11-3-2006

Occipital White Matter Volumes Predict Visual Motor Outcome in Preterm Infants with Retinopathy of Prematurity (ROP)

Renu Chundru
Yale University

Occipital White Matter Volumes Predict Visual Motor Outcome in Preterm Infants with Retinopathy of Prematurity (ROP)

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Renu Chundru

2006

Table of Contents

Acknowledgements:

Thesis Advisor: Dr. Laura Ment, Department of Pediatrics, Yale University
Karol Katz, Yale University
Dr. Betty Vohr, Department of Pediatrics, Brown University
Dr. Shelli Kesler, Department of Psychiatry, Stanford University

Abstract:

OCCIPITAL WHITE MATTER VOLUMES PREDICT VISUAL MOTOR OUTCOME IN PRETERM INFANTS WITH RETINOPATHY OF PREMATURITY (ROP).
Chundru, Renu, Vohr, Betty, Kesler, Shelli, and Ment, Laura R. Section of Neurology, Department of Pediatrics, Yale University, School of Medicine, New Haven, CT.

Although very low birth weight preterm (VLBW) infants with grade 3,4 retinopathy of prematurity (ROP) are at high risk for unfavorable visual outcomes, the middle school vision motor integration (VMI) skills and cognitive outcome scores of these children remain largely unknown. Data for 323 very VLBW survivors of the Multicenter Randomized Indomethacin IVH Prevention Trial (BW 600 – 1250 g) were analyzed to test the hypothesis that grades 3, 4 ROP would be an important predictor of cognitive and VMI skills. 3 subgroups were evaluated: ROP negative (N = 163), ROP grades 1,2 (N = 137) and ROP grades 3,4 (N = 23) were evaluated prospectively at 12 years of age with a neurocognitive battery. High-resolution volumetric MRI scans were quantified for 40 of the study subjects, and occipital brain volumes were correlated with Beery VMI scores. Children with ROP 3-4 had ↑ vision impairment and lower test scores. Whole brain volumes were significantly less for children with any grade of ROP ($p = 0.02$), occipital white matter volumes tended to be less for the same study subjects ($p = 0.08$) and both total occipital brain volumes and occipital white matter volumes were significantly correlated with Beery VMI scores ($r=0.610$, $p = 0.009$ and $r = 0.652$, $p =0.005$, respectively). Prematurely-born children with a history of grade 3-4 ROP continue to have ↑ vision impairment, special needs and lower performance on cognitive, language and visual motor integration scores at age 12 years. Both whole occipital brain volumes and occipital white matter volumes were predictive of VMI scores for children with ROP. (supp by NS 27116)

Objective: Data for 323 very VLBW survivors of the Multicenter Randomized Indomethacin IVH Prevention Trial (BW 600 – 1250 g) were analyzed to test four hypotheses:

(1.) There exist many risk factors for retinopathy of prematurity.
(2.) Grades 3, 4 ROP are important predictors of negative visual sequelae.
(3.) Grades 3, 4 ROP are important predictors of cognitive and VMI skills.
(4.) Any stage ROP results in structural changes of the brain persisting into childhood.

Introduction:

Retinopathy of prematurity (ROP) is the leading cause of childhood blindness in the United States (7) and has been estimated to cause visual loss in 1300 children and severe visual impairment in 500 children each year in the United States (47). Retinopathy of prematurity was first described in 1942 as a proliferative retinopathy which affects premature infants of low birth weight and young gestational age. It has been found that up to 30% of very low birth weight infants will develop severe retinopathy of prematurity and 8% will progress to blindness (7). In infants <1251 grams, the incidence of retinopathy of prematurity was found to be a staggering 68% (41). The findings of the previous study were compared to those of infants born in 1986/1987 in the CRYO-ROP Study and it was found that the overall incidence of retinopathy of prematurity is similar in both studies. In addition, the gestational age of onset, rate of progression and the time of onset of prethreshold disease has changed very little since the CRYO-ROP study which was performed years ago (41).

During normal retinal development, vessels migrate from the optic disc to the ora serrata (the area at which the choroid and retina end) at around 16 weeks of gestation. By 36 weeks of gestation, mature vessels differentiate from these vessels and extend to the nasal side, and by 39-41 weeks these vessels extend temporally (50). The fundamental process underlying the development of retinopathy of prematurity is the incomplete vascularization of the retina (1). The location of the interruption of normal vaculogenesis is determined by the time of premature birth. The abnormal neovascularization of retinopathy of prematurity is believed to be a result of hypoxia (1). There has been a plethora of angiogenic factors which are believed to be released after tissue hypoxia,

including basic fibroblast growth factor (bFGF), transforming growth factor–α (TGF-α), and tumor necrosis factor–α (TNF-α) and which are believed to play a role in retinopathy of prematurity. However, some of the greatest attention has been focused on the vascular endothelial growth factor (VEGF), which is found to be elevated in patients with many proliferative retinopathies, including retinopathy of prematurity (50). VEGF is an angiogenic factor which is specific to endothelial cells and its production is increased by hypoxia and is believed to play a major part in mediating active intraocular neovascularization in patients with ischemic retinal diseases (51). VEGF is believed to be induced by retinal ischemia, diffusible, more concentrated in vitreous than in the aqueous humor, increased during active proliferation, reduced during quiescent proliferation, and diminished after successful laser therapy (51).

It has been found that in ocular tissue the production of VEGF is induced by hypoxia in retinal pigment epithelial cells (49). One study which examined VEGF concentration in various retinal diseases found that VEGF stimulated the growth of retinal endothelial cells in vitro, as did vitreous fluid containing measurable VEGF. The stimulation of the growth of retinal endothelial cells was inhibited by VEGF-neutralizing antibodies (51).

In this same study, the VEGF concentrations in samples of aqueous and vitreous humor from patients with neovascular disorders were compared with those in samples from patients without neovascularization. VEGF was detectable in more patients with revascularization, and the concentration of VEGF in these patients was very high (51). In addition, this study found that the concentration of VEGF declined in all patients who had decreased neovascular activity after laser photocoagulation. It is believed that it is the

reduction in retinal ischemia after laser therapy that reduces the production of angiogenic factors and suppresses neovascularization (51).

Of course, as previously discussed, it is believed that VEGF solely is not responsible for the neovascularization that occurs during retinopathy of prematurity, but also involves other proliferative factors and their interaction with VEGF, including basic fibroblast growth factor, insulin-like growth factors, and pigment-epithelium derived factor (PEDF).

In a different study, the relationship between IGF-1 and VEGF was examined. It was found that IGF-1 is required for VEGF activation of vascular endothelial cell proliferation and survival pathways (39). The IGF-1 levels were found to be deficient after premature birth, allowing for retinal vascular loss and subsequently retinopathy of prematurity (39.). It was postulated that the restoration of IGF-1 to levels found in utero may possibly be used in the future for the prevention of retinopathy of prematurity (39).

In one study cultured monkey retinal pigment epithelial (RPE) cells were exposed to low oxygen concentration in order to stimulate hypoxia (36). In this study, it was found that the level of the pigment epithelium-derived factor (PEDF), a protein secreted by the retinal pigment epithelium was decreased in the RPE/choroids of the monkey cells (36). PEDF is believed to act on retinal survival and angiogenesis, and both hypoxia and VEGF are thought to downregulate PEDF through proteolytic degradation (36). A better understanding of the role of VEGF and other proliferative factors is needed in order to better understand and treat retinopathy of prematurity.

Recently the role of genetic factors in the development of severe ROP has been studied. In a recent study, genetic analysis was performed on sixteen children. Missense

mutations (R121W and L108P) in the third exon of the ND gene were found in 4 patients affected by ROP (3). These mutations were not present in 50 unrelated healthy control subjects, suggesting that mutations in the ND gene may play a role in the development of severe ROP in premature infants (3).

In a more recent study, it was found that 2 patients in a cohort of 100 patients with ROP demonstrated the presence of ND mutations. These mutations were not found in any of the controls. Although the ND gene is not frequently involved in advanced ROP, this study demonstrates that genetic influences may play an important role in the development of severe ROP in some premature infants (4).

The classification of retinopathy of prematurity is based on several key observations which are essential to the description of retinopathy of prematurity (42). The first key observation used involves the location of retinal involvement by zone. To define the location of the retinopathy, 3 concentric zones of retinal involvement have been defined – each zone is centered on the optic disc (42). Because there is a direct correlation between severity of disease and amount of avascular retina, the location of the border between vascularized and avascular retina is an important prognostic sign (51).

The second key observation used is the extent of retinal involvement recorded as hours of the clock or as 30 degree sectors (42).

