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Cerebral injury and retinopathy as risk factors for blindness in extremely preterm infants

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ABSTRACT

Objective This study investigates whether and to what extent cerebral injury is associated with bilateral blindness in extremely preterm infants, which has been attributed mainly to retinopathy of prematurity (ROP).

Design Multicentre analysis of children born from 1994 to 2021 at gestational age 22 0/7 to 28 6/7 weeks with follow-up at 18–26 months. Logistic regression examined the adjusted association of bilateral blindness with severe ROP and/or cerebral injury among extremely preterm infants.

Exposures Severe ROP and cerebral injury, the latter defined as any of the following on cranial imaging: ventriculomegaly; blood/increased echogenicity in the parenchyma; cystic periventricular leukomalacia.

Main outcome measures Bilateral blindness, defined as a follow-up examination meeting criteria of 'blind—some functional vision' or 'blind—no useful vision' in both eyes.

Results The 19 863 children included had a mean gestational age of 25.6±1.7 weeks, mean birth weight of 782±158 g and 213 (1%) had bilateral blindness. Multiplicative interaction between ROP and cerebral injury was statistically significant. For infants with only severe ROP (n=3130), odds of blindness were 8.14 times higher (95% CI 4.52 to 14.65), and for those with only cerebral injury (n=2836), odds were 8.38 times higher (95% CI 5.28 to 13.28), compared with the reference group without either condition. Risks were not synergistic for infants with both severe ROP and cerebral injury (n=1438, adjusted OR=28.7, 95% CI 16.0 to 51.7, p<0.0001).

Conclusions In a group of extremely preterm infants, severe ROP and cerebral injury were equally important risk factors for blindness. Besides ROP, clinicians should consider cerebral injury as a cause of blindness in children born extremely preterm.

Trial registration number NCT00063063.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Extremely preterm infants are at risk for blindness, which has been primarily attributed to retinopathy of prematurity (ROP) but could also be due to cerebral injury, the leading cause of paediatric visual impairment in developed countries.

WHAT THIS STUDY ADDS

⇒ In this retrospective analysis of prospectively collected data on 19 863 extremely preterm infants, severe ROP and cerebral injury were associated with similar and significant increases in the risk for blindness (adjusted ORs 8.14 and 8.38, respectively).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Besides ROP, clinicians should have a high index of suspicion for cerebral injury when considering risk factors for blindness in children born extremely preterm.

INTRODUCTION

Infants born preterm are at increased risk of blindness relative to those born at term.[1] Approximately 1% of extremely preterm infants develop severe visual impairment.[2] Retinopathy of prematurity (ROP), a disruption of retinal vascularisation, is the most widely recognised cause of visual impairment affecting preterm infants.[1 3] Approximately 13% of extremely preterm infants develop severe ROP needing treatment.[2 4] Among infants with severe ROP, 6.4% develop bilateral blindness with no functional vision.[5 6]

While many clinicians and researchers may largely attribute blindness in infants born preterm to severe ROP, the leading cause of visual impairment among all children in developed countries is cerebral in nature.[7] Risk factors for cerebral visual impairment (CVI) among all infants include intracranial haemorrhage, immature cerebrovascular development, inadequate autoregulation of cerebral blood flow and insults in utero.[8] Preterm infants are especially vulnerable to cerebral damage due to a fragile network of cerebral blood vessels called the germinal matrix, which is at risk for haemorrhage with ventricular extension or periventricular parenchymal involvement.[9] White matter ischaemia and/or inflammation may manifest as periventricular leukomalacia (PVL) in preterm infants. Hypoxic ischaemic encephalopathy (HIE), PVL and hydrocephalus are well-known causes of paediatric CVI, with perinatal or postnatal HIE being the most common cause of CVI in preterm and term infants.[7]

The relative contribution of severe ROP and CVI to blindness in children born extremely preterm remains unclear. While cerebral injury is appropriately recognised in the general paediatric

