Original Article

Prevalence and Prognosis of Glaucoma/Elevated Intraocular Pressure in Patients with Uveitis

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Abstract

Objectives: To evaluate the prevalence and clinical course of elevated intraocular pressure (EIP) and glaucoma in different types of uveitis.

Materials and Methods: A retrospective chart review was performed for patients who were treated for any kind of uveitis at Ege University Ophthalmology Department between January 2003 and January 2023. Patients with transient/persistent increase in intraocular pressure (IOP), who were already under treatment with antiglaucoma medications at the initial examination, or who were diagnosed with glaucoma during follow-up were included. Demographic features, uveitis type, time between uveitis and glaucoma/EIP diagnoses, topical and systemic treatments for uveitis, and antiglaucoma medications and surgeries were recorded.

Results: A total of 2176 patient files (1206 anterior uveitis [AU], 247 intermediate uveitis [IU], 165 posterior uveitis [PU], 558 panuveitis [PanU]) were reviewed and 594 eyes of 440 (20.2%) patients (205 female, 235 male) were included in the study (292 eyes with AU, 80 eyes with IU, 44 eyes with PU, and 178 eyes with PanU). Glaucoma was observed in 220 eyes (37.0%) and EIP in 374 eyes (63.0%). Glaucoma was present in 120 eyes with AU, 23 eyes with IU, 13 eyes with PU, and 64 eyes with PanU. IOP was controlled with medical treatment in 458 eyes (77.1%) while glaucoma surgery/laser was needed in 113 eyes (19.0%). No treatment was required for 23 eyes (3.9%).

Conclusion: The prevalence rate of glaucoma/EIP was 20.2%. Glaucoma was most observed in eyes with AU (41.1%), while EIP was most common with IU (71.2%).

Keywords: Behçet's disease, glaucoma surgery, uveitic glaucoma

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Introduction

Uveitis is characterized by inflammation of the uveal structures (iris, ciliary body, choroid). However, the current definition of uveitis also includes inflammation of the retina, vitreous, and optic nerve.[1] Inflammation of these ocular structures might result from various diseases. Uveitis-related elevated intraocular pressure (EIP) is associated with an intraocular pressure (IOP) above 21 mmHg, while uveitic glaucoma is associated with high IOP and optic nerve damage and/or visual field defects.[2]

The mechanism of increased IOP in uveitis can vary. Trabeculitis, peripheral anterior synechia, posterior synechia resulting in pupillary block, corticosteroid exposure, or obstruction of the trabecular meshwork by inflammatory cells might lead to the elevation of IOP in uveitis patients.[3]

The mean annual incidence rate of EIP in adults with non-infectious uveitis is 14.4%.[4] Since uveitis has highly heterogeneous etiologies, the prevalence and mechanism of EIP and its progression to glaucoma depends heavily on the etiology and the localization of the inflammation. Anterior uveitis was reported to be the main cause of elevated IOP in many studies.[5,6] However, there are also reports suggesting no significant difference between anterior and posterior uveitis.[7,8]

The current study aimed to investigate the prevalence and course of EIP and glaucoma in various types of uveitis and evaluate the treatment outcomes of uveitic glaucoma.

Materials and Methods

A retrospective chart review was carried out for uveitis patients who were examined at the Uvea Department of Ege University between January 2003 and January 2023. Patients with an IOP above 21 mmHg in any of the follow-up visits and/or were diagnosed with uveitic glaucoma were included in the study. Ethics committee approval was obtained from the Ege University Ethics Committee for Medical Studies (decision no: 24-9T/9, date: 05.09.2024). Written informed consent was obtained from all patients for the use of data from their medical files.

In the current study, EIP was defined as an IOP measurement above 21 mmHg using Goldmann applanation tonometer. Glaucoma was defined as the presence of glaucomatous optic nerve damage (detected by fundus examination, peripapillary retinal nerve fiber layer thickness analysis using optical coherence tomography, and/or visual field tests) associated with the increase in IOP. All patients with transient or persistent IOP elevation, patients who were already taking antiglaucoma medications at the first visit, and patients diagnosed with uveitic glaucoma were included in the study. Patients who were followed up for less than 3 months and patients with incomplete data were excluded.

