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Research Article

Contribution of Chemical Composition of Vitreous on Development of Hypertensive Pain Syndrome in Terminal Glaucoma

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Abstract

Purpose: To identify a possible link between hypertensive pain syndrome in the eyes with terminal glaucoma of different origin and the difference of urea concentrations between the vitreous and blood serum.

Methods: The research included study of vitreous samples that were taken from 31 patients (31 eyes) with IOP over 35 mm Hg during the surgical treatment for terminal glaucoma of different origin. The principle of surgery was drainage of the vitreous chamber for pain relief. Vitreous and venous blood samples were obtained in order to measure urea concentrations (SPOTCHEM-EZ SP 4430 biochemistry analyzer). The patients were divided into 3 groups depending on the features of pain. The first group included 8 eyes with severe pain just before the surgery; the second - 14 eyes with a history of pain but no pain prior to surgery; the third - 9 eyes with no history of pain.

Results: In 25 cases (81%) the urea concentration in the vitreous was higher than in blood serum and in 4 cases (13%) the concentrations were almost equal. In only 2 cases (6%) it was lower than in the blood serum. The high urea concentration in vitreous accompanies steady increase of IOP. Pain was registered when the difference between urea concentrations exceeded the critical level of 6.1 mmol/L.

Conclusion: If the concentration of the osmotically active urea in the vitreous exceeds that of blood serum, it may be the reason for IOP steady increase in some cases of refractory glaucomas. If the difference of concentrations is over the critical threshold, it can be the reason of pain.

Keywords: *Glaucoma; Pain; IOP; Vitreous; Urea; Blood Serum; Hemodialysis*

Introduction

High intraocular pressure (IOP) in terminal glaucoma is sometimes associated with severe pain. The pain in those cases is dull, excruciating and long lasting. It can irradiate into the bony structures of the head and responds poorly to non-opioid anesthetics. Glaucomas of these types are refractory to surgical treatment because of the secondary increase in IOP [1] and relapse of pain shortly after the surgery. Association of this kind of pain with high IOP in patients with terminal glaucoma allows us to define this condition as hypertensive pain syndrome (HPS).

The cause of pain in such cases is believed by some researchers to be high IOP compressing nociceptors located in the ciliary processes. However, we assumed that the origin of pain may be different because the abovementioned point of view offers no explanation for the absence of pain or discomfort in the vast majority of patients with glaucoma and high IOP.

In order to clarify the link between high IOP and severe pain in HPS, we first studied the association between patients' subjective complaints and high IOP. In previous studies, in a group of patients with subretinal neovascular membranes we used transciliary intravitreal injections with 0.05 ml VEGF inhibitor (under local anesthesia, 1.0% Alcaini, 30G needle). Right after the procedure, we measured IOP and interviewed the patients. We found that for a short period, just after the injection IOP could increase up to 60 mm Hg. Despite that, none of the patients presented any complaints of pain that would be similar to that in HPS [2].

Thus, excruciating pain that was the subject of our previous study only developed in the eyes with high IOP. However, high IOP itself in most cases was not associated with eye pain which means that high IOP is an obligatory condition for HPS but it not necessarily a direct cause of pain.

To understand the real underlying mechanism of HPS we used the data obtained while monitoring two patients with terminal glaucoma, pyelonephritis, renal failure and uremia. Both these patients were on the kidney transplant waiting list in nephrological clinics. Both were receiving haemodialysis (HD) (3.5 - 4.0 hours per session) and suffered from excruciating pain in the affected eyes typical of HPS. In both cases, the pain was associated with the time of HD session: there was no pain before HD but it gradually appeared 50-80 minutes after the start of every HD session. It increased and did not respond to anesthetics. Closer to the end of HD, the pain in the eye was sometimes unbearable and the patients asked to finish HD earlier. Pain intensity always slowly decreased after HD and disappeared completely by the beginning of the next HD session. The same situation repeated with every HD session [3].

Several authors already reported IOP increase in glaucoma during HD [4-9]. We theorized that the increase in IOP, pain and changes in its intensity were due to the variation of the concentrations of osmotically active substances between the blood in the capillaries of the ciliary processes and the fluid contents of the vitreous separated from each other by a semipermeable biological membrane - the walls of the ciliary processes.

