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THE ROLE OF CORTISOL, PROLACTIN, CD_4 AND CD_8 IN INDUCTION OF ANTERIOR CHAMBER ASSOCIATED IMMUNE DEVIATION (ACAID) IN CASE OF CATARACTS

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Abstract

As a result of performed clinical and para-clinical studies in the pre-surgical period IgG, high level of cortisol and prolactin were revealed in intraocular fluid of patients with cataract on the background of glaucoma; the findings allow to consider mentioned indices as informative criteria for diagnosis and, especially, prognosis of disease course.

The mere fact of IgG revealing in intraocular fluid should be considered as a consequence of "baring" (uncovering) of antigenic determinants in extra-barrier membranes of an eye and in the first place in tissues of lens.

The increase of cortisol levels in intraocular liquid bears, on the one hand, an adaptive character as in the extra-barrier membranes of an eye cortisol-dependent mechanisms of inhibition of regional antibody formation processes are involved, being mediated by CD_8 activation, and, on the other hand, activation of cytotoxic sub-populations of T-killer lymphocytes is fraught with emergence of dystrophic processes in the same membranes of the eye.

The relatively high level of prolactin in intraocular liquid should be considered as a factor that selectively activates the synthesis of pro-inflammatory cytokines, which possess not the least role in a process of abolition of immune deviation in extra-barrier membranes of an eye.

On the basis of performed experimental and clinical studies we propose the hypothesis, according to which in pathogenesis of induction and abolition of anterior chamber associated immune deviation (ACAID) there are engaged hormonal-immune loops conditioned by modulating action of cortisol and prolactin towards the immunocompetent cells localized in extra-barrier membranes of eyes.

Intraocular liquid obtained from the anterior chamber of an eye during surgical intervention should be considered as an informative biological object for diagnosis, course duration, and prognosis of cataract and glaucoma due to determination of a number of indices, which characterize specific stages of ACAID formation and deviation.

Keywords: cataract, anterior chamber associated immune deviation (ACAID), immune-endocrine disorders.

Introduction

The term "immune privilege of an eye" implies the entire complex of regional immune cell-mediated and humoral reactions aimed at prevention of inflammatory and dystrophic processes development in membranes and liquid sections (slices) of an eye under conditions of a wide range of ophthalmologic maladies.

At the same time, this term first of all reflects the state of "local immune homeostasis" under conditions of normal functioning of an eye. The complete cascade of local protective/adaptive mechanisms is aimed to form immunological processes, which in total are defined as anterior chamber associated immune deviation (ACAID).

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To our mind, based on available scientific publications, the general scheme of immunopathological process can be presented as the following chronologically occurring stages:

1. As a result of interaction of different pathogenetic factors there occurs "baring" (uncovering) of antigenic determinants [*Orge Y., Gungor S., 1984*; *D'Orazio T., Niederkorn J., 1998*; *Sonoda A. et al. 2000*; *Camelo S. et al., 2005*].

2. As a response to acquiring the antigenic properties by tissues of an eye in the region of damage (injury) there occurs no activation of the antibody formation process, as reactions of active immunological tolerance prevail to dominate [*Murray P. et al., 1990*; *Lightman S., Towler H., 1992; Fu T. et al., 2004; Kitaichi N. et al., 2005*].

3. No formation of immune complexes occurs, as under conditions of pathology there is engaged the regional mechanism preventing activation of the compliment [*Streilein J., Stein-Streilein J., 2000*].

4. Mechanisms of immune suppression (inhibition of antibody formation) are conditioned by directed activation of T-suppressor and killer subpopulations [*Wilbanks C., Streilein J., 1990; Muhaya M. et al., 1999]*.

5. Directed activation of T-killer lymphocytes occurs due to production of TGF-β [*Abrahamyan A. et al., 1995; Streilein J. et al, 1992; Fleenor D. et al., 2006*].

6. The high level of CD_8 is mainly conditioned by the fact that in the region of eye tissues damage there occurs activation of the main histocompatibility class I complex, which functions as the initial factor ensuring triggering of receptor mechanisms underlying activation and proliferation of T-killer lymphocyte populations [*Nishi O. et al., 1992; Martin W. et al., 1995; Bakunowicz L. et al., 1997; Muhaya M. et al., 1999*].

It should be emphasized that certain pathogenetic mechanisms/links underlying induction and course of ACAID in case of non-complicated and complicated cataracts are currently the subject of a wide discussion [*Orge Y., Gungor S., 1984; Uenoyama K. et al., 1989; Zhou Z. et al., 1996; Cinatl et al., 2000; Robinson M. et al., 2000; Streilein J. et al, 1992; Kawakami M. et al., 2005*].