The third observation used is the staging of the severity of the retinopathy at the junction of the vascularized and avascular retina. This classification is the most pertinent to our study, as we separated the three groups of premature infants based on the stage of severity of the retinopathy of prematurity. 5 stages are used to describe the abnormal vascular response at the junction of the vascularized and avascular retina. As more than 1

stage of retinopathy of prematurity may be present in the eye, the stage of the eye is determined by the most severe manifestation which is present (42). Stage 1 is considered the demarcation line, which is a thin line which separates the avascular retina from the vascularized retina. The abnormal vessels that lead to the demarcation line are relatively flat and lie within the plane of the retina. Although vascular changes can be apparent prior to the development of the demarcation line, such as the dilation of the peripheral retinal vessels, these changes are insufficient for the diagnosis of ROP (42).

The second stage of retinopathy of prematurity is defined as a ridge which arises in the area of the demarcation line, but has a height and width, extending above the plane of the retina. The ridge may change from white to pink and vessels may leave the plane of the retina posterior to the ridge to enter it (42).

Stage three retinopathy of prematurity is defined by neovascularization that extends from the ridge into the vitreous, and can cause a ragged appearance as the proliferation becomes more extensive. The severity of a stage 3 lesion can be subdivided into mild, moderate, or severe depending on the extent of extraretinal fibrovascular tissue infiltrating the vitreous (42).

Stage four is defined by a partial retinal detachment. This stage is divided into stage 4A (extrafoveal) and stage 4B (foveal) partial retinal detachments (42). Typically, the retinal detachments begin at the point of the fibrovascular attachment to the vascularized retina (42).

The final stage of retinopathy of prematurity is stage 5, total retinal detachment, which is generally tractional and may occasionally be exudative and usually funnel shaped, the configuration of which permits a subdivision of this stage (42).

The final key observation used in the classification of retinopathy of prematurity is the presence or absence of dilated and tortuous posterior pole vessels, which is significant for plus disease (42). "Plus disease" occurs when the peripheral vascular shunting of blood is so overwhelming that it leads to marked venous dilation and arterial tortuosity in the posterior pole. Plus disease is the hallmark of rapidly progressive ROP and is notated by adding a plus sign after the number of the ROP stage (51).

Key Classification criteria for retinopathy of prematurity:

(1) the location of retinal involvement by zone

(2) the extent of retinal involvement by clock hour

(3) the state or severity of retinopathy at the junction of the vascularized and avascular retina

(4) the presence or absence of dilated and tortuous posterior pole vessels (plus disease).

The first international classification of retinopathy of prematurity was published in 1984 (42). Recently in 2005, an international group of pediatric ophthalmologists and retinal specialists modified some aspects of the International Classification of Retinopathy of Prematurity (ICROP) done in 1984, using recent evidence since the original publication (42).

Some of the changes to the original classification include the addition of a more virulent form of retinopathy which is observed in the smallest babies. In addition, an intermediate level of plus disease as well as a practical tool for estimating the extent of zone 1 was added (42).

As the treatment of threshold retinopathy of prematurity can lead to a better visual outcome in some infants, screening examinations of premature infants have become increasingly important. It has been suggested that screening for ROP should be performed in all infants with a birth weight < 1500g, a gestational age ≤ 28 weeks, and in infants weighing between 1500g and 2000g with an unstable clinical course. In most cases, at least two examinations should be performed. The first examination should occur between 4 and 6 weeks chronological age or between the 31st and 33 weeks of postconceptional age, whichever occurs later and should be continued until 45 weeks of postmenstrual age, or the progression of retinal vascularization into zone III (5, 50). Infants at high risk for progression to threshold disease should be examined weekly. Infants with less severe disease in zone 2 or disease restricted to zone 3 should be examined every 2 weeks until the fundus matures (51).

The ultimate goals in the treatment of threshold ROP is the prevention of any retinal detachment or scarring and optimization of visual outcome. Treatment involves ablation of avascular retina by either cryotherapy or laser photocoagulation. The laser has become the instrument of choice for ophthalmologists throughout the world for the treatment of threshold retinopathy of prematurity (2, 50). In order to determine when treatment is indicated, the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) sought to determine threshold ROP, the severity of ROP for which a given eye had an equal chance of spontaneous regression or progression to untoward outcome. Threshold disease has become the accepted point at which treatment should begin. Currently threshold disease is considered stage III+ ROP in zone 1 or 2 occupying at least 5 contiguous clock hours or 8 noncontiguous clock hours of retina

(51). Overall, in one study it was found that 65.8% of premature infants developed some degree of ROP and 6% reached threshold retinopathy of prematurity (48). Infants with threshold ROP should receive peripheral ablative therapy within 72 hours of diagnosis (51).

With an increasing number of premature infants being born, a more complete understanding of retinopathy of prematurity has become all the more important. In this study we have sought to understand the risk factors for retinopathy of prematurity, as well as the sequelae of retinopathy of prematurity, focusing on the visual and cognitive outcome of the children at 12 years of age, as well as looking at the effect on the brain itself through MRI scans at 12 years of age.

The various risk factors for the development of retinopathy of prematurity have been examined numerous times. There has been agreement for some – a decreasing gestational age, decreasing birthweight, and increasing apneic episodes. However, there is still some argument for the significance of other risk factors studied – including race, sex and surfactant use, among others. In one study which examined 425 premature babies for ROP between January 1994 and December 1998 in Seoul, Korea retinopathy of prematurity was found in 20.7% of the premature infants examined (6). The risk factors found in this study included a gestational age $\leq$ 28 weeks, a birthweight $\leq$ 1000 g, ventilator care for $\geq$ 48 hours, surfactant use, and apnea. In addition, it was found that frequent apneic attacks increased the progression of pre-threshold ROP to threshold ROP (6).

Likewise, another study which looked at the risk factors for retinopathy of prematurity found that infants who developed retinopathy of prematurity had a lower

gestational age, a lower birth weight, a higher number of days on oxygen/ventilator, more days in the ICU, a greater need for steroids, and a higher incidence of sepsis when compared to infants who did not develop ROP (7). In this study the variables which were found to be statistically significant were age, weight, days on oxygen, days on the ventilator, days in the ICU, the need for certain medications (such as steroid use, surfactant, antibiotics, theophylline), and complications of prematurity (sepsis, seizures, intraventricular hemorrhage) (7). An increased risk of retinopathy of prematurity in infants weighing less than 1600 g, included intraventricular hemorrhage. (52)

In one study it was found that significant risk factors for retinopathy of prematurity included lower gestational age, decreased birth weight, and the number of erythrocyte transfusions within the first 4 weeks of life (38).

Although there are many elements which are known to be risk factors of retinopathy of prematurity, there are also many risk factors of which a consensus has yet to be found. There have been many studies which looked at race and the incidence of retinopathy of prematurity, yet no consensus has been reached on this subject. A recent study which looked at Chinese, Indian, and Malay children in Singapore found no correlation between race and the incidence of retinopathy of prematurity (53). In one study, no correlation was found between the race of the infant or the sex of the infant and the risk of developing retinopathy of prematurity. A lower incidence of retinopathy of prematurity was found in the Hispanic patient compared to that of the non-Hispanic patient, but it was not statistically significant (7). However, race was found to be significant in other studies on the incidence of retinopathy of prematurity. One study found that African-American infants are less prone to severe outcome ROP than white

infants (12). In addition, another study found that Alaskan natives developed threshold ROP earlier than non-natives (37). In this study all Alaskan infants who weighed less than 1500 grams were examined from 1989 through 2003. Alaskan natives had a higher incidence of threshold retinopathy of prematurity as compared with non-Alaskan natives, and were found to progress to treatment at a younger age. 69% of Alaskan native males had threshold ROP (69%), compared with 51% of non-Alaskan native males (51%). Although the Alaskan natives had a higher incidence of threshold retinopathy of prematurity, they surprisingly were found to have a greater birth weight and required less time on ventilation, both of which are believed to be independent risk factors for retinopathy of prematurity (37).

The possible implication that gender may have on the incidence of retinopathy of prematurity is still unknown. Two studies have reported that twice the number of male infants are affected with retinopathy of prematurity (53,54). In one study it was suggested that there was an increased risk of cryotherapy in boys (10).

Another possible risk factor of retinopathy of prematurity is indomethacin use. Indomethacin is a nonsteroidal anti-inflammatory agent which acts by inhibiting prostaglandin production. It is thought that indomethacin may improve retinopathy when administered during a period of hyperoxia injury because of its effect on prostaglandin synthesis and consequently on retinal neovascularization. In a mouse model, the use of indomethacin given concurrently with oxygen administration showed an improvement in oxygen induced retinopathy, but showed no effect when indomethacin was given without supplemental oxygen (8).

