Severe visual impairment in children with mild or moderate retinal residua following regressed threshold retinopathy of prematurity

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PURPOSE
To describe clinical features of patients from the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) trial who, after developing severe ROP in infancy, had minimal or moderate retinal residua in at least one eye but a visual acuity of worse than 20/200 in both eyes at the 10 year examination.

METHODS
Data from the 10 year CRYO-ROP Trial follow-up exams were evaluated to identify all patients with retinal outcomes of no retinopathy of prematurity (ROP) residua, straightened temporal vessels, or macular heterotopia in at least one eye, but visual acuity less than 20/200 in both eyes. Presence of optic atrophy, nystagmus, and optic disk cupping and developmental survey results were examined.

RESULTS
Of 247 patients examined at 10 years, 16 met our inclusion criteria. At the last age at which the following data were recorded, seven had optic atrophy at the 10 year examination, one had optic disk cupping >0.5 at the 5½ year examination, and eight had nystagmus under binocular conditions at the 24 month examination. Nine patients had a below-normal developmental test score on the Functional Independence Measure for Children (WeeFIM). After clinical data interpretation, we concluded that the predominant cause of visual impairment was postgeniculate disease in five patients, ROP in six patients, and combined anterior and posterior visual pathway disease in two patients; in three patients data were insufficient to make a determination.

CONCLUSIONS
Poor visual function with mild to moderate retinal residua of severe ROP in at least one eye is relatively rare. In such patients, anterior, posterior, or combined visual pathway disease can occur. (J AAPOS 2007;11:148-152)

The clinical scenario of a full-term infant with poor visual acuity and a normal structural eye examination is often encountered by pediatric ophthalmologists. As a general rule, if such a patient has nystagmus, anterior visual pathway disease is suspected1 and electroretinography is recommended to rule out a retinal dystrophy (eg, Leber’s congenital amaurosis, rod monochromatism). When nystagmus is absent, anterior visual pathway disease is unlikely and therefore neuroimaging is recommended to assess for central or cortical causes of visual impairment (CVI).

The clinical scenario for the child born prematurely is more complex, as there are additional risks that may produce both anterior and posterior visual pathway disease. Retinopathy of prematurity (ROP) is an important etiology of anterior visual pathway (ocular) causes of visual loss in preterm babies,2-7 and a variety of insults may affect the developing visual cortex (eg, perinatal hypoxia, intraventricular hemorrhage, periventricular leukomalacia, and hydrocephalus).8 When the child has nystagmus, severe retinal residua of ROP (retinal detachment, macular fold), and an intact visual cortex, the etiology of the visual loss is straightforward and likely isolated to the anterior visual pathway, as a diagnosis of congenital “motor” nystagmus would be untenable in the presence of profoundly decreased vision acuity. However, if a prematurely born child with poor visual acuity has only minimal or moderate retinal residua of ROP, in the presence of varying degrees of neurological insult and global developmental delay, it can be difficult to assign the relative contributions of anterior (ie, ROP) versus posterior (cortical) visual pathway disease. The purpose of this report was to describe the
clinical characteristics of patients who developed threshold ROP, who were participants in the randomized trial of the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Trial, and who had substantial visual impairment associated with minimal or moderate ROP residua.

Subjects and Methods

Two hundred ninety-one children who developed threshold ROP in one or both eyes when they were newborns participated in the CRYO-ROP Trial, in which eyes were randomly assigned to observation or to ablation of the retinal periphery with cryotherapy. At age 10 years, 247 (96.9%) of the 255 surviving children were examined by a study-certified ophthalmologist and had monocular visual acuity measured by a study-certified vision acuity tester with Early Treatment of Diabetic Retinopathy Study (ETDRS) logMAR visual acuity charts. In this report a small subset of 16 children was identified at the 10 year examination who, as defined by the CRYO-ROP study, had an unfavorable visual outcome (20/200 or worse) in both eyes despite a favorable structural outcome (retinal residua of macular heterotopia or less, with no history of retinal detachment or vitrectomy) in at least one eye.