Table 1 Baseline characteristics by group

	Neither (n=12 459)	Cerebral injury (n=2836)	Severe ROP (n=3130)	Both (n=1438)	Total (n=19 863)
Maternal age, year*	n=12 458 27.8±6.6	n=2833 27.2±6.5	n=3130 27.7±6.5	n=1438 27.6±6.6	n=19 859 27.7±6.6
Race, n/total n (%)*†	n=12 295	n=2788	n=3091	n=1412	n=19 586
Black	5590 (45)	1270 (46)	1112 (36)	507 (36)	8479 (43)
White	6175 (50)	1427 (51)	1772 (57)	834 (59)	10 208 (52)
Other	530 (4.3)	91 (3.3)	207 (6.7)	71 (5.0)	899 (4.6)
Hispanic or Latino ethnic group, n/total n (%)†*	n=12 186 1871 (15)	n=2771 441 (16)	n=3050 568 (19)	n=1404 317 (23)	n=19 411 3197 (16)
Mother's education, n/total n (%)	n=12 459	n=2836	n=3130	n=1438	n=19 863
Less than high school diploma	2888 (23)	656 (23)	737 (24)	359 (25)	4640 (23)
High school diploma	3659 (29)	875 (31)	854 (27)	421 (29)	5809 (29)
Partial college/trade/technical	2972 (24)	656 (23)	776 (25)	313 (22)	4717 (24)
College degree or more	2716 (22)	594 (21)	700 (22)	311 (22)	4321 (22)
Unknown	224 (1.8)	55 (1.9)	63 (2.0)	34 (2.4)	376 (1.9)
Received any antenatal glucocorticoids, n/total n (%)*	n=12 437 10 813 (87)	n=2824 2246 (80)	n=3118 2652 (85)	n=1432 1118 (78)	n=19 811 16 829 (85)
Public maternal medical insurance, n/total n (%)‡	n=12 457 7100 (57)	n=2833 1681 (59)	n=3130 1726 (55)	n=1436 822 (57)	n=19 856 11 329 (57)
Prenatal care, n/total n (%)	n=12 452 11 797 (95)	n=2830 2660 (94)	n=3124 2954 (95)	1434 1344 (94)	n=19 840 18 755 (95)
Diabetes prior to pregnancy (2016+), n/total n (%)	n=2151 100 (4.6)	n=456 15 (3.3)	n=509 22 (4.3)	n=238 12 (5.0)	n=3354 149 (4.4)
Insulin-dependent diabetes, n/total n (%)	n=12 420 510 (4.1)	n=2827 102 (3.6)	n=3117 110 (3.5)	n=1429 46 (3.2)	n=19 793 768 (3.9)
Gestational diabetes mellitus (2016+), n/total n (%)	n=2126 101 (4.8)	n=454 27 (5.9)	n=504 17 (3.4)	n=238 12 (5.0)	n=3322 157 (4.7)
Maternal hypertension, n/total n (%)*	n=12 443 3719 (30)	n=2827 575 (20)	n=3123 696 (22)	n=1433 250 (17)	n=19 826 5240 (26)
Chorioamnionitis (2006+), n/total n (%)§	n=6620 1055 (16)	n=1453 271 (19)	n=1569 265 (17)	n=704 127 (18)	n=10 346 1718 (17)
Histological chorioamnionitis (2006+), n/total n (%)*	n=5867 3090 (53)	n=1258 737 (59)	n=1403 743 (53)	n=622 371 (60)	n=9150 4941 (54)
Antenatal antibiotic exposure, n/total n (%)‡	n=12 400 8789 (71)	n=2816 2016 (72)	n=3110 2277 (73)	n=1427 1042 (73)	n=19 753 14 124 (72)
Magnesium sulfate exposure (2011+), n/total n (%)*	n=4466 3746 (84)	n=923 728 (79)	n=1019 817 (80)	n=461 344 (75)	n=6869 5635 (82)
Mode of delivery, n/total n (%)*	n=12 443	n=2831	n=3126	n=1435	n=19 835
Vaginal vertex	3655 (29)	1028 (36)	949 (30)	509 (35)	6141 (31)
Vaginal breech	433 (3.5)	154 (5.4)	201 (6.4)	101 (7.0)	889 (4.5)
C-section	8355 (67)	1649 (58)	1976 (63)	825 (57)	12 805 (65)
Birth weight, g*	n=12 459 812±155	n=2836 790±154	n=3130 696±136	n=1438 699±136	n=19 863 782±158
Gestational age, week*	n=12 457 26.0±1.7	n=2836 25.4±1.6	n=3130 24.8±1.4	n=1438 24.5±1.3	n=19 861 25.6±1.7
Sex, n (%)*	n=12 458	n=2836	n=3129	n=1437	n=19 860
Male sex	5774 (46)	1458 (51)	1614 (52)	801 (56)	9647 (49)
Female sex	6675 (54)	1376 (49)	1514 (48)	636 (44)	10 201 (51)
Ambiguous sex	9 (0.1)	2 (0.1)	1 (0.03)	0 (0)	12 (0.1)
Small for gestational age, n (%)*	n=12 456 1585 (13)	n=2836 218 (7.7)	n=3129 340 (11)	n=1436 91 (6.3)	n=19 857 2234 (11)
Multiple birth, n (%)*	n=12 459 2872 (23)	n=2836 661 (23)	n=3130 785 (25)	n=1438 391 (27)	n=19 863 4709 (24)
Median 5 min Apgar score (5th–95th percentiles)*	n=12 377 7 (6–8)	n=2798 7 (5–8)	n=3111 7 (5–8)	n=1422 6 (4–7)	n=19 708 7 (6–8)
5 min Apgar score ≤5, n/total n (%)*	n=12 377 2508 (20)	n=2798 875 (31)	n=3111 913 (29)	n=1422 550 (39)	n=19 708 4846 (25)

Plus–minus values are means±SD. Percentages may not total 100 because of rounding.
Missing data: maternal age=4, race=277, Hispanic or Latino ethnic group=452, mother's education=376 (unknown), antenatal glucocorticoids=52, gestational age=2, sex=3, 5 min Apgar score=155, SGA=6, public maternal medical insurance=7, prenatal care=23, diabetes prior to pregnancy=16 509, insulin-dependent diabetes=70, gestational diabetes mellitus=16 541, hypertension=37, chorioamnionitis=9517, histological chorioamnionitis=10 713, antenatal antibiotic exposure=110, magnesium sulfate exposure=12 994, mode of delivery=28.
*Significant at p<0.01 (χ^2, Wilcoxon or median test).
†Race and ethnic group were reported by the parent or guardian. 'Other' includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or more than one race.
‡Significant at p<0.05 (χ^2 test).
§Chorioamnionitis as documented in the mother's medical record.
ROP, retinopathy of prematurity; SGA, small for gestational age.

