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Glaucoma in the Early Treatment for Retinopathy of Prematurity (ETROP) study

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Abstract

Purpose—To report the clinical characteristics of infants with severe retinopathy of prematurity (ROP) and glaucoma based on review of the Early Treatment for Retinopathy of Prematurity (ETROP) study.

Methods—All infants randomized in the ETROP trial were included. Each infant developed high-risk prethreshold ROP in at least one eye. Infants were examined until 6 years postnatal age. The following data were collected: corneal clarity, depth of the anterior chamber, status of the optic nerve and cup/disk ratio, retinal structure, and visual acuity. The diagnosis of glaucoma was based on the investigators best clinical judgment. All infants diagnosed with glaucoma were included in the study.

Results—A total of 12 of 718 eyes (1.67%) were diagnosed with glaucoma. Of these, 5 were first reported as having glaucoma at 9 months, 2 at 2 years, 1 each at 3 and 4 years, and 3 at 5 years. The anterior segment was shallow in 7 eyes. Three eyes had normal retinal structure, 1 had macular dragging, and 8 had retinal detachments involving the fovea (stage 4B or worse). At the six-year follow-up examination only one eye with glaucoma had measurable vision.

Conclusions—Although earlier treatment of significant ROP has resulted in better retinal structure and visual acuity outcomes, nearly 2% of the eyes with high-risk prethreshold ROP developed glaucoma at some point during the first 6 years of life.

Childhood glaucoma is a heterogeneous and relatively rare group of disorders that presents with elevated intraocular pressure (IOP) in young children. It can be the result of a variety of distinct pathologies, congenital defects or anomalies, and various insults such as trauma or inflammation.[1,2]

The incidence of primary congenital glaucoma in the Western world is reported as 1:10,000–1:30,000 live births.[3,4] Secondary angle closure glaucoma in former premature infants with retinal detachments resulting from retinopathy of prematurity (ROP) is well recognized. Smaller studies of heterogeneous populations of infants with ROP before there

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was a treatment option available reported that the incidence of secondary glaucoma in children with a poor outcome was near 30%.[5–11] The purpose of this study was to report the available data on the clinical features of glaucoma in a large population of premature infants with severe ROP.

Methods

A total of 401 infants with birth weights ≤1251 g, enrolled at 26 centers in the United States between October 1, 2000, and September 30, 2002, participated in the randomized Early Treatment for Retinopathy of Prematurity (ETROP) trial. Details of enrollment, randomization, and treatment have been described elsewhere.[12] The institutional review boards of all participating institutions approved the study protocol and the study was conducted in accordance with guidelines of the Health Insurance Portability and Accountability Act. Parents or guardians of all participants gave informed consent before enrollment in the randomized trial and upon entry into the follow-up phase of the study.

Study-certified examiners performed examinations when infants reached 6 and 9 months corrected age and annually at 2 through 6 years of age. As part of the examination, a comprehensive set of data was recorded, including corneal opacity (present, absent, or uncertain), depth of the anterior chamber (normal, shallow, abnormally deep, or questionable), status of the optic nerve, including pallor (absent, questionable, partial, severe, view obscured) and cup/disc ratio ≥0.5 (yes or no). The summary diagnosis reflected the retinal structure at each examination. Visual acuity was measured according to study protocol.[13,14] Information regarding additional treatments or surgeries was also collected. Measurement of IOP was not required by the protocol but could be reported. While this was not a glaucoma study, examiners were asked whether in their best clinical judgment the child had glaucoma and recorded their response as either “present (yes)” or “not suspected (no).”

Results

Of the 718 eyes included in this study, 12 developed glaucoma within the first 6 years of life. Five were in the early treatment group and 7 were in the conventionally managed group. Of the 12, 5 were first reported as having glaucoma at 9 months, 2 at 2 years, 1 each at 3 and 4 years, and 3 at 5 years. Seven of the 12 eyes had additional retinal surgery before the 9 month examination. Eleven eyes received laser therapy for their ROP (Table 1).

