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Risk of Ocular Hypertension in Adults with Noninfectious Uveitis

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Purpose: To describe the risk and risk factors for ocular hypertension (OHT) in adults with noninfectious uveitis.

Design: Retrospective, multicenter, cohort study.

Participants: Patients aged ≥18 years with noninfectious uveitis seen between 1979 and 2007 at 5 tertiary uveitis clinics.

Methods: Demographic, ocular, and treatment data were extracted from medical records of uveitis cases.

Main Outcome Measures: Prevalent and incident OHT with intraocular pressures (IOPs) of ≥21 mmHg, ≥30 mmHg, and increase of ≥10 mmHg from documented IOP recordings (or use of treatment for OHT).

Results: Among 5270 uveitic eyes of 3308 patients followed for OHT, the mean annual incidence rates for OHT ≥21 mmHg and OHT ≥30 mmHg are 14.4% (95% confidence interval [CI], 13.4−15.5) and 5.1% (95% CI, 4.7−5.6) per year, respectively. Statistically significant risk factors for incident OHT ≥30 mmHg included systemic hypertension (adjusted hazard ratio [aHR], 1.29); worse presenting visual acuity (≤20/200 vs. ≥20/40, aHR, 1.47); pars plana vitrectomy (aHR, 1.87); history of OHT in the other eye: IOP ≥21 mmHg (aHR, 2.68), ≥30 mmHg (aHR, 4.86) and prior/current use of IOP-lowering drops or surgery in the other eye (aHR, 4.17); anterior chamber cells: 1+ (aHR, 1.43) and ≥2+ (aHR, 1.59) vs. none; epiretinal membrane (aHR, 1.25); peripheral anterior synechiae (aHR, 1.81); current use of prednisone >7.5 mg/day (aHR, 1.86); periocular corticosteroids in the last 3 months (aHR, 2.23); current topical corticosteroid use [≥8×/day vs. none] (aHR, 2.58); and prior use of fluocinolone acetonide implants (aHR, 9.75). Bilateral uveitis (aHR, 0.69) and previous hypotony (aHR, 0.43) were associated with statistically significantly lower risk of OHT.

Conclusions: Ocular hypertension is sufficiently common in eyes treated for uveitis that surveillance for OHT is essential at all visits for all cases. Patients with 1 or more of the several risk factors identified are at particularly high risk and must be carefully managed. Modifiable risk factors, such as use of corticosteroids, suggest opportunities to reduce OHT risk within the constraints of the overriding need to control the primary ocular inflammatory disease. *Ophthalmology 2017;■:1−13 © 2017 by the American Academy of Ophthalmology*

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Elevated intraocular pressure (IOP) or ocular hypertension (OHT) in uveitis is commonly attributed to resistance to aqueous outflow related to trabecular meshwork exposure to filtered inflammatory cells, cytokines, iris pigment, corticosteroids, or possibly other factors.[1] Ocular hypertension can lead to glaucoma with optic nerve damage; therefore, understanding the risk and predictors of OHT is of great clinical importance.[2−4] Ocular hypertension and glaucoma are common in severe cases of uveitis, such as those enrolled in the Multicenter Uveitis Steroid Treatment Trial, in which 24% of uveitic eyes that manifested an IOP increase by 10 mmHg or more developed glaucomatous optic neuropathy within 2 years.[5] Fluctuation in IOP is known to increase the trabecular meshwork extracellular matrix and may compromise an eye with uveitis, increasing the risk of glaucoma.[6] The corticosteroid therapy used as the mainstay for quelling active intraocular inflammation is associated with a higher incidence of OHT, although the extent of risk with various corticosteroid therapeutic approaches requires further clarification, especially over longer follow-up times.[7−10] Friedman et al[5] have reported that fluocinolone acetonide implant therapy is associated with a 4-fold risk of developing IOP elevation of ≥10 mmHg and of incident glaucomatous optic neuropathy compared with systemic anti-inflammatory therapy.

Ocular hypertension is considered the most important risk factor for glaucoma; lowering IOP is the main strategy for preventing glaucoma in patients who are at risk and for slowing progression in those with established glaucoma.[11−13] However, management of uveitic glaucoma

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is particularly challenging because the treatment aims both to reduce inflammation and to lower IOP, objectives that may be at odds. The success of glaucoma surgery is decreased in eyes with uveitic glaucoma, and surgical interventions are associated with a higher incidence of postoperative complications,[14–17] which entails a further management challenge.

To better characterize the risk of OHT and its risk factors, we assessed the prevalence and incidence among adult patients with uveitis in the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) cohort study, a large retrospective cohort study of cases of noninfectious inflammatory eye diseases.[18,19]

Methods

The study was conducted in accordance with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. The institutional review boards of each of the participating tertiary uveitis centers approved the retrospective study methods, including waiver of informed consent. The SITE study was registered as a cohort study (http://www.clinicaltrials.gov, identifier NCT00116090, June 26, 2005).