For uveitis screening, all patients underwent basic tests including complete blood count, erythrocyte sedimentation rate, C-reactive protein levels, chest X-ray, and interferon gamma release assay, along with serological tests for *Treponema pallidum* and human immunodeficiency virus. Additional tests such as tissue type classification for HLA-B27 and HLA-B51, sacroiliac joint X-ray, and serological tests for *Toxoplasma gondii, Brucella,* or *Bartonella henselae* were performed when appropriate.

Uveitis was classified as acute or chronic. Acute uveitis was defined as the sudden or gradual start of inflammation with complete resolution with treatment, with or without recurrences. Chronic uveitis was defined as persistent inflammation lasting more than 3 months and/or relapsing within 3 months after the termination of therapy.[9]

Age, gender, localization of uveitis, presence of any associated systemic diseases, exposure to corticosteroids, ophthalmological examination findings pertaining to the iridocorneal angle, IOP, best corrected visual acuity (in decimal), the course of the IOP increase, treatment of EIP and glaucoma, number and type of antiglaucoma medications used, and glaucoma surgeries and complications were recorded and analyzed.

Statistical Analysis

The Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.) was used for statistical analyses. Descriptive statistics are presented as mean, standard deviation, median, range, and percentage values. The Shapiro-Wilk test was used to test the normality assumptions of the quantitative data. Chi-square test was used for the comparison of categorical variables. The statistical significance value was defined as $p<0.05$.

Results

The medical records of 2176 patients were reviewed and 594 eyes of 440 patients (20.2%) were included in the study. Gender distribution, mean age, mean follow-up time, and ophthalmological findings are summarized in Table 1.

In 334 eyes (56.2%), either IOP was increased at the first visit or the patient had already been started on antiglaucoma medications by another ophthalmologist due to high IOP identified with uveitis. The mean duration between the first diagnosis of uveitis and IOP elevation was 299.7±849.5 days (range: 0-8030). A total of 41 patients (9.3%) were under 18 years of age at the time of EIP or glaucoma diagnosis.

The presence of any associated systemic and ocular diseases and treatment of uveitis are summarized in Table 2.

Acute uveitis was present in 145 patients (33.0%), while chronic uveitis was found in 295 patients (67.0%). An IOP

Table 1. Demographic features and clinical findings of all study eyes

Total number of patients	440
Female, n (%)	205 (46.5)
Male, n (%)	235 (53.1)
Total number of eyes	594
Age, years, mean ± SD (range)	48.9±20.5 (7-104)
Follow-up period, months, mean ± SD (range)	62.09±88.3 (3-192)
IOP, mean±SD, mmHg (range)	35.6±10.9 (22-60)
BCVA, first visit, logMAR, mean ± SD (range)	0.29±0.3 (2.28-0)
BCVA, last visit, logMAR, mean ± SD (range)	0.26±0.31 (2.28-0)
Iridocorneal angle, eyes, n (%)*	
Open	509 (85.7)
Peripheral anterior synechia	61 (10.3)
Pupillary block	28 (4.7)
Uveitis localization, eyes, n (%)	
Anterior	292 (49.2)
Intermediate	80 (13.5)
Posterior	44 (7.4)
Panuveitis	178 (30.0)

*Eyes could be included in multiple categories.
BCVA: Best corrected visual acuity, IOP: Intraocular pressure, SD: Standard deviation