The effect that surfactant therapy has had on the incidence of retinopathy of prematurity has been examined in previous studies. One study examined the effects of surfactant replacement therapy, high-frequency oscillatory ventilation (HFOV), and the general improvement in quality of care on the incidence of severe retinopathy of prematurity. It found that of all these recent developments in neonatology only surfactant replacement therapy was associated with a decreased risk for severe retinopathy of prematurity (12).

The effect that postnatal steroids have on the incidence of retinopathy of prematurity has yet to be determined. One study found that infants treated with prolonged, (greater than 24 days) of dexamethasone therapy had a significantly reduced incidence of cryotherapy when compared with those treated for a shorter period of time (10).

However, in another study the use of post-natal steroids was found to be a risk factor for retinopathy of prematurity. In one study, of 21 different factors examined only the use of steroids for lung disease was associated with the need for cryotherapy (11).

It has been postulated that preeclampsia or eclampsia may reduce the incidence of retinopathy of prematurity, since the resulting hypertension results in intrauterine stress and possibly subsequent maturation of the eyes. In one study it was found that maternal pre-eclampsia leads to a more favorable outcome for premature infants (12), but more studies are needed to confirm the possible effect that preeclampsia, and/or eclampsia may have on the incidence of retinopathy of prematurity.

Although substance abuse during pregnancy has multiple negative effects on the infant, it does not seem to have any affect on the incidence of retinopathy of prematurity.

Multiple studies have found no correlation between substance abuse and the incidence of retinopathy of prematurity. In one study no relationship was found between ROP and maternal smoking, alcohol intake, or even prenatal care (12). Similarly in another study, IV drug abuse, alcohol abuse, and no prenatal care were not found to be statistically significant predictors of ROP (7).

In the past hyperglycemia has been found to be a risk factor for the incidence of retinopathy of prematurity (46). An increased risk of retinopathy of prematurity was correlated with each 10 mg/dl increase of mean glucose (46) but further studies are needed to make any generalized conclusions.

Dopamine has also been examined as a possible risk factor for retinopathy of prematurity. In one study it was found that dopamine use may be an indicator for the development of prethreshold and threshold retinopathy of prematurity. 18/41 infants were treated with dopamine for hypotension. It was found that a higher percentage of the dopamine treated infants reached prethreshold retinopathy of prematurity and threshold retinopathy of prematurity. In the dopamine treated group 67% of infants reached prethreshold retinopathy of prematurity and 39% reached threshold retinopathy of prematurity. Comparatively, in the non-dopamine treated group only 13% reached prethreshold retinopathy of prematurity, and only 4% reached threshold retinopathy of prematurity (13). In another study, it was found that an increased risk of retinopathy of prematurity was correlated with a history of dopamine infusion (52).

One study which examined the use of vitamin E supplementation in the prevention of morbidity and mortality in preterm infants found that in very low birth weight infants, vitamin E supplementation increased the risk of sepsis, and reduced the

risk of severe retinopathy and blindness among those examined (14). In another study it was found that a decreased risk of retinopathy of prematurity was correlated with each IU/kg/day of vitamin E supplementation (46).

Although there has been great strides in understanding the various risk factors of retinopathy of prematurity, we are still far from being able to understand the interplay and importance that each risk factor ultimately has on the incidence of retinopathy of prematurity. For example, although there has been a decrease in the gestational age and birthweight in recent years, there has also been a decrease in the incidence of retinopathy of prematurity. One study found that between the years 1989 and 1998, despite there being a decrease in the mean gestational age and birthweight there was also a significant reduction in the incidence of retinopathy of prematurity (1). The reduced incidence of retinopathy of prematurity was attributed to improvements in ventilation techniques and the overall care of the neonate, in particular the use of prenatal steroids and surfactant (1), thereby demonstrating that although we may be able to demonstrate the effect that various risk factors may have on the incidence of retinopathy of prematurity, we are still far from being able to determine which factors are ultimately the most important in the occurrence of retinopathy of prematurity in the premature infant.

As we have previously discussed many risk factors have an effect on the incidence of retinopathy of prematurity. In turn, ROP itself is believed to be a risk factor for negative visual and cognitive sequelae for the infant. Prematurity on its own has long been seen to have a tremendous effect on the cognitive sequelae of the infants into their child and adulthood, and when ROP is factored in the effect is even more pronounced.

The relationship of cognitive sequelae to retinopathy of prematurity has been examined previously, but to our knowledge ours is the oldest group to be studied.

In one study severe retinopathy of prematurity was shown to have the strongest association with 18-month outcome (17). In another study it was found that among extremely premature infants (less than 28 weeks), with normal neonatal cranial ultrasounds, both serum bilirubin as well as the incidence of retinopathy of prematurity were associated with developmental impairment at 5 years of age. Retinopathy of prematurity was associated with a poor outcome for vision, hearing, and cerebral palsy (15). Interestingly enough in this study gestational age and birth weight were not associated with a poorer developmental outcome (15).

In one of the first studies in which health related quality of life was measured in formerly premature children with and without significant visual impairments, it was found that threshold ROP was associated with functional limitations in health attributes and reduction in health related quality of life scores at 10 years of age (16). In this study the parental perspectives on the health status and the health-related quality of life was examined in children at 10 years of age, who had a birth weight less than 1251 g and participated in the multicenter cryotherapy for retinopathy of prematurity (CRYO-ROP) study. Moreover it was found that among those children with threshold ROP, a greater reduction in health related quality of life scores were found among those children with a poor visual outcome as compared to those with better sight. Overall, the highest health related quality of life scores were found for the group of children who did not develop ROP, who consequently had birth weights that were 262 g higher and gestational ages that were 3.3 weeks greater than those of children with retinopathy of prematurity (16).

It is understandable that children with threshold retinopathy of prematurity would have higher rates of developmental, educational, and social challenges in childhood. In the CRYO-ROP Multicenter study, the educational status and special education services among children who had threshold retinopathy of prematurity was examined at 8 years of age. In this study, 33% of children who had threshold retinopathy of prematurity had major disabilities and a similar number had suffered from academic and social challenges (18).

Of 8-year-old children with a history of threshold ROP, there were significant developmental, educational, and social skill differences between those who had favorable versus unfavorable visual status in the better eye. Of the children with favorable visual status, 52 % were at grade level in academic skills, and only around ¼ required special education services. In comparison, the majority of children with unfavorable visual status required special education placements, had below-grade-level academic skills, and demonstrated social challenges involving independent play, peer interaction, and participation in age-related sports. In addition, significantly higher rates of developmental delays/disabilities, cerebral palsy, autism, and seizure disorders occurred in children with unfavorable visual status compared with favorable visual status (18). In this study it was found that favorable visual status, favorable functional ratings at 5.5 years, markers of higher socio-economic status (such as private health insurance), and non-black race were associated with significantly lower rates of both special education placement and below-grade-level academic performance at 8 years of age. The factors associated with significantly increased risk of below-grade-level performance on univariate analysis included black ethnicity, male gender, early abnormal neurologic

status, supplemental security insurance at 5.5 years, and lack of access to a car at 5.5 years (18).

As retinopathy of prematurity can interfere with the normal development of the eye, it is not surprising that it may result in a number of negative visual outcomes. It has been noted that two percent of the prematurely born children are visually impaired (<20/60) (19). The incidence of refractive errors in premature infants is 4 times more common in 10-year olds when compared with full-term controls, 29.6% versus 7.8% respectively. Astigmatism and anisometropia were more common and more severe in premature children. In addition, it has been shown that those prematurely born children with retinopathy of prematurity who were cryotreated, had the highest incidence of refractive error, followed by prematurely born children without ROP, 64% versus 26.2% respectively (19).

Although the incidence of refractive error in premature infants with retinopathy of prematurity itself is higher than controls, the stage of retinopathy of prematurity has not been shown to have an effect on the refractive error in the child (40). In one study, the development of refraction was examined in premature infants at 6 months, 2.5 years, and 10 years of age (40). No significant difference was found between the various stages of retinopathy of prematurity and similar refraction was found at 6 months, 2.5 years, and 10 years of age regardless of the stage of retinopathy of prematurity (40).

