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Risk Factors for Secondary Glaucoma in Herpetic Anterior Uveitis

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• PURPOSE: To determine the incidence of elevated intraocular pressure (IOP) and secondary glaucoma in herpetic anterior uveitis (AU), owing to either herpes simplex or varicella zoster virus, by using the Standardization of Uveitis Nomenclature (SUN) criteria, and to identify risk factors for the development of glaucoma.

• DESIGN: Retrospective observational cohort study.

• METHODS: Patients with herpetic AU presenting themselves between 2001 and 2013 at the ophthalmology department of the University Medical Center Groningen were included. Main outcome measures were the incidence of elevated IOP and glaucoma and risk factors for the development of glaucoma.

• RESULTS: Seventy-three herpetic AU patients were included. Ocular complications most commonly seen during follow-up for uveitis were elevated IOP (75%), keratitis (59%), dry eyes (34%), posterior synechiae (34%), cataract (32%), and glaucoma (15%). Glaucoma patients, in comparison to non–glaucoma patients, had a higher number of IOP peaks during their follow-up for uveitis ($P < .001$). The majority of patients with elevated IOP (91%) had this already at the start of the uveitis. Nineteen percent of the patients needed glaucoma surgery.

• CONCLUSIONS: Using the SUN criteria, our study confirmed that elevated IOP and secondary glaucoma are major complications in herpetic AU. If an elevated IOP occurred, it was usually already present at the start of a uveitis episode. A risk factor for the development of glaucoma was the number of endured IOP peaks. Future studies are needed to evaluate whether early and prolonged use of antiviral and IOP-lowering medication may prevent glaucoma. (Am J Ophthalmol 2017;181: 55–60. © 2017 Elsevier Inc. All rights reserved.)

ELEVATED INTRAOCULAR PRESSURE (IOP) AND secondary glaucoma (IOP-related damage to the optic nerve head and accompanying visual field loss) are major ocular complications in uveitis. Reported incidences of elevated IOP and glaucoma in uveitis vary widely between as well as within the different uveitis entities. In herpetic anterior uveitis (AU), reported incidences of elevated IOP vary from 47% to 90%,[1–3] whereas reported incidences of secondary glaucoma vary between 2% and 54%.[1,2,4–6] Possible explanations for this include nonuniform definitions and variable follow-up times.

Variability in definitions is a general problem in uveitis studies. Therefore, the Standardization of Uveitis Nomenclature (SUN) working group has defined criteria for uveitis classification and follow-up, including uniform definitions of elevated IOP and glaucoma.[7]

The main objective of this study is to determine the incidence of elevated IOP and secondary glaucoma in herpetic AU, owing to either herpes simplex virus (HSV) or varicella zoster virus (VZV), by using the SUN criteria. The second objective is to identify risk factors for the development of glaucoma. Identifying these risk factors can help to determine how therapeutic modalities can prevent glaucoma in this patient group.

METHODS

• ETHICS STATEMENT: The Medical Ethical Committee of the University Medical Center of Groningen approved the conduction of this study.

• PATIENTS: The patients included in this study were selected from an existing database, containing all uveitis patients from 2001 until 2013 who had been treated or are currently being treated for uveitis at the ophthalmology department of the University Medical Center Groningen (a tertiary referral center). We included patients with herpetic AU owing to HSV or VZV. At the time of inclusion, all patients were 18 years or older. In the absence of specific SUN criteria for herpetic AU, the diagnosis was made by clinical presentation (keratitis—dendritic herpes branch—followed by AU, elevated IOP at presentation, iris sector atrophy developing over time, and/or clear facial varicella zoster infection [ophthalmic branch of fifth cranial nerve] with subsequent keratouveitis or a positive anterior chamber tap for local antibody production or the presence of virus DNA by polymerase chain reaction [pcr]). Facial skin lesions were considered as a strong indication of VZV-related uveitis. Keratitis can be associated

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with both HSV and VZV infection, but larger herpetic corneal branches were considered indicative of HSV. Because most patients were diagnosed by their clinical presentation, they were classified as "presumable" HSV or VZV AU.

Patients with multiple causes of anterior uveitis, including a possibly herpetic uveitis, and patients who had an elevated IOP or glaucoma before the onset of the uveitis were excluded.

