Author's response to reviews

Title: Quantitative relations between the eyeball, the optic nerve, and the optic canal important for intracranial pressure monitoring

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Replies to Reviewer Samson Gwer.

We ask the Reviewer to please accept our thanks for the analysis of our paper. We are grateful for his having so clearly pointed out a number of issues that needed to be addressed in order to enhance the clarification of our paper, and we have done so for each citation as follows:

1. What are the baseline characteristics of individuals selected for the study e.g. what were the reasons for admission to the department of radiology – why did they need “routine” ct-scans?, are there other measurements of physiological parameters e.g. blood pressure, head circumference, how many individuals belonged to the various age groups?

Initially, we selected our cases from a cohort of patients who were admitted to our Emergency Department, were referred to CT investigations but no pathology was found. The reasons for CT scans were most various: head trauma in the history but no cranial pathology was detected, complaints on severe headache but no cranial pathology was detected, vomiting of unclear etiological origin, complaints on severe dizziness and vertigo but no cranial pathology was diagnosed, condition after road accident but a patient appeared to be healthy, etc. At the Emergency Department, routine blood pressure taking, blood tests, etc. we obtained. Head circumference was not measured. We clarified this paragraph as follows (p. 5, two upper paragraphs):

"We examined the patients who were admitted to the Emergency Department, were referred to the CT investigation that included the head and neck region, and appeared to be neurologically and ophthalmologically healthy.

Exclusion procedure was organized in two steps. First, the patients with documented ophthalmological, cerebral, or neuroophthalmological disorders were excluded as well as patients with injuries around the orbits. At this stage, we also checked the data of the blood tests to exclude intoxications that might affect CNS. Second, the selected patients were examined by an ophthalmologist and by a neurologist in order to exclude overlooked eye disorders or cerebral
pathology. Special attention was paid in order to exclude cases with ischemic, toxic, hereditary, nutritional, or compressive neuropathies, glaucoma, cataract, etc. Therefore, four criteria were used to include a case into our study: 1) a neurologist did find any CNS-specific pathology; 2) an ophthalmologist did find any eye/optic nerve-specific pathology; 3) CT investigation did not detect any cranial pathology or existing pathology of the optic nerve; 4) blood tests did not indicate any toxic elements that might affect the CNS".

Information on age groups was also provided (p. 7, first paragraph of the Results):

"In our cohort, there were 214 females and 186 males, age range was from 18 to 94 (mean 46). Distribution among age groups: group I(18-30) - 89; group II(30-65) - 156; group III(65+) – 155".

2. Can there be a clearer description of the methods used to include or exclude patients – were similar protocols used for instance to rule out for instance toxic neuropathies, were they different observers, are there references to standard procedures if any?

That is correct, there were different observers. Specifically for toxic neuropathies, toxicology blood tests were obtained at the Emergency Department as a part of their protocol. We indicated this in the text (see the answer to the question 1).

3. Please provide a reference for the standard Philips protocols for head and neck imaging used in this study

This information is now provided (refs. 13-15).

4. It is not very clear why the ONSD /ETD should be used. There may be rationale for this but this does not come out clearly in the background or discussion. As much as there is little variation in this index, what is its clinical import? Why this index and not ONSD/head circumference for instance?

Our research is divided into two parts – normative database (current manuscript) and pathology. That is why we did not put everything in the discussion section of this manuscript. Currently, the ONSD method to monitor intracranial pressure is not precise. If only the optic nerve itself is taken into account, standard deviation of pathological data and standard deviation of the normative data can overlap and a physician will be unable to make a decision. The index is much more precise: 0.19±0.02 in health. In various pathological conditions that affect intracranial pressure, it can be from 0.22 to 0.3 without any standard deviation overlap.

Head circumference is hard to use for this index because people with brachycephalic and dolichocephalic skulls have the same normal ONSD. At the very beginning of our research, we tried the skull as well but abandoned this idea.
Replies to Reviewer Michael Shterenshis.

We wish to express our gratitude to the Reviewer for expending so much effort in providing such specific guidelines to help us enhance our paper. We thank the Reviewer for his/her encouraging remarks and hope that our many revisions will have done justice to his/her kind words. Our replies are as follows:

1. Please indicate more precisely how the transverse diamenter of the eyeball was measured - retina to retina or sclera to sclera.
   It was retina to retina – we inserted this information into the text (p. 6, paragraph 2).

2. You did not find differences in measurements between age groups. please explain why.
   Thank you for this remark. We added in the Discussion (p. 9):
   "We did not find statistically significant differences in ONSD correlated with age. The optic nerves experience the age-dependent nerve fiber loss as any other nerve in the human body. However, while total axon count in the optic nerve decreases with age, mean axon diameter increases with age.21 At the same time, the thickness of dura mater increases with age.22 While all these processes take place at the same time, we might assume that the ONSD remains approximately the same during a lifetime".

3. The CT scans were used in the research. Please explain how this measurements can be obtained by MRI or ultrasound that also are used for intracranial pressure detection via ONSD.
   We used CT for this research. MRI is hard to obtain from a healthy person. Your remark is correct and we added limitation of the research as follows (p. 10):
   Limitations of the research. All the CT scans were obtained by the 256-slice CT Philips scanner. It might be possible that scanners of different trademarks could provide slightly different results of measurements as well as MRI or sonographic evaluation.

4. The title of the article is somewhat long. I do not insist, but perhaps you can rephrase it.
   Another title we had in mind is The eyeball, the optic nerve, and the optic canal in intracranial pressure monitoring: normative database.
   We will be happy to change the title of the manuscript if the Editor-in-Chief will not object.