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Epidemiology, pathophysiology and diagnosis of uveitic glaucoma and ocular hypertension secondary to uveitis

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ABSTRACT

Uveitic glaucoma (UG) encompasses a broad spectrum of disorders leading to an increase in intraocular pressure (IOP) and glaucomatous damage to the optic nerve in patients with concomitant uveitis. The treatment of glaucoma in patients with uveitis requires a meticulous diagnostic and therapeutic approach, often involving a multidisciplinary team, to achieve adequate control of the inflammatory response and IOP. As researchers have been able to pinpoint the risk factors for elevated IOP in patients with uveitis, it has become possible to identify groups of patients who require special attention in clinical practice. The variety of mechanisms underlying the development of UG is associated primarily with the type of uveitis. Most patients with active inflammation experience a decrease in IOP due to reduced production of the aqueous humor and increased uveoscleral outflow. In some cases, however, IOP is elevated, for example during active trabeculitis, chiefly in patients with uveitis of herpetic origin. Chronic inflammation may cause scarring and remodeling within the Schlemm's canal, collecting channels, and trabecular meshwork, leading to an increased resistance to the outflow of the aqueous humor. IOP elevation due to the filtration angle closure mechanism in patients with active uveitis occurs most commonly through the formation of posterior synechiae, anterior synechiae or neovascular membranes in the filtration angle itself. In addition, the possibility of iatrogenic IOP elevation in patients with uveitis during treatment with glucocorticoids (mainly topical, but also systemic) must be considered. Making a correct diagnosis of uveitis and regular patient follow-up for glaucomatous damage are of crucial importance. Accurate diagnosis allows for prompt implementation of appropriate anti-inflammatory treatment, helping to avoid long-term effects of smoldering inflammation.

KEY WORDS: glaucoma, uveitic glaucoma, intraocular pressure, ocular hypertension, uveitis, secondary glaucoma.

INTRODUCTION

Uveitis is a heterogeneous group of conditions in which the pathological process affects primarily the uveal layer of the eye, i.e. the iris, the ciliary body and/or the choroid. Secondary manifestations of the disease may include the involvement of the cornea, sclera, vitreous body, retina, and optic nerve. The uveal inflammatory process may be due to either autoimmune or infectious factors. Because of diagnostic and therapeutic difficulties, despite its relatively rare occurrence, uveitis accounts for approximately 10% of cases of legal blindness in developed countries [1]. The most common causes of vision loss in patients with uveitis include cystoid macular edema, cataract, and glaucoma. Uveitic glaucoma (UG) is defined as damage to the optic nerve occurring in patients diagnosed with uveitis, presenting with characteristic glaucomatous visual field defects corresponding to the areas of damage, caused by elevated intraocular pressure (IOP) [2]. The very definition of the disease reveals the first fundamental difference between UG and primary open-angle glaucoma (POAG). Uveitic glaucoma is always associated with high IOP. Other features distinguishing UG from POAG include lower patient age, greater IOP fluctuations, more difficult diagnostic process (poor view, problems with obtaining good quality test results), possibility of disease course alternating with periods of hypotony, poorer response to IOP-lowering drugs, worse prognosis after anti-glaucoma surgical interventions, and faster progression rate that quickly leads to severe damage to the optic nerve [3]. In addition to UG, patients with uveitis may experience transient increases in IOP > 21 mmHg. The condition, if not accompanied by changes in the optic

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nerve, is referred to as ocular hypertension [4]. Naturally, repeated episodes of elevated IOP in patients with recurrent or chronic inflammation may over time lead to glaucomatous neuropathy. Therefore, patients with uveitis and ocular hypertension require a close follow-up [5].