Table 2. Associated systemic and ocular conditions

Etiology - systemic, patients, n (%)	
Spondyloarthropathies	57 (12.8)
Behçet's disease	82 (18.5)
Undifferentiated connective tissue disorders	8 (1.8)
JIA	17 (3.8)
Sarcoidosis	14 (3.1)
TINU	2 (0.4)
Vogt-Koyanagi-Harada syndrome	5 (1.1)
Multiple sclerosis	2 (0.4)
Etiology - ophthalmic, eyes, n (%)	
Herpetic uveitis	32 (5.3)
Fuchs uveitic syndrome	5 (0.8)
CMV uveitis	2 (0.3)
Posner-Schlossmann syndrome	4 (0.7)
Toxoplasmosis/toxocariasis	11 (1.8)
Uveitis treatment, eyes, n (%)	
Topical corticosteroids	594 (100)
Systemic treatment	
Corticosteroids	358 (60.3)
Conventional immunosuppressives	98 (16.4)
Anti-TNFα agents	87 (14.5)
Intravitreal dexamethasone implant	34 (5.7)
Anterior	2 (0.3)
Intermediate	7 (1.2)
Posterior	4 (0.7)
Panuveitis	21 (3.5)

JIA: Juvenile idiopathic arthritis, TINU: Tubulointerstitial nephritis and uveitis syndrome, CMV: Cytomegalovirus, TNF: Tumor necrosis factor

increase of at least 10 mmHg over baseline was observed in 88 eyes (14.8%) after the initiation of systemic/topical/intravitreal corticosteroids. These eyes were defined as "steroid responders".

EIP was identified in 374 eyes (63.0%), while glaucoma was identified in 220 eyes (37.0%). The incidence of EIP and glaucoma according to the localization of uveitis and the applied treatments are summarized in Table 3. Glaucoma was most frequently associated with anterior uveitis (41.1%), but the relationship did not reach statistical significance (p=0.057). EIP was most frequently associated with intermediate uveitis compared to the other uveitis locations (p=0.03). Surgical and/or laser treatment were required in 113 eyes (19.0%) while medical treatment was adequate for the control of IOP in 458 eyes (77.1%). The treatment modality (surgery/laser/medication) and incidence of surgery did not differ significantly between the patients (p=0.3). Pupillary block was observed in 28 eyes and laser iridotomy was applied to all of them in addition to medical treatment. No treatment was applied to 23 (3.9%) eyes. Thirty-one eyes (5.2%) were found to be legally blind (visual acuity ≤20/200 and/or visual field smaller than the central 20 degrees) at the first visit. At the last visit (median 72 months), 77 eyes (13.0%; 37 medically treated and 40 surgically treated eyes) were found to be legally blind. The incidence of blindness was lower in the medical treatment group compared to the surgically treated group (8.0% vs. 35.4%, p=0.03). In total, 17 eyes (2.9%) underwent vitrectomy. Vitreoretinal surgery was carried out for diagnostic purposes in 2 eyes, tractional membranes/tractional retinal detachment in 2 eyes, vision-reducing dense vitreous membranes/opacities in 3 eyes, macular hole in 2 eyes, and rhegmatogenous retinal detachment in 8 eyes.

The number of antiglaucoma medications used, surgeries performed, and number of surgeries are shown in Table 4. The complications and numbers of eyes requiring revision and repeat surgeries are summarized in Table 5.

Table 3. Frequencies of EIP and glaucoma and applied treatments according to uveitis localization

	Anterior, n (%)	Intermediate, n (%)	Posterior, n (%)	Panuveitis, n (%)	Total, n (%)
Glaucoma	120 (41.1)	23 (28.8)	13 (29.6)	64 (36.0)	220 (37.0)
EIP	172 (58.9)	57 (71.2)	31 (70.4)	114 (64.0)	374 (63.0)
Treatment					
Surgery/laser	60 (20.2)	13 (16.2)	11 (25.0)	29 (16.3)	113 (19.0)
Medical	216 (74.3)	62 (77.5)	32 (72.7)	148 (83.1)	458 (77.1)
None	16 (5.4)	5 (6.3)	1 (2.3)	1 (0.6)	23 (3.9)