One study, which examined the etiology of the high myopia associated with retinopathy of prematurity, concluded that it is pathophysiologically distinct from the high myopia seen in full-term patients. In full-term patients, increasing myopia was associated with axial length, with smaller contributions from increased lens thickness

and lens power. However, in patients with retinopathy of prematurity, their lens-thickness/anterior-chamber-depth ratio is almost 50% higher than full-term individuals, suggesting that the etiology of the high myopia in children with previous retinopathy of prematurity is due to a disturbance in anterior segment development (20).

In one study, the visual function in very low birth weight children was compared with that of controls. It was found that the visual function in very low birth weight children was much poorer than that of controls. 63% of VLBW children had reduced visual function, compared with 36% of controls. The VLBW infants had a higher incidence of a variety of adverse visual outcomes: increased need for corrective lenses, lower corrected visual acuity, a higher incidence of strabismus, and poor contrast sensitivity. This study found that low birthweight, presence of an intraventricular hemorrhage, and a low 1-minute Apgar score predicted reduced visual function (21). In addition, it was found that among the very low birth weight children poor visual function was predictive of lower IQ, and those children with reduced visual function were more likely to have significantly impaired motor skills. Two possible explanations for the association between visual impairment and neurodevelopmental impairment were offered in the study. One possible explanation is that both impairments are a result of neurological damage. Alternatively, poor visual function may have an adverse affect on the development of motor and cognitive skills (21).

Finally, in another study it was found that ocular morbidity was significantly higher among children who were of a very low birthweight. They were found to have worse visual acuity, a higher incidence of strabismus, and a higher incidence of ROP.

Interestingly enough, a history of seizures in the perinatal period was correlated very highly with poor visual acuity (22).

As retinopathy of prematurity is thought to have enormous effects on both cognitive and visual function persisting at least until childhood, we believed that being able to structurally examine the changes that occur in the brain through magnetic resonance imaging (MRI) would be especially enlightening. In the past there have been studied performed which have looked at regional brain volumes in premature infant, but to our knowledge ours is the first study to look at the brain volumes in children who had retinopathy of prematurity.

In one of the first quantitative MRI studies of long-term outcome of regional brain volumes in preterm infants it was found that regional cortical volumes in preterm children were significantly smaller than that of controls. This difference was most significant in the sensorimotor regions, but also occurred in the premotor, midtemporal, parieto-occipital, and subgenual cortices. Subcortical gray matter in the basal ganglia, white matter in the posterior corpus callosum, and cortical grey matter in the amygdala and hippocampus were also reduced. The regional volumes were correlated significantly with gestational age at birth, 5-minute Apgar scores, and IHV within 6 hours of birth (23). In addition, it was found that full-scale, verbal, and performance IQ scores were associated positively with regional volumes, and most strongly and consistently with volumes of sensorimotor and midtemporal brain regions (23). This study found that preterm birth itself is associated with regionally specific, reductions in brain volume persisting into childhood, and that these structural changes are associated with a poorer cognitive outcome in the child (23).

Methods:

The Randomized Indomethacin IVH Prevention Trial was conducted at Women and Infants' Hospital, Providence, RI; Maine Medical Center, Portland; and Yale New Haven Hospital, New Haven, Conn. The protocols were reviewed and approved by the institutional review boards of each institution. Informed consent was obtained from all parents and children.

Between September 5, 1989, and August 31, 1992, 505 infants weighing 600 to 1250 g at birth were admitted within 6 hours of birth to 2 parallel randomized, prospective, low-dose indomethacin IVH prevention trials (24,25). All infants were examined using cranial echoencephalography (ECHO) between 5 and 11 hours after birth. Of the 505 enrolled infants, 431 had normal ECHO studies and were considered early IVH negative. Seventy-four infants had ECHO evidence for IVH at this time; these were called early IVH positive.

Subsequent scans were performed 24 and 48 hours after the first scan; 4, 5, 7, 14, and 21 days after birth; and at 40 weeks' postmenstrual age. Scans were interpreted by the institutional radiologist and independently verified by a central radiologist. In cases of disagreement, data were reexamined by all participating radiologists and a consensus was reached.

Radiologic assessment was performed without prior knowledge of the infant's clinical condition. The grading system for hemorrhages was as follows (24,25) grade 1 (blood in the germinal matrix regions); grade 2 (blood within the lateral ventricular system without ventricular dilation); grade 3 (blood within and distending the lateral ventricles); and grade 4 (blood within the ventricular system and parenchymal

involvement). Ventriculomegaly was assessed at 40 weeks' postmenstrual age (or if not available 21 days after birth). Moderate and severe ventriculomegaly were defined as measurements of 1.0 to 1.5 cm and more than 1.5 cm, respectively, at the midbody of the lateral ventricle on sagittal scan. Studies were also evaluated for focal echolucencies. All cases showing focal echolucencies had cystic areas consistent with periventricular leukomalacia (PVL) on the ultrasound performed at 40 weeks' postmenstrual age. A study infant was defined as having significant central nervous system (CNS) injury if he/she had 1 or more of the following 3 ultrasound findings: grade 4 IVH at any time following the first scan at 5 to 11 hours; PVL at term; or ventriculomegaly at term.

All infants underwent gestational age assessment using a modification of the Ballard scale (26). Prenatal, perinatal, and neonatal data were obtained by maternal interviews and review of the maternal and neonatal charts. Randomization to low-dose indomethacin was categorized as present/absent. An infant was diagnosed with bronchopulmonary dysplasia (BPD) if he/she both required oxygen supplementation and had an abnormal chest radiograph at 28 days of life (27); BPD was categorized as present/absent.

At 12 years of chronologic age, children were evaluated with the PPVT-R and the Wechsler Intelligence Scale for Children–Third Edition (WISC-III) (28), a norm-referenced instrument for assessing the intellectual function of children aged 6 years 0 months through 16 years 11 months. The WISC-III also provides 3 IQ scores: PIQ, VIQ, and full-scale IQ, with a mean (SD) of 100 (15).

Serial neurodevelopmental follow-up evaluations were performed on all study participants. At 12 years of corrected age (ie, months past the obstetric due date), each

child was tested with the Peabody Picture Vocabulary Test–Revised (PPVT-R) (30), an age-normed test that requires no verbal responses from the child and measures receptive vocabulary words of individuals aged 2½ years through adulthood. Raw scores are converted to standard scores with a mean (SD) of 100 (15) points. The PPVT-R does not require a motor response and is thus an excellent instrument for use with children with motor disabilities (31).

The Peabody Individual Achievement Test-Revised (PIAT-R) (32) is a battery of academic achievement tests for children ages 5 years 0 months to 18 years 11 months. The reading recognition, mathematics, and spelling subtests were administered. Demographic questionnaires, which included information on household composition, languages spoken in the home, educational level of the biological or adoptive/foster parent, school placement of the child, resource utilization, and need for medications, were administered to the parent/caregiver.

A standard neurologic examination was performed by the pediatric neurologist/developmental pediatrician at each site. The neurologic examination included determinations of height, weight, and occipitofrontal head circumference, assessment of visual field testing, pupillary function, eye movements, and facial strength. Tone, strength, reflexes, and cerebellar function were determined. A determination of normal, suspect, or abnormal neurologic status was made. Abnormal or suspect assessments were secondarily assessed for the presence of microcephaly, spastic diplegia, hemiplegia, or quadriplegia.

Demographic information was obtained from the primary caregivers. Maternal education was categorized as less than high school or high school graduate or higher.

Residence in a 2-parent household at 96 months of CA was coded yes/no, and parents were defined as birth mother, adoptive mother, stepmother, and/or birth father, adoptive father, and stepfather. Early intervention services including occupational therapy, physical therapy, speech, and/or language therapy were obtained from parent/caregiver report. A child was considered positive for these special services if he/she received 1 or more services at 36 months of CA, consistent with previous studies (33,34).

Study participants were divided into ROP (-), ROP grade 1-2, and ROP grade 3-4 to evaluate scores. The PPVT-R scores were selected as our primary outcome measure prior to statistical analysis, because the same test was used at all 4 measurements. The IQ scores were a secondary outcome measure. Finally, z scores were calculated for the full-scale IQ, VIQ, and PIQ scores for each child at each age.

To understand important biological or environmental factors that may be associated with testing scores, factors reported to be associated with the occurrence of retinopathy of prematurity were evaluated: Birth weight (g), gestational age (wk), male sex, 1 and 5 minute Apgar scores, administration of antenatal steroids, randomization to indomethacin, randomization to indomethacin and steroids, preeclampsia +/- eclampsia, IVH (both within first 6 postnatal hrs and at post-natal day 5), Grade 3-4 IVH post-natal day 5, administration of pressor drugs, administration of caffeine, aminionitis, BPD, Assisted ventilation for >12hrs, RDS, apnea, pneumothoraces, hypoglycemia, hyperglycemia, PVL, ventriculomegalay, and seizures at discharge.

