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Inflammatory glaucoma. Elements of etiology and pathology

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Abstract

Background: Inflammatory glaucoma, also known as uveitic glaucoma is a multifactorial process of inflammation that causes the rising of intraocular pressure (IOP) accompanied by morphological and physiological modifying similar to open angle glaucoma. The mechanisms by which ocular inflammation causes an increase of the IOP are not integrally comprehended, and many of the relevant pathways and features are still covered with a veil of mystery. The eyes of uveitic patients are defined by complex interactions between the angles (open or closed), trabecular outflow, fluctuations in the aqueous production and the response to steroids. Regarding the elevation of IOP in these individuals, it is mostly attributed to the increased outflow resistance, which distorts the equilibrium between aqueous production and outflow.

Conclusions: Inflammatory glaucoma is a multifactorial pathology that needs a careful diagnosis and therapeutical approach in order to obtain a good management of inflammatory process and intraocular pressure. There are a lot of pathological pathways that influence the evolution of inflammatory glaucoma and make treatment more difficult. Last years, glaucoma treatment has significantly improved, but to better understand pathogenesis of uveitic glaucoma more scientific studies are necessary.

Key words: inflammatory glaucoma, uveitic glaucoma, secondary glaucoma.

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Introduction

Inflammatory glaucoma, also known as uveitic glaucoma is a multifactorial process of inflammation that causes the rising of intraocular pressure accompanied by morphological and physiological modifying similar to open angle glaucoma. Glaucoma and uveitis were described together for the first time in 1813, by Joseph Beer. Later, in 1891, Priestley Smith proposed first modern classification of uveitic glaucoma [1].

The overall prevalence of glaucoma in eyes with uveitis varies from 10 to 20%, but it is much more common in chronic uveitis and can be as high as 46% [2]. , the prevalence of uveitis has been estimated at approximately 115 people per 100000 population. Approximately 20% of uveitis patients develop glaucoma. At internation scale, prevalence of uveitis has been estimated at 38-730 people per 100000 worldwide. Approximately 20% of uveitis patients develop glaucoma [3].

The mechanisms by which ocular inflammation causes an increase of the intraocular presure (IOP) are not integrally comprehended, and many of the relevant pathways and features are still covered with a veil of mystery. In contrast with primary glaucoma, where pressure-independent mechanisms may be related, uveitic glaucoma is usually correlated with increased IOP, although the elevation of IOP may happen intermittently. The eyes of uveitic patients are defined by complex interactions between the angles (open or closed), trabecular outflow, fluctuations in the aqueous production and the response to steroids. Regarding the elevation of IOP in these individuals, it is mostly attributed to the increased outflow resistance, which distorts the equilibrium between aqueous production and outflow [4].

The wide spectrum of variations in the underlying trabecular function in different individuals also adds to the perplexity of the uveitis. It is expected that the trabecular meshwork function may be affected while aging and therefore older patients are more susceptible to intraocular inflammation in comparison with younger individuals. Probably, the accumulation of pathological alterations secondary to the chronic inflammatory activity may also be relevant to the IOP rise in older uveitic patients. Interestingly, the management of uveitic glaucoma in our patients appears to be more difficult and challenging in the younger age group. Whereas, younger individuals may have a stronger optic nerve that can withstand high pressure for a more extended period of time, it appears that older patients develop severe optic nerve damage even during shorter intervals of raised IOP and consequently more visual disabilities [5, 6].

Factors increasing intraocular pressure:

1. Concentration of aqueous proteins, inflammatory cells, and debris
2. Trabeculitis
3. T-cells, IL, cytokines and other immune factors
4. Hypersecretion of prostaglandin
5. Genetic background
6. Corticosteroid-induced elevation of IOP
7. Vascula endothelian grown factor (VEGF) and iris neovascularization etc.

