Peer Review File

Inter-ocular asymmetry of retinal parameters in Caucasian healthy children and young adults measured with optical coherence tomography

Reviewer: 1

This manuscript studies retinal parameters in a population using spectral-domain OCT. The authors focus on the asymmetries that these parameters show between the right and the left eye. The paper is well written and presented. However, I am not sure about the importance of this work. Authors should try and clarify the aim of the work, as well as to explain in a better way why knowing the asymmetry of retinal parameters is or can be related to myopia progression. The authors acknowledge that the sample size is small at the end of the discussion. I agree with them, the sample size is small for this kind of studies.

ANSWER: Thank you for these kind words. We have revised the introduction and discussion of the manuscript to provide a better explanation of our study aims and of the relevance of exploring inter-ocular asymmetry in the context of myopia onset and progression. Indeed, the sample is rather small for the purpose of the study. However, given the temporal constraints imposed by the ethical review board we were unable to recruit further subjects to increase statistical power. This limitation shall be addressed in further studies.

I think the authors should consider the possibility of adding the word “inter-ocular” to the title, as in “Inter-ocular asymmetry of retinal parameters…”

ANSWER: The reviewer is correct. We have added this word to the title.

Reviewer: 2

Abstract

I would remove the first sentence “OCT is a useful technique to assess the retina”, as it does not add anything for the aim of the study. In fact, I would start directly with “To evaluate…”.

Replace the word “uncover” from Results. It sounds odd.

In the Conclusion, authors state: “…may be an effective approach to further the understanding of myopia…” Replace by “to further understand”.

ANSWER: Thank you for these suggestions. The manuscript has been edited accordingly.

Introduction

Page 1, Line 39. Replace “Besides” by “In addition”.

Page 1, Line 41. Replace “This gives support to” by “This supports the”.

ANSWER: The manuscript has been edited to implement these changes.

Here authors claim: “Besides, myopia onset and progression has been associated with an increase in axial length and with thinning of retinal structures. This gives support to the need for exploration of normal asymmetry in the absence of inter-ocular differences in refractive error as a means to better understand the changes occurring in myopia…”

Could you elaborate a bit more that reasoning? I do not really see the link between myopia onset and the asymmetries in retinal parameters. Please, elaborate.

ANSWER: Previous research has documented an association between myopia progression and retinal thinning and axial elongation. However, how and why myopia develops in certain
individuals is far from understood. Is there some anatomical/structural predisposition towards myopia onset and progression? The study of inter-ocular asymmetry in patients without anisometropia, and subsequent research on patients with different degrees of anisometropia may assist in understanding the development of these retinal alterations.

Page 1, Line 45. What is considered “normal” in the asymmetries of retinal parameters?

**ANSWER:** As noted below, this refers to the range of normal inter-ocular asymmetry which may be encountered in the absence of significant anisometropia and in the absence of unilateral or asymmetrical pathological conditions. Therefore, by normal we mean “average or physiological”. We have added these terms to the manuscript for clarity.

Page 1, Line 56. What is the age group at risk of myopia onset progression?

**ANSWER:** Although many risk factors have been described in the context of myopia onset and progression, including hereditary factors, outdoor activities, prolonged close work, etc., it is common to associate myopia onset and progression with school age. We have added this information to the revised manuscript, together with a relevant reference (Pärssinen O, Kauppinen M, Viljanen A. The progression of myopia from its onset at age 8-12 to adulthood and the influence of heredity and external factors on myopic progression. A 23-year follow-up study. Acta Ophthalmol 2014;92(8):730-739).

The goal of the study is not clearly stated in my opinion and can lead to confusion. What do you mean exactly when you say that you are going to define the thresholds for physiological asymmetry? Please, clarify.

**ANSWER:** We are referring to the range of normal inter-ocular asymmetry which may be encountered in the absence of significant differences in ocular refraction and in the absence of unilateral or asymmetrical pathological conditions. We have added this information to the revised manuscript.

Subjects and methods

Page 2, Line 6. Indicate the number of patients that were recruited here.

**ANSWER:** This information is provided in the revised manuscript.

Page 2, Line 7. Why that particular range in ages (12 to 23 years old).

**ANSWER:** As noted before, the age between the onset of puberty and emerging adulthood is particularly relevant to study myopia onset and progression. Also, we observed a notorious lack of published research on inter-ocular asymmetry of retinal parameters as measured with OCT devices for this age range.

Page 2, Line 8. Since you are relating this work to myopia progression, I feel like it would have been better to include more myopic patients and maybe even patients with higher degree of myopia.