EPIDEMIOLOGY OF UVEITIC GLAUCOMA

According to population-based studies, the prevalence of UG in patients with uveitis varies widely, ranging from 5 to 41% [3, 6-8]. Such a large discrepancy results from the application of different research methodologies. In the studies reporting a higher prevalence of UG, the group of patients with glaucoma also included transient increases in IOP, where the development of glaucoma was observed in 22.7% of patients with chronic uveitis during a 10-year follow-up [6]. Thus, ocular hypertension appears to be a very common condition in patients with uveitis, whereas glaucomatous damage affects only about 20% of uveitis-affected patients [5]. UG is more common in patients with chronic and recurrent (16.6%) than acute (7.4%) uveitis. Depending on the affected part of the uvea, UG is most frequently found in patients with anterior uveitis: chronic (26.4%) and acute (48.1%) variants [6]. The lowest risk of UG is noted in patients with intermediate uveitis: 15.4% for the chronic and 9.3% for the acute forms of the disease [6]. The etiology of uveitis has an effect on the incidence of IOP spikes. The infectious causes of uveitis that predispose patients to elevated IOP include herpes simplex virus, toxoplasmosis, syphilis, and Lyme disease. Among non-infectious causes, IOP elevation is most commonly seen in patients with Fuchs uveitis syndrome, Posner-Schlossman syndrome, sarcoid uveitis as well as uveitis associated with juvenile idiopathic arthritis, Behçet's disease, Vogt-Koyanagi-Harada (VKH) syndrome, and sympathetic ophthalmia [7, 9]. The largest available source of information for evaluating the risk of ocular hypertension and glaucoma in adult patients with uveitis is the study conducted by The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Research Group [10]. The researchers reviewed medical data for a total of 11,452 eyes in 7,062 patients diagnosed with uveitis, receiving therapy at five centers specializing in the treatment of the condition between 1978 and 2007. Based on accumulated data, a number of risk factors predisposing to the development of elevated IOP (> 30 mmHg) in patients with uveitis were identified including:

- concomitant hypertension;
- visual acuity < 0.5 in the uveitic eye (likely due to more severe inflammation);
- history of vitrectomy;
- presence of peripheral anterior synechiae (PAS), with no such correlation found for posterior synechiae;
- history of elevated IOP in the fellow eye (if the IOP rise in the fellow eye was within the range of 21–29 mmHg, the risk increased twofold; if the IOP elevation in the fellow eye exceeded 30 mmHg, the risk of IOP spike in the affected eye rose fivefold);
- need for glucocorticosteroid therapy (a higher risk was seen in patients receiving topical compared to systemic treatment). The highest (tenfold) increase in the risk of IOP elevation was associated with fluocinolone acetonide intravitreal implants (Retisert, Iluvien). Periocular depot injection of GCs in the previous 3 months was associated with a 2.3-fold increase in the risk of IOP spike. The elevated risk of ocular hypertension in patients using GC-containing eye drops was found to be linked to the frequency of administration. It was already evident with once-daily dosing, and it reached a peak (2.5 times greater risk) when the dosage exceeded 8 drops per day. Chronic treatment with systemic GCs (at doses > 7.5 mg prednisone equivalent/day) was associated with a 1.8-fold higher incidence of IOP > 30 mmHg. Interestingly, the use of GCs at doses lower than 7.5 mg of prednisone per day (or another GC at an equivalent dose) was not found to increase the risk of ocular hypertension.

The study mentioned above also provided evidence that the duration of the inflammatory process influenced the incidence of elevated IOP. Two years after diagnosis, an increase in IOP > 21 mmHg was found in one-third of patients and an elevation in IOP > 30 mmHg in 14% of patients. After 10 years of disease duration, the patient proportions rose to over 50% for IOP > 21 mmHg and to more than 30% for IOP > 30 mmHg. After 10 years of disease, IOP > 21 mmHg was seen in more than half of patients, and IOP > 30 mmHg in more than one-third of patients.

PATHOMECHANISM OF UVEITIC GLAUCOMA

Just as the etiology of uveitis is heterogeneous, so are the mechanisms underlying the development of UG and ocular hypertension secondary to uveitis. Patients may be affected both by open- and closed-angle glaucoma [3].

An increase in IOP in patients with uveitis may occur as a result of the mechanisms described below.