Of the 12 eyes, 9 were reported to have elevated IOP. Intraocular pressure was not reported in 3 eyes; however, in these eyes, specific comments were made to the effect that glaucoma was diagnosed based on the appearance of the optic nerve head. At the reported onset of glaucoma, 4 of 12 eyes had both elevated IOP and corneal opacity; 7 eyes had shallow anterior chambers, 1 was questionably shallow, and 4 were considered normal depth (Table 2).

At the reported onset of glaucoma, 3 eyes had normal retinal structure, 1 had macular dragging, and 8 had retinal detachments involving the fovea (stage 4B or worse). In the 6 eyes in which the cup/disc ratio could be evaluated at the time glaucoma was diagnosed, 3 had a cup/disc ratio ≥0.5. Optic nerve atrophy was questionable in 2 eyes, partial in 3, and absent in 2 eyes at the time of reported onset (Table 3).

The majority of eyes (8/12) had no glaucoma treatment recorded. Of the 4 remaining eyes, 2 were started on medical management. One of these eyes did well with medical treatment, whereas the other required surgical intervention. Of the 3 eyes that received surgical

treatment, 2 had a primary lensectomy for angle closure glaucoma and 1 had an Ahmed Glaucoma Valve (New World Medical, Rancho Cucamonga, CA) placed.

At the 6-year follow-up examination, 1 patient with bilateral glaucoma was deceased. Of the 10 remaining eyes, 1 patient did not have ETDRS visual acuity measured by a certified tester, 1 patient was unable to perform the ETDRS protocol secondary to poor neurodevelopment, and 1 eye had visual acuity of 20/400. The remaining 7 eyes were all no light perception (Table 1).

Discussion

The glaucoma often described in ROP has been a narrow anterior angle with a shallow anterior chamber associated with a retrolental membrane pushing the iris–lens diaphragm forward or simply a swollen lens.[6,15–18] Treatment typically involves a peripheral iridectomy or lensectomy to deepen the anterior chamber.[8,19,20]

Although gonioscopy was not performed as part of the study, we believe that none of the study babies had primary “newborn” congenital glaucoma, or primary glaucoma associated with anterior segment anomalies. Infants with these problems would have been excluded from participating in the ETROP study. While we cannot exclude primary congenital glaucoma of the “infantile” and “juvenile” type, most of our cases can be categorized as secondary glaucomas. Seven eyes had shallow anterior chambers, of which 5 had retinal detachments at the time of reported onset. These eyes had the classical form of glaucoma associated with ROP.

Although a normal anterior chamber depth does not preclude a diagnosis of angle closure, the remaining 5 eyes did not have shallow anterior chambers. Given the lack of gonioscopic data, the mechanism for glaucoma in these cases is difficult to classify. Four eyes had laser treatment and 2 of these eyes had vitrectomies before 9 months of age. One possible mechanism in these 4 eyes is inflammation associated with previous ocular surgeries (Sawchyn AK, McGregor ML, Fellows RR. Pupillary block after laser photocoagulation for retinopathy of prematurity. J AAPOS 2009;13:e27–e28 [Abstract 108].). The fifth eye (no. 12), had no laser, normal depth of the anterior chamber, and normal retinal structure. It is possible that this eye had late-onset primary congenital glaucoma because it was first diagnosed at the 5-year examination. Additionally, the three eyes diagnosed with glaucoma based on the optic nerve head appearance may also represent other entities known to occur in preterm infants including optic atrophy or cupping from anterior or posterior visual pathway diseases and myopic discs.[21,22]

In 186 children with bilateral threshold ROP enrolled in the CRYO-ROP study, glaucoma was diagnosed in 2.9% of the treated eyes and 6.1% of the control eyes at the 55-year examination.[23] In our study, we do not report the incidence of glaucoma at any particular time; therefore it is impossible to compare CRYO-ROP and ETROP data. However, we do know that 718 eyes were originally enrolled in the ETROP study, and 12 eyes (12/718, 1.67%) were reported to have glaucoma at some point in the first 6 years of life. This percentage is well below the historic levels of glaucoma reported before ROP treatment was instituted.