Osmotically active substances of the vitreous body include urea or carbamide [10-12], which was the focus of our interest since its concentration changed dramatically during the HD session. Urea plays an important role in the metabolism of nitrogenous compounds in animals. Because of high osmolarity, carbamide was earlier used as a kind of diuretic [13]. Under normal conditions, the level of urea in the blood (and the osmotic pressure of the blood serum) is much higher than in the intraocular fluids (or cerebrospinal fluid) due to its poor transport through the haemato-ophthalmic barrier.

We hypothesised that such mechanism could be responsible for HPS in patients who received HD. The volume of fluid moving through the eye is generally great enough [14]. There is a certain correlation between concentrations of low molecular substances in the blood serum and the fluid contents of the eyeball due to the haemato-ophthalmic barrier. However, aqueous outflow is practically absent in terminal glaucoma and the substances inside the vitreous become trapped and have no way of leaving the eye. At the same time, the concentrations of metabolites (including urea) in the blood serum change substantially during a HD session.

As a result, osmotically active urea in the vitreous chamber reaches high levels which may be an important factor in drawing and keeping the water inside the eye leading to increased IOP. Also, the difference in concentrations of the osmotically active substances on different sides of the walls of the ciliary processes may result in abnormal tension. The walls of the ciliary processes contain numerous nociceptors. We surmise that such abnormal tension on ciliary walls may irritate nociceptors and generate pain.

In order to manage HPS in blind eyes of both patients we used a surgical technique based on the drainage of the vitreous chamber [15].

The drainage of the vitreous chamber to eliminate pain in terminal secondary glaucoma (including neovascular glaucoma) had been practiced at our clinic for many years long before the invention of laser cyclophotocoagulation. The efficacy and simplicity of the surgery to save the aching blind eye as cosmetically important part of body is the reason why we continue using it until now. The eyes included in this study were operated on by one surgeon (Ermolaev A) skilled in this type of surgery (300 cases over the last 25 years).

This surgery also makes it possible to obtain vitreous samples *in vivo* for research. There are several modifications of the surgical technique but they all share the following features:

- The position of a superficial scleral flap basis is shifted from the limbus towards the equator by 2 mm compared with conventional trabeculectomy so the center of scleral bed is located in the projection of the pars plana of the ciliary body;
- A single piece of deep scleral layer is removed to make a scleral well (3.5 mm from the limbus; the size of the scleral well is approximately 1 x 1 mm);
- Thermoperforation of the pars plana is made through the scleral well;
- Approximately 0.5-1.0 ml of the vitreous under the drainage well, around it, as well as from the central and postcentral parts of the vitreous chamber is removed before the free flow of liquid begins;
- The scleral flap is closed and fixed not tightly to allow permanent drainage from the vitreous chamber;
- The conjunctiva is sutured.

The concentrations of urea in the blood serum of both patients before and after the last HD session preceding the surgery were measured (Table 1a.). A vitreous sample and a new blood sample from the ulnar vein were taken during surgery to measure and compare the urea levels (Table 1b). The details of this study had been published earlier [3].

Patients	A		B	
	Urea concentration in blood serum before and after HD (mmol/l)		Urea concentration in the vitreous and blood serum during surgery (mmol/l)	
	Before HD	After HD	Vitreous	Blood serum
M.*	44.2	9.6	25.0	9.7
K.**	46.4	12.4	36.4	29.5

Table 1: *(A, B) Urea concentration in two patients with uraemia.*

HD: Haemodialysis.

A. The blood samples were taken before and after the last session of HD before the surgery.

B. The vitreous samples were taken as a part of surgery aimed at draining the vitreous cavity; blood samples were taken during surgery.

**: Patient M. was treated 3 hours after HD when the pain was still severe.*

***: Patient K. was treated 24 hours after HD when pain was much milder.*

All samples were centrifuged, blood serum and the supernatant of the vitreous contents were analysed.

Similar results were described by Ghaffariyeh., *et al*. [16] when they sampled the vitreous while making a transciliary endovitreal injection of avastin between the HD sessions. The data reported in these articles allowed us to define the line of further studies.

Purpose of the Study

The purpose of the study was to identify a possible link between HPS in the eyes with terminal glaucoma of different origin and the difference of urea concentrations between the vitreous and blood serum.