• **DEFINITIONS:** Active uveitis was defined as ≥0.5+ cells in the anterior chamber, inactive uveitis as <0.5+ cells in the anterior chamber (regardless of medication use for uveitis), and remission as <0.5+ cells in the anterior chamber without medication use for uveitis.[7] Glaucoma was defined as the presence of visual field defects typical for glaucoma that were reproducible and could not be explained by other pathology, with or without glaucomatous disc abnormalities and with or without elevated IOP.[7] An IOP peak was defined as an IOP > 21 mm Hg, before the start of IOP-lowering medication[7]; in case of multiple measurements the highest IOP was recorded. The following definitions of IOP variables that were not defined by the SUN working group were added: Elevated IOP at the beginning of a uveitis episode was defined as an IOP > 21 mm Hg in the first week of a new uveitis episode and elevated IOP during a uveitis episode was defined as an IOP > 21 mm Hg after the first week of a new uveitis episode. Elevated IOP during follow-up was defined as elevated IOP (>21 mm Hg) that was recorded at least once during follow-up (beginning of first uveitis episode until the end of the last uveitis episode). Short-term use of IOP-lowering medication corresponded to the use of IOP-lowering medication during an active uveitis episode. Long-term use of IOP-lowering medication corresponded to the use of IOP-lowering medication during an active uveitis episode and its continued use thereafter.

• **DATA:** The following information was collected from the medical records: age at the time of first uveitis episode (further referred to as "onset"), sex, unilateral or bilateral uveitis, date of first and last uveitis episode, number of uveitis episodes, follow-up time in months of active uveitis (time between the start of the first and the end of the last uveitis episode), total follow-up time in months (time between the start of the first uveitis episode and the last recorded date in the patient record), Snellen visual acuity (VA) at onset and at the end of total follow-up, the cup-to-disc ratio of the optic disc at the end of total follow-up and ocular complications that developed during follow-up for uveitis (glaucoma, elevated IOP, scleritis, keratitis, cataract, posterior capsule opacification, papillitis, cystoid macular edema, dry eyes, posterior synechiae, and other ocular complications). Anterior chamber fibrin, corneal edema, and keratic precipitates were also recorded. If glaucoma developed in the nonuveitic eye, this was also recorded.

Known or presumed risk factors for developing open-angle glaucoma were registered, namely a low central corneal thickness, myopia, positive family history of glaucoma, African descent, and steroid use.[8–12] In case of elevated IOP, additional information was gathered, including the time point of elevated IOP in relation to the uveitis episode (at the start of an episode, during an episode, during inactive uveitis, or during uveitis in remission). Also, the total number of IOP peaks (elevated IOP > 21 mm Hg with normal IOP before and after), and the highest measured IOP were recorded. In glaucoma patients, the interval between the start of the first uveitis episode and the diagnosis of glaucoma was calculated in years. Further, the medical treatment and surgical interventions with regard to elevated IOP and glaucoma were collected, such as the number of patients treated with IOP-lowering medication, type of medication and number of agents used simultaneously, duration of use of IOP-lowering medication, number and type of surgical IOP-reducing interventions, and the interval between the start of the first uveitis episode and IOP-reducing intervention in years.

• **STATISTICS:** Descriptive statistics were used, such as percentages, mean ± SD (range) for normally distributed data, and median (interquartile range; range) for non-normally distributed data. For the comparison of proportions the χ^2 test or the Fisher exact test was used, when appropriate. For the comparison of continuous variables between 2 groups, the independent-samples *t* test (if data were normally distributed) or the Mann-Whitney *U* test (if not) was used. For statistical analysis, Snellen VA was converted to the logarithm of the minimum angle of resolution (logMAR) equivalent and subsequently reconverted for presentation. Data were analyzed using SPSS Statistics 20.0.0.1 (IBM Corp, Armonk, New York, USA). A *P* value of .05 or less was considered statistically significant.