Study Population

The design and methods used in the SITE Cohort Study have been described.[18,19] In brief, patients with noninfectious ocular inflammation not known to have human immunodeficiency infection who presented to the study centers during the study period were evaluated using retrospective chart review. For this report, all children aged <18 years on entry into the cohort were excluded, because they have been reported separately.[20] Data were extracted from the case records of the patients seen between January 1978 and December 2007 from 5 specialty uveitis centers. All adults who had been diagnosed as having any form of uveitis as the primary inflammatory eye disease at presentation were included.

Data Collection

Data collection was performed by trained, certified, expert reviewers who reviewed the medical charts of the eligible patients and input information into a custom Microsoft Access Database (Microsoft Corporation, Redmond, WA). Data included demographic characteristics at baseline and ocular and treatment characteristics for each eye at each visit.

Main Outcome Measures

The IOP was recorded for each eye during each follow-up visit, because it had been measured for clinical care. Use of medications to treat OHT was also recorded. The prevalence of OHT (at the levels of IOP ≥21 mmHg and IOP ≥30 mmHg, use of IOP-lowering medications, or prior IOP-lowering surgery) at the first clinic visit and the incidence of OHT among those without prevalent OHT during follow up (IOP ≥21 mmHg and IOP ≥30 mmHg, an increase in IOP from the first visit by ≥10 mmHg, new use of IOP-lowering medications, or new IOP-lowering surgery) were assessed. To avoid missing events when cases presented taking IOP-lowering therapy or started IOP-lowering therapy in the interval between uveitis clinic visits, cases taking IOP-lowering therapy (or post IOP-lowering surgery) at a given visit were counted as having the respective events at that point of observation. Incidence rates of and risk factors for the development of OHT were primary outcome measures. The 3 categories of incident OHT were analyzed separately. All outcomes were assessed at each available follow-up visit. Incident IOP elevation was counted as an event on observation at a single visit without a requirement that IOP elevation be sustained (which was not feasible with the use of time-varying covariate).

The following variables were assessed for their potential association with all 3 categories of OHT: (1) demographic and habit characteristics, such as age, gender, race, and smoking characteristics; (2) systemic diseases, such as systemic hypertension, diabetes mellitus, hyperlipidemia, sarcoidosis, juvenile idiopathic arthritis, spondyloarthritis, and Behçet disease; (3) duration and type of uveitis; (4) ocular inflammatory signs, such as overall inflammatory activity, anterior chamber cell grade, vitreous cell grade, vitreous haze grade, hypopyon, keratic precipitates, chorioretinal lesions, snowballs, vascular occlusions, epiretinal membrane band keratopathy, posterior synechiae, and peripheral anterior synechiae (PAS); (5) OHT in the opposite eye; (6) systemic, oral, topical, periocular, intraocular corticosteroids, and corticosteroid implants (for intraocular/periocular injection to be counted a limit of 30 days was used); (7) other anti-inflammatory drugs and biologics. Variables that change over time, such as ocular inflammatory signs, OHT in the contralateral eye, and treatment status, were evaluated as time-varying covariates. For these variables, the values at the same time as the outcome of interest was assessed were used.[21] For depot corticosteroid injections (periocular or intravitreous), medication was assumed to be present for 3 months after the injection.[22,23]

Statistical Analyses

Eye-specific data were used for this analysis. Prevalence of OHT was evaluated as the proportion meeting each outcome definition at the first visit; risk factor analysis was based on crude and adjusted odds ratios (aORs) for covariates of interest calculated using logistic regression that incorporated generalizations of generalized estimating equations to account for correlation between the eyes of individual patients.

Incidence of OHT was evaluated on the basis of the number of events per eye-year at risk, with observation beginning at the time of cohort entry; risk factor analysis was based on crude and adjusted hazard ratios (aHRs) for covariates of interest calculated using Cox proportional hazards models with a robust sandwich estimate to account for correlation between the eyes of individual patients. Individual strata could not be evaluated using a Kaplan–Meier approach for time-varying variables; therefore, the overall cumulative incidence and the assumption of proportionality between strata were used to calculate strata-specific cumulative incidence. This was done for all variables, including those that are time-invariant. This approach allowed estimation of nonlinear OHT rates and confidence intervals (CIs) consistent with the hazard ratios while accounting for correlation between eyes of the same patient.

Each OHT outcome (≥21 mmHg and ≥30 mmHg for prevalence and incidence, and +10 mmHg for incidence) was modeled independently, and 95% CIs were provided for all point estimates. *P* values were nominal and 2-sided. To select characteristics included in all adjusted logistic regression (prevalence) and Cox proportional hazards (incidence) models, a backward stepwise selection process was used simultaneously in the respective IOP ≥30 models, where characteristics with $P > 0.05$ in both models were stepwise excluded, and those remaining were adjusted for in all 5 models (to adjust for the same covariates in all multiple regressions). Intraocular and periocular corticosteroid use within the last 3 months were retained in the Cox models despite not having enough data at baseline to test them in the logistic regression