AMERICAN ACADEMY OF OPHTHALMOLOGY®

Ocular Hypertension in Adults with a History of Prematurity

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Purpose: To determine the ocular hypertension (OHT) incidence in patients with a history of prematurity and the effect of intervention for acute retinopathy of prematurity (ROP) in infancy on OHT incidence.

Design: Retrospective case series at a single tertiary referral vitreoretinal practice.

Participants: A total of 407 eyes of 213 patients were included, with ROP stage 0 to 5.

Methods: A retrospective chart review was conducted of patients aged ≥15 years, seen from 1973 to 2013, with a history of premature birth (gestational age <32 weeks). Data were collected from patient charts, including gender, date of birth, gestational age at birth, birth weight, stage of ROP at presentation, management (including laser, cryotherapy, lens-sparing vitrectomy [LSV], or lensectomy-vitrectomy). Ocular hypertension (if present) data included age of onset, timing of glaucoma surgery (if performed), lens status, and last follow-up examination.

Main Outcome Measures: Development of OHT, defined as eyes requiring a glaucoma medication for more than 6 consecutive months or surgical intervention for elevated intraocular pressure.

Results: Of included eyes, 155 (38.1%) developed OHT within 69 years of follow-up. Subgroup analyses revealed an OHT incidence of 23.2% (36/155 eyes) in eyes without a history of any treatment for acute ROP (spontaneously regressed), 23.3% (10/43 eyes) in eyes that underwent ablative therapy alone, and 58.5% (76/130 eyes) in eyes requiring acute incisional retinal surgery ($P < 0.01$). Stage 4 eyes had a lower OHT incidence compared with stage 5 eyes (40.5% [17/42] vs. 66.7% [54/81], $P < 0.01$); however, among stage 4 and stage 5 eyes, phakic eyes at last follow-up had a decreased OHT incidence compared with aphakic eyes (27.8% [5/18] vs. 69.8% [60/86], $P < 0.01$).

Conclusions: Patients with a history of extreme prematurity are at an increased risk of OHT and glaucoma, even if they did not receive acute ROP treatment. More severe acute ROP is associated with higher incidence of OHT, and this is associated with an increased incidence of incisional surgical intervention. Awareness of the increased lifelong risk of adverse ocular sequelae in patients with a history of prematurity will help guide appropriate monitoring. *Ophthalmology Retina 2017;■:1–7 © 2017 by the American Academy of Ophthalmology*

Retinopathy of prematurity (ROP) is a vasoproliferative vitreoretinopathy that occurs in premature, low birth weight infants. Laser photoablation and, more recently, intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents are effective treatment modalities for severe acute ROP[1,2]; however, the majority of cases of mild ROP spontaneously regress.[3,4] In managing patients with a history of preterm birth, it is critical to recognize that ROP is a lifelong disease. Well-established late sequelae of ROP include myopia,[5–7] early development of cataract,[8–10] glaucoma,[11–16] macular ectopia,[17,18] lattice-like degeneration,[6,19,20] retinal tears,[12,19,20] and rhegmatogenous and exudative retinal detachments.[20–22] The increased long-term survival rates of extremely premature infants over the past 3 decades will likely yield a surge of adult patients in the coming years with a history of ROP,[23–25] for whom it will be important to understand, recognize, and appropriately screen for these potentially vision-threatening sequelae.

Glaucoma has long been recognized as an important cause of visual impairment in ROP[13,14]; however, the long-term risk for the development of glaucoma and ocular hypertension (OHT) in these patients has not been determined. The Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study investigated cryotherapy versus no cryotherapy in infants with bilateral threshold ROP. They reported a glaucoma incidence of 2.9% for treated patients at 5.5 years (n = 186) and 4.7% for treated patients at 10 years (n = 240).[26,27] Bremer et al[28] analyzed infants from the Early Treatment for Retinopathy of Prematurity (ETROP) study for incidence of glaucoma during the first 6 years of life and reported a glaucoma incidence of 1.67% (12/718 eyes). Other studies have reported a range of glaucoma incidence in patients with a history of ROP ranging from 10.6 to 26.9%.[12,14,15,29] To date, the incidence of glaucoma and OHT in adults with a history of prematurity is unknown. We report the long-term incidence and the effect of early ROP treatment on OHT in adults with a history of ROP.

Methods

Patient Selection and Data Collection

This study was conducted according to a protocol approved by the Beaumont Health System Research Institute Human Investigation Committee and complied with the standards set forth by the Declaration of Helsinki. A retrospective chart review was conducted

https://doi.org/10.1016/j.oret.2017.10.005
ISSN 2468-6530/17

of all patients carrying a diagnosis of ROP and aged at least 15 years seen at a single institution (Associated Retinal Consultants, PC, Royal Oak, MI) from October 1973 to August 2013.

Data collected from patients' charts included baseline demographic data, including gender, birth weight, gestational age, baseline examination, severity, and management of acute ROP. Also collected were data regarding OHT (if present), including age of onset and timing of glaucoma surgery, lens status, and last follow-up examination.