In addition to the evaluation at age 10 years, each child had undergone periodic study examinations performed by study-certified ophthalmologists. Data on retinal and optic nerve anatomy were accrued via examiners’ clinical assessment of findings on binocular indirect ophthalmoscopy; although baseline photographs were taken in the first year of life, serial fundus photographs were not obtained throughout the course of the study. Information recorded included presence or absence of optic atrophy at age 3 months, 12 months, 24 months, and 10 years; presence or absence of optic disk cupping >0.5 at 5.5 years (the first age at which it was recorded) and 10 years; and presence or absence of nystagmus at ages 3, 12, and 24 months. Answers to questions about developmental status were obtained from the child’s parent or guardian as part of the 12 and 24 month study examinations; these questions were included on the ophthalmologic examination forms and were not part of a larger neurodevelopmental assessment battery. The questions were designed to identify those children with moderate to severe delays as most children should be able perform the task queried. At age 5½ years, the child’s neurodevelopmental functional status was assessed using the WeeFIM. At 10 years, a questionnaire concerning the child’s health-related quality-of-life (the Health Utilities Index [HUI]) was administered to parents. However, because visual function is an integral part of the HUI3 outcome score, these results cannot be used as a measure of a child’s neurodevelopmental status independent of visual acuity, and thus, are not presented in this article.

Prior to analyzing the data, we decided that, in cases in which both eyes had a favorable structural outcome, data for retinal residua of ROP, optic atrophy, and cup/disk ratio would be reported from the eye with better visual acuity; in cases where both eyes had equal visual acuity, data would be reported from one eye chosen randomly to avoid selection bias. However, data analysis indicated that, in all cases, only one eye had a favorable structural outcome; so, in each case, data were reported for that eye. Nystagmus was judged present based on the recorded responses of the study-certified examiners. In some cases where data were missing, clinical inferences were made (see e-Supplement 1 and corresponding notes, available at jaapos.org).

Results

Sixteen patients were identified who met the inclusion criteria of a poor visual outcome in both eyes and a favorable retinal structural outcome in at least one eye. Of interest, all 16 had a favorable structural outcome in only one eye; the fellow eye had undergone vitrectomy following a total retinal detachment or was graded as having an unfavorable structural outcome (partial or total retinal detachment) on at least one examination. The supplemental table (e-Supplement 1, available at jaapos.org) presents the ocular findings from the eye with the favorable structural outcome for each child, as well as the developmental findings for these 16 children.

Optic nerve evaluation focused on the presence of optic atrophy and increased cupping of the optic disk. Optic atrophy was present or questionably present at the 10 year examination in nine children; it was present or questionably present at 3 months in only two of these children, at 12 months in six of these children, and at 24 months in four of these children. Two children with optic atrophy or questionable optic atrophy at 10 years had normal-appearing discs at all ages at which data were previously recorded. Increased cupping of the optic nerve (>0.5) was noted in only one patient at 5.5 years and in none of the remaining patients at 10 years.

Nystagmus under binocular conditions was present in 2 of 12 patients with data at the 3 month examination, 5 of 13 patients at the 12 month examination, and 8 of the 14 patients for whom data were recorded at the 24 month examination; one patient with nystagmus at 3 and 12 months had “absent” recorded at 24 months.

To provide an indication of overall developmental status for these children, results of the developmental questions asked at each examination were reviewed. At 12 months, only 50% (8/16) of the children were able to sit unassisted, but 75% (12/16) were able to grasp objects. At 24 months, 63% (10/16) of the children could feed themselves; 63% (10/16) could walk, and 75% (12/16) could speak at least three words. At age 5.5 years, a normal WeeFIM score (>95) was present in 44% (7/16), and a WeeFIM score compatible with severe disability (<77) was present in 56% (9/16); no children fell into the intermediate category.

Discussion

Parents of a premature infant with severe ROP are understandably quite concerned about the child’s future visual potential. The role of the ophthalmologist is to counsel the family regarding the short- and long-term ocular se-
quele of ROP, as well as the possibility that postgeniculate disorders may preclude normal visual acuity. Although many premature children have poor visual acuity that is clearly due to ROP residua, others show visual disability that seems out of proportion to the retinal abnormalities, and in some eyes that have very poor visual acuity, the posterior pole appears completely normal. In this report, we have documented the retinal anatomy, optic disk appearance, presence or absence of nystagmus, and neurodevelopmental status over a 10 year period for 16 patients from the CRYO-ROP Trial in whom the visual disability is out of proportion to the ROP residua. This report provides insight into the possible etiologies of visual acuity loss in these children by assimilating the variety of clinical parameters recorded for each patient.

An association between central nervous system (CNS) damage and prematurity has been well described in the literature. Fledelius reported a 51% incidence of CNS problems in infants born in Denmark at gestational ages 25 to 35 weeks, regardless of whether they developed ROP. However, another Danish study documented a three-fold increase in CNS damage in premature infants with ROP as opposed to those without ROP. Jacobson and colleagues have reported major neurological impairment (mental retardation, cerebral palsy, epilepsy) in 75% of children blinded from ROP.