The visual outcome for the 8 eyes with glaucoma that survived to 6 years of age and had their vision tested by a study-certified visual acuity tester was devastating. Only one eye had vision better than no light perception, and that eye was legally blind, with best-corrected visual acuity of 20/400. In 7 of the 8 eyes the poor visual outcome was felt to be due to the poor retinal outcome associated with ROP; in 1 eye it was felt to be due to cerebral visual impairment. In no case was glaucoma felt to be the primary reason for poor visual outcome.

One weakness of the present study is that the diagnosis of glaucoma was based on the pediatric ophthalmologist's best clinical judgment. There was not a strict set of criteria to be followed for making the diagnosis. This lack of diagnostic criteria may have introduced inter-examiner variability and created a risk for either under- or overdiagnosis.

Our report suggests that children with ROP develop glaucoma at higher rates than healthy children and that routine monitoring for the development of glaucoma is warranted. Improved treatment strategies for ROP may decrease the rate of glaucoma in preterm infants requiring treatment. Physicians who care for preterm infants with severe ROP should be mindful of the variability in the presenting clinical characteristics as well as the age of onset of glaucoma in this population.

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Table 1

Ocular features of eyes developing glaucoma in the ETROP study

Eyes	Exam when glaucoma first reported	Glaucom a treatment	6-year (final) VA	Treatment group	Laser	Non-glaucoma procedures before 9 mos
1[a]	9 mo	N	Died	ET	Y	
2[a]	9 mo	N	Died	CM	Y	VTX
3	9 mo	N	NLP	ET	Y	VTX
4	2 yr	N	NLP	CM	Y	VTX
5[b]	2 yr	N		CM	Y	Scleral buckle
6	9 mo	Y	NLP	CM	Y	
7	4 yr	N	NLP	ET	Y	VTX
8	9 mo	Y	NLP	CM	Y	Lensectomy/ VTX
9	3 yr	Y	NLP	ET	Y	Scleral Buckle
10	5 yr	Y	20/400	CM	Y	
11	5 yr	N	NLP	ET	Y	
12[b]	5 yr	N		CM	N	

CM, conventionally managed; *ET*, early treated; *NATP*, not able to perform; *NLP*, no light perception; *VA*, visual acuity; *VTX*, vitrectomy.

[a]Patient died before 6-year follow-up.

[b]VA could not be tested.

Table 2

Anterior segment changes at the reported onset of glaucoma

Eyes	Intraocular pressure	Corneal opacity	A/C chamber depth
1[a]		absent	shallow
2[a]		absent	shallow
3	Elevated (50 mm Hg)	present	shallow
4	Elevated [b]	absent	questionable
5	Elevated (55 mm Hg)	present	shallow
6	Elevated (44 mm Hg)	absent	shallow
7	Elevated (30 mm Hg)	absent	normal
8	Elevated [b]	absent	shallow
9	Elevated (38mg Hg)	present	shallow
10	Elevated [b]	absent	normal
11	Elevated (47 mg Hg)	present	normal
12[a]		absent	normal

A/C, anterior chamber.

[a]No information available on intraocular pressure; glaucoma diagnosis based on optic nerve appearance.

[b]diagnosis based on optic nerve appearance.

Table 3

Posterior pole changes at the reported onset of glaucoma

Eyes	Retinal structure (summary diagnosis)	C/D ratio ≥0.5	ON atrophy(pallor)
1	Normal	No	Questionable
2	Macular ectopia	No	Questionable
3	All view of the posterior pole and near periphery blocked due to total cataract or corneal opacity (due to ROP)	UG	UG
4	All view of the posterior pole and near periphery blocked due to total cataract or corneal opacity (due to ROP)	UG	UG
5	Stage 5 retinal detachment or retinoschisis	UG	UG
6	Stage 4B retinal detachment or fold involving macula	UG	UG
7	Stage 4B retinal detachment or fold involving macula	Yes	Partial
8	Stage 5 retinal detachment or retinoschisis	UG	UG
9	Stage 4B retinal detachment or fold involving macula	Yes	Partial
10	Stage 4B retinal detachment or fold involving macula	No	Normal
11	Normal	Yes	Normal
12	Normal	UG	Partial

C/D, cup/disk; *ON*, optic nerve; *ROP*, retinopathy of prematurity; *UG*, unable to grade.