Table 2 Risk factors for blindness

Risk factor	No cerebral injury (n=15 589)			Cerebral injury* (n=4274)		
	n with blindness/n total	Adjusted OR† (95% CI)	P value	n with blindness/n total	Adjusted OR† (95% CI)	P value
No severe ROP (n=15 295)	27/12 459 (0.2%)	1.0 (reference group)		47/2836 (1.7%)	8.38 (5.3 to 13.3)	<0.0001
Severe ROP‡ (n=4568)	53/3130 (1.7%)	8.14 (4.5 to 14.6)	<0.0001	86/1438 (6.0%)	28.7 (16.0 to 51.7)	<0.0001§

In each cell, data are displayed as (infants with primary outcome/total infants in category).
*The marginal adjusted OR for any cerebral injury in the presence of severe ROP was 3.53 (95% CI 2.26 to 5.50), p<0.0001.
†The adjusted ORs and p values are from a logistic regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, cerebral injury, severe ROP, the interaction between cerebral injury and severe ROP, and centre as a cluster effect. Additionally, the following variables were removed during backward stepwise selection: maternal public insurance, gestational age, birth year, antenatal steroids, Hispanic ethnicity, maternal hypertension and maternal insulin-dependent diabetes. Multiplicative interaction between cerebral injury and ROP was found to be statistically significant (p=0.01).
‡The marginal adjusted OR for any severe ROP in the presence of cerebral injury was 3.43 (95% CI 2.31 to 5.09), p<0.0001.
§Compared with children with neither risk factor, the presence of both cerebral injury and severe ROP was associated with an adjusted OR of 28.73 (95% CI 15.96 to 51.71), p<0.0001. This comes from a logistic regression model assessing cerebral injury and severe ROP as a four-level variable (cerebral injury only, severe ROP only, both, neither) with no interaction term.
GEE, generalised estimating equation; ROP, retinopathy of prematurity.

population, its association with blindness in premature infants may be underappreciated. This study was designed to test the hypothesis that cerebral injury is associated with bilateral blindness in extremely preterm infants and can account for some of the variance not explained by severe ROP alone.

METHODS

The current study is a retrospective analysis of prospectively collected data on extremely preterm infants with birth weight of 401–1000 g or gestational age of 22 weeks 0 day to 28 weeks 6 days who received care at one of 28 Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN) centres from 1994 to 2021 and participated in the NRN follow-up study at 18–26 months with complete assessment of visual outcomes by a certified examiner. NRN registry databases include in-hospital and follow-up outcomes for infants born before 29 weeks' gestational age. Trained research coordinators prospectively collect maternal and neonatal data from birth until discharge home, transfer, death or 120 days. For infants transferred or still hospitalised at 120 days, vital status is collected until 1 year of age. Surviving infants are eligible for comprehensive follow-up assessment at 18–26 months' corrected age. The institutional review board at each participating hospital approved data collection protocols and participation in the registry. Waiver of consent for registry enrolment was granted at most affiliated hospitals, but parental consent was required at five hospitals. Most hospitals required written parental consent for participation in the follow-up study, but five hospitals allowed participation under waiver of consent. Follow-up data were collected from 1995 to 2023. Infants with genetic syndromes, congenital neurological malformations or ocular malformations and those who did not participate in follow-up were excluded, as were infants missing data on blindness, cerebral injury or severe ROP. Gestational age was determined by best obstetric estimate or, if unavailable, by neonatal estimate. Infants were classified as small for gestational age based on a birth weight below the 10th percentile for gestational age according to the Alexander growth curve. Sex was reported as female, male or ambiguous, requiring confirmation of ambiguous genitalia by genetics consult. Race and ethnic group were reported by the parent or guardian. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[10]

Outcomes

Bilateral blindness was defined based on follow-up examinations meeting criteria of 'blind—some functional vision' or 'blind—no useful vision' in both eyes. Before 2006, the NRN criterion was 'blind—no useful vision', defined as refraction of <20/200 (legally blind) in both eyes. For infants born in 2006 or later, bilateral blindness was defined as both eyes with either 'blind–no useful vision' or 'blind—some functional vision', a condition that requires the child to have an object held directly in front of their face to see it, consistent with a refraction of <20/200.

Exposures

Criteria for severe ROP included the following: either eye with stage 3 ROP or worse; retinal detachment; Plus disease; receipt of peripheral retinal laser ablation, scleral buckling, vitrectomy and/or treatment with anti-Vascular Endothelial Growth Factor (VEGF) drugs. Cerebral injury was determined by cranial imaging (ultrasound, magnetic resonance, CT) through 36 weeks' postmenstrual age that demonstrated any of the following: ventriculomegaly with or without hydrocephalus; blood/increased echogenicity in the parenchyma; and/or cystic PVL. In additional analysis, severe cerebral palsy (CP) was defined as a Gross Motor Function Classification System level of 4 or 5, and grade 3 bronchopulmonary dysplasia (BPD) was defined as invasive mechanical ventilation administered at 36 weeks' postmenstrual age.[11]

Statistical analysis

Covariates including birth year, sex, gestational age, birth weight, multiple birth, NRN centre (as a cluster effect), antenatal corticosteroids, maternal race and ethnicity, maternal insurance, maternal hypertension and maternal insulin-dependent diabetes were considered in a backward selection model using stepwise regression to develop the final model. Sex, birth weight, multiple birth, centre and race were retained in the final logistic regression model that compared the outcome of bilateral blindness among infants with two potential risk factors (cerebral injury, severe ROP), using generalised estimating equations to account for centre effects. The model included an interaction term for cerebral injury with severe ROP. A separate model used linear regression to assess risk differences (RD) and fit an additive interaction model. Linear regression was used only for the RD model with additive interactions to avoid convergence issues in the binomial model, acknowledging the limitation that the

Table 3 Secondary investigation using adjusted OR (aOR) and 95% CI for visual outcomes based on type of cerebral injury, relative to no cerebral injury