RESULTS

THE MEDICAL RECORDS OF 73 HERPETIC AU PATIENTS WERE analyzed. The median age of onset of uveitis was 50 (range: 5–85) years. Fifty-four (74%) patients had a presumably HSV-associated and 19 (26%) patients a presumably VZV-associated AU. The median age of HSV patients was 48 (range: 5–85) years and of VZV patients 60 (range: 24–85) years, *P* = .03. In 19 (26%) patients an anterior chamber tap was performed, which tested positive for local antibody production or the presence of virus DNA by PCR in 14: in 12 patients for HSV and in 2 for VZV. There were 28 (38%) female patients. All patients had a unilateral AU; the fellow eye was affected in none of the patients.

Table 1 shows the ocular characteristics. Patients had a median of 3 (range: 1–27) uveitis episodes. Twenty-four of

TABLE 1. Ocular Characteristics of Herpetic Anterior Uveitis Patients (N = 73)

Total uveitis episodes	3 (1, 1–6, 27)
Single uveitis episode, no recurrence	24 (34%)
Follow-up (active uveitis) (y)[a]	2.7 (0.01, 0.1–9.8, 43.8)
Follow-up (total) (y)[b]	9.1 (0.1, 3.8–15.2, 44.9)
Remission time (y)[c]	3.3 (0.1, 1.9–5.3, 16.3)
LogMAR VA uveitis eye (onset uveitis)	0.17 (−0.18, 0.00–0.40, 2.52)
(Snellen VA onset uveitis)[d]	*(0.67 [HM, 0.40–1.00, 1.50])*[f]
LogMAR VA uveitis eye (end total follow-up)	0.10 (−0.10, 0.00–0.22, 1.77)
(Snellen VA end total follow-up)[d]	*(0.80 [FC, 0.60–1.0, 1.26])*[f]
Anterior chamber fibrin[e]	8 (11%)
Corneal edema[e]	37 (51%)
Keratic precipitates[e]	65 (89%)

FC = finger counting; HM = hand movement; VA = visual acuity.

Results are n (% of total) or median (min, interquartile range, max).

[a]Time between the start of the first and the end of the last uveitis episode.

[b]Time between the start of the first uveitis episode and the last recorded date in the patient record.

[c]Time between the end of the last uveitis episode and the last recorded date in the patient record.

[d]Difference in visual acuity at onset of uveitis and end of total follow-up was statistically significant ($P = .008$).

[e]At the time of active uveitis.

[f]LogMAR visual acuity converted to Snellen visual acuity.

TABLE 2. Ocular Complications of Herpetic Anterior Uveitis Patients (N = 73)

Complication	N (%)
Elevated IOP	55 (75)
Keratitis	43 (59)
Dry eye[a]	25 (34)
Posterior synechiae	25 (34)
Cataract	23 (32)
Glaucoma	11 (15)
Posterior capsule opacification	7 (10)
Cystoid macular edema	3 (4)
Scleritis	1 (1)
Papillitis	0 (0)
Other	2 (3)[b]

IOP = intraocular pressure.

[a]Medically treated.

[b]Retinal detachment, retinal angiomatous proliferation/macular degeneration.

73 patients had a single uveitis episode, 14 (58%) of whom had a presumably HSV-associated and 10 (42%) a presumably VZV-associated AU, $P = .048$. Median Snellen VA was significantly better at the end of total follow-up, compared with at first uveitis presentation, 0.80 (range: finger counting [FC] to 1.26) vs 0.67 (range: hand movement [HM] to 1.50, $P = .008$). During follow-up for uveitis, the following events were noted at least once (Table 1): anterior chamber fibrin in 8 (11%), corneal edema in 37 (51%), and keratic precipitates in 65 (89%) patients. Table 2 shows the ocular complications most commonly seen during follow-up for uveitis; these were elevated IOP (75%), keratitis (59%), dry eyes (34%), posterior synechiae (34%), cataract (32%), and glaucoma (15%). The majority of patients with elevated IOP (91%) had elevated IOP at the start of 1 or more uveitis episodes. Glaucoma developed during follow-up for uveitis after a median interval of 3.9 (range: 0.2–22.7) years. None of the patients with glaucoma in the eye with uveitis developed glaucoma in their fellow eye. There was no significant difference in the incidence of glaucoma (9/54 [17%] vs 2/19 [11%], $P = .7$) or elevated IOP (42/54 [78%] vs 13/19 [68%], $P = .5$) between HSV and VZV patients, respectively.