Materials and Methods

Thirty-one patients (31 eyes) with terminal glaucoma of different origin were studied and operated on. Cases with gross vitreoretinal pathology, haemophthalmos and tumors were excluded. The purpose of surgery aimed at the drainage of the vitreous space was to try and cure HPS and to refrain from enucleating blind eyes. IOP in all eyes exceeded 35 mm Hg. We did not attempt to make accurate IOP measurements since in cases with such high IOP a measurement error could be significant. The details of the surgery were described earlier [15].

During surgery, penetrating sclerectomy (1x1mm) under the flap was made. Local incision of choroid and retina were made under the superficial scleral flap through scleral well 3.5 mm from limbus. We aspirated about 0.5 ml of the vitreous from the postcentral part of the vitreous chamber through this well using a 21G injection needle.

We also took blood samples from the ulnar vein during surgery. Vitreous and blood samples were studied in the clinical laboratory upon completing the surgery. The samples were centrifuged for 6 minutes at 1500 rpm. Then the blood serum and the supernatant of the vitreous were analysed for urea (SPOTCHEM-EZ SP 4430, USA, automated biochemistry analyzer).

All patients had high IOP resistant to antiglaucoma treatment. They were divided into 3 groups depending on the intensity of pain before the surgery. The first group included 8 eyes with severe pain just before the surgery; the second - 14 eyes with a history of pain but no pain prior to surgery; the third - 9 eyes with steady high IOP but without history of pain. The results of laboratory tests were matched with subjective pain intensity in the patients' eyes.

Group number	Quantity of patients (eyes)	IOP (mm Hg)	Pain in the eye
1	8	> 35	Severe pain just before surgery
2	14	> 35	History of pain; no pain prior to surgery
3	9	> 35	No history of pain

Table 2: *Glaucoma patient groups.*

The patients were divided into 3 groups depending on the features of pain.

Results and Discussion

During the aspiration, we noticed that the samples from the anterior and posterior parts of the vitreous chamber had different densities. As for the anterior part, aspiration was challenging because it was very compact. In contrast, the aspiration of the postcentral part of the vitreous chamber was easy and required minimal effort.

We believe that difficulties during aspiration from the anterior part of the vitreous chamber stem from a particular feature of vitreous body anatomy - a complex compact enough structures and higher density in this area [17]. Another explanation of the different densities

of the anterior and posterior parts of the vitreous chamber was syneresis where the anterior vitreous becomes compact while the central and posterior parts undergo liquefaction [18]. Clinical signs of vitreous syneresis include posterior vitreous detachment and the appearance of the retrovitreous space found in all terminal glaucoma cases on ultrasound regardless of the patient's age [19]. Earlier, vitreous syneresis was thought to be associated with age-related changes in the body [20,21]. The consistent finding of vitreous syneresis in all cases of terminal glaucoma gives us a reason to suppose that glaucoma may be considered as factor accelerating involution of the vitreous.

The aspirated vitreous sample was transparent and more liquid than the native vitreous. In two cases it contained traces of fresh blood, perhaps, as a result of surgical trauma. We think the aspirated substance obtained during surgery was a mixture of the retrovitreous fluid and little fragments of posterior layers of the vitreous altered by syneresis.

Urea concentration in the vitreous was higher than in blood serum in 25 cases (81%) and almost equal in 4 cases (13%). And only in 2 cases (6%) it was lower than in the blood serum (the ratio close to normal). The IOP in all cases was over 35 mm Hg and and did not respond to IOP-lowering drops.

Severe pain before the surgery was registered in 8 cases. The difference in urea concentrations between the vitreous and blood serum in those cases was higher and exceeded 6.1 mmol/L. It was the critical level separating groups with pain and without in our research.

The levels of urea in the vitreous and blood serum in groups of patients are given in figure 1.