Data were not uniformly available on optic nerve cup-to-disc ratios, visual field testing, gonioscopy, or other optic nerve imaging parameters. For the purposes of this study, a diagnosis of OHT was applied to an eye if it (1) underwent a surgical intervention aimed at lowering intraocular pressure or (2) required glaucoma medications for more than 6 consecutive months excluding the early postoperative period. Once this definition was met, onset of OHT was then defined by the date that glaucoma drops were started or the date of first glaucoma surgery. For our patient cohort, the type of glaucoma associated with OHT was recorded only if specifically indicated in the chart by correspondence from a consulting glaucoma specialist. Eyes that were phthisical on presentation were included in this study only if they had a clearly documented history of OHT before the development of phthisis.

Statistical Analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC) and Microsoft Excel (Microsoft Corp, Redmond, WA). Patients from our series were divided into 3 subgroups based on the treatment that an eye received for acute ROP as follows: no treatment, ablative treatment (i.e., cryotherapy or laser), or incisional surgery for acute retinal detachment repair. Of note, this series predates the advent of intravitreal anti-VEGF therapy for acute ROP. Incidence of OHT was assessed for the whole series and for each subgroup. Incidence of OHT was also calculated for eyes on the basis of the highest stage of acute ROP, the type of acute ROP intervention, and whether an eye required lensectomy. Statistical analyses used the Student *t* test and Fisher exact test. The different subgroups were evaluated by Kaplan–Meier plots for OHT-free time in years. *P* values <0.05 were considered statistically significant.

Results

A total of 426 eyes of 213 patients met inclusion criteria. Of these, 19 eyes were excluded because they were phthisical on presentation and without a clear history as to whether or not they carried a diagnosis of OHT or glaucoma before the development of phthisis. Of the included eyes, 7 were phthisical on presentation with a documented history of OHT or glaucoma before the development of phthisis. An additional 51 eyes became phthisical or no light perception during the course of follow-up and were included; 28 of these eyes developed OHT before phthisis.

A total of 407 eyes of 213 patients (104 male, 109 female) were included in the study. Mean gestational age was 26.5 weeks (median, 26 weeks; data available for 74.7% of the cohort), and mean birth weight was 967 g (median, 907 g; data available for 76.9% of the cohort). The ROP stage ranged from stage 0 to 5. Mean follow-up was 14.3 years, ranging from a single visit up to 35.7 years. Mean age at last follow-up was 31.6 years, with a range of 15 to 69 years. The majority of OHT eyes (84.5%) were not able to be further subdivided on the basis of type of glaucoma from the chart review. Of those that were subdivided, angle-closure glaucoma (ACG, including acute ACG, chronic ACG, and phacomorphic) (n = 11, 7.1%) and neovascular glaucoma (n = 11, 7.1%) were the most common. Mean age of diagnosis for ACG eyes was 18.5 years (range, 1.3–49.5), and 8 underwent glaucoma surgery at a mean age of 16.7 years. Mean age of diagnosis for neovascular glaucoma eyes was 24.1 years (range, 2.5–50.5), and 4 underwent glaucoma surgery at a mean age of 38.3 years. There were also 2 cases of OHT (1.3%) associated with silicone oil. Table 1 displays the glaucoma surgeries performed for the overall cohort where reported.

Of the 407 eyes, 155 developed OHT for an overall incidence of 38.1% over 69 years of follow-up. For the entire cohort, the incidence increased at each decade. The proportion of eyes with OHT was 18.2% at 10 years, 22.6% at 20 years, 25.6% at 30 years, 27.5% at 40 years, 29.0% at 50 years, and 31.0% at 60 years. Subgroup analysis based on acute ROP treatment revealed an OHT incidence of 23.2% (36/155 eyes) in eyes without a history of any treatment for acute ROP (including spontaneously regressed), 23.3% (10/43 eyes) in eyes receiving ablative therapy alone (laser photoablation or cryotherapy), and 58.5% (76/130 eyes) in eyes requiring incisional surgery ($P < 0.01$). Table 2 summarizes the subgroup incidence and age of onset data. No eyes in the current study were treated with intravitreal anti-VEGF agents in infancy. Among eyes that required incisional surgery for acute ROP, stage 4 eyes demonstrated a lower incidence of OHT compared with stage 5 eyes (40.5% [17/42] vs. 66.7% [54/81], $P < 0.01$); however,

Table 1. Specific Characteristics for Eyes Requiring Glaucoma Surgery

Subgroup	N	Incidence*	Age, Mean†	Age, Median	Age, Range
Topical glaucoma medication only	103	66.4%	N/A	N/A	N/A
PI only	8	5.2% (15.4%)	30 yrs	43.5 yrs	11.5–43.5 yrs
Trabeculectomy/Tube shunt only	4	2.6% (7.7%)	22.5 yrs	20 yrs	3.5–46.5 yrs
Cycloablation only‡	20	12.9% (38.5%)	13.3 yrs	11.5 yrs	1.4–50.5 yrs
Cataract extraction only	5	3.2% (9.6%)	19.3 yrs	14.5 yrs	0.6–53.5 yrs
Multiple procedures§	7	4.5% (13.5%)	N/A	N/A	N/A
Other/unknown	8	5.2% (15.4%)	N/A	N/A	N/A

N/A = not applicable; OHT = ocular hypertension; PI = peripheral iridotomy.
*Incidence out of all OHT eyes. Percentage of eyes undergoing a particular surgery out of all eyes requiring glaucoma surgery in parentheses.
†Age at surgery.
‡Cyclocryotherapy or cylcophotocoagulation.
§Three cases of cataract extraction with PI, 3 cases of cataract extraction with cycloablation, and 1 case of tube shunt with cycloablation.