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Hyperemia in Glaucoma Patients

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Introduction

Although the evaluation of a glaucoma patient on medical therapy complaining of red eyes may not have the cachet of performing nonpenetrating surgery or laser angle therapy, it is nevertheless an essential component of the successful care and management of patients with this disease. Indeed, red eyes can prove particularly troublesome if they become persistent and therefore affect the tolerability of the agent -- which in turn affects compliance. Poor compliance can result in treatment failure due to a decrease in overall intraocular pressure (IOP) control. Because glaucoma is the second leading cause of blindness worldwide[1] and currently pharmacologic IOP lowering is the first-line therapeutic option for glaucoma, the advent of red eyes in a patient is not uncommon. It is therefore of the utmost importance to be able to identify red eyes, to distinguish the cause of the red eyes -- whether from a true allergic reaction, ocular surface disease, or irritation from the medication itself -- and to act to alleviate the problem so that adherence and treatment efficacy are not compromised.

Distinguishing Hyperemia From Underlying Disorders

Hyperemia, or redness alone in clinical terms, is only a sign of a problem, and may be associated with a broad group of ocular diseases or, possibly, be part of a response to allergic inflammation or irritation. Within the eyes, the redness that we see is caused by the vasodilatation of the conjunctival blood vessels against the white background of the sclera.[2] The presentation of red eyes, however, is only a starting point in the diagnostic sleuthing necessary to find and treat its underlying cause. Allergists will generally treat obvious atopic conjunctivitis, but they refer to ophthalmologists for more extensive differential diagnosis.

To make the diagnosis, there are various grading systems available, including standard photographic charts[3] and the Corneal and Contact Lens Research Unit (CCLRU) grading scale.[2] They include verbal descriptions and photographs that illustrate increasing levels of conjunctival hyperemia. Although conjunctival hyperemia is an important clinical sign of ocular disease or inflammation, it is important to note that even a normal eye has a degree of hyperemia; it is more common in males than females; and the area of the nasal bulbar has the highest grading. It is thus the degree of hyperemia, not its presence alone, which separates normal from abnormal.

Hyperemia is a symptom; allergy, on the other hand, refers to a specific process that stimulates inflammation. True allergic (atopic, type I) reactions stem from hypersensitivity to a substance (allergen). There is an antibody-antigen interaction, and a cascade of events follow associated with the release of inflammatory mediators from cells;

hyperemia is commonly an outcome of the event. There is some difficulty in distinguishing a true ocular allergy. Grading systems of ocular allergies are not consistent because the presentation and location can be quite variable. The other difficulty is the issue of defining what a true allergy is. Hyperemia, pruritus, folliculosis, and conjunctival allergy have been all or partially included under the umbrella of ocular allergy, and the presence or absence of some of those will influence the measured incidence of allergy in a particular study. For the conjunctival reaction, it may be proper to include all 3 -- hyperemia, pruritus, and conjunctival follicles -- to fully describe the allergic reaction. Periocular dermatitis, a type IV delayed cell-mediated hypersensitivity associated with scaling, crusting, and erythema around the area of involvement, is a clinical diagnosis not requiring a grading system.

The importance of tolerability as it affects adherence to medication usage cannot be underestimated. Therefore, patients with red eyes require a systematic evaluation of symptoms and signs to be successfully diagnosed and treated. A comprehensive ocular-visual assessment should begin with first principles to determine the source of the problem.

Initially, it is essential that problems such as marginal blepharitis, meibomian gland dysfunction, and underlying dry eyes be identified and managed. A significant percentage of glaucoma patients are women older than the age of 50, and this group of patients tends to be much more predisposed to dry eyes.[4] It has also become clear that the use of multiple medications, either because of the medications themselves or the associated preservatives, will aggravate this dry eye condition.[5,6] The use of Schirmer's evaluation, fluorescein, and rose Bengal staining to evaluate the tear film can confirm an underlying dry eye problem. The dry eye can then be managed with the use of nonpreservative tears and gel, and ideal lid hygiene.

Contact type allergies (type IV) have extension of erythema well beyond the lid margin, and can occur with many medications, but tend to be more common with sulfa-based preparations. An underlying problem, blepharitis, is commonly associated with the elderly population, and the earlier the identification and intervention -- with improvement of lid hygiene -- the more rapidly symptoms can be controlled.

A final point of confusion is seasonal allergies. Airborne allergens, including pollen, dust, and molds, cause inflammation on the ocular surface, especially for patients who already have dry eyes. It is imperative that this problem be differentiated from responses to glaucoma medications. This is usually accomplished by attention to the patient's history and transient nature of the symptoms. It then can be treated with appropriate anti-allergic medications not requiring the discontinuation of the patient's ocular medications.