Possible risk factor	Blindness n/N (%)	aOR* (95% CI)	P value
Reference group: no cerebral injury	80/15 586 (0.5)	1.0	–
a. Ventricular size enlarged (with or without concurrent/prior blood)	33/2141 (1.5)	2.23 (1.49 to 3.33)	<0.0001
b. Blood/echodensity in parenchyma with or without midline shift†	0/200 (0)	N/A	
c. PVL	15/294 (5.1)	8.94 (4.60 to 17.4)	<0.0001
d. Combination of ≥2 above cerebral injury criteria	45/1149 (3.9)	5.58 (3.33 to 9.36)	<0.0001
e. Any of criteria A–D with shunt for hydrocephalus	40/476 (8.4)	12.7 (8.86 to 18.2)	<0.0001

*The adjusted ORs and p values are from a logistic regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, type of cerebral injury (none; ventricular size enlarged only; PVL only; two or more of the following: ventricular size enlarged, PVL, blood/echodensity in the parenchyma; one of the above with shunt for hydrocephalus), severe ROP and centre as a cluster effect. The model does not include an interaction term between type of cerebral injury and severe ROP because we also assessed this interaction in a separate logistic regression model and found no significant interaction (p=0.15).
†Infants with blood/echodensity in parenchyma (only) were excluded from the regression since none of these infants had the outcome of blindness.
GEE, generalised estimating equation; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

parameter space for the estimated probabilities is not restricted to (0, 1).

Logistic regression modelling was again used to explore the odds of blindness associated with each type of defined cerebral injury. This included a category for infants with two or more types of injury, and a category for severe hydrocephalus, defined as placement of a ventricular shunt in the setting of other cerebral injury. As CP[12 13] and BPD are known to coexist with late cerebral injury, ROP and blindness, sensitivity analysis explored the relationship between cerebral injury and blindness independent of these diagnoses. Such analysis incorporated CP and BPD statuses into the model as covariates and was limited to infants born in 2006 or after due to limitation in determining grade 3 BPD status.

Given the augmented NRN blindness data in 2006, we also examined the odds of blindness during the epochs before and after the definition change. Because some infants may have had cerebral injuries falling outside this study's definition, additional analysis compared those with cerebral injury to infants with normal brain imaging. Post hoc analysis was performed using criteria for cerebral injury which did not include parenchymal blood/echodensity in the definition.

Table 4 Adjusted OR (aOR) and 95% CI for blindness, adjusting for severe CP and grade 3 BPD (2006–2021 births)

	No cerebral injury		Cerebral injury*	
Risk factor	Adjusted OR† (95% CI)	P value	Adjusted OR† (95% CI)	P value
No severe ROP	1.0 (reference group)		3.72 (1.93 to 7.17)	<0.0001
Severe ROP‡	4.44 (2.57 to 7.67)	<0.0001	7.93 (3.61 to 17.4)	<0.0001§

*The marginal adjusted OR for any cerebral injury in the presence of severe ROP was 1.79 (95% CI 1.05 to 3.03), p=0.03.
†The adjusted ORs and p values are from a logistic regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, cerebral injury, severe ROP, the interaction between cerebral injury and severe ROP, centre as a cluster effect, severe CP (GMFCS level 4 or 5) and grade 3 BPD (Jensen 2019 pragmatic definition). Multiplicative interaction between cerebral injury and ROP was found to be statistically significant (p=0.03).
‡The marginal adjusted OR for any severe ROP in the presence of cerebral injury was 2.13 (95% CI 1.45 to 3.13), p=0.0001.
§Compared with children with neither risk factor, the presence of both cerebral injury and severe ROP was associated with an adjusted OR of 7.93 (95% CI 3.61 to 17.4), p<0.0001. This comes from a logistic regression model assessing cerebral injury and severe ROP as a four-level variable (cerebral injury only, severe ROP only, both, neither) with no interaction term.
BPD, bronchopulmonary dysplasia; CP, cerebral palsy; GEE, generalised estimating equation; GMFCS, Gross Motor Function Classification System; ROP, retinopathy of prematurity.

A sample size analysis was not performed in this secondary analysis of available registry data for all infants meeting certain criteria. A two-sided p<0.05 was used to indicate statistical significance. Analyses were performed using SAS V.9.4 between July and December 2023. All continuous variables are presented as mean±SD except 5 min Apgar score (median and 5th–95th percentiles). Because blindness is a rare outcome, an adjusted OR (aOR) was deemed adequate to closely approximate the relative risk of blindness.[14]

RESULTS

NRN follow-up data were available for 21 745 infants during the study period. Of these, 696 (3.2%) were excluded due to birth defects, 55 (0.3%) were excluded due to missing data on blindness and 1131 (5.2%) were excluded due to missing data on cerebral injury and/or severe ROP (online supplemental eFigure 1 and eTable 1). The 19 863 children in the final study population had a mean gestational age of 25.6±1.7 weeks and mean birth weight of 782±158 g (table 1, online supplemental eTables 2 and 3).

Of infants included, 23% (4568/19 863) had severe ROP, and 22% (4274/19 863) had cerebral injury. Overall, 1% (213/19 863) of children had bilateral blindness. Of blind children, 25% (53/213) had severe ROP only, 22% (47/213) had cerebral injury only, 40% (86/213) had both and 13% (27/213) had neither (table 2). Multiplicative interaction between cerebral injury and ROP was found to be statistically significant (p=0.01), indicating that the association of ROP (or cerebral injury) with blindness depended on whether the infant also had cerebral injury (or ROP). In infants without severe ROP, cerebral injury was associated with an 8.38-fold increase in adjusted odds of blindness (95% CI 5.28 to 13.28). In those without cerebral injury, severe ROP was associated with an 8.14-fold increase in adjusted odds of blindness (95% CI 4.52 to 14.65). Those with both severe ROP and cerebral injury were 28.7 times more likely to be blind (95% CI 15.96 to 51.71) using a four-level variable model (cerebral injury only, severe ROP only, both, neither) with no interaction term.