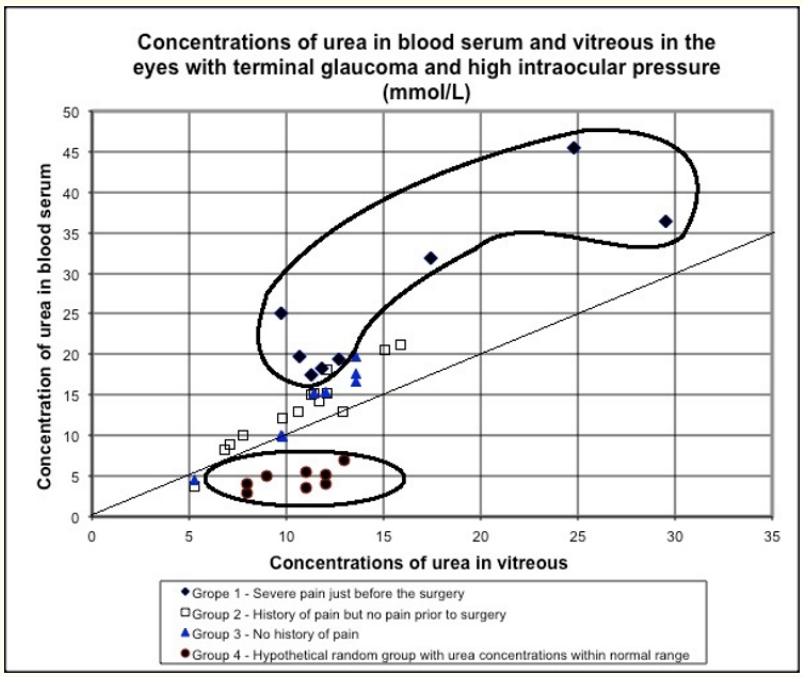

Figure 1: *Difference of urea concentrations between the vitreous and blood serum in terminal glaucoma.*

A - The line depicts equal urea concentrations in the blood serum and vitreous.

B - The hypothetical group with urea concentrations within normal range in both substances is below the equimolar line (circled at the bottom of the graph).

C - All dots representing the group with severe pain just before the surgery are located high above the equimolar line (circled at the top of the graph).

D - IOP in all cases exceeded 35 mm Hg. The concentration of urea in the vitreous is higher than in blood serum or close to equimolar.

Figure 1 shows 3 main groups which represent correlations between the urea concentrations in the vitreous and blood serum in the eyes with terminal glaucoma. For comparison, we added to the graph a hypothetical 4th group which represented randomly chosen concentrations of urea in blood serum and vitreous body within the normal range. To illustrate it, we added the line which shows the condition of equimolar concentrations of urea between the vitreous and blood serum. This line divides the graph into two fields: dots below the line represent patients with normal ratio of concentrations, wherein urea concentration in the blood is higher than in the vitreous. Dots above the line represent cases with abnormal difference in urea concentrations wherein it is higher in the vitreous.

All 8 cases from the 1st group with hypertensive pain syndrome were located considerably above the equimolar line. The difference of concentrations of urea between the blood serum and the vitreous in the group with pain was 6.1 mmol/l and higher.

The dots which represent the patients with high IOP but without pain (the 2nd and 3rd groups) are located below the 1st group on the graph. These patients also had increased urea level in the vitreous. The majority of the dots are located above the equimolar line and only a few are near the line or slightly lower [22].

Conclusion

We suggested that the penetration of a substantial quantity of urea into the vitreous chamber may be the result of apparent or subclinical increase of urea level in the blood. In terminal glaucoma, the outflow is practically blocked, and the urea which entered the vitreous chamber cannot leave the eye. After the return of urea level in the blood to normal values, the urea concentration in the vitreous begins to exceed the level of urea in blood. This condition can undoubtedly only develop under predisposing factors (e.g. kidney disease).

Osmotically active urea which accumulated inside the vitreous chamber draws water from the blood and retains it inside the eye. It could be the reason for the steady increase of IOP in some cases of refractory glaucoma. This mechanism is akin to that of a diaper which absorbs and retains liquid because osmotically active particles are placed into the bag made of a semi permeable membrane.

If the urea concentration was high but the difference between the vitreous and blood serum was below the critical level, the result would only be a steady increase in IOP. But if the difference in concentration exceeded the critical level, it would result in hypertensive pain syndrome due to abnormal tension on the walls of the ciliary processes.

If this mechanism really exists in eyes with refractory glaucoma, it would explain many unsuccessful surgery outcomes. The reason for quick scarring of surgically created outflow pathways may not only be associated with excessive repair at the surgical site. Insufficient outflow of liquid through surgically made channels (as a result of water being trapped in the vitreous by osmotically active substances) would be one of the reasons for quick scarring.

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