As a rule, the main reason of ACAID induction is 1- or 2-stage surgical intervention as a result of which there occurs "baring" (uncovering) of antigenic determinants of lens tissues. As a result, in "immunocompetent" membranes of an eye there occurs the synthesis of specific autoantibodies targeted to tissues of lens, by which local procedures of autoimmune-aggression are caused; these latter are conditioned by the damaging action of both autoantibodies and locally formed immune complexes.

The activation of reactions of local humoral immunity is accompanied by a significant increase of IgG levels in intraocular liquid (in anterior and posterior chamber of eyes) due to which the intraocular liquid is a rather informative media for studies on mechanisms of both formation and abolition of ACAID. At the same time all the above-mentioned links underlying abolition of ACAID in case of cataracts are studied rather insufficiently.

According to modern view, in specific eye membranes (sclera, corneal membrane, ciliary body) the cells of epithelial genesis and fibroblastic origin besides their main function are also endowed with the hormone producing function: synthesis and secretion of cortisol.

At present there dominates the point of view, according to which the fundamental function of cortisol in eye membranes consists in maintenance of the optimal level of intraocular pressure [*Jacob E. et al., 1996*].

The role of prolactin appears more disputable, as it is determined in anterior chamber of an eye and retina both in normal state and under cataracts, uveites and retinopathies [*Player U. et al., 1991*; *Duenas Z. et al., 2004*].

To our mind, the role of *in situ* produced hormones such as cortisol and prolactin in tissues of an eye is more versatile and is far beyond the frames of functions ensuring the regulation processes of ion exchange and intra-ocular pressure.

We propose the hypothesis, in accordance with which cortisol and prolactin play an important role in formation of ACAID by modulation of immunological processes either in the aspect

of activation of T- and B-populations or targeted synthesis of cytokines of adaptogenic spectrum of action. This assumption is also sustained by data of scientific publications, according to which in the mammalian organism both cortisol and prolactin are endowed with immunomodulating functions. Thus, it is considered to be established that physiological concentrations of prolactin and cortisol ensure consistency of immune homeostasis. However, at high concentrations cortisol acts as a factor that selectively activates specific subpopulations of T- killer lymphocytes [*Pazirandeh A. et al., 2002; Lindemann D., Racke K., 2003; Visser J., 2003*], while prolactin activates the synthesis of a number of cytokines (interleukins I, II, VI, TNF, as well as γ-IFN) in central and peripheral organs of immunogenesis [*Matera L., 1986*].

Therefore one cannot exclude that under conditions of a number of eye diseases both hormones can actively participate in deviation of reactions ensuring formation of ACAID. No studies of similar aspects were found in available literature.

The aim of the present research was to study the role of cortisol and prolactin in ACAID pathogenesis in case of cataracts.

The following tasks were set forth in concern with the formulated goal:

1. to establish peculiarities of the clinical course and character of complications in patients with senile and complicated cataract;

2. to reveal shifts in content of immunoglobulins of G, M and A class, CD_4, and CD_8, prolactin and cortisol, sodium, potash and calcium in intraocular liquid of patients with senile and complicated cataracts using methods of immune (Manchini reaction), immune-enzyme (ELISA) and ion-selective analyses;

3. based on the performed complex research to propose certain corrections to the known scheme of ACAID induction and deviation in case of complicated and non-complicated cataracts.

Material and Methods

At the University Ophthalmologic Clinics of YSMU we analyzed 100 cases of patients operated for cataract by specialists of the Clinics. All patients exposed to surgery were divided into 3 groups:

Group I: patients with senile cataract (n=53);

Group II: patients with complicated cataract on the background of arterial hypertension (n=31);

Group III: patients with complicated cataract on the background of primary open-angle, closed-angle and mixed-type glaucoma (n=16).

The analysis was performed with the use of main clinical laboratory methods of research, including comprehensive anamnesis and complaints, external inspection of the eye, visometry (with correction for far and near distance), biomicroscopy, tonometry (with individual usage of Maklakov, Goldman tonometers, tonopen, transpalpebral tonometer), ophthalmoscopy (direct and reverse methods), ophthalmometry, ultrasound examination (A- and B-scanning with the function of intraocular level (IOL) force calculation), bacteriological and bacterioscopic analysis of the contents of conjunctival cavity.