In the linear regression model incorporating additive interaction, the RD for cerebral injury was 1.4% (RD=0.9–1.8%), indicating that those with cerebral injury had 14 (95% CI 9 to 18) additional cases of blindness per 1000 infants compared with

those who did not have cerebral injury (online supplemental eTable 4). The RD for severe ROP was also 1.4% (RD=0.8–2.0%), indicating that those with severe ROP had 14 (95% CI 8 to 20) additional cases of blindness per 1000 infants compared with those who did not have severe ROP. There was a significant additive interaction (p<0.001) with an additional RD of 2.9% (RD=1.2–4.5%), such that children with both risk factors had 29 (95% CI 12 to 45) additional cases of blindness per 1000 infants compared with those with neither risk factor.

Among cerebral injuries, hydrocephalus requiring shunt in the setting of other defined cerebral injury was associated with the greatest increase in the risk of blindness (aOR=12.7, 95% CI 8.86 to 18.2), followed by PVL (aOR=8.94, 95% CI 4.60 to 17.4) (table 3). None of the 200 infants with blood/echodensity in the parenchyma as the sole abnormality were blind. Severe CP was found to be a significant risk factor for blindness (aOR=40.6, 95% CI 27.9 to 58.9, p=0.002), but there was no association between grade 3 BPD and blindness (p=0.62) (table 4). During the epoch before the augmented NRN blindness data in 2006, severe ROP had a stronger association with blindness than cerebral injury (aOR 10.2 vs 5.0) (online supplemental eTable 5). During the later epoch, cerebral injury had a stronger association with blindness than severe ROP (aOR 10.7 vs 6.2). Additional sensitivity analyses yielded overall similar results (online supplemental eTables 6–9).

DISCUSSION

This retrospective analysis of extremely preterm infants with 18–26 months' follow-up evaluated severe ROP and cerebral injury as possible risk factors for the outcome of bilateral blindness. The results suggest that cerebral injury is associated with blindness and accounts for variance not explained by severe ROP alone. Furthermore, cerebral injury and severe ROP are equally important risk factors for blindness. These results highlight the potential for diverse mechanisms for blindness in extremely preterm infants and emphasise the likelihood that some blindness is cerebral in nature. While both conditions are risk factors for blindness, studies have also demonstrated that ROP[15 16] and severe ROP[17 18] are associated with cerebral injury and structural brain abnormalities. Thus, the link between severe ROP and blindness may be partially mediated through cerebral injury, possibly through common mechanisms that result in both ROP and cerebral injury. While both exposures increase the odds of blindness, the actual risk remains rather low, with 1.7% of infants with only cerebral injury and 1.7% of those with only severe ROP demonstrating blindness. Even among infants with both risk factors, 94% were not blind. Among those with bilateral blindness, 13% had neither severe ROP nor cerebral injury, supporting that other factors affect this outcome.

Extremely preterm infants account for about 1% of all births,[19] and approximately 1% of these infants develop severe visual impairment.[2] ROP is the most widely recognised cause of visual impairment affecting preterm infants,[1] with increasing incidence at lower gestational ages.[3 20] ROP outcomes range from resolution with normal vision to bilateral blindness.[3] Infants with mild to moderate ROP typically have normal vision. More advanced and progressive ROP can cause retinal detachment and is associated with a higher risk of blindness.[3 21] Approximately 13% of extremely preterm infants develop severe ROP needing treatment.[2 4] Among those with severe ROP, 6.4% develop bilateral blindness with no functional vision.[5 6]

A known cause of visual impairment in both term and preterm infants is CVI, for which risk factors include intracranial haemorrhage, immature cerebrovascular development, inadequate autoregulation of cerebral blood flow and various insults in utero.[8] A prior meta-analysis identified retinal pathologies and CVI as the top two causes of severe visual impairment and blindness among children in nations of high socioeconomic index,[22] and CVI is now the leading cause of paediatric visual impairment in developed countries.[7] However, these data describe the general paediatric population. It has been unclear to what extent cerebral causes are similarly responsible for visual impairment in children born extremely preterm.

Because ROP is a familiar and unique aetiology of visual impairment among preterm infants, blindness in this population is often attributed to ROP. Thus, while cerebral injury is appropriately recognised in the general paediatric population, its significance as a cause of blindness in preterm infants may be underappreciated. An individual participant meta-analysis demonstrated that, among infants born before 28 weeks' gestation, an oxygen-targeting intervention that lowered the incidence of severe ROP did not reduce blindness,[2] suggesting that other contributing factors may be overlooked.

Prior studies of preterm infants have demonstrated that PVL portends a poor visual prognosis[23] due to injury to visual association fibres and optic radiations,[24] but it is not known whether other more common cerebral abnormalities in extremely preterm infants are associated with visual impairment. This study found the strongest risk factors for blindness to be a combination of cerebral injury and hydrocephalus requiring shunt, followed by PVL and ventriculomegaly.