In the past, clinicians have grouped all retrogeniculate causes of visual loss together under the umbrella of “cortical visual impairment.” The term “postgeniculate visual loss” may be more appropriate. Although many preterm infants have diffuse or global brain injuries, advances in neuroimaging of the in utero anatomy of developing neural vasculature have led to the ability to segregate perinatal injuries into those affecting the gray matter (cortical) from white matter (subcortical) disease. In term infants, hypoxic damage affects primarily the watershed zones of the cerebral cortex, that is, the frontal and parieto-occipital regions. However, embryologically, the deep venous drainage system of the brain develops earlier than the cortical systems, and, as a result, the watershed zone in preterm infants is the subcortical area. Thus, premature infants, in contrast to term babies, are more likely to sustain periventricular injury (periventricular leukomalacia, or PVL).

Although Brodsky and colleagues have delineated various clinical characteristics, including strabismus, gaze abnormalities, and optic nerve hypoplasia, that can help differentiate between cortical and subcortical central visual loss, optic atrophy is a nonspecific finding, occurring in about one-fourth of patients with either cortical or subcortical insults. Hoyt and Good have stated that both optic atrophy and optic nerve hypoplasia in children may occur as a result of prenatal brain damage, particularly when hypoxia is the cause, as a result of transsynaptic degeneration across the lateral geniculate nucleus; development of such optic atrophy is not instantaneous, but rather progressive over time, as conveyed in an antegrade fashion across the synapse. Van Buren has reported acquired transsynaptic degeneration following occipital ablation with subsequent optic atrophy in adolescent primates, but Miller and Newman reported a normal fundus almost six decades after a cortical stroke in a human. Another potential ophthalmoscopic sequela of subcortical visual loss (PVL) is nonglaucomatous optic disk cupping, attributed to bilateral damage to the optic radiations with retrograde transsynaptic degeneration of axons. However, no incidence data for this finding are available in the literature, nor is it clear whether the temporal profile of the development of these changes differs in premature versus term infants.

We segregated our study population into the four following clinical subgroups: group 1: patients likely to have postgeniculate disease as the sole or primary cause of visual loss; group 2: patients likely to have ROP or other anterior visual pathway disease as the primary cause of visual loss; group 3: patients with combined anterior and posterior visual pathway disease; and group 4: those in whom insufficient data are available to make a determination.

Part of our subgroup classification relied on the presence or absence of binocular nystagmus. Although classic teaching has been that nystagmus in children with poor visual acuity generally signifies bilateral prechiasmal disease and is very rare in cortical visual loss, various authors have reported nystagmus in the latter group of patients. In their seminal review of cortical visual impairment, Good et al state that “fixation nystagmus does not occur in CVI, unless bilateral anterior visual pathway defects coexist,” and Fielder and Evans state that “a functioning geniculo-locistiate system is a prerequisite for the development of horizontal nystagmus.” However, various others have reported the presence of nystagmus in patients with cortical visual loss at rates from 11% to 84%. Huo et al noted nystagmus in 11% of such patients, but they included children with optic nerve and retinal disease; they themselves state that, in their cohort, “the nystagmus was presumably caused by concurrent anterior visual pathway disease.” O’Keefe et al noted nystagmus in 17.6% of patients who suffered intraventricular hemorrhage, but comorbid anterior visual pathway disease in their cohort included optic nerve atrophy or hypoplasia in 38%, and ROP in almost 50% (Stage 3 or worse in one-third of these). Thus, the frequency of nystagmus in patients with normal fundi would be very low, if present at all, Jacobson et al similarly reported nystagmus in 16/19 children who suffered periventricular leucomalacia. However, of these 16 cases, “easily recognizable” nystagmus was present in only six patients (38%); nine patients (56%) had “clinically detectable” latent nystagmus, while another four children (25%) had eye movement recordings consistent with latent nystagmus. Only two (12%) of their cohort had an eye movement tracing consistent with the infantile nystagmus syndrome. It is unclear whether these patients had any concomitant anterior visual pathway disease, and the authors themselves state that some of their cohort could “be corresponding to the motor form of congenital nystagmus.
Development of binocular nystagmus may indicate a consistent with retrogeniculate visual loss. However, the eye, with optic atrophy and a very low WeeFIM score, all patient 12 had a normal posterior pole in the favorable acuity.