The levels of aqueous proteins have been found to be elevated in uveitic patients, indicating that they may be associated with the trabecular outflow. Previous studies have investigated the role of aqueous proteins during acute intraocular inflammation [7, 27–31]. However, due to the fact that these studies have explored acute uveitis, it was not feasible to define the long-term effect of elevated aqueous proteins in uveitic eyes. It is a well-established knowledge that the protein concentration in the anterior chamber is increased in acute uveitis, causing a drop of trabecular outflow. This could probably happen more extensively in individuals with clinical entities that present with the acute rise of IOP [4]. Though it must be underlined that in Posner-Schlossman syndrome, which presents with acutely raised IOP, the levels activity in the anterior chamber remain normally low, implying that other mechanisms (e.g., trabeculitis) contribute in the increased IOP. The increased number of trabecular precipitates that include proteins, inflammatory cells, and debris in the anterior chamber of uveitic eyes may decrease trabecular outflow by clogging of the trabecular meshwork. Evidence that inflammatory cells lead to clogging of the trabecular meshwork derive from studies that recorded acute rises in IOP after Nd: YAG laser capsulotomy. Moreover, there is evidence that the acute inflammatory processes that follow Nd: YAG laser can also lead to chronic ocular hypertension (OHT), underlining that the clogging of trabecular meshwork that occurs during an episode of intraocular inflammation may have long-term effects on trabecular outflow and subsequently on IOP. Gonioscopy of the trabecular meshwork can reveal its obstruction by inflammatory precipitates in several pathological entities, such as in Grant's syndrome, pseudoexfoliations, and pigmentary glaucoma. The inflammation of the trabecular meshwork, which is known as trabeculitis, may also cause a rise in IOP. Herpetic uveitis consists one of the most characteristic examples. Two older studies by Hogan et al. and Townsend et al. have described the histological alterations caused in enucleated human eyes and rabbits with herpetic inflammation, respectively [4, 7, 8].

Both studies highlighted that trabeculitis could play a critical role in the elevation of IOP in uveitis, especially when caused by *herpes simplex* virus (HSV). However, it is yet to be defined whether trabeculitis interferes in types of uveitic glaucoma with a more chronic course, such as those related to Fuch's heterochromic cyclitis or juvenile idiopathic arthritis (JIA) [4].

Interestingly, T-cells consist the largest cell population in the aqueous, vitreous, retina and the uveal tract of uveitic patients. More specifically, Th-1 cells might have a substantial contribution in the pathophysiology of uveitis, but their role in uveitic glaucoma remains uncertain [9]. A study by Murray et al. investigated the aqueous humor obtained from patients with and without uveitis during a cataract extraction surgery. Individuals with uveitis demonstrated an inflammatory response mediated by T-cells. There was a prevailing expression of IL-2 and IFN-γ, which are Th-1 related cytokines and their levels were significantly lower in non-uveitic individuals [10]. Nonetheless, the levels of proinflammatory cytokines have been associated with the activity of inflammatory activity in various types of uveitis. Ohira et al. analyzed the effects of factors on the levels of aqueous humor proinflammatory cytokines and growth factors in uveitic eyes. According to the results mean interleukin (IL)-6, IL-8, monocyte chemotactic protein (MCP)-1, tumor necrosis factor (TNF)-α and VEGF were found to be higher in cases with uveitic glaucoma than those in cataract (non-glaucomatous) cases. Additionally, IL-6, MCP-1, and VEGF were all higher in uveitic glaucoma than in patients with primary open angle glaucoma (POAG). The uveitic cases with a history of phacoemulsification indicated higher levels of IL-6, IL-8, MCP-1 and PDGF-AB/BB in comparison with the phakic eyes. Finally, the presence of cells in the anterior chamber was associated with higher levels of TNF-α, IL-8 and PDGF-AB/BB. As for PDGF-AB/BB level, it was found to be higher in infectious rather than in non-infectious uveitis [4, 11, 12].

Mechanisms of intraocular pressure elevation in secondary open angle glaucoma:

1. Trabecular meshwork obstruction is the most common mechanism and can be caused by: Disruption of the blood aqueous barrier, which allows entry of inflammatory cells into the aqueous humor and entrapment of normal serum components in the aqueous outflow system. Swelling of trabecular lamellae and endothelial cells with both a physical narrowing of trabecular pores and dysfunction also leads to aqueous outflow obstruction, ultimately leading to permanent damage and scarring of the trabecular meshwork [13-15].

2. Hypersecretion caused by PGE_1- and PGE_2-mediated increase in the rate of aqueous secretion or by a breakdown in blood-aqueous barrier (BAB), with an associated increase in aqueous protein concentration and thus aqueous viscosity [16].

3. Corticosteroid-induced elevation of IOP.

Steroid-induced glaucoma is a form of secondary open angle glaucoma that results from the use of steroids. Corticosteroids are believed to decrease outflow by inhibiting degradation of extracellular matrix material in the trabecular meshwork (TM), leading to aggregation of an excessive amount of the material within the outflow channels and a subsequent increase in outflow resistance. The amounts of glycosaminoglycans, elastin, and fibronectin have been shown to increase in tissue culture preparations in response to dexamethasone treatment while the levels of tissue plas-