Categorical data with no expectation of a linear trend among groups (e.g., sex) were analyzed using Fisher exact test. Categorical data with an a priori expectation of a linear trend among groups were analyzed by the $[chi]^2$ test for linear trend. The 2-sample

Wilcoxon rank sum test was used for between-group comparisons of continuous data. Because PPVT-R scores were not always normally distributed, summary statistics for this factor were reported using medians and ranges.

Hierarchical multivariate regression models were used to examine the effect of several factors simultaneously. All significant higher-order interaction terms required inclusion of all lower order (i.e., main effect) factors in the model. The first model evaluated the main effects only to determine which factors played an independent role in predicting the occurrence of ROP. Using this reduced set of important factors, a second model was developed in which the main effects and the interaction of these factors with one another were explored. A significant interaction implies that the effect of one factor on PPVT-R scores varies significantly according to the level of the other factor. All statistical analyses were performed using SAS software version 8.2 (SAS Institute Inc, Cary, NC). All P values are 2-sided and statistical significance was assigned at $P<.05$. All statistical analyses were performed by Karol Katz.

Results:

As shown in **Table 1**, there was a significant difference in the gestational ages, birth weights, 1-minute and 5-minute Apgar scores, IVH at 5 days, pressor drugs, amnionitis, bronchopulmonary dysplasia, assisted ventilation for >12hrs, respiratory distress syndrome, and periventricular leukomalacia between the ROP (-) (n=163), ROP (1,2) (n=137), and ROP (3,4) (n=23).

As show in Table 1, there were no significant differences in male sex, administration of antenatal steroids, administration of indomethacin, administration of indomethacin and steroids, preeclampsia +/or eclampsia, IVH (within first 6 postnatal hrs), grade 3-4 IVH post-natal day 5, caffeine, apnea, pneumothoraces, hypoglycemia, hyperglycemia, ventriculomegaly, and seizures at discharge between the ROP (-) (n=163), ROP (1,2) (n=137), and ROP (3,4) (n=23).

Table 1:

Characteristics	**ROP (-) (n=163)**	**ROP (1,2) (n=137)**	**ROP (3,4) (n=23)**	**p-value**
Birth weight, g	1035.2	864.6	841.7	<.0001
Gestational age, wk	28.5	27.1	27.0	<.0001
Male	82(50.31)	81(59.12)	15(65.22)	0.0823
1-Minute Apgar score, median	4.9	3.9	3.4	0.0003
5-Minute Apgar score, median	6.9	6.2	6.2	0.0012
Antenatal Steroids	59(36.20)	47(34.31)	8(34.78)	0.8009
Indomethacin	73(44.79)	73(53.28)	9(39.13)	0.8317
Indomethacin and Steroids	27(16.56)	26(18.98)	4(17.39)	0.7560

Preeclampsia +/or Eclampsia	21(12.88)	7(5.11)	3(13.04)	0.3436
IVH (within first 6 postnatal hrs)	16(9.82)	22(16.06)	5(21.74)	0.0515
Any IVH at post-natal day 5	31(19.02)	42(30.66)	11(47.83)	.0008
Grade 3-4 IVH post-natal day 5	5(3.07)	4(2.92)	3(13.04)	0.0593
Pressor Drugs	13(7.98)	16(11.68)	9(39.13)	<.0001
Caffeine	100(61.35)	78(56.93)	13(59.09)	0.6158
Amnionitis	16(9.88)	25(18.66)	6(26.09)	0.0105
Bronchopulmonary dysplasia	51(31.29)	90(66.18)	21(91.30)	<.0001
Assisted Ventilation for >12hrs	119(73.01)	124(90.51)	22(95.65)	0.0001
Respiratory Distress Syndrome	128(79.01)	119(86.86)	23(100.00)	0.0044
Apnea	72(44.17)	55(40.44)	9(39.13)	0.5180
Pneumothoraces	4(2.47)	5(3.65)	2(8.70)	0.1385
Hypoglycemia	26(15.95)	25(18.25)	3(13.04)	0.9544
Hyperglycemic	89(54.60)	88(64.23)	13(56.52)	0.3905
Periventricular leukomalacia	6(3.70)	5(3.68)	4(17.39)	0.0187
Ventriculomegaly	9(5.56)	8(5.88)	2(8.70)	0.5935
Seizures at discharge	10(6.17)	0(0)	3(13.04)	0.8980

As shown in **Table 2**, the was a significant difference in the incidence of corrective lenses at 12 years of age, services for blind at 12 years of age, normal vision at 12 years of age, decreased vision at 12 years of age, absent vision at 12 years of age, full and equal eye movements at 12 years of age, and abnormal eye movements at 12 years of age between the ROP (-) (n=163), ROP (1,2) (n=137), and ROP (3,4) (n=23).

Table 2:

Characteristics	ROP (-) (n=163)	ROP (1,2) (n=137)	ROP (3,4) (n=23)	p-value
Corrective Lenses @12	31/102 (30.39)	41/106 (38.68)	15/2 (171.43)	0.0007
Services for Blind@12	1/102 (0.98)	0	7/21 (33.33)	<.0001
Normal vision at 12	56/93 (60.22)	46/90 (51.11)	2/20 (10)	<.0001
Decreased vision at 12	36/93 (38.71)	44/90 (48.89)	16/20 (80)	<.0001
Absent vision at 12	1/93 (1.08)	0	2/20 (10)	<.0001
Full and equal eye movements	39(97.5)	43(95.56)	5(55.56)	0.0020
Abnormal Eye Movements	1/40(2.5)	2/45(4.4)	4/9(44.4)	0.0020

Using the Cox regression model, multivariate analyses were performed to identify those perinatal characteristics shown in Table 1 that were significantly associated with retinopathy of prematurity. As shown in **Table 3,** we found that birthweight (P = .0330), periventricular leukomalacia (P = <.0001), indomethacin (P = .0363), indomethacin and Steroids (P = .003), and less than high school (P = .0008) were independent and significant predictors.

Table 3: **Multivariate Analysis**

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr>F
ROP, Stage 3-4	-11.48	4.01	2214.64	8.18	.0045
Birth-weight	.0117	.0055	1241.82	4.59	.0330

Periventricular Leukomalacia	-21.55	4.69	5714.93	21.10	<.0001
Indomethacin	-4.58	2.178	1197.44	4.42	.0363
Indomethacin and Steroids	10.44	2.83	3694.99	13.64	.003
Less than high school	-10.29	3.03	3106.27	11.47	.0008

Cognitive test scores for the 3 study groups at 12 years are shown in **Table 4**. Children in both the ROP (-) and ROP 1,2 had significantly higher verbal IQ, performance IQ, full-scale IQ, and PPVT standard scores for reading recognition, reading comprehension, and math than those in ROP 3,4.

Table 4: Cognitive and Educational Test Results at 12 Years of Age

Characteristics	**ROP (-) (n=163)**	**ROP (1,2) (n=137)**	**ROP (3.4) (n=23)**	**p-value**
N	163	136	23	<.0001
Verbal IQ	91.2 ±18.5	90.6±19.8	80.7±23.4	<.0001
Performance IQ	89.2 ±17.0	84.9±17.7	69.3±19.9	<.0001
Full-Scale IQ	89.2 ±18	86.8±18.2	72.6±23.4	<.0001
PPVT	92.9 ±23.4	92.5±26.7	74.3±35.1	<.0001
Full scale <70	17(5.38)	22(6.96)	10(3.16)	<.0001
Verbal scale <70	16(4.98)	17(5.30)	7(2.18)	0.0093
Performance <70	18(5.64)	26(8.15)	11(3.45)	<.0001
PPVT-R <70	16(5.05)	20(6.31)	9(2.84)	0.0004

Our brain volume data can be found in **Table 5**. In our study, we found that the whole brain volumes were significantly less for children with any grade of ROP (p = 0.02), occipital white matter volumes tended to be less for the same study subjects (p = 0.08) and both total occipital brain volumes and occipital white matter volumes were significantly correlated with Beery VMI scores (r=0.610, p = 0.009 and r = 0.652, p =0.005, respectively).