One mechanism involves a sharp increase in IOP associated with an active inflammatory process. The condition is referred to as hypertensive uveitis. Most cases of uveitis are associated with a slight reduction in IOP (sometimes IOP values are within the normal range, but nevertheless lower than in the healthy eye), which is attributed to the fact that one of the primary features of the inflammatory process is the loss of function in the affected organ. In patients with uveitis, this applies to the ciliary body which, as one of its functions, produces the aqueous humor [11, 12]. For this reason, elevated IOP during active uveitis also represents an important diagnostic clue. An increase in IOP during active infection occurs when the inflammatory process spreads to the trabecular meshwork (trabeculitis) [13]. Trabecular edema fills up intertrabecular spaces, causing an increased resistance to the outflow of the aqueous humor and, as a consequence, inducing a spike in IOP. Trabeculitis typically develops in association with uveitis of herpetic origin [14, 15]. It is less frequent in uveitis caused by syphilis, toxoplasmosis, Posner-Schlossman syndrome [16], and Fuchs uveitis syndrome [17].

The other mechanism leading to an increase in IOP involves changes in the trabecular meshwork and the aqueous outflow tracts in patients with chronic or recurrent uveitis. Prolonged inflammatory process in the eye is known to cause scarring within the Schlemm's canal and collecting channels, followed by a collapse and occlusion of these structures. Also, persistent inflammation causes changes within the trabecular meshwork itself, presenting as scarring, hyalinization, dysfunction of the vascular endothelium, and filling of intertrabecular spaces by inflammatory cells [18-20]. All of the changes listed above ultimately lead to an increase in the resistance to the aqueous humor outflow and cause chronic elevation of IOP.

Recent studies have shown that in patients with ocular sarcoidosis chronically elevated IOP may be associated not only with the mechanisms outlined above, but also increased levels of angiotensin-converting enzyme (ACE) detected not only in the blood serum but also in the aqueous humor [21]. ACE converts angiotensin I into angiotensin II. Angiotensin II (Ang II) has been shown to increase trabecular meshwork cell proliferation and collagen synthesis, contributing to an increased resistance to the aqueous humor outflow. In addition, the administration of Ang II into the anterior chamber has been found to reduce outflow by the unconventional route, though the mechanism underlying this process has not yet been fully elucidated. Furthermore, angiotensin-converting enzyme is known to act on the plasma kinin-forming system by breaking down bradykinin. Bradykinin increases the synthesis of prostaglandins, which have an IOP-lowering effect by increasing the uveoscleral outflow. In addition, bradykinin causes vasodilation through an increase in nitric oxide (NO) production. NO has been shown to inhibit the formation of vasoconstrictive endothelin-1 (ET-1) [22]. Numerous studies have demonstrated that patients with POAG, and especially with normal tension glaucoma (NTG), have an increased level of ET-1, which not only contributes to an elevation of IOP, but also reduces blood flow in the optic nerve, speeding up the rate of damage [23].

An ongoing inflammatory process within the uveal layer may lead to acute filtration angle closure. Angle closure in patients with uveitis can occur either with pupillary block as the underlying mechanism or without pupillary block. Pupillary block is most commonly observed in cases of uveitis that are characterized by a massive fibrin response resulting in the development of extensive (often circular) posterior synechiae, causing seclusion of the pupil and leading to the formation of "iris bombé" [24]. A particularly prominent tendency to the development of posterior synechiae is known to be associated with uveitis of sarcoid and herpetic origins, with a positive HLA-B27 antigen test, and coexisting with JIA. Filtration angle closure due to the anterior "pull" mechanism without pupillary block (at the iris base) occurs in connection with extensive anterior synechiae or shrinkage of the neovascular fibrous membrane [25]. The causes underlying PAS formation are similar to those leading to the development of posterior synechiae. In contrast, neovascularization within the filtration angle is usually secondary to peripheral retinal hypoxia, which may be associated with:

- retinal vasculitis (e.g. Eales' disease, sarcoidosis, Birdshot chorioretinopathy);
- extensive peripheral chorioretinal granulomas (sarcoidosis, toxocariasis, syphilis);
- massive snow banking (*pars planitis*) [26].

In turn, in VKH syndrome and sympathetic ophthalmia, angle closure occurs via the posterior "push" mechanism without pupillary block (outside the lens). This is due to choroidal effusion syndrome leading to the detachment and anterior rotation of the ciliary processes [27, 28].