minogen activator, stromelysin, and the activity of several TM metalloproteases have been shown to fall. Furthermore, excessive accumulation of glycosaminoglycans has been identified in human trabecular meshwork specimens obtained from steroid-responders, confirming similar findings in a rabbit model [17, 18]. In support of the evidence for extracellular matrix deposition, dexamethasone treatment has also been shown to inhibit TM cell arachadonic acid metabolism and reduce phagocytic activity. It is hoped that recent advances in novel molecular genetic methods will allow a better understanding of the mechanisms causing the steroid-induced glaucoma. By gene deletion or overexpression studies, the exact role of individual genes responsible for the modulation of meshwork extracellular material may be identified in the near future [19]. An increase in the IOP related to the corticosteroids that are used for the control of inflammatory reactions in uveitis has been recorded in 18–36% of patients; these individuals are described as steroid responders. Clinically, a response to steroids is expected to develop within 2 to 6 weeks after starting therapy, but can potentially happen at any time.

Shrestha et al. monitored and studied 116 consecutive new uveitic patients, recording the IOP at presentation, at 1 week, 3 and 6 weeks. They recorded that 20% of these eyes developed ocular hypertension, which was at a percentage of 64.5% attributed to corticosteroids (37.03% of the oral group, 14.28% of the posterior sub-tenon group and 8.57% of the topical group). The same study indicated that timely medical treatment might avert the necessity of early surgical intervention for the control of eye pressure [4].

Interestingly, as a response to decreased pressure gonocytes, which consist of fibro-elastic cells in the anterior chamber of the normal human eye secrete polymerized mucopolysaccharides. This results in swelling of the cells of the trabecular meshwork and a subsequent decrease in the trabecular outflow. To curtail these effects and reduce IOP hyaluronidase breaks down the polymerized mucopolysaccharides. However, the release of hyaluronidase may be restricted due to the use of steroids, causing inhibition of mucopolysaccharides depolymerization. Some studies have investigated the genetic background of steroid responders, showing that a gene that may play some role is responsible for a protein named Myocilin, which is produced by the cells of the human trabecular meshwork [20]. Despite the fact that there are not any known Myocilin mutations associated with steroid responders, it appears that the cells of human trabeculum increase the production of Myocilin in response to the administration of dexamethasone. Consequently, although genes might contribute in defining steroid responders more studies are required to confirm this hypothesis [4].

Pathogenesis of Neovascular Inflammatory Glaucoma (NVG) is unclear too. Extremely high levels of VEGF are present in patients with NVG [21]. In addition to VEGF, several other molecules have been associated with the development of NVG, including basic fibroblast growth factor, platelet-derived growth factor, insulin-like growth factor-1 and interferon-α [22]. Vascular proliferation first occurs with endothelial budding at the capillary level not only of the vasculature of the minor arterial circle of the iris but also the major arterial circle at the iris base. These endothelial buds progress to glomerulus-like vascular tufts, resembling renal micro-vasculature. The new vascular tissue is composed of endothelial cells without a muscular layer and with little adventitial or supportive tissue. The vessels are thin walled and tend to be located near or on the iris surface but can be seen histologically at any level within the iris. The fibrovascular membrane in neovasularization of the iris (NVI) also contains proliferating myofibroblasts with smooth muscle differentiation. This clinically transparent and contractile membrane causes a flattening and effacement of iris surface architecture, ectropion uveae, development of peripheral anterior synechiae (PAS) and subsequent secondary angle closure [23].

Most common causes of uveitic glaucoma:

1. Juvenile rheumatoid arthritis is an autoimmune disease typically affecting children under the age of 16 years and lasts more than six months. The uveitis is typically bilateral, nongranulomatous, asymptomatic anterior uveitis, usually preceded by arthritis [24]. It has been shown that individuals with persistent low-grade uveitis are at a higher risk of developing glaucoma. JIA-related glaucoma often occurs with open angles, but secondary angle-closure caused by pupillary block as a result of the formation of posterior synechiae is relatively common. Apart from glaucoma, the main complications that can lead to loss of vision are a cataract, band keratopathy, and cystoid macular edema [25]. Regarding medication, the therapeutic scheme includes a topical steroid, cycloplegics that may be followed by systemic steroid therapy and possibly regional injection of steroids. In persistent and more severe cases immunomodulation (e.g., methotrexate) can be incorporated in the management of the disease, resulting in low toxicity and high efficacy. According to recent studies adalimumab, which is an anti-TNF-α agent, has shown efficacy in treating refractory uveitis in multiple settings, including juvenile idiopathic arthritis [26-28]. With regard to the treatment of glaucoma patients are initiated on antiglaucoma medications, but in complicated and severe cases surgical treatment (e.g., trabeculectomy or tube shunt surgeries) may be unavoidable. Unfortunately, many of them might require medication even after surgery.