Table 5: MRI findings at 12 years of age

Characteristics	ROP (-) (n=23)	ROP (+) (n=17)	p-value
Total brain volume	1420.8 ±82.3	1343.5 ±136.0	.022
Occipital lobe, white	61.36 ±9.45	55.22 ±11.07	.078
Occipital lobe, gray	68.277 ±8.63	64.86 ±9.63	.976
Occipital lobe, total	129.63 ±12.33	120.08 ±17.48	.391
Cerebellum, total	135.2 ±10.6	129.5 ±14.0	.55

Discussion:

Retinopathy of prematurity remains the leading cause of childhood blindness in the United States. It has been estimated that anywhere from 20% to 68% of premature infants may develop retinopathy of prematurity (6,41) and up to 8% of cases may progress to blindness. In our study, we found the incidence of any stage retinopathy of prematurity to be 160/323 = 49.5%. The reasons for the differing incidences in the

studies is unclear, but could perhaps related to the difference in the diagnosis of retinopathy of prematurity by the various ophthalmologists, and differing care in the neonatal intensive care unit in the various sites.

The various risk factors for retinopathy of prematurity have been studied in many previous studies. There has been a consensus for many of the risk factors of retinopathy of prematurity, including a decreasing gestational age, decreasing birthweight, and increasing apneic episodes. However many other risk factors remain controversial, including race, sex, and indomethacin use among others. We have sought to study both the agreed upon risk factors, in order to add to the existing literature, as well as the controversial risk factors in hopes of being able to further elucidate the many risk factors of retinopathy of prematurity.

Gestational age is a well known risk factor for retinopathy of prematurity. Many previous studies have found that infants who developed retinopathy of prematurity had a lower gestational age (6, 7, 38). Our study, not surprisingly showed that retinopathy of prematurity is associated with a lower gestational age. However, we found that an increase in the stage of the retinopathy of prematurity was in fact not associated with a lower gestational age. The average gestational age found in our study for ROP (-) was 28.5 week, for ROP (1,2) was 27.1, and ROP (3,4) was 27.0 weeks. Therefore a lower gestational age may be associated with an increased incidence of retinopathy of prematurity, but not necessarily with an increase in the severity of the retinopathy of prematurity.

The birthweight of the infant is another well known risk factor for the occurrence of retinopathy of prematurity. In previous studies it has been found that the birthweight

for those infants with retinopathy of prematurity is lower than that of controls (6, 7, 38). In our study, we too found that a decreased birth weight was correlated not only with an increased incidence of retinopathy of prematurity, but also with an increase in severity of the retinopathy of prematurity. We found that the ROP (-) infants had an average birth weight of 1035.2 g, the ROP (1,2) infants had an average birthweight of 864.6 g, while the ROP (3,4) infants had an average birthweight of 841.7 g.

However important birthweight may be a factor in retinopathy of prematurity, it is not the only factor involved. Between the years 1989 and 1998 despite a decrease in the mean gestational age and birthweight of premature infants, there was also a decrease in the incidence of retinopathy of prematurity (1). This reduced incidence of ROP is possibly attributed to improvements in ventilation techniques and the overall care of the neonate, in particular the use of prenatal steroids and surfactant (1). Thus the incidence of retinopathy of prematurity in the infant is a complicated interaction of many variables.

As hypoxic injury is the original stimulus for retinopathy of prematurity, apnea is thought to be a risk factor for the occurrence of retinopathy of prematurity. In previous studies it has been found that an infant being on ventilator care for $\geq$ 48 hours has been a risk factor for retinopathy of prematurity and that frequent apneic attacks increased the progression of pre-threshold ROP to threshold ROP (6). In addition, another study found that the higher number of days on oxygen/ventilator and more days in the ICU were also risk factors for the incidence of retinopathy of prematurity (7). In our study, assisted ventilation for >12hrs was found to be significantly correlated with the incidence of retinopathy of prematurity ($p = .0001$). In addition, respiratory distress syndrome was also correlated with an increased incidence of retinopathy of prematurity ($p = 0.0044$).

However, apnea itself was not correlated with an increased incidence of retinopathy of prematurity in our study (p = .5180).

The role of indomethacin in the prevention of retinopathy of prematurity has not been fully understood in the past. Indomethacin is a nonsteroidal anti-inflammatory agent which acts by inhibiting prostaglandin production. Indomethacin is thought to improve retinopathy during periods of hyperoxia injury, because of its effect on retinal neovascularization (by inhibiting prostaglandin production). One study performed in the 1980's found that indomethacin did not impact the incidence of retinopathy of prematurity (44). However a study performed in 1999, which looked at a mouse model, demonstrated an improvement in oxygen induced retinopathy with indomethacin treatment (8). In addition, one study performed in 2003 examined the effect of ibuprofen (a nonsteroidal anti-inflammatory agent similar to indomethacin) on oxygen-induced retinopathy in a mouse model and also demonstrated an improvement in oxygen induced retinopathy (45). In addition, post-natal steroid use has been found to be a risk factor in retinopathy of prematurity. In one study, of 21 factors were examined, and only steroid use for lung disease was associated with the need for cryotherapy (11). However, our study did not show a significant statistical difference in the incidence of retinopathy of prematurity in both the indomethacin group, as well as the indomethacin + steroids group (P = .8317 and P = .7560l, respectively).

Two previous studies have reported that twice the number of male infants are affected with retinopathy of prematurity (53, 54). In one study it was suggested that there was an increased risk of cryotherapy in boys (12). In our study, we too found an increased incidence of retinopathy of prematurity in male infants. While ROP (-) was

approximately split half and half (50.31%), 59.12% of stage 1,2 ROP infants were male and 65.22% of stage 3,4 ROP infants were males.

In previous studies, it was found that maternal pre-eclampsia may lead to a more favorable outcome for premature infants, perhaps due to the fact that hypertension causes intrauterine stress and subsequent maturation of the eyes (*12*). However, in our study we found no statistically significant difference in the incidence of any stage ROP with the incidence preeclampsia +/- eclampsia in the mother.

In previous studies it has been found that an increased risk of retinopathy of prematurity was correlated with each 10 mg/dl increase of mean glucose (46). However, in our study we did not find any statistically significant difference in the infants with either hypoglycemia, or hyperglycemia (p values of .9544 and .3905 respectively).

In one study it was found that a higher percentage of the dopamine treated infants reached prethreshold retinopathy of prematurity (67% versus 13%), as well as threshold retinopathy of prematurity (39% versus 4%) (12). An additional study found an increased risk of retinopathy of prematurity was correlated with a history of dopamine infusion (52). In our study we found a statistically significant difference ($p<.0001$) in those infants treated with pressor drugs versus those of controls and the incidence of retinopathy of prematurity stage 3,4.

It has been found that an increased risk of retinopathy of prematurity was correlated with an intraventricular hemorrhage. (52). In our study we found that intraventricular hemorrhage was indeed correlated with retinopathy of prematurity. We looked first at intraventricular hemorrhage occurring within the first 6 postnatal hours, and found it to be correlated with an increased incidence of retinopathy of prematurity (p

= 0.051). In addition, we looked at intraventricular hemorrhage occurring at post-natal day 5, and found that it too was correlated with an increased incidence of retinopathy of prematurity (p = .0008). Finally, we looked at grade 3-4 IVH at post-natal day 5, and found that it also was correlated with retinopathy of prematurity (p = 0.0593).

In our multivariate analyses we found that birthweight (P = .0330), periventricular leukomalacia (P = <.0001), indomethacin (P = .0363), indomethacin and steroids (P = .003), and less than high school (P = .0008) were independent and significant predictors**.**

It has been noted that two percent of the prematurely born children are visually impaired (<20/60) (17). The visual function in very low birth weight children has been found to be much poorer than that of controls (21). In addition, the very low birth weight infants have a higher incidence of a variety of adverse visual outcomes including worse visual acuity and a higher incidence of strabismus (19,21). In our study, we sought to examine the difference in incidence of various visual outcomes in premature infants with retinopathy of prematurity using premature infants without ROP as the controls. We found that there was a significantly higher incidence in services for blind at 12 years of age (P = <.0001), decreased vision at 12 years of age (P = <.0001), absent vision at 12 years of age (P = <.0001), and abnormal eye movements at 12 years of age (P = .002), in the ROP (3,4) group.

The incidence of refractive errors in premature infants has been found to be 4 times more common in 10-year olds when compared with full-term controls (19). Interestingly enough, the high myopia associated with ROP is thought to be pathophysiologically distinct from the high myopia in full-term patients (20). Although the incidence of refractive error in premature infants with retinopathy of prematurity

itself is higher than controls, in a previous study, the stage of retinopathy of prematurity did not have an effect on the refractive error (40). In our study we found an increased incidence of corrective lenses in children with a previous history of retinopathy of prematurity (P = .0007). In our study, we found a statistically significant difference in the incidence of corrective lenses in the ROP stage (3,4) infants when compared to ROP (-), as well as that of ROP stage (1,2), which differs from the findings of the previous study (40).

