Author’s response to reviews

Title: Acute Emotional Stress as a Trigger for Intraocular Pressure Elevation in Glaucoma

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To facilitate review, a point-by-point response in Word format was provided as Supplementary Material.

Please find a copy below.

** Editor Comments

We thank the editor for their thoughtful and detailed comments. While the near-complete resolution of the hypertensive episode as well as its timing in relation with a severe emotional episode suggests an association between stress and IOP regulation, persistent decompensation indicates a probable mixed mechanism. We have revised our submission to highlight the uncertain nature of this relationship, especially in view of the unpredictable nature of pseudo-exfoliative glaucoma (line 125-127, line 209). CyPass withdrawal occurred a few days after the original manuscript was submitted, disrupting the patient's management plan. The end of the report was edited accordingly (line 117-118). We have also addressed all comments from the reviewers, as detailed below.

** Reviewer 1 - Xiangmei Kong:

We would like to thank the reviewer for her attentive comments. We have included additional material and figures, including images of the optic discs, visual fields and OCT. The discussions regarding the difference in IOP between both eyes has been significantly broadened (line 132-171) and the potential impact of disease severity was included as suggested by the reviewer (line 164-171).

** Reviewer 2 - Chiara Posarelli:
We would like to thank the reviewer for her thorough review and thoughtful comments. We have revised the manuscript according to the comments below:

1- "First why did you change the topical medications to control the IOP spike and you didn't just add oral acetazolamide to the patient?"

Considering the existing functional defect in the left eye and the amplitude of the IOP rise (48 mmHg), the decision was made to initiate both topical and oral therapy as a first line measure to normalise IOP as promptly as possible and subsequently titrate down the treatment. This was added to the report (line 104-105).

2- "Did you change the medications in both eyes or only in the left one? After the IOP spike is still the patient using timolol and dorzolamide and brimonidine?"

Topical medications were only initiated in the left eye and titrated down as the IOP decreased. At the end of the follow-up period, both acetazolamide and brimonidine were stopped. This was clarified in the manuscript (line 102-103, line 112-113).

3- "Line 111 please correct familial with familiar;"

Familial is the word we intended to use, in reference to the turmoil in her family.

4- "Line 113-114 Contact lens sensor didn't provide IOP measurements but register signal fluctuations, I believe that the reader should be aware of this concept which is very important and need to be better clarified also in the figure 2"

This is a very good point - Triggerfish contact lens sensors measure variations in corneal shape and only provide a representation of the variations in IOP, not actual pressure values. The explanation was added (line 113-116, Legend-Fig. 2).

5- "Did you perform an UBM or only AS-OCT? Did the examination confirm the slit lamp appearance of the bleb?"

Only the AS-OCT was performed, which confirmed the biomicroscopic appearance of a functioning bleb. This was clarified (line 91-92).

6- "I believe that in order to better clarify the differences between the two eyes is important to clarify for the Reader the ExPress surgical techniques; where still the scleral sutures on site at the time of IOP spike? Sometimes releasable sutures are used to close the scleral flap and removed to control wound healing process during the first 2-3 weeks."
Thank you for these insightful comments. We have added an explanation of the surgical principles of the ExPRESS shunt (line 139-145). Two scleral sutures were still in situ at the time of the first presentation - this crucial observation was added (line 86-87).

7- "Fig 1 please add the axis of the graph what they refer to."

Both axes of Figure 1 were labeled.

8- "Did you find any paper that observe, as you do, such a difference between the two eyes? It's very difficult this different behavior."

Several studies described discrepancies in IOP between both eyes of patients who underwent bilateral glaucoma surgery, some of which even found a statistically significant difference between the first and the second eye. Other studies, specifically on eyes with PEXG, have directly correlated maximum IOPs both to the amount of PEX material within Schlemm's canal and to the amount of axonal damage.

Your comment prompted us to develop and broaden our discussion about this difference in IOPs between the two eyes, and suggest more theories potentially underlying this process (line 132-171).