There were five children in whom postgeniculate disease was most likely the sole or primary cause of poor vision acuity (Patients 1-5). Two of these patients had completely normal retinal anatomy in the favorable eye; two had straightening of the temporal vessels without macular heterotopia, and one had macular heterotopia. None of these five patients had nystagmus under binocular conditions at 24 months, and only one had definite optic atrophy that was detected only at age 10 years. In another whom optic atrophy was questionable, nonglaucomatous cupping was observed. Four of these five children had very low WeeFIM scores; although this is not diagnostic of cortical visual impairment, it is consistent with profound CNS dysfunction. One might argue that some of these children were capable of ocular resolution of better acuity, but could not perform testing due to neurologic abnormalities. Nevertheless, the poor visual acuity scores of these children, as measured with study procedures, is still due to central issues rather than ocular disease. Although patient cooperation may always be an issue in evaluating such children, none of the subjects in this study were unable to be examined.

ROP or other anterior pathway disease was likely the primary cause of visual loss in another six patients (Patients 6-11). Retinal evaluation of the favorable eye revealed macular heterotopia in each case. All of these patients had nystagmus present under binocular conditions at 24 months. Two of these patients had definite optic atrophy at 10 years, with questionable optic atrophy in another. It is not possible to discern whether this optic atrophy is a result of retinal or postgeniculate disease, but the presence of nystagmus is supportive of the hypothesis that the cause of their visual loss is weighted more heavily toward anterior visual pathway disease. We cannot be certain whether the nystagmus represents the infantile nystagmus syndrome, manifest latent nystagmus, or both. However none of these possibilities is consistent with nystagmus generated from cortical disease. Five of these six children had a normal WeeFIM score, which is inconsistent with diffuse or global CNS injury and supports a minimal role, if any, of neurologic disease in the etiology of the poor vision acuity.

Combined anterior and posterior visual pathway disease was likely present in two children (Patients 12 and 13). Patient 12 had a normal posterior pole in the favorable eye, with optic atrophy and a very low WeeFIM score, all consistent with retrogeniculate visual loss. However, the development of binocular nystagmus may indicate a component of prechiasmal disease as well. Patient 13 had macular heterotopia and nystagmus, consistent with visual loss from ROP, but also developed optic atrophy and had a WeeFIM score of 43, which may reflect a component of postgeniculate visual loss.

Insufficient data were available to make a determination for three patients (Patients 14-16). Patients 14 and 15 had straightened vessels, and one developed optic atrophy and had a very low WeeFIM score. However, no data are available regarding the presence of nystagmus at 12 or 24 months, making it unwise to render a judgment regarding the likelihood of anterior visual pathway disease. Patient 16 had retinal residua of straightened vessels and also developed optic atrophy. Binocular nystagmus was present at 3 and 12 months but not noted at 24 months. Because this would be a very unusual clinical presentation, and because we do not have detailed information regarding neurologic status, these data do not allow us to assign a diagnostic category.

Although our data set is incomplete, we believe the following conclusions are generalizable to those very low birth weight children who develop severe ROP and have a favorable retinal outcome in at least one eye but poor visual function in both eyes. First, a poor visual outcome in both eyes with a normal posterior pole in at least one eye after regressed threshold ROP was rare. Among the 247 patients from which our study population is drawn, none had a poor visual outcome in both eyes with a normal retinal examination in both eyes at 10 years of age, and only 3 of the entire cohort had a poor visual outcome in both eyes with a normal posterior pole in one eye. It remains unclear why none of our subject population had a favorable structural outcome in both eyes.

Second, among patients with a favorable retinal outcome in at least one eye but poor vision acuity in both eyes, presumed postgeniculate disease and anterior visual pathway disease occurred with similar frequency. This may be in part because macular abnormalities that could significantly impair visual acuity (eg, pigmented disturbances, atrophy) are included in the study definitions of favorable retinal anatomy.

Third, when nystagmus occurs in relation to anterior visual pathway disease, it may not be present in early infancy; only one of eight patients with nystagmus at 24 months had definite nystagmus at 3 months, but four had nystagmus by age 12 months. Thus, the absence of nystagmus at birth or in the first several months of life cannot be used as a clinical marker for postgeniculate visual loss and does not rule out anterior visual pathway disease. Our results demonstrate, not surprisingly, that nystagmus due to ROP may not develop for several months, similar to nystagmus associated with congenital cataracts, congenital retinal dystrophies, or congenital optic nerve abnormalities.