Limitations

NRN data do not include information on pupillary reflex, a physiological response left intact in the setting of cerebral blindness but often impaired or absent in ROP.[25 26] Because we lacked information regarding the location of abnormalities in cranial imaging studies, it was not possible to localise cerebral injuries—for example, to the occipital lobe, which houses the visual cortex. The data also do not capture the spectrum of severity in cerebral injury, so varying degrees of injury were not considered. Assessing vision in young children with severe cerebral injury is challenging, potentially leading to overestimation or underestimation of visual impairment. A certified neurological examiner assessed vision outcomes at follow-up using history and observation, but there was no formal evaluation by an ophthalmologist; any resulting bias should have a small effect. Our data are not generalisable to all extremely preterm infants because we excluded infants with genetic syndromes, congenital neurological and/or ocular malformations, and those who did not receive care at NRN centres. Due to the large sample size and the relatively few excluded infants, this bias likely exerts a modest effect. Strengths include a large database and population, multiple variables collected and robust follow-up.

CONCLUSIONS

In this retrospective analysis of extremely preterm infants, cerebral injury and severe ROP were equally important risk factors for blindness. Besides ROP, clinicians should consider cerebral injury among causes of blindness in this population.

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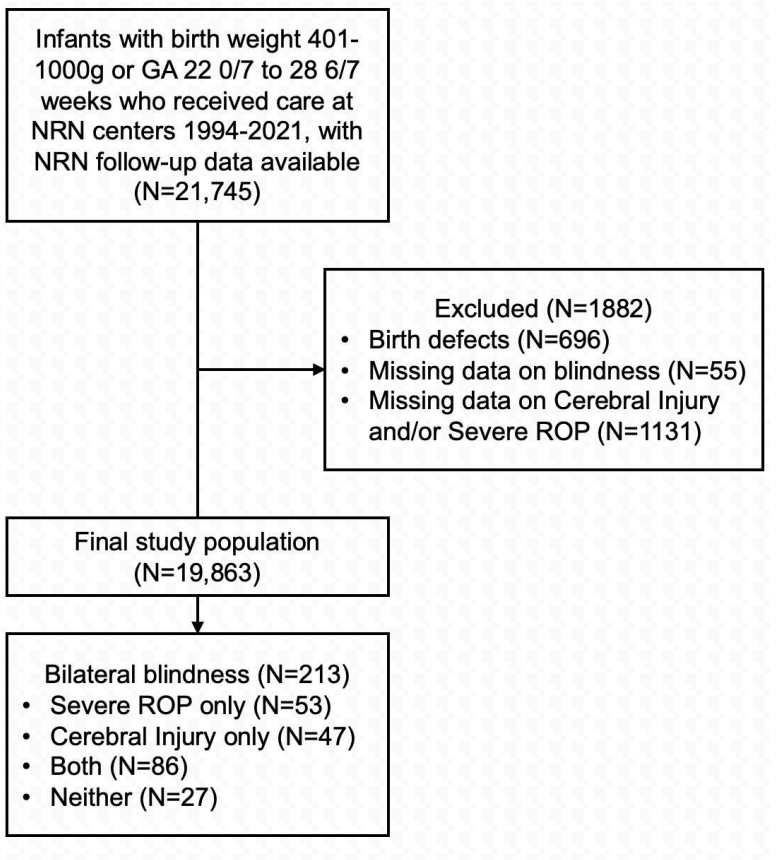
Supplemental Material

This supplementary material has been provided by the authors to give readers additional information about their work.



eFigure 1. Participant Flow Diagram

21,745 infants who received care at NRN centers fulfilled eligibility criteria in terms of birth weight or gestational age, as well as sufficient follow-up data on visual outcomes. There were 1882 infants excluded from the study due to genetic syndromes, congenital neurological malformations, or ocular malformations, or missing data on the outcome or exposures. This resulted in a final study population of 19,863.

Abbreviations: GA, Gestational Age; NRN, Neonatal Research Network; ROP, Retinopathy of Prematurity.

eTable 1. Characteristics of Surviving Children Born at 22 0/7 to 28 6/7 Weeks' Gestational Age Excluded due to Missing Data versus Included in Analysis

	Excluded due to missing data N=1,186	Included in analysis N=19,863
Maternal age — yr	N=1185 27.3 ± 6.6	N=19859 27.7 ± 6.6
Race — no./total no. (%)[a,b] Black White Other	N=1175 453 (39%) 675 (57%) 47 (4.0%)	N=19586 8479 (43%) 10208 (52%) 899 (4.6%)
Hispanic or Latino ethnic group — no./total no. (%)[a,b]	N=1166 154 (13%)	N=19411 3197 (16%)
Mother's education — no./total no. (%) Less than high school diploma High school diploma Partial college/trade/technical College degree or more Unknown	N=1186 289 (24%) 359 (30%) 253 (21%) 253 (21%) 32 (2.7%)	N=19863 4640 (23%) 5809 (29%) 4717 (24%) 4321 (22%) 376 (1.9%)
Received any antenatal glucocorticoids — no./total no. (%)[b]	N=1181 928 (79%)	N=19811 16829 (85%)
Public maternal medical insurance — no./total no. (%)[b]	N=1184 629 (53%)	N=19856 11329 (57%)
Prenatal care — no./total no. (%)	N=1182 1102 (93%)	N=19840 18755 (95%)
Diabetes prior to pregnancy (2016+) — no./total no. (%)	N=91 2 (2.2%)	N=3354 149 (4.4%)
Insulin-dependent diabetes — no./total no. (%)	N=1182 42 (3.6%)	N=19793 768 (3.9%)
Gestational diabetes mellitus (2016+) — no./total no. (%)	N=90 4 (4.4%)	N=3322 157 (4.7%)
Maternal hypertension — no./total no. (%)[b]	N=1182 391 (33%)	N=19826 5240 (26%)
Chorioamnionitis (2006+) — no./total no. (%)[c]	N=226 30 (13%)	N=10346 1718 (17%)
Histologic chorioamnionitis (2006+) — no./total no. (%)	N=203 96 (47%)	N=9150 4941 (54%)
Antenatal antibiotic exposure — no./total no. (%)[b]	N=1177 702 (60%)	N=19753 14124 (72%)
Magnesium sulfate exposure (2011+) — no./total no. (%)	N=163 134 (82%)	N=6869 5635 (82%)
Mode of delivery — no./total no. (%) Vaginal vertex Vaginal breech C-section	N=1185 346 (29%) 47 (4.0%) 792 (67%)	N=19835 6141 (31%) 889 (4.5%) 12805 (65%)
Birth weight — g[b]	N=1186 840 ± 142	N=19863 782 ± 158
Gestational age — wk[b]	N=1185 26.9 ± 2.4	N=19861 25.6 ± 1.7
Sex — no (%) Male sex Female sex Ambiguous sex	N=1185 541 (46%) 642 (54%) 2 (0.2%)	N=19860 9647 (49%) 10201 (51%) 12 (0.1%)