EIP: Elevated intraocular pressure, n: Number of eyes

Table 4. Number of antiglaucoma medications and number of performed surgeries

	Anterior n (%)	Intermediate n (%)	Posterior n (%)	Panuveitis n (%)	Total n (%)
Number of antiglaucoma medications					
0	18 (6.1)	40 (50.0)	19 (43.2)	89 (50)	166 (27.9)
1	15 (5.1)	1 (1.25)	3 (6.8)	3 (1.6)	22 (3.6)
2	76 (25.6)	21 (26.2)	7 (15.9)	48 (26.7)	152 (25.4)
3	160 (54.7)	10 (12.5)	14 (31.8)	27 (15.2)	211 (35.5)
4	21 (7.1)	6 (7.5)	1 (2.3)	9 (5.0)	37 (6.3)
5	2 (0.7)	2 (2.5)	0	2 (1.1)	6 (1.1)
Surgical treatment					
Trabeculectomy	32 (10.8)	4 (5)	10 (22.7)	6 (3.4)	52 (46)
Trabeculectomy+phacoemulsification	3 (1)	-	-	2 (1.1)	5 (4.4)
Deep sclerectomy	3 (1)	4 (5)	-	6 (3.4)	13 (11.5)
Ex-Press/XEN glaucoma implant	3 (1)	4 (5)	-	3 (1.7)	10 (8.8)
Glaucoma drainage devices	7 (2.4)	3 (3.7)	-	1 (0.5)	11 (9.7)
GATT	2 (0.7)	2 (2.5)	1 (2.3)	1 (0.5)	6 (5.3)
Cryo-cyclodestruction	2 (0.7)	-	1 (2.3)	3 (1.7)	6 (5.3)
Number of surgeries					
1	35 (11.8)	4 (5)	8 (18.1)	10 (5.6)	57 (50.4)
2	7 (2.4)	1 (1.2)	-	1 (0.5)	9 (7.9)
>3	5 (1.7)	5 (6.2)	2 (4.6)	4 (2.2)	16 (14.1)
Laser treatment					
Laser iridotomy	12 (4)	3 (3.7)	1 (2.3)	12 (6.7)	28 (24.8)
Selective laser trabeculoplasty	5 (1.7)	-	-	2 (1.1)	7 (6.2)

GATT: Gonioscopy-assisted transluminal trabeculotomy, n: Number of eyes

Table 5. Complications and revisions related to glaucoma surgeries (n=113)				
Glaucoma surgery	**n (%)**	**Related complications**	**n (%)**	**Eyes needing revisions/ reoperations, n (%)**
Trabeculectomy with MMC	57 (50.4)	Hypotony Choroidal detachment Hyphema Bleb encapsulation	16 (28.1) 3 (5.2) 3 (5.2) 7 (12.3)	11 (19.3)
Deep sclerectomy	13 (13.5)	Bleb encapsulation	1 (7.7)	3 (23.1)
XEN-45 implantation	5 (4.4)	None	0	5 (100.0)
Ex-Press mini shunt	5 (4.4)	None	0	3 (60.0)
GATT	6 (5.3)	Hyphema	2 (33.3)	0
Ahmed glaucoma valve implantation	11 (9.7)	Hypotony Bleb encapsulation	2 (18.2) 2 (18.2)	2 (18.2)
Cryo-cyclodestruction	6 (5.3)	None	0	0
MMC: Mitomycin C, GATT: Gonioscopy-assisted transluminal trabeculotomy, n: Number of eyes				

Discussion

Uveitic glaucoma was first described in 1813 by Beer.[10] Since then, many studies have evaluated and reported on this condition, adding to our knowledge. It is now known that the etiology of uveitis plays a major role in the increase in IOP, with various mechanisms contributing towards EIP in uveitis. Herpetic uveitis and Posner-Schlossman syndrome are most associated with uveitic glaucoma/EIP, while for non-infectious uveitis, juvenile idiopathic arthritis is one of the most common etiologies.[11] In the current study, the prevalence of EIP/glaucoma was 20.2% among eyes with any type of uveitis. In a multicenter study, the prevalence of uveitic EIP/glaucoma was reported to be 15.8% with an annual incidence rate of 14.4%.[4] In another study, the incidence rate of glaucoma/EIP in uveitis patients was reported to be 6.5% in 1 year and 11.1% in 5 years.[5] Additionally, the prevalence of glaucoma/EIP in uveitis patients was reported as 20% in England,[12] 47.7% in Thailand,[13] 8.8% in Germany,[14] 16.4% in the USA,[15] 8.4% in Taiwan,[16] and 25.4% in Japan.[17] Incidentally, a study from the UK reported the prevalence of uveitic glaucoma as 41.8%, which is higher compared to most of the other published reports.[18]

The prevalence of EIP/secondary glaucoma in childhood uveitis was observed to be 35% in a 5-year prospective study[19] and 8.8% in another report.[13] In our study, 9.3% of the affected patients were under 18 years old. Sharon et al.[20] reported that 41.2% of the patients with high IOP were under 16 years old.