Although retinopathy of prematurity has become a relatively common finding in the era of extremely premature infants, there is a scarcity of studies performed to look at the correlation of retinopathy of prematurity and cognitive function in older children who previously had retinopathy of prematurity. In one study severe retinopathy of prematurity showed the strongest association with 18-month outcome (15). In another study it was found that among extremely premature infants (less than 28 weeks, with normal neonatal cranial ultrasounds), serum bilirubin and retinopathy of prematurity were associated with developmental impairment at 5 years of age. Interestingly enough in this study, gestational age and birth weight themselves were not associated with a poorer developmental outcome (13).

In the past, in the CRYO-ROP Multicenter study, the educational status and special education services among children who had threshold retinopathy of prematurity were examined at 8 years of age. Threshold retinopathy of prematurity was associated with higher rates of developmental, educational, and social challenges in middle childhood . In addition, of the 8-year-old children with a history of threshold ROP, there

were significant developmental, educational, and social skill differences between those who had favorable versus unfavorable visual status in the better eye (18).

In a different study it as found that VLBW children with reduced visual function were more likely to have significant impairment of motor skills, and poor visual function was predictive of lower IQ (21). In one of the first studies in which health related quality of life was looked at in formerly premature children, it was found that threshold ROP was associated with functional limitations in health attributes, as well as in reductions in health related quality of life scores at 10 years of age. In addition, like many previous studies, those children who had poor visual outcome, had a worse health related quality of life score than those with better sight (14).

In this study we sought to examine the hypothesis that retinopathy of prematurity would result in decreased cognitive ability at 12 years of age when compared to that of premature infants without retinopathy of prematurity. We believe that this is the oldest cohort in which the correlation of retinopathy of prematurity and IQ has been examined. We looked at performance, verbal and full scale IQ for 12 year old who were previously ROP (-), ROP stage 1,2, and ROP stage 3,4. In our study, children in both the ROP (-), and ROP stage 1,2 had significantly higher verbal IQ, performance IQ, full-scale IQ, and PPVT standard scores for reading recognition, reading comprehension, and math than those with previous ROP stage 3,4. There are several possible explanations for this correlation. The first of which is that children with previous retinopathy of prematurity have a higher incidence of impaired vision, and as shown in previous studies impaired vision is correlated with decreased cognitive ability (18,21). Another possible explanation is that the visual deprivement that occurs during infancy from the retinopathy

of prematurity has lasting effects on the brain itself. Finally, we have shown that the infants with retinopathy of prematurity are sicker infants, with lower birthweights and lower gestational ages, so it is possible that the lower IQ's are a result of neurological damage unrelated to the ROP.

In the first quantitative MRI study of long-term outcome of regional brain volumes in preterm infants it was found that regional cortical volumes in preterm children were significantly smaller than controls and that the regional volumes were correlated significantly with gestational age at birth, 5-minute Apgar scores, and IHV within 6 hours of birth. In addition, it was found that preterm birth was associated with regionally specific, long-term reductions in brain volume, and that these morphological abnormalities were in turn associated with poorer cognitive outcome (23).

To our knowledge, there have been no prior neuroimaging studies of children with retinopathy of prematurity that employ statistical analysis. In our study, we found that the whole brain volumes were significantly less for children with any grade of ROP ($p = 0.02$), occipital white matter volumes tended to be less for the same study subjects ($p = 0.08$) and both total occipital brain volumes and occipital white matter volumes were significantly correlated with Beery VMI scores ($r=0.610$, $p = 0.009$ and $r = 0.652$, $p =0.005$, respectively). This is an extremely interesting finding, as it is all stages of ROP which showed a significant difference in brain volume, both whole and occipital white matter volume, regardless of the visual outcome of the infant. As most stage 1,2 retinopathy of prematurity regresses on its own, it is especially interesting to note there is a difference in the occipital lobe brain volumes in all stages of retinopathy of prematurity, including that of stage 1,2 retinopathy of prematurity.

One possible explanation for this difference in brain and occipital lobe volume is that the infants with retinopathy of prematurity are sicker infants, with a lower birthweight and gestational age. However, we need to explain the difference in occipital lobe volumes that exists between children who previously had retinopathy of prematurity, and those who have not, when no difference exists between these two groups in other areas of the brain, including the cerebellum. As the cerebellum is known to be extremely sensitive to hypoxia, the finding that there is no difference in the cerebellar volumes between these two groups leads us to conclude that the difference in brain volumes is a result of the difference in occipital lobe volumes, and not from hypoxia. Moreover, we believe that it is the visual deprivation that occurs because of the retinopathy of prematurity (either during infancy, or persisting later into childhood in more severe stages), which results in this difference in the occipital lobe volumes.

The human visual system is an important example of neuronal plasticity during development. In humans, visual input is required in order for the visual system in the brain to reach its full development . For example, binocular vision is extremely sensitive to visual experiences during the first months of life. If the vision of one or both eyes is impaired through cataracts, high refractive error, or a deviated eye during infancy a permanent reduction in the quality of vision may result (43). It has been postulated in previous studies that the abnormal visual experience during critical developmental periods and the resulting visual deficits are associated with structural changes in visual portions of the brain (43). In the past these hypothesis have been looked at in children with amblyopia or visual deprivation due to cataracts or high refractive error. However, in this study we believe that we are able to demonstrate that the visual deprivation caused

by the existence of any stage retinopathy of prematurity in the infant during a critical development period, causes structural changes in the brain which persist at least through childhood. It is extremely interesting that structural changes can be seen in the brain at 12 years of age in children with previous ROP.

Conclusion:

We believe that we have added to the already abundant body of knowledge of various risk factors for retinopathy of prematurity. We have also looked at the cognitive sequelae in the oldest subset of children with previous retinopathy of prematurity, and have shown that children with previous stage 3,4 retinopathy of prematurity have lower performance on cognitive, language and visual motor integration scores at age 12 years of age. We are the first study to look specifically at the brain volumes of children with a previous history of retinopathy of prematurity, compared to that of premature controls. We believe that the results of this study are very important as they may further elucidate the consequence that retinopathy of prematurity may have on the developing brain. This will be invaluable to further understanding the mechanism of the developing visual system and our ability to better understand retinopathy of prematurity for future generations.

References:

(1.) Rowlands, Ionides, Chinn, Mackinnon, Davey. 2001. "Reduced incidence of retinopathy of prematurity". Br J Ophthalmology. 85(8):933-5.

(2.) Recchia, Capone. 2004. "Contemporary understanding and management of retinopathy of prematurity" Retina, the Journal of Retinal and Vitreous Diseases. 24(2) 283- 292.

(3.) Shastry, Pendergast, Hartzer, Liu, Trese. 1997. "Identification of missense mutations in the Norrie disease gene associated with advanced retinopathy of prematurity." Archives of Ophthalmology. 115(5):651-5.

(4.) Hiraoka, Berinstein, Trese, Shastry. 2001. "Insertion and deletion mutations in the radionucleotide repeat region of the Norrie disease gene in patients with advanced retinopathy of prematurity." Journal of Human Genetics. 46(4):178-81.

(5.) Reynolds, Dobson, Quinn, et al. 2002. "CRYO-ROP, LIGHT-ROP Cooperative Groups. Evidence-based screening criteria for retinopathy of prematurity: Natural history data from the CRYO-ROP and LIGHT-ROP studies. Arch Ophthalmology.120: 1470-1476.

(6.) Kim, Sohn, Pi, Yoon. 2004. Postnatal risk factors of retinopathy of prematurity. Pediatric and Perinatal Epidemiology. 18(2):130-4

(7.) Brown, Thach, Song, Marx, Kwun, Frambach. 1998. "Retinopathy of prematurity: evaluation of risk factors" Int Ophthalmol. 22(5):279-83.

(8.) Nandgaonkar, Rotschild, Yu, Higgins. 1999. Indomethacin Improves Oxygen-Induced Retinopathy in the Mouse. Pediatric Research 46(2): 184-188

(9.) Termote, Schalij-Delfos, Brouwers, Donders, Cats. 2000. New developments in neonatology: less severe retinopathy of prematurity? Journal of Pediatric Ophthalmology & Strabismus. 37(3):142-8

(10.) Sobel, Philip. 1992. Prolonged dexamethasone therapy reduces the incidence of cryotherapy for retinopathy of prematurity in infants of less than 1 kilogram birth weight with bronchopulmonary dysplasia. Pediatrics. 90(4):529-33.