2. Fuch's heterochromic iridocyclitis was first described by Fuch in 1906, FHIC is an idiopathic, painless, chronic, low-grade iridocyclitis with heterochromia, due to iris stromal atrophy. The typical age of onset is 20 - 40 years of age, with men and women affected equally.

It is typically unilateral, but in 13% of the cases it has presented bilaterally [29, 30]. Infiltration of TM by mononuclear inflammatory cells, typically lymphocytes and plasma cells, causes rubeosis, trabeculitis, and collapse of the Schelmm's canal, leading to TM obstruction and rise in IOP. Interestingly, iris angiography can detect leakage of the iris vessels and ischemic alterations of the iris. Reported incidence of glaucoma varies from 13-59%, with higher fig-

ures seen on long-term follow-up. The glaucoma typically persists after uveitis has subsided and does not respond to steroids. Fuch's cyclitis rarely causes synechiae formation. Unless glaucoma develops, Fuch's cyclitis is a benign disorder and does not require therapy. Use of steroids may only accelerate PSC formation and increase IOP [31].

The glaucoma associated with FHI resembles primary open-angle glaucoma. Gonioscopic evaluation may reveal multiple fine blood vessels, arranged either radially or concentrically in the trabecular meshwork. Cataract is a constant feature of FHI, whereas glaucoma has been reported to occur in 6-47% of cases. Low-grade inflammation does not need treatment with anti-inflammatory or immunosuppressive agents [2].

3. Posner-Schlossman syndrome is characterized by a number of unusual features, including unilateral involvement, recurrent attacks of often very mild cyclitis, marked elevation of IOP, open angle, and occasional heterochromia. IOP may elevate up to 40 to 70 mm Hg during an acute episode. The condition typically affects individuals aged 20-50 years and resolves spontaneously regardless of treatment [2].

This rise in the eye pressure has been correlated with the aqueous levels of prostaglandins and usually resolves spontaneously. The pathogenetic mechanisms have not been clarified yet. Some of the possible etiologic factors include HSV and cytomegalo virus (CMV) infections, an immunogenetic factor that involves HLA-Bw gastrointestinal disease and several allergic factors (i.e., eczema, urticaria, asthma, rhinitis, contact dermatitis, angioneurotic edema, intolerance to aspirin and food allergies). The prognosis is benign, with only exception for the patients that develop glaucomatous alterations, which is recorded in about 25% of cases. Clinical findings include small, flat, fine, non-pigmented KP detected in the inferior corneal endothelium. In gonioscopy, the angle appears to be open with some occasional trabecular precipitates. The therapeutic approach includes steroids and antiglaucoma medication (beta-blockers and carbonic anhydrase inhibitors). It has been shown that oral indomethacin, prostaglandin inhibitors and subconjunctival polyphloretin (prostaglandin antagonist) are effective in lowering the IOP during acute attacks. Surgical treatment is indicated in patients that glaucoma persists after maximal medical treatment [4].

4. The development of secondary glaucoma consists the most common complication of herpetic uveitis. It has been reported that 28–45% of patients with HSV keratouveitis demonstrate transient increased IOP and 10–54% may present with uveitic glaucoma. Disciform keratouveitis and necrotic stromal keratitis are associated more commonly with elevated IOP than epithelial keratitis [32]. Active iridocyclitis accompanied by an acute increase in eye pressure are the main features of herpetic infection and in most cases, HSVs or VZVs are the etiologic factors. These spikes in the IOP occur as a result of the trabecular meshwork inflammation, similarly to hypertensive episodes of Posner-Schlossman syndrome that has been described above.

This explains why the IOP returns to normal levels while responding to topical corticosteroids. It must be underlined though, that the elevated IOP can occur secondarily to the obstruction and swelling of the trabecular meshwork. Episodes of herpetic uveitis are typically unilateral, acute and in severe cases may present with hyphema, hypopyon, fibrin deposition and formation of anterior synechiae [4].

Conclusions

1. Inflammatory glaucoma is a multifactorial pathology that needs a careful diagnosis and therapeutical approach in order to obtain a good management of inflammatory process and intraocular pressure.

2. There are a lot of pathological pathways that influence the evolution of inflammatory glaucoma and make treatment more difficult.

3. Previous years, glaucoma treatment has significantly improved, but to better understand pathogenesis of uveitic glaucoma more scientific studies are necessary.

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VC, NB and VC designed the study and drafted the first manuscript. VC, LD and LG revised the manuscript and completed the final design. All the authors approved the final version of the manuscript.

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