	Excluded due to missing data N=1,186	Included in analysis N=19,863
Small for gestational age — no. (%)[b]	N=1184 284 (24%)	N=19857 2234 (11%)
Multiple birth — no. (%)	N=1186 261 (22%)	N=19863 4709 (24%)
Median 5-min Apgar score (5th to 95th percentile)[b]	N=1174 7 (6-8)	N=19708 7 (6-8)
5-min Apgar score ≤5 — no./total no. (%)[b]	N=1174 200 (17%)	N=19708 4846 (25%)

The middle column is comprised of 55 infants missing information on blindness and 1131 missing information on cerebral injury and/or severe ROP. Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.

[a] Race and ethnic group were reported by the parent or guardian. “Other” includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or more than one race.

[b] Significant at p<0.01 (Chi-square, Wilcoxon, or Median test).

[c] Chorioamnionitis as documented in the mother’s medical record.

No characteristics were significant only at p<0.05 (Chi-square or Wilcoxon test).

Missing data: Maternal age=5, Race=288, Hispanic or Latino ethnic group=472, Mother’s education=408 (Unknown), Antenatal glucocorticoids=57, Gestational age=3, Sex=4, 5-min Apgar score=167, SGA=8, Public maternal medical insurance=9, Prenatal care=27, Diabetes prior to pregnancy=17604, Insulin-dependent diabetes=74, Gestational Diabetes Mellitus=17637, Hypertension=41, Chorioamnionitis=10477, Histologic chorioamnionitis=11696, Antenatal antibiotic exposure=119, Mg sulfate exposure=14017, Mode of delivery=29.

eTable 2. Study Population by Gestational Age

Gestational Age	N	%
19 weeks	1	0.0%
20 weeks	2	0.0%
21 weeks	6	0.0%
22 weeks	184	0.9%
23 weeks	1347	6.8%
24 weeks	3484	18%
25 weeks	4720	24%
26 weeks	5273	27%
27 weeks	2357	12%
28 weeks	1437	7.2%
29 weeks	514	2.6%
30 weeks	296	1.5%
31 weeks	132	0.7%
32 weeks	75	0.4%
33 weeks	18	0.1%
34 weeks	11	0.1%
35 weeks	4	0.0%
Total	19,861[a]	100%

[a] 2 infants are missing gestational age.

eTable 3. Study Population by Birthweight, 100g Increments

Birthweight	N	%
300 – 399g	30	0.2%
400 – 499g	529	2.7%
500 – 599g	1905	9.6%
600 – 699g	3766	19%
700 – 799g	4362	22%
800 – 899g	4291	22%
900 – 999g	3719	19%
1000 – 1099g	795	4.0%
1100 – 1199g	283	1.4%
1200 – 1299g	128	0.6%
1300 – 1399g	41	0.2%
1400 – 1499g	9	0.0%
1500 – 1599g	2	0.0%
1600 – 1699g	2	0.0%
1700 – 1799g	1	0.0%
Total	19,863	100%

eTable 4. Risk Differences for Blindness

Risk Factor	RD[a] (95% CI)	p-value
Cerebral Injury	1.4% (0.9-1.8%)	<0.001
Severe ROP	1.4% (0.8-2.0%)	<0.001
Additive Interaction	2.9% (1.2-4.5%)	<0.001

Abbreviation: ROP, Retinopathy of Prematurity.
[a] The Risk Differences and p-values are from a linear regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, cerebral injury, severe ROP, the additive interaction between cerebral injury and severe ROP, and center as a cluster effect.

eTable 5. Adjusted Odds Ratios (aOR) and 95% Confidence Interval for Blindness Before and Since 2006

	1994-2005 births (N=9483)		2006-2021 births (N=10,380)	
Risk Factor	**aOR[a] (95% CI)**	**p-value**	**aOR[a] (95% CI)**	**p-value**
Cerebral Injury, with Severe ROP present	1.98 (1.12-3.51)	0.02	5.90 (3.67-9.47)	<0.0001
Cerebral Injury, with Severe ROP absent	5.00 (2.50-9.97)	<0.0001	10.7 (5.69-20.1)	<0.0001
Severe ROP, with Cerebral Injury present	4.06 (1.80-9.14)	0.0007	3.39 (2.21-5.20)	<0.0001
Severe ROP, with Cerebral Injury absent	10.2 (4.70-22.2)	<0.0001	6.15 (3.47-10.9)	<0.0001
Cerebral Injury*Severe ROP Interaction	--	0.11	--	0.07
Both Cerebral Injury and Severe ROP vs. Neither[b]	20.3 (8.42-48.8)	<0.0001	36.3 (17.6-74.8)	<0.0001