With the aim of prophylaxis, instillations of medicinal substances into the conjunctival cavity were performed: antibiotics of wide spectrum of action and non-steroid anti-inflammatory preparations were administered. Instillations were done a few days prior to operation even in those cases when negative results were obtained due to bacteriological analysis of conjunctival cavity.

Additional methods of research were applied in case the clinical analysis was hindered or there were concomitant diseases of eyes. These methods involved gonioscopy, perimetry, topography, and electroretinogram (ERG). General analyses of blood and urine were performed. The obligatory consultations of the therapist and anesthesiologist were taken.

In case of necessity, the consultations of endocrinologist, cardiologist, otorhinolaringologist, neuropathologist and stomatologist were appointed.

In all patients under study, the extracapsular extraction of cataract was done with implantation of posterior chamber polymethylmethacrylate intraocular lens under retrobulbar anesthesia with general premedication 40 *min* prior to surgery intervention.

The procedure of chamber liquid extraction was done intra-operatively under conditions of sterility.

The corneocentis was done by insulin syringe through the upper limb; 0.1-0.2 *ml* of intraocular liquid was taken. The liquid remained in a syringe until laboratory research was performed immediately after delivery of the material to the Laboratory of Morphological Research at the Scientific-Research Center of the Yerevan State Medical University.

All patients operated by us were intently observed, got appropriate treatment indicated according to the individual scheme. We observed the patients in the early postoperative period.

The intraocular liquid of patients from all 3 Groups (by 16 samples in each) were exposed to immunological, immune-enzyme and biochemical analyses.

The content of cortisol, CD_4, and CD_8 in intraocular liquid was determined with the use of the appropriate kits (DRG-International Inc., USA-Germany); prolactin was determined using a special kit (Biotech Research, Czech Republic).

The immune-enzyme analysis was performed on automatic spectrophotometer "Stat-Fax 3200" (USA) in the absorbance wavelength range 420-450 *nm*. The content of cortisol was expressed as *pg/ml*; CD_4 and CD_8 were measured as *unit/ml*, while prolactin was expressed as *ng/ml*.

Determination of immunoglobulins G, M, A class levels was done according to generally accepted procedure proposed by Manchini. The content of immunoglobulines was expressed as *UI/ml*. Measurements of sodium, potash and calcium ions content were done by the method of ion-selective analysis with the use of an analyzer (Kone-microlyte, Finland). The level of ions was expressed as *mmol/l*. The obtained results of immune-enzyme and ion-selective analyses were exposed to statistical analysis using Student's criteria.

Results

As a result of performed clinical studies, it was revealed that the frequency and character of pre-, intra-, and postoperative complications in patients with complicated cataracts significantly exceeded those in patients with senile cataracts.

Thus, in Group I (patents with senile cataracts) in 10 patients during the postoperative period there was observed insignificantly expressed inflammatory process as iridocyclitis (+1 cell in anterior chamber) that was coped by the end of day 2. In 1 patient with senile cataract and expressed pseudo-exfoliative syndrome in intra-operative period there occurred a prolapse of vitreus body, which was associated with the lytic and destructive action of pseudo-exfoliative "material" to the lens zonule of Zinn. Five patients of Group II had difficulties connected with achieving medicamentous mydriasis as a result of expressed atherosclerotic changes of vessels of iris, which caused its rigidity. In 2 patients of this study group in intraoperative period there occurred complications as bleedings (hemorrhages) from vessels of the iris, which were coped by the end of surgery interention. In postoperative period in 5 patients of Group II there was diagnosed iridocyclitis with inflammatory cellular reaction in anterior chamber of an eye (presence of liquid +2 inflammatory cells) with exudate of fibrin, miosis, painful palpation of sclera in projection of ciliary body. We managed to cope the regional inflammatory process after general and local therapy only by the end of the 1st week. Fibrous opacity of posterior capsule originated in 2 of the mentioned 5 patients. The cornea-edema (edema of cornea) was revealed in other 2 patients on the background of moderately expressed inflammatory process in postoperative period; this state was coped by the end of the 1st week due to medicamentous treatment. In pre-operationl period complications were also observed in 2 patients of Group III with closed-angle and mixed-type glaucoma as it was impossible to achieve maximum medicamentous mydriasis.

In 6 cases (3 patients with open–angle glaucoma, 2 patients with mixed-type and 1 patient with angle-closure) glaucoma there were complications in postoperative period: expressed iridocyclitis with the presence of inflammatory cells in the anterior chamber of an eye (+2, + 3), exudate of fibrin, miosis of 1.5 *mm*, painfulness upon palpation of sclera in projection of ciliary body.