In addition, patients with uveitis may experience an iatrogenic IOP rise induced by GC treatment. In fact, an increase in IOP after GC treatment is observed in just over one-third of the population. Approximately 5% of the population respond with a significant increase in IOP (> 15 mmHg or > 31 mmHg) to the administration of GCs. These patients are referred to as high-responders (highly sensitive to GCs). In addition, 33% of the population are moderate responders (with medium sensitivity to GCs). In this group, a moderate hypertensive response to GCs (an increase of 6–15 mmHg or IOP > 20 mmHg) is expected [29]. The group of individuals at increased risk of GC-induced IOP elevation includes patients with POAG, first-degree relatives of patients with POAG, patients with NTG, and patients in extreme age groups (i.e. under 6 years of age and the elderly), highly myopic individuals as well as patients with connective tissue disorders, type I diabetes mellitus, and Fuchs endothelial dystrophy [30]. In predisposed individuals, GC-induced IOP elevation occurs, as a rule, within 2-6 weeks after starting treatment. As mentioned earlier, topically administered GCs (drops, periocular and intravitreal injections) are substantially more likely to cause a spike in IOP than systemic (oral or intravenous) GCs. Topically administered GCs vary in their effect on IOP. In general, the most potent topical GCs, i.e. prednisolone acetate or dexamethasone alcohol, also have the greatest potential to raise IOP. In turn, loteprednol etabonate, rimexolone and fluorometholone are topical GCs known to have a minor effect on IOP. Unfortunately, they are not considered suitable for the treatment of uveitis because of their insufficient anti-inflammatory activity. GCs are believed to cause a spike in IOP through an increase in the aqueous humor outflow resistance mainly at the level of the trabecular meshwork [9]. Two types of steroid receptors, GRα and GRβ, have been identified on the surface of trabecular cells. GRα is the primary factor responsible for increasing resistance to the outflow of the aqueous humor as a result of:

- increased deposition of the extracellular matrix within the trabecular meshwork through the activation of the myocilin gene and the inhibition of metalloproteinases and phagocytic capacity;
- increased rigidity through the cross-linking of actin filaments;
- inhibited migration of inflammatory cells and increased tightness of intercellular junctions.

In contrast, GRβ elicits a decrease in the activity of GRα by inhibiting its transcription. GRα overexpression with a concurrent decline in GRβ activity were noted in patients responding to GC treatment with an increase in IOP [29, 31].

Of note, though, it is sometimes very difficult to determine unequivocally whether elevated IOP seen in patients with uveitis is due to the effects of GCs or the inflammatory process itself. It is important to highlight that an increase in IOP in patients with ongoing inflammation should not be considered as a reason to discontinue treatment with anti-inflammatory drugs. Naturally, in such cases efforts should be made to establish the minimum effective dose to control inflammation. In a large proportion of patients, proper control of inflammation also leads to IOP normalization. In cases where prolonged anti-inflammatory treatment is anticipated, it is worth considering early initiation of immunosuppressive therapy (IMT), as it has no known effects on IOP. However, it should be emphasized that IMT must be continued for several (2–6) weeks to achieve its full anti-inflammatory effect, which is why GCs are irreplaceable in induction therapy. Delaying the initiation of anti-inflammatory treatment due to concerns about the risk of ocular hypertension may lead to irreversible damage to the eye.

DIAGNOSTIC PROCEDURE

Patients with coexisting uveitis and elevated IOP urgently require the diagnosis of the underlying disease and monitoring of progression towards glaucomatous damage. In many cases, accurate identification of the etiology of uveitis contributes to effective treatment that helps achieve normalization of IOP. In addition, correct diagnosis of uveitis allows assessment of the risk of IOP problems in the future. It has been shown that elevated IOP in patients with uveitis is associated with a faster progression towards optic nerve damage. Consequently, prompt diagnosis for glaucomatous damage plays a vital role. Unfortunately, additional examinations routinely included in the diagnostic work-up for primary glaucoma are markedly more difficult to interpret in patients with uveitis. A common problem is poor transparency of the optical media (inflammatory exudate in the anterior chamber, synechiae, complicated cataract, inflammatory reaction in the vitreous), which makes it difficult or even impossible to obtain results of acceptable quality. Furthermore, it is often difficult to determine whether the observed abnormalities are associated with glaucomatous damage or the inflammatory process. Consequently, the role of in-depth physical examination cannot be overestimated. In patients with uveitis, the physical examination must always include a thorough evaluation of the anterior segment and the fundus together with a meticulous assessment of the optic nerve, and IOP measurement by applanation tonometry. Each patient with uveitis and elevated IOP requires gonioscopy to assess the degree of opening of the filtration angle, but also visualize existing anterior synechiae and inflammatory cells within the trabecular meshwork, nodules, or the presence of angle neovascularization [13]. In cases where gonioscopy is not possible because of corneal lesions or a severe reaction in the anterior chamber, it may be necessary to perform AS-OCT imaging, or possibly UBM. However, despite providing information about the degree of opening of the angle, these examinations are not suitable for revealing any other potential pathologies that may be present there [3].