Medication and Red Eyes

More difficult problems in effective treatment arise when the red eyes prove to be a response to the medications themselves. Various sources have noted the association of conjunctival hyperemia with virtually all topical IOP-lowering medications -- alpha-adrenergic agonists, beta-adrenergic antagonists, carbonic anhydrase inhibitors, prostaglandin analogs, and prostamide analogs.[7,8] The class that is associated with the highest incidence of hyperemia is the prostaglandin analogs. Although the incidence of initial hyperemia when starting the 3 medications is different -- latanaprost is noted at 5%-15%,[9] bimatoprost at 15%-45%,[10] and travoprost at 35%-50%[11] -- incidence rates have been shown to change over time. For example, hyperemia peaks with bimatoprost at day 1 while the vast majority of cases return to near baseline levels by day 28.[12] It is theorized that the aqueous may need sudden access to the ocular circulation on initiation of treatment, thereby resulting in an autoregulatory vasodilatation. After a new homeostasis becomes established, the vessels gradually adapt and the vasodilatation decreases. Several cross-over studies[13,14] have also noted that patients who have had previous exposure to prostaglandins display less hyperemia when switched to another drug in the class, a phenomenon that may be explained by this chain of events.

Based on these findings, it should be emphasized how important it is to educate patients starting on this class of glaucoma medications that the hyperemia, if it occurs, is usually mild and of short duration. Given the effective IOP

reduction associated with this class, patient management of the early symptoms while maintaining the same medication may be the best approach.[15] Also of note is the presence of preservatives in glaucoma medications. They can be a potential agent for erythema and may be considered in the event of red eye.[16,17]

The alpha-adrenergic agents have been shown to have the highest incidence of true allergic reactions, although that rate varies widely depending on study. The drug apraclonidine has a reported rate of 14%-48% depending on the concentration from 0.5 to 1%.[3,18] Brimonidine 0.2% has a reported rate between 4.2-25.7% if both allergic conjunctivitis and contact dermatitis are included. As with defining ocular allergy, the problem lies with the various interpretations of what comprises an allergic reaction. For example, a study[19] looking at allergic reactions to brimonidine required only hyperemia and follicular conjunctivitis for a diagnosis; pruritus, weeping, discharge, or discomfort were not necessary for the diagnosis of allergic conjunctivitis. The use of such a broad definition may help explain why there was such a high reported rate of allergic reactions at 25.7%.

In a pivotal study comparing the fixed combination 0.2% brimonidine/0.5% timolol given twice a day with monotherapy with either timolol or brimonidine given 3 times a day, there was a noted significant difference in treatment-related adverse events.[20] It was shown that there was a significantly lower rate of hyperemia (22.8% to 14.5%) and allergic conjunctivitis (9.4% to 5.2%) in the fixed combination group compared with the brimonidine one. This low rate of treatment-related adverse events in the brimonidine/timolol group has been seen in Canada where the drug has been in use for over 3 years.[21,22] The lower level also appears to be sustained over time.[23] There have been several theories put forward to try to explain this difference; the most persuasive is by Alvarado based on previous research.[24,25] He has shown in a cell culture model that alpha-adrenergic agonists cause cells to shrink, thereby opening intercellular spaces within the conjunctiva that would allow a path for pro-inflammatory mediators, such as drugs, preservatives, airborne allergens, lipid secretion, and other potential toxic agents, to reach the subconjunctival space. The addition of a beta-blocker has been shown to prevent this cell shrinkage, thereby stabilizing the conjunctival epithelium as a barrier to the subconjunctival space. Because it is in the subconjunctival space where the cellular and vascular response to inflammation is developed, the maintenance of the natural barrier effect of the conjunctiva may explain the statistically significant reduction in all components of allergy and inflammation comparing the fixed combination of brimonidine/timolol vs brimonidine alone in the 1-year pivotal study by Sherwood.[20] Indeed, there is speculation about the role that beta-blockers may play regarding the local allergic effects of the other glaucoma drug classes. Interesting results have been seen in combining beta-blockers with prostaglandins as fixed combination in Canada and Europe, where it has been suggested that the beta-blocker effect may extend to minimizing the hyperemia effect of second-generation prostaglandins such as travoprost and bimatoprost.[3,7,8,26-28]

Conclusion

Hyperemia in glaucoma patients is not uncommon, particularly among patients taking 2 or more medications. What is important, however, is that physicians be able to adequately diagnose and manage the hyperemia. Is it the result of a seasonal allergy or some other underlying disorder? Or does it stem directly from the medication itself? Distinguishing between different causes will direct treatment. If the hyperemia is found to result from a seasonal allergy or underlying ocular disorder, that condition can be directly treated and the patient should be able to remain on the existing medication. On the other hand, if the hyperemia results directly from the medication, steps can be taken to ease the hyperemia and improve tolerability. If the hyperemia is seen early, especially with the use of a prostaglandin, its severity should decrease after 6-12 weeks. In such cases, patients may be fine remaining on the same drug. However, if the hyperemia persists, then switching drugs is an option. The first step is usually to switch within the class, while another alternative is to change to another class of medications. The patient also may be switched to a fixed combination, where research suggests the addition of a beta-blocker may help minimize allergic reactions. Once such a successful determination is made, medication tolerability should be improved, along with patient adherence -- resulting in the maintenance of long-term stability of IOP control.

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