Fourth, although optic atrophy as a marker for retrogeniculate disease may occur, its absence does not rule out this diagnosis; of the five patients likely to have central disease as the main cause of their visual loss, optic atrophy
was definitely present in only one case, and questionably present in another. Similarly, optic disk cupping as a marker of CVI or PVL appears to be fairly uncommon, occurring in only one of our cases, which were culled from a group that represents the very population in whom this finding would be most likely. We cannot comment on the pattern of optic disk pallor (eg, diffuse, sectoral, “bow-tie”) or rate of development of optic atrophy in our cohort since these data were not collected.

Deficiencies of this study include those inherent in retrospective data reviews. We do not have information on results of neuroimaging, electrophysiology, or detailed neurologic evaluation of these patients, all of which would be needed to accurately separate ocular from cortical disease. Furthermore, the topic of this article was neither a primary nor a secondary outcome of the CRYO-ROP Trial, and data collection was not designed with this particular subpopulation in mind. This article cannot address the incidence of cortical visual impairment in the entire population of premature infants, and our data are representative only of those infants with poor vision acuity following severe ROP with a favorable retinal outcome in at least one eye. Nevertheless, these data provide useful information for clinicians who examine and treat very low birth weight babies with severe ROP.

References
### e-Supplement 1. Clinical characteristics of study population

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<thead>
<tr>
<th>Subject</th>
<th>Eye with favorable retinal residua at 10 yr</th>
<th>Optic atrophy</th>
<th>Cupping &gt;0.5</th>
<th>Manifest nystagmus</th>
<th>Development at 12 mo</th>
<th>Development at 24 mo</th>
<th>Speaks three words</th>
<th>Sitting</th>
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Group 2: Likely predominantly ROP or other anterior visual pathway disease

|         | OS   | MH  | —  | N  | N  | Q  | —  | A  | —  | P  | P  | 1  | 1  | 1  | 1  | 1  | 119  |
|         | OS   | MH  | N  | N  | N  | N  | A  | A  | —  | A  | P  | 1  | 1  | 1  | 1  | 1  | 125  |
|         | OS   | MH  | N  | Q  | N  | P  | A  | A  | P  | P  | P† | 1  | 1  | 1  | 1  | 1  | 103  |
|         | OD   | MH  | N  | N  | N  | N  | A  | A  | A  | P  | P† | 1  | 1  | 1  | 1  | 1  | 70    |
|         | OD   | MH  | N  | Q  | P  | P  | A  | A  | A  | P  | P  | 1  | 1  | 1  | 1  | 1  | 105   |
|         | OD   | MH  | N  | N  | N  | N  | A  | A  | A  | A  | —  | P  | 1  | 1  | 1  | 1  | 1  | 100   |

Group 3: Likely combined anterior and posterior visual pathway disease

|         | OD   | N  | N  | N  | N  | P  | A  | A  | A  | A  | P  | 3  | 2  | 1  | 1  | 2  | 50    |
|         | OD   | MH  | N  | Q  | Q  | P  | A  | A  | —  | A  | P  | 3  | 2  | 2  | 2  | 3  | 43    |

Group 4: Data insufficient for determination

|         | OD   | SV  | N  | N  | N  | N  | A  | A  | A  | A  | A† | —  | —  | 2  | 1  | 1  | 1  | 1  | 103   |
|         | OD   | SV  | N  | N  | Q  | P  | —  | A  | A  | —  | —  | 3  | 1  | 1  | 1  | 1  | 53    |
|         | OD   | SV  | Q  | N  | P  | P  | A  | P  | P  | A† | —  | 1  | 1  | 2  | 1  | 2  | 35    |

**OD**: right eye; **OS**: left eye; **mo**: months; **yr**: years; **NL**: normal posterior pole retina; **SV**: straightened vessels; **MH**: macular heterotopia; **N**: no; **Q**: questionable; **A**: absent; **P**: present; **1**: yes; **2**: questionably; **3**: no. WeeFIM scores out of maximum 126; >95 considered normal; <77 considered severe disability. —: missing data

*No score recorded for binocular nystagmus, but presumed to be absent since nystagmus recorded as present OD and absent OS.
†No score recorded for binocular nystagmus, but presumed to be present since nystagmus recorded as present OD and present OS, and binocular nystagmus was recorded at the preceding (12 month) examination.
‡No score recorded for binocular nystagmus, but presumed to be absent since nystagmus recorded as absent OD and absent OS.