**ANSWER:** The reviewer is correct. The research described in the present article is only a small part of a large body of research exploring anatomical and functional asymmetry in normal eyes and eyes with high myopia (but without pathological complications). The results of our research
on high myopic patients has been published elsewhere (Alzaben Z, Cardona G, Zapata MA, Zaben A. Inter-ocular asymmetry in choroidal thickness and retinal sensitivity in high myopia. Retina 2017. doi: 10.1097/IAE.0000000000001756).

Page 2, Line 36. Why did you place the ETDRS chart at 4 meters? Did you account for the possible 0.25 D of accommodation when looking at an object located at 4 m?

**ANSWER:** The reviewer is right in his/her concern. However, we followed published recommendations regarding ETDRS chart placement distance. Thus, the differences between the Bailey–Lovie chart and the EDTRS chart are the standard testing distance (6 m versus 4 m), and the choice of letter families (1968 British Standard letters versus Sloan letters). The choice of letters means the ETDRS chart has wider spacing (5 units versus 4 units) between adjacent letters within rows. At the recommended testing distances, the range of acuity values on both charts covers the same range from logMAR = 1.00 to logMAR = −0.30 (6/60 to 6/3 and 4/40 to 4/2). (see, for example, Bailey IL, Lovie-Kitchin JE. Visual acuity testing. From the laboratory to the clinic. Vis Res 2013;90:2-9).

Page 2, Line 51. Use the Greek letter rho.

**ANSWER:** Done.

**Results**

Table 1. There is something I do not understand about this Table. You stated in Methods that only subjects who have visual acuity better or equal to 0 logMAR were selected for this study. However, in Table 1 you show that there were participants with worse visual acuity. How is this possible?

**ANSWER:** Thank you for pointing this error to us. Values are either 0.000 or negative. This has been corrected in the revised manuscript.

Please, write the range in a different way, e.g. [-3.75, +0.50]. It is very confusing when there are a hyphen and a plus sign together.

**ANSWER:** This has been edited in the manuscript.

Page 3, Line 22. Authors state: “Statistically significant differences were found between males and females in age (median of 19 years in males versus 15 years in females, p = 0.018)…” I do not think this is needed for this paper. It does not add anything to this study.

**ANSWER:** This information has been deleted from the manuscript.

Tables 2 and 3. I would suggest again to modify the way you present the ranges, it is confusing sometimes, e.g. see first row of Table 3: Range -9.00 -6.00. It is hard to understand if it is a -6 or a 6.

**ANSWER:** This has been edited in the manuscript.

Table 3. Why duplicate the information? The range and the percentiles are the same.

**ANSWER:** This is probably a consequence of our reduced sample of participants. Indeed, the range and 2.5th and 97.5th percentiles columns display the same values, with the exception of central macular thickness. We have opted not to modify the table as previous research commonly
presents both range and percentiles. However, if the reviewer expresses further concern about this issue, the range column may be safely deleted.

Discussion
Page 4, Line 17. What are the limits of normal retinal asymmetry? The range showed in Table 3? Please, clarify.
ANSWER: It is common to present limits of normal retinal asymmetry as the 2.5th and 97.5th percentiles. Therefore, these are the key values from Table 3. We have added this information to this sentence of the discussion.

I would like to see some possible reasons as to why the authors think some parameters present asymmetry between eyes. Why do you think those particular parameters are asymmetrical and other are not?
ANSWER: Published literature offers a number of explanations to address interocular asymmetry. Mainly, authors link interocular asymmetry to changes in retinal and choroidal vasculature morphometry. However, a recently published review on this topic states that “Setting reliable criteria by which to judge the symmetry of the retinal vasculature is challenging. We know that the overall shape of the retinal vasculature in the left and right eye is broadly symmetrical, but detailed properties of the vasculature much less so: that is the specific path and shape of individual vessels, the location of bifurcations and junctions, and the values of various morphometric indices commonly found in the literature of retinal biomarkers of nonocular disease, such as tortuosity, branching angles and geometry, and vessel calibres (or widths).” (Cameron JR, et al. Lateral thinking - Interocular symmetry and asymmetry in neurovascular patterning, in health and disease. Prog Retin Eye Res. 2017;59:131-157).
We have added a very brief note in this regards to the revised manuscript, pointing the interested reader to the relevant reference.

Line 51. “Interestingly, statistically significant differences were encountered between males and females in both age and mean RNFL thickness in the right eye” Finding significant differences between males and females in age is not interesting.
ANSWER: This information has been deleted from the manuscript.