Abbreviation: ROP, Retinopathy of Prematurity.
[a] The adjusted odds ratios and p-values are from a logistic regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, cerebral injury, severe ROP, the interaction between cerebral injury and severe ROP, and center as a cluster effect. Additionally, the following variables were removed during backward stepwise selection: maternal public insurance, gestational age, birth year, antenatal steroids, Hispanic ethnicity, maternal hypertension, and maternal insulin-dependent diabetes.
[b] The adjusted odds ratio and p-value for Both cerebral injury and severe ROP vs. Neither is from the same logistic regression model but using different reference levels for the two risk factors, assessing Cerebral injury and Severe ROP as a 4-level variable (Cerebral injury only, Severe ROP only, Both, Neither) with no interaction term.

eTable 6. Adjusted Odds Ratios (aOR) and 95% Confidence Interval for Blindness, Comparing Cerebral injury vs. Normal imaging[a]

(N=15,578)		
Risk Factor	**aOR[b] (95% CI)**	**p-value**
Cerebral Injury, with Severe ROP present	3.47 (2.20-5.49)	<0.0001
Cerebral Injury, with Severe ROP absent	10.8 (6.11-19.3)	<0.0001
Severe ROP, with Cerebral Injury present	3.41 (2.33-4.98)	<0.0001
Severe ROP, with Cerebral Injury absent	10.6 (5.00-22.6)	<0.0001
Cerebral Injury*Severe ROP Interaction	--	0.01
Both Cerebral Injury and Severe ROP vs. Neither[c]	36.9 (18.7-72.9)	<0.0001

Abbreviation: ROP, Retinopathy of Prematurity.

[a] Infants without normal imaging and without cerebral injury (N=4285) are excluded.

[b] The adjusted odds ratios and p-values are from a logistic regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, cerebral injury, severe ROP, the interaction between cerebral injury and severe ROP, and center as a cluster effect.

[c] The adjusted odds ratio and p-value for Both cerebral injury and severe ROP vs. Neither is from the same logistic regression model but using different reference levels for the two risk factors, assessing Cerebral injury and Severe ROP as a 4-level variable (Cerebral injury only, Severe ROP only, Both, Neither) with no interaction term.

eTable 7. Risk Factors for Blindness, Cerebral Injury vs. Normal Imaging

(N=15,578)	
Risk Factor	**Blind**
Cerebral Injury Normal imaging	133/4274 (3.1%) 53/11304 (0.5%)
Severe ROP No Severe ROP	122/3544 (3.4%) 64/12034 (0.5%)
Cerebral Injury only Severe ROP only Both Neither	47/2836 (1.7%) 36/2106 (1.7%) 86/1438 (6.0%) 17/9198 (0.2%)
If Severe ROP: Cerebral Injury No Cerebral Injury	N=3544 86/1438 (6.0%) 36/2106 (1.7%)
If No Severe ROP: Cerebral Injury No Cerebral Injury	N=12034 47/2836 (1.7%) 17/9198 (0.2%)
If Cerebral Injury: Severe ROP No Severe ROP	N=4274 86/1438 (6.0%) 47/2836 (1.7%)
If Normal imaging: Severe ROP No Severe ROP	N=11304 36/2106 (1.7%) 17/9198 (0.2%)

Abbreviation: ROP, Retinopathy of Prematurity.

eTable 8. Adjusted Odds Ratios (aOR) and 95% Confidence Interval for Blindness, with Blood/Echodensity in Parenchyma not Included in Cerebral Injury Definition

Risk Factor	aOR[a] (95% CI)	p-value
Cerebral Injury, with Severe ROP present	3.73 (2.40-5.79)	<0.0001
Cerebral Injury, with Severe ROP absent	8.97 (5.71-14.1)	<0.0001
Severe ROP, with Cerebral Injury present	3.35 (2.26-4.97)	<0.0001
Severe ROP, with Cerebral Injury absent	8.06 (4.50-14.4)	<0.0001
Cerebral Injury*Severe ROP Interaction	--	0.01
Both Cerebral Injury and Severe ROP vs. Neither[b]	30.1 (16.8-53.6)	<0.0001

Abbreviation: ROP, Retinopathy of Prematurity.

[a] The adjusted odds ratios and p-values are from a logistic regression model using GEE; the model adjusted for sex, birth weight, multiple birth, maternal race, cerebral injury, severe ROP, the interaction between cerebral injury and severe ROP, and center as a cluster effect. Additionally, the following variables were removed during backward stepwise selection: maternal public insurance, gestational age, birth year, antenatal steroids, Hispanic ethnicity, maternal hypertension, and maternal insulin-dependent diabetes.

[b] The adjusted odds ratio and p-value for Both cerebral injury and severe ROP vs. Neither is from the same logistic regression model but using different reference levels for the two risk factors, assessing Cerebral injury and Severe ROP as a 4-level variable (Cerebral injury only, Severe ROP only, Both, Neither) with no interaction term.

eTable 9. Risk Factors for Blindness, with Blood/Echodensity in Parenchyma not Included in Cerebral Injury Definition

Risk Factor	Blind
Cerebral Injury	133/4074 (3.3%)
No Cerebral Injury	80/15789 (0.5%)
Severe ROP	139/4568 (3.0%)
No Severe ROP	74/15295 (0.5%)
Cerebral Injury only	47/2687 (1.7%)
Severe ROP only	53/3181 (1.7%)
Both	86/1387 (6.2%)
Neither	27/12608 (0.2%)
If Severe ROP:	N=4568
Cerebral Injury	86/1387 (6.2%)
No Cerebral Injury	53/3181 (1.7%