Table 1.

The content of cortisol and prolactin in intraocular liquid and blood serum of patients with senile and complicated cataracts

Study Groups	Cortisol content		Prolactin content	
	Intraocular liquid	Blood serum	Intraocular liquid	Blood serum
Group I	12.9 ± 0.64	56.9 ± 4.15	0.34 ± 0.045	7.0 ± 0.36
Group II	14.1 ± 0.61 p> 0.5	115.6 ± 6.88 p< 0.001	0.3 ± 0.046 p > 0.5	7.48 ± 0.57 p> 0.5
Group III	23.38 ± 1.46 p< 0.001	64.84 ± 7.28 p> 0.5	1.1 ± 0.08 p< 0.001	9.5 ± 1.6 p> 0.5

We managed to cope this state by the end of the 1st week due to comprehensive general and topical medicamentous therapy. In later period, in 2 patients of the same study group the fibrous opacity of the posterior capsule of lens occurred on the background of the developed iridocyclitis. In 1 patient with the latent lens subluxation and pseudoexfoliative syndrome in intraoperative period there took place the prolapse of vitreous body. In this patient due to expressed edema of the cornea there was the danger of developing "endothelial-epithelial" dystrophy of cornea in the postoperative period. This threat was averted with the help of helium-neon laser.

The results of clinical studies were compared by us with a number of immunological (levels of immunoglobulines G, M and A class), endocrinological (levels of cortisol and prolactin) and biochemical (ion-selective analysis for determination of potash, sodium and calcium) indices of intraocular liquid of patients of the 3 study groups.

As shown by results of performed immune-enzyme analysis approximately similar indices of cortisol and prolactin were determined in intraocular liquid of Group I and II patients; the levels were similar to those in intraocular liquid of healthy contingent. Upon analysis of intraocular liquid in Group III patients (complicated cataract on the background of glaucoma) we registered relatively high indices of both tested hormones. Thus, the levels of cortisol and prolactin exceeded those in intraocular liquid in Group I patients (senile cataract) 1.8 and 3.2 times, appropriately (Table 1).

As obvious from Table 2, levels of ions of sodium, potassium, and calcium in patients of Groups I and II were similar to those in intraocular liquid of practically healthy contingent that is

Table 2.

The content of ions of sodium, potassium, and calcium in intraocular liquid of patients with senile and complicated cataracts

Study Groups	Ionic content of intraocular liquid		
	Na^+	K^+	Ca^{++}
Group I	133.3 ± 4.4	5.0 ± 0.21	0.99 ± 0.06
Group II	128.4 ± 4.2 p > 0.5	5.35 ± 0.42 p > 0.5	1.15 ± 0.1 p > 0.5
Group III	177.6 ± 7.2 p < 0.001	2.3 ± 0.26 p < 0.001	1.99 ± 0.18 p < 0.001

confirmed by studies of A. Pirie and R. van Heyningen [*Pirie A., van Heyningen R., 1968*].

In persons with the diagnosis of "complicated cataract on the background of glaucoma" relatively high indices of sodium and potassium ions were determined exceeding the levels of mentioned ions in intraocular liquid of Group I patients 1.5- and 2-fold, appropriately. Simultaneously a tendency began to develop towards a decrease of potassium levels in intraocular liquid.

Thus, there was revealed a direct correlation dependance of cortisol high levels, on the one hand, and the content of sodium and potassium ions, on the other hand. Based on obtained findings it is possible to draw a conclusion, according to which the increase of intraocular pressure in individuals suffering complicated cataract on the background of glaucoma is mostly conditioned by disorders of ionic transfusion between the ciliary body and the intraocular liquid and processes of cortisol "hyper production" by hormone producing cells in extra-barrier membranes of an eye.

To our mind, the immune-enzyme studies performed by us in order to determine the levels of prolactin and cortisol in blood serum of the same patients are of a definite interest.

As obvious from Table 1, in blood serum of patients from all study groups almost identical level of prolactin was revealed being similar to that in blood serum of actually healthy subjects.

The levels of cortisol in blood serum of Study Groups I and III were approximately similar and were within the range in which cortisol was determined in blood serum of practically healthy subjects. In patients with the diagnosis of "complicated cataract on the background of arterial hypertension" the level of cortisol compared to Study Groups I and III increased approximately 2-fold. At the same time, as evident from obtained results, the increase of cortisol level in blood serum of patients of Group II was not accompanied by its increase in intraocular liquid. However, in patients of Group III (complicated cataract on the background of glaucoma) the marked increase of cortisol was observed in intraocular liquid at its relatively low indices in blood serum. This circumstance, though indirectly, signifies in favour to local synthesis of cortisol by cells of extra-barrier tissues of an eye, which besides their main functions ensure also the processes of cortisol secretion *in situ*.