Similarly to POAG, a visual field test is the primary examination for the diagnosis of optic nerve damage caused by elevated IOP in patients with uveitis. The presence of characteristic defects in the visual field, corresponding to the changes identified in the optic nerve, allows for the diagnosis of UG. In their study, Liu *et al*. found that changes in the visual field progressed significantly faster in patients with UG than in the population of patients with POAG (–0.49 dB/year and –0.37 dB/year in the respective patient groups) [32]. In addition, the percentage of patients with rapid progression of visual field changes, i.e. >1.5 dB/year, was found to be almost twice as high in patients with glaucoma and uveitis than in patients with glaucoma but without uveitis (11% vs. 7%) [33]. Consequently, patients with uveitis coexisting with ocular hypertension or glaucoma should undergo a perimetry test frequently enough to allow early identification of patients at risk of rapid progression of glaucomatous abnormalities. However, as mentioned above, it should be borne in mind that retinal changes caused by the inflammatory process also have an adverse effect on the visual field. Kiss *et al*. reported that patients with active cystoid macular edema (CMO) presented with a significant decline in the sensitivity of the central retina determined by perimetry, compared to patients without CMO. Following the resolution of edema, the sensitivity of this retinal region improves, but it nevertheless remains permanently impaired compared to eyes that have never been diagnosed with CMO [34].

Being widely available and easy to perform, OCT has become an indispensable component of the diagnosis and follow-up of glaucoma. Moore *et al*. found that the thickness of the retinal nerve fiber layer (RNFL) in patients with uveitis was statistically significantly higher than in the healthy population even during the remission of inflammation. This may result in the atrophy of nerve fibers going unnoticed, as the parameters may remain 'normal' in relation to the normative database (so-called "green disease") [35]. Furthermore, RNFL thickness was observed to be significantly higher in the same eye during the period of active inflammation compared to the phase of remission. This pattern carries the risk of overdiagnosis of glaucoma in some patients, when the resolution of RNFL edema is interpreted as the onset of a glaucomatous defect (so-called "red disease"). For this reason, OCT-based assessment for glaucomatous changes in patients with uveitis should be performed exclusively during remission. Also, the parameters measured in a patient should be compared to the results obtained in the same patient over time, and the interpretation of findings in relation to a normative database should be avoided. Dinn *et al*. found that the most sensitive OCT parameter for detecting glaucomatous changes in patients with uveitis was progressive RNFL thinning

in the inferior quadrants [36]. Studies are also underway on the application of angio-OCT in patients with UG [37].

CONCLUSIONS

Uveitic glaucoma is a very complex and challenging condition, both diagnostically and therapeutically. Knowledge of the basic aspects of the differential diagnosis of uveitis and the pathophysiological mechanisms that may have an impact on IOP elevation contributes to a better management of glaucomatous lesions. Patients at an increased risk of ocular hypertension, and hence more prone to developing UG, should be provided with easy access to appropriate diagnostic tools and regular medical check-ups with a glaucoma specialist. Prompt initiation of anti-inflammatory and IOP-lowering treatment can significantly reduce the risk of vision loss in this specific group of patients. Further research is needed to gain a greater understanding of the pathophysiology of inflammatory processes involved in different types of uveitis. Improved knowledge of the mechanisms leading to an increase in IOP in patients with active inflammation will contribute to the development of modern diagnostic and therapeutic methods, and reduce the time from diagnosis to the initiation of treatment.

DISCLOSURE

The authors declare no conflict of interest.

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