There was no significant difference in known or presumed risk factors for the development of open-angle glaucoma (corneal thickness of less than 500 μm, high myopia [<−3 dpt], and a positive family history for glaucoma) between patients with and without glaucoma. The majority of patients (97%) were white (missing data: corneal thickness 51%, myopia 5%, family history positive for glaucoma 56%, ethnicity 53%).

Overall, 66 of 73 patients (90%) were treated with systemic antiviral medication; of those 66 patients, 38 (58%) started during the first uveitis episode, 11 (17%) started during the second uveitis episode, and 17 (26%) started after the second uveitis episode. In addition, 47 of the 73 patients (64%) received IOP-lowering medication at least once; 33 of them (33/73; 45%) were treated with IOP-lowering medication solely and 14 (14/73; 19%) needed a surgical pressure-reducing intervention, consisting mainly of an implantation of a Baerveldt glaucoma drainage device (11/14; 79%). The median interval between the first uveitis episode and the pressure-reducing intervention was 5.4 (range: 0.01–25.6) years. The total follow-up time did not differ between patients with IOP-lowering medication solely and patients who needed a surgical pressure-reducing intervention, 12.4 ± 11.7 (range: 0.4–44.6) vs 11.0 ± 7.6 (range: 2.1–27.2; $P = .7$) years. The median number of IOP-lowering agents used simultaneously was 2 (range: 1–5); the most commonly used type was a β-blocker (44/47; 94%). Most patients used the IOP-lowering medication for a short period of time (30/47; 64%). All patients were treated with topical corticosteroids at the time of active uveitis, with a maximum of 16 drops a day. In case of a persistent and severe uveitis, additional oral corticosteroids (6/73, 8%) or periocular corticosteroid injections (8/73, 11%) were given.

TABLE 3. Patient and Ocular Characteristics of Patients With and Without Secondary Glaucoma

	Total Group	Eyes With Glaucoma[a]	Eyes Without Glaucoma[b]	*P* Value, Glaucoma vs Nonglaucoma
Clinical characteristics				
Number of eyes	73	11	62	
Sex (male/female)	45 (62%)/28 (38%)	9 (82%)/2 (18%)	36 (58%)/26 (42%)	.19
Age of onset of uveitis	50 (5, 32–64, 85)	52 (28, 39–66, 75)	50 (5, 31–64, 85)	.54
Age at end of total follow-up	63 (25, 51–76, 90)	71 (39, 43–77, 81)	61 (25, 52–76, 90)	.47
HSV/VZV	54 (74%)/19 (26%)	9 (82%)/2 (18%)	45 (73%)/17 (27%)	.72
Number of uveitis episodes				.17
1	26 (36%)	1 (9%)	25 (40%)	
2–4	24 (33%)	6 (55%)	18 (29%)	
>4	21 (29%)	4 (36%)	17 (27%)	
Unknown	2 (3%)	0 (0%)	2 (3%)	
Follow-up (y)	7.9 (0.01, 0.1–9.8, 43.8)	6.0 (0.8, 1.6–7.8, 25.6)	1.6 (0.01, 0.06–10.3, 43.8)	.40
Average cup-to-disc ratio end follow-up[c]	0.3 (0.1, 0.1–0.5, 0.9)	0.8 (0.4, 0.7–0.8, 0.9)	0.3 (0.1, 0.1–0.4, 0.7)	<.001*
IOP				
Number of IOP peaks				<.001*
0	17 (23%)	0 (0%)	17 (27%)	
1–2	24 (33%)	0 (0%)	24 (39%)	
>2	23 (32%)	7 (64%)	16 (26%)	
Unknown	9 (12%)	4 (36%)	5 (8%)	
Highest IOP measured (mm Hg)	38 ± 10 (22–65)	46 (36, 40–48, 48)	35 (22, 29–44, 65)	.19
Systemic antiviral medication				
Start uveitis episode 1 or 2/start after uveitis episode 1 or 2 or no antiviral treatment	49 (67%)/24 (33%)	7 (64%)/4 (36%)	42 (68%)/20 (32%)	.79
Antiglaucoma medication				
Number of patients treated with antiglaucoma medication	47 (64%)	11 (100%)	36 (58%)	.006*
Number of antiglaucoma agents used simultaneously	2 (1, 1–3, 5)	3 (2, 3–4, 5)	2 (1, 1–3, 4)	<.001*
Duration of treatment with antiglaucoma medication				
Short-term use/long-term use[d]	30 (64%)/16 (34%)	0 (0%)/10 (91%)[e]	30 (83%)/6 (17%)	<.001*
Surgical intervention	14 (19%)	10 (91%)	4 (7%)	<.001*