Table 3.

CD_4 and CD_8 content in intraocular liquid of patients with senile and complicated cataractss

Study Groups	CD_4	CD_8
Group I	10.7 ± 2.1	52.7 ± 6.5
Group II	13.0 ± 2.4 p >0.5	43.8 ± 9.05 p > 0.5
Group III	26.1 ± 4.3 p < 0.001	21.75 ± 5.6 0.01 > p > 0.002

The following results were obtained due to Manchini reaction for determination of immunoglobulines of G, M, and A class in intraocular liquid in studied contingent.

In patients of Groups I and II the results of immunological analysis of intraocular liquid for G class immunoglobulines were negative. Analyses of biological samples of intraocular liquid in all 16 patients of Study Group III revealed the presence of IgG, the level of which made 39.7 ± 5.9 *UI/ml*.

The next stage of our studies was the immune-enzyme analysis for determination of CD_4 and CD_8 content in intraocular liquid.

As obvious from Table 3, in patients of Groups I and II in intraocular liquid almost similar indices of CD_4 were determined. At the same time in patients of Group III the level of CD_4 markedly increased exceeding 2.4 and 2.0 times the analogous indices in intraocular liquid in patients of Groups I and II, appropriately. In intraocular liquid of patients of Group II a tendency was traced towards the decrease of CD_8 content (compared to Study Group I). In intraocular liquid of Group III patients the low levels of CD_8 were determined being 2.4-fold below the analogous index in Study Group I.

As mentioned above, in intraocular liquid of

operated contingent within Group III patients the relatively high indices of immunoglobulines class G, CD_4, sodium and calcium ions were determined to be exceeding similar indices in Study Groups I and II. As noted earlier, in Study Group III patients' contingent there was registered an expressed inflammatory process with the presence of fibrin threads, inflammatory cells in intraocular liquid. It is precisely in this contingent of patients, irrespectively of glaucoma character (open-angle, angle-closure or mixed-type) that we determined the highest indices of immunoglobulines G (68.3 ± 4.3 *UI/ml*) and (37.7 ± 5.2 *UI/ml*), cortisol (19.5 ±0.8 *pg/ml*), ions of sodium and calcium (169.5 ± 5.1; 1.8 ± 0.2 *mmol/l*, appropriately) and rather low level of CD_8 (18.2 ± 2.5 u*nit/ml*).

Conclusion

The obtained results signify to the fact that in persons with complicated cataract on the background of primary open–angle and angle-closure glaucoma in immune competent membranes of the eye there occurs activation of reactions of humoral immunity on the background of a marked decrease of T-killer lymphocytes activity; to this latter testify relatively high indices of CD_4 and IgG, as well as low level of CD_8 in intraocular liquid.

It was in this contingent of patients that we found highest indices of IgG, CD_4, cortisol and prolactin on the background of decreased "killer-activity", which already in the early postoperative period under disturbance of the integrity of a capsule might be factors of risk for induction of autoimmune aggression in response to "baring" antigenic determinants of lens.

On the base of thus obtained data, the role of *in situ* produced cortisol and prolactin in ACAID induction and abolition in case of cataracts should be considered from qualitatively new standpoint.

Apparently, the entire chronological process of surgical intervention on the background of already existing regional immuno-pathological and endocrine perturbations should be considered a provoking factor as in the course of operation the antigenic determinants of lens tissues are uncovered.

Due to our studies, we also managed to ascertain that the known engaged mechanism of TGF-mediated stimulation of CD_8 in extra-barrier membranes of an eye is not the fundamental one. Thus, surgical interventions in concern of complicated cataracts (in our case: complicated cataracts on the background of glaucoma) are fraught with disorders of local endocrine homeostasis, which negatively affects ACAID induction processes. Our studies allowed also to reveal that in extra-barrier membranes of the eye there are obviously engaged earlier unknown hormonal-immune loops ensuring formation and course of ACAID. One cannot exclude that precisely regional dyshormonal disorders and, in the first place, "hyper-production" of cortisol and prolactin by structural components of extra-barrier membranes of the eyes in case of complicated cataracts on the background of glaucoma are initial in disturbance of immune-endocrine interactions, which condition abolition of reactions responsible for ACAID formation.

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