(11.) Batton, Roberts, Trese, Maisels. 1992. "Severe Retinopathy of Prematurity and Steroid Exposure" Pediatrics. 90(4):534-6.

(12.) Wheatley, Dickinsonm Mackey, Craig, Sale. 2002 Retinopathy of prematurity: recent advances in our understanding British Journal of Opthalmology. 86: 696-700

(13.) Mizoguchi, Chu, Murphy, Willits, Morse. 1999. Dopamine use is an indicator for the development of threshold retinopathy of prematurity. British Journal of Ophthalmology. 83(4):425-8

(14.) Brion, Bell, Raghuveer. 2003 Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. Cochrane Database of Systematic Reviews

(15.) Sampath, Bowen, Gibson. 2005. "Risk Factors for Adverse Neurodevelopment in Extremely Low Birth Weight Infants with Normal Neonatal Cranial Ultrasound." J Perinatol. 25(3):210-5.

(16.) Quinn, Dobson, Saigal, Phelps, Hardy, Tung, Summers, Palmer, CRYO-ROP Cooperative Group. 2004. "Health-Related Quality of Life at Age 10 Years in Very Low-Birth-Weight Children With and Without Threshold Retinopathy of Prematurity" Arch Ophthalmol. 122(11):1659-66.

(17.) Schmidt B. Asztalos EV. Roberts RS. Robertson CM. Sauve RS. Whitfield MF. 2003. Trial of Indomethacin Prophylaxis in Preterms (TIPP) Investigators. Impact of bronchopulmonary dysplasia, brain injury and severe retinopathy on the outcome of extremely low-birth weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. JAMA. *289(9):1124-9.*

(18.) Msall, Phelps, Hardy, Dobson, Quinn, Summers, Tremont. 2004. Cryotherapy for Retinopathy of Prematurity Cooperative Group. "Educational and Social Competencies at 8 Years in Children with Threshold Retinopathy of Prematurity in the CRYO-ROP Multicenter Study" Pediatrics. 113(4):790-9

(19.) Larsson, Agneta, Holmstrom. 2003. A Population-Based Study of the Refractive Outcome in 10-Year-Old Preterm and Full-Term Children Archives of Opthalmology 121: 1430-1436.

(20.) Garcia-Valenzuela, Kaufman. 2005. "High myopia associated with retinopathy of prematurity is primarily lenticular." AAPOS. 9(2):121-8

(21.) Powls, Botting, Cooke, Stephenson, Marlow. 1997. "Visual impairment in very low birthweight children." Archives of Diseases in Childhood. 76:F82-F87

(22.) McGinnty, Halliday. 1993. "Perinatal predictors of ocular morbidity in school children who were very low birthweight." Pediatric and Perinatal Epidemiology. 7(4):417-25, 1993

(23.) Peterson, Vohr, Stai, Cannistraci, Dolberg, Schneider, Katz, Westerveld, Sparrow, Anderson, Duncan, Makuch, Gore, Ment. 2000. "Regional Brain Volume Abnormalities and Long-term Cognitive Outcome in Preterm Infants" JAMA. 284(15)

(24.) Ment LR, Oh W, Ehrenkranz RA, Philip AGS. 1994. Low dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics*. 93:543–550

(25.) Ment LR, Oh W, Ehrenkranz RA. 1994. Low dose indomethacin and extension of intraventricular hemorrhage: a multicenter randomized trial. *J Pediatr.* 124:951–955

(26.) Constantine NA, Kraener HC, Kendall-Tackett KA. 1987. Use of physical and neurologic observations in assessment of gestational age in low birth weight infants. *J Pediatr.* 110:921–928.

(27.) Northway WHJ, Rosan RC, Porter DY. 1967. Pulmonary disease following respirator therapy of hyaline-membrane disease: bronchopulmonary dysplasia. N Engl J Med. 276:357–368.

(28.) Wechsler D. Wechsler Intelligence Scale for Children–Third Edition. 1991. New York, NY: Psychological Corp.

(30.) Dunn LM, Dunn LM. 1981. PPVT: Peabody Picture Vocabulary Test-Revised Form. Circle Pines, Minn: American Guidance Service.

(31.) Levine SC, Huttenlocher P, Banich MT, Duda E. 1987. Factors affecting cognitive functioning of hemiplegic children. Dev Med Child Neurol. 29:27–35.

(32.) Markwardt FC. 1989. Peabody Individual Achievement Test-Revised Manual. Circle Pines, MN: American Guidance Service. 1–243.

(33.) McCarton C, Brooks-Gunn J, Wallace I, Bauer C. 1997. Results at age 8 years of early intervention for low-birth-weight premature infants. JAMA. 277:126–132.

(34.) Brooks-Gunn J, McCarton CM, Casey PY, et al. 1994. Early intervention in low-birth- weight premature infants: results through age 5 years from the Infant Health and Development Program. JAMA. 1994;272:1257–1262.

(36.) Notari, L, Miller A, Martinez A, Amaral J, Ju M, Robinson G, Smith LE, Becerra SP. Pigment epithelium –derived factor is a substrate for matrix metalloproteinase type 2 and type 9: implications for downregulation in hypoxia.

(37.) Lang DM, Blackledge J, Arnold RW. Is Pacific race a retinopathy of prematurity risk factor? Archives of Pediatrics & Adolescent Medicine. 2005. 159(8):771-3.

(38.) Termote JU, Donders AR, Schalij-Delfos NE, Lenselink CH, Derkzen van Angeren CS, Lissone SC, Cats BP. Can Screening for retinopathy of prematurity be reduced? 2005. Biology of the Neonate. 88(2):98-100.

(39.) Smith LE. IGF-1 and retinopathy of prematurity in the preterm infant. Biology of the neonate. 2005. 88(3): 237-44.

(40.) Homstrom GE, Larsson EK. Development of spherical equivalent refraction in prematurely born children during the first 10 years of life: a population based study. Archives of Ophthalmology. 2005. 123(10):1404-11.

(41.) Good WV, Hardy RJ, Dobson V, Palmer EA, Phelps DL, Quintos M, Tung B. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. 2005. Pediatrics 116(1):15-23.

(42.) An International Committee for the Classification of Retinopathy of Prematurity. 2005. The International Classification of Retinopathy of Prematurity Revisited. Archives of Ophthalmology. 123:991-999.

(43.) Mendola J, Conner I, Roy A, Chan S, Schwartz T, Odom V, Kwong K. 2005. Voxel-based analysis of MRI detects abnormal visual cortex in children and adults with amblyopia. Human Brain Mapping. 25: 222-236.

(44.) Bandstra ES, Montalvo BM, Goldberg RN, Pacheco I, Ferrer PL, Flynn J, Gregorios JB, Bancalari E. 1988. Prophylactic indomethacin for prevention of intraventricular hemorrhage in premature infants. Pediatrics. 82(4):533-42.

(45.) Sharma J. Barr SM. Geng Y. Yun Y. Higgins RD. 2003. Ibuprofen improves oxygen-induced retinopathy in a mouse model. Current Eye Research. 27(5):309-14.

(46.) Garg R, Agthe AG, Donohue PK, Lehmann CU. 2003. Hyperglycemia and retinopathy of prematurity in very low birth weight infants. Journal of Perinatology. 23(3): 186-94.

(47.) Phelps DL. 1981. Retinopathy of prematurity: an estimate of vision loss in the United States—1979. Pediatrics. 67:924–6.

(48.) Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. Ophthalmology. 1991;98:1628–40.

(49.) Adamis AP, Shima DT, Yeo KT, et al. Synthesis and secretion of vascular permeability factor/vascular endothelial growth factor by human retinal pigment epithelial cells. Biochem Biophys Res Commun 1993;193:631-638.

(50.) Yanoff: Ophthalmology, 2nd edition. 2004. Mosby, Inc

(51.) Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med. 1994;331:1480–7.

(52.) Lui P, Fang P, Huang C, Kou H, Chung M, Yang Y, Chung C. 2005. Risk Factors of Retinopathy of Prematurity in Premature Infants Weighing Less Than 1600 g. Amer J Perinatol 22: 115-120.

(53.) Wheatley CM, Dickinson JL, Mackey DA, Craig JE, Sale MM. 2002. Retinopathy of prematurity: recent advances in our understanding. Br J Ophthalmol. 86:696 –700.

(54.) Nodgaard H, Andreasen H, Hansen H, Sorensen HT. 1996. Risk factors associated with retinopathy of prematurity (ROP) in northern Jutland, Denmark. Acta Ophthalmol Scand. 74:306 –310.