IOP = intraocular pressure.
Data are n (% of total) or median (min, interquartile range, max).
Asterisk indicates statistically significant *P* values.
[a]Date of diagnosis of glaucoma is end of follow-up.
[b]End of last uveitis episode is end of follow-up.
[c]End of last uveitis episode.
[d]Short-term use of IOP-lowering medication corresponded to the use of IOP-lowering medication during an active uveitis episode. Long-term use of IOP-lowering medication corresponded to the use of IOP-lowering medication during an active uveitis episode and thereafter as the uveitis was quiet.
[e]One patient missing.

Table 3 shows the patient and ocular characteristics of patients with and without glaucoma. Glaucoma patients, in comparison to nonglaucoma patients, are more often characterized by a higher number of IOP peaks during follow-up for uveitis. Glaucoma patients were more often medically treated with IOP-lowering medication, needed more IOP-lowering agents, and used these IOP-lowering agents more often for a longer period of time. Use of steroids (topical, oral, or ocular injections) did not differ between the 2 groups. In addition, there was no significant difference in corneal edema (64% vs 48%; $P = .4$), anterior chamber fibrin (27% vs 8%; $P = .08$), keratic precipitates (82% vs 90%; $P = 1.0$), keratitis (45% vs 61%; $P = .3$), posterior synechiae (45% vs 32%; $P = .5$), and iris transillumination (36% vs 50%; $P = .4$) between patients with and without glaucoma.

DISCUSSION

USING THE SUN CRITERIA, OUR STUDY CONFIRMED THAT elevated IOP and secondary glaucoma are major complications in herpetic AU patients. In the majority of the patients, the elevated IOP was measured at the start of a uveitis episode. Risk factors for the development of glaucoma were the number of IOP peaks. Also, use and prolonged use of IOP-lowering medication, and the number of IOP-lowering agents used simultaneously, were higher in glaucoma patients. A large proportion (19%) of the herpetic AU patients needed a surgical pressure-reducing intervention.

In herpetic AU, outflow obstruction owing to swelling of inflamed trabecular meshwork structures and depositioning of inflammatory cells and debris are considered to be important in the pathogenesis of increased IOP and glaucoma.[13] Another common mechanism is secondary angle-closure glaucoma related to the formation of peripheral anterior synechiae. Steroid-induced glaucoma is an important contributor in any type of uveitis, because the application of steroids is the mainstay of uveitis treatment. In the majority of our patients, the elevated IOP was measured at the start of a uveitis episode, which supports the mechanism of obstruction owing to inflammation.

The incidence of secondary glaucoma in our study was 15% after a median follow-up of 7.9 years. This is much higher than that of primary open-angle glaucoma in a normal Dutch population aged 55 years and older ($n = 3842$), where a 5-year risk of probable open-angle glaucoma was found to be 1.2% and of definite open-angle glaucoma 0.6%.[14] The 10-year risk of primary open-angle glaucoma was found to be 2.8% in the same cohort, with a mean age of 65.8 years ($n = 2571$).[15]

The frequency of elevated IOP in herpetic AU as reported in the literature varies, which is mainly owing to the variation in definitions used. In our study, following the SUN classification,[7] elevated IOP was defined as a measured IOP > 21 mm Hg, resulting in an incidence of 75%. Wensing and associates reported IOP > 30 mm Hg in 18 of 39 (46%) HSV and in 5 of 10 (50%) VZV AU eyes,[4] van der Lelij and associates an IOP > 23 mm Hg in 28 of 31 (90%) herpetic AU eyes,[3] Tugal-Tutkun and associates an IOP > 22 mm Hg in 58 of 114 (51%) herpetic AU eyes,[1] and Sungur and associates a temporary rise in IOP during an active uveitis period in 36 of 76 (47%) herpetic AU eyes.[2] Despite these apparent differences, elevated IOP is generally reported in at least half of herpetic AU eyes. Because elevated IOP at the start of a uveitis episode is considered to be indicative of a herpetic cause of the uveitis, studies may overreport elevated IOP owing to selection bias. In other words, in case elevated IOP at the start of a uveitis episode is absent, these eyes are less likely to be diagnosed as herpetic AU.

