td>
<td>1.000*</td>
<td>1.000*</td>
</tr>
</tbody>
</table>

H : High myopia, M : Low to Moderate Myopia, E : Emmetropia

*Multivariate regression analysis with adjustment for age, gender, spherical equivalent, Axial length, and intraocular pressure.

8) Discussion page 12, 2nd paragraph. The sample size is too small to draw valid inferences about the proportion of male and female.

The limitation of small population number was added as follows.

While an interesting finding, we are unable to make any definitive conclusions from this, given the retrospective hospital based cross sectional nature and relatively small number of
subjects of our study.

9) Discussion page 12, 2nd paragraph. Contrary to what the authors stated, it is likely that the magnification influenced the size of the retinal defect, and therefore of the angular measurement. Thus it is critical that authors provide a mathematical model of measurement before and after magnification correction to support their claim.

The method we used was to analyze RNFL defects around optic disc. Disc is a round circle, and the circle can not be over 360 degree even if it is expanded. Therefore, it is not necessary to verify the one expanded with the same ratio. There are large population based studies that concluded the method using ratio did not affect the results. However, if the case is partially distorted somehow, errors can be found in measured values. But we only used good images without distortions, so there will be no disputes on them. Also, our methods are commonly used in other related studies, leaving no doubt about it.

MINOR ESSENTIAL REVISIONS

1) Methods section, 2nd paragraph, line 4. Insert reference(s) after "described technique"

Done

2) In the discussion, page 9, 2nd paragraph. the sentence " The MD values.....emmetropia groups." contradicts the results presented on page 7-8.

The word “larger” seemed confusing, so it was replaced by “reduced.”
MD of Humphrey C24-2 perimetry was significantly larger reduced in the high myopia group (-7.57 ± 4.04 dB) (95% CI: -8.92, -6.22) than in the low to moderate myopia group (-5.15 ± 3.75 dB)(95% CI: -5.98, -4.32) and in the emmetropia group (-4.38 ± 4.02 dB)(95% CI: -5.47, -3.30) (p=.014, p<.001).

3) Discussion page 10. The 2nd paragraph is full of redundancies.

We deleted that paragraph.

There are several ways to examine the RNFL in patients with glaucoma. However, commonly used imaging studies have shown a low diagnostic credibility for patients with high myopia due to problems with reproducibility and artifacts. It has been reported that OCT, confocal scanning laser ophthalmoscopy, and scanning laser polarimetry cannot discriminate sufficiently between non-glaucomatous and glaucomatous subjects that have high myopia.[8, 9] VF testing also has limitations in detecting early glaucoma due to the confounding effects of chorioretinal degeneration, which occurs frequently in myopic eyes. In contrast, red-free photography is quite useful for finding RNFL defects in myopic Asian patients. While a lack of retinal pigmentation renders some difficulties in detecting RNFL defects in the Caucasian population, especially in high myopia, East Asians frequently display detectable RNFL defects, even in high myopia, made more easily visible by their fundus pigmentation. Thus, red-free photography can be utilized for the detection of glaucoma in patients with high myopia.
DISCRETIONARY REVISIONS

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

No conflict of interest to report