The high variations in the prevalence rates in the reported studies might result from differences in the duration of exposure to corticosteroids and/or the dosage used, as well as the differences in etiologies. Our study encompasses a period before the newer treatment options (such as anti-tumor necrosis factor alpha drugs) were available; therefore, corticosteroids were more commonly used for longer durations. Additionally, since the current study was conducted at a university hospital, which is a tertiary referral center that serves a very large population, our results are strongly affected by the severity of the cases.

The most common disease associated with uveitic glaucoma in the current study was Behçet's disease, followed by spondyloarthropathies. Behçet's disease is already known to be one of the most common etiologies for uveitis in Türkiye (32%),[21] which is also supported by the current study. In another study from Türkiye, the most common localization was anterior (43.6%) and Behçet's disease was the second most common etiology (26%).[22] Although infectious uveitis with herpesviruses, Posner-Schlossman syndrome or Fuchs uveitis syndrome are known to have the highest risk for increase in IOP, Behçet's disease has also been reported to be commonly associated with uveitic glaucoma.[13,17]

In the current study, 63% of uveitic eyes with high IOP had only EIP, whereas 37% of them had glaucomatous degeneration of the optic nerve associated with high IOP. In contrast to our results, Pathanapitoon et al.[13] reported that 61.4% of uveitic eyes with high IOP had glaucoma whereas 38.6% had EIP without any glaucomatous findings. The same study reported that the prevalence of glaucoma in all uveitic eyes was 29%.[13] Heinz et al.[14] reported a very low prevalence (8.8%) of high IOP in uveitic eyes, although 71.5% of the eyes evaluated had glaucomatous degeneration. Similarly, Merayo-Lloves et al.[15] reported that 58.2% of uveitic eyes with high IOP had glaucomatous findings.

Anterior uveitis was the most common type of uveitis among all study patients in the current study (49.2%) and glaucomatous degeneration was most observed in eyes with anterior uveitis (n=120, 41.1%), followed by panuveitis (n=64, 36.0%). The frequency of glaucoma in intermediate and posterior uveitis was 28.8% and 29.6%, respectively. Supporting this, Kanda et al.[17] reported that anterior uveitis was the most common type with EIP (34.6%). Interestingly, these authors did not observe EIP/glaucoma in any of the eyes with posterior uveitis, which may be related to the relatively low number of samples with posterior uveitis (only 23 eyes). Supporting our findings, Pathanapitoon et al.[13] reported that most patients with glaucoma had anterior uveitis (61%) or panuveitis (25%). Herbert et al.[18] also reported that anterior uveitis was the most common type associated with high IOP (38%). Sharon et al.[20] reported that 83% of their

patients with uveitic EIP had anterior uveitis. Contrary to these data, Neri et al.[5] reported that there was no significant difference in the prevalence of EIP between anterior, intermediate, and posterior uveitis.

Since the use of corticosteroids is an unavoidable part of uveitis treatment, corticosteroid-induced EIP is commonly reported.[4] Friedman et al.[23] reported that an IOP increase of at least 10 mmHg was observed in 65% of uveitis patients who received fluocinolone acetonide implants and 24% of those treated with systemic corticosteroids. Glaucomatous optic nerve damage was reported in 26% of patients in the implant group, compared to 6% in the systemic treatment group.[23] Shrestha et al.[24] reported that corticosteroids were the main cause of EIP in most of the new uveitic cases with high IOP (65%) within the first 6 weeks of treatment.