Our incidence of secondary glaucoma (15%) is comparable to those in the study of Sungur and associates in herpetic (HSV and VZV) AU and of Wensing and associates in HSV AU eyes. They found secondary glaucoma in 10 of 76 (13%) and 7 of 38 (18%) eyes, respectively.[2,4] Wensing and associates used a definition related to ours, an IOP of more than 21 mm Hg and the presence of disc abnormalities, of visual field defects typical for glaucoma, or both.[4] Sungur and associates used a different definition, namely a permanent IOP rise during the remission period—irrespective of disc abnormalities and/or visual field defects.[2] Other studies differ from ours and vary among each other with regard to the reported incidences of secondary glaucoma. Tugal-Tutkun and associates reported secondary glaucoma in 2 of 114 (2%) herpetic AU eyes,[1] Miserocchi and associates in 24 of 44 (54%) HSV and 9 of 24 (38%) VZV uveitis eyes,[6] Wensing and associates in 3 of 10 (30%) VZV AU eyes,[4] and Takahashi and associates in 7 of 23 (30%) herpetic AU eyes.[5] Takahashi and associates defined secondary glaucoma as an IOP higher than 21 mm Hg at 2 consecutive visits and the need for IOP-lowering medication.[5] In the studies of Miserocchi and associates[6] and Tugal-Tutkun and associates[1] there are no specified definitions of secondary glaucoma or elevated IOP. In the study of Miserocchi and associates, it is not clear if secondary glaucoma and elevated IOP are considered to be synonymous, but this would explain the high incidence of secondary glaucoma in their study.[6]

It is well known that elevated IOP is a risk factor for the development of secondary glaucoma.[9,16] However, information on specific aspects of the elevated IOP that influence the development of secondary glaucoma is lacking. It is supposed that the level of IOP[17–19] and the reduced diurnal-to-nocturnal change of habitual IOP[20] are important factors. In our study, patients who developed secondary glaucoma had elevated IOP more often during follow-up for uveitis and endured significantly more IOP peaks than patients without glaucoma, supporting the concept that elevated IOP during follow-up for uveitis and IOP peaks may cause significant problems in the long run. It has proved to be difficult to determine what is the most harmful, more IOP peaks or elevated IOP for a long period of time, in particular because these parameters are strongly correlated, the number of IOP measurements is limited (that is, IOP is undersampled), and different statistical approaches give different outcomes.[21] However, even without knowing which IOP parameter is most important, the results indicate that in patients with recurrent uveitis, frequent IOP measurements and low-threshold treatment of elevated IOP may be beneficial—given the high incidence of secondary glaucoma. In addition, knowing that 35 of 73 (48%) patients needed 2 or more IOP-lowering agents simultaneously and 14 of 73 (19%) patients finally needed a surgical pressure-reducing intervention makes it important to prevent these serious complications by early treatment. Future studies are needed to evaluate whether such measures indeed reduce the incidence.

In addition to frequent IOP measurements and low-threshold treatment of elevated IOP, therapeutic modalities consisting of long-term antiviral treatment to prevent new uveitis episodes and IOP peaks may be beneficial. The optimum starting point and duration of treatment with antiviral medication should be established in future studies.

Our study is mainly retrospective and has all the shortcomings related to this. Our patients were seen at a tertiary referral center and therefore this population may not represent the general uveitis population. Furthermore, most patients were diagnosed by their clinical presentation. Our study evaluated a relatively large group of patients and it adhered to the SUN Working Group criteria, thus contributing to more uniform reporting on uveitis outcomes.

In conclusion, elevated IOP and secondary glaucoma are frequent complications of viral AU. Future studies are needed to evaluate whether early and prolonged use of antiviral and antiglaucoma medication may prevent glaucoma. In addition, the described variability between studies regarding the definitions of elevated IOP and secondary glaucoma, and the resulting variation in reported incidences of these complications, underline the need for standardized criteria such as developed by the SUN working group.[7]

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