In our study, 60.3% of eyes were treated using systemic corticosteroids during the follow-up period and only 5.7% received intravitreal dexamethasone implants. Feng et al.[25] reported that intravitreal dexamethasone implants did not cause any significant IOP increase when used as combination with phacoemulsification cataract surgery in pediatric uveitis patients. The results of a systematic review and meta-analysis indicated that intravitreal dexamethasone implants cause EIP and increase the number of antiglaucoma medications needed but do not increase the need for glaucoma surgery.[26] It is not always possible to differentiate steroid-induced ocular hypertension from an increase in IOP secondary to the inflammation in uveitis patients. However, we observed an increase in IOP immediately after the initiation of topical/systemic/intravitreal corticosteroid treatment in almost 15% of eyes, which were classified as "steroid responders". An IOP reduction after steroid cessation was not considered a criterion for steroid responsiveness. This is because it is not always possible to completely stop treatment in uveitic patients and IOP does not always decrease when exposure to steroids ends, possibly due to irreversible changes in the trabecular meshwork.[24]

Spondyloarthropathies were the second most common associated systemic condition in this study. Although spondyloarthropathy-associated uveitis is known to result in a decrease in IOP, pupillary block and chronic corticosteroid exposure combined with the inflammatory damage to the trabecular meshwork might cause EIP and/or glaucoma.

In the current study, only 23 eyes (3.9%) did not require treatment of any kind. Most of the eyes with EIP needed antiglaucoma medications at least temporarily. Almost 20% of the eyes in our cohort needed glaucoma surgery/laser treatment. Previous studies have reported the incidence of surgery in this patient group to be approximately 30% (Pathanapitoon et al.[13]), 47% (Merayo-Lloves et al.[15]), 23.2% (Neri et al.[5]), and 30.3% (Herbert et al.[18]). Jones[12] reported that glaucoma surgery was needed mostly in eyes with chronic anterior uveitis, corresponding to 32% of the eyes that underwent glaucoma surgery. The need for glaucoma surgery in the current study was the highest in eyes with posterior uveitis (25%). This may be related to a more extensive systemic exposure to steroids or the severity of the uveitis itself.[27]

The iridocorneal angle was open in most eyes (85%), and two or more topical anti-glaucoma medications were being used on most eyes (67.8%) at the time of surgery in the current study. Postoperative complications were mostly observed after trabeculectomy (50.8%), and bleb encapsulation was common after trabeculectomy, deep sclerectomy, and Ahmed glaucoma valve implantation. Hypotony (15.9%) was the most common postoperative complication, as in previous reports in the literature.[28] Theoretically, deep sclerectomy and XEN-45/Ex-Press mini-shunt implantations are expected to provide better outcomes with fewer complications and more stable IOP.[28,29] In the current study, the incidence of complications was significantly lower with these surgeries, as expected, with no hypotony observed. However, the need for revisions or repeat surgeries was also higher compared to trabeculectomy with mitomycin C and Ahmed glaucoma valve implantation.

Study Limitations

The main limitations of this study are its retrospective design and the heterogeneity of uveitis etiologies. A very important factor in EIP and glaucoma is corticosteroid exposure, which varied between patients and eyes in this study.

Conclusion

In conclusion, we report that high IOP was relatively common in all types of uveitis (~20%). Almost 40% of these cases developed glaucomatous neurodegeneration, with approximately 20% requiring glaucoma surgery. Only about 4% of these eyes required no treatment of any kind. IOP elevation can be seen even years after the initial diagnosis of uveitis, therefore IOP measurements should be carried out at each visit. As children comprise a considerable proportion of patients with uveitis, the extra effort needed for reliable IOP measurements should not be avoided.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ege University Ethics Committee for Medical Studies (decision no: 24-9T/9, date: 05.09.2024).

Informed Consent: Written informed consent was obtained from all patients for the use of data from their medical files.

Declarations

Authorship Contributions

Surgical and Medical Practices: M.E.B., S.G.Y., H.A., Concept: M.E.B., H.A., Design: M.E.B., H.A., Data Collection or Processing: M.E.B., Analysis or Interpretation: S.G.Y., Literature Search: M.E.B., Writing: M.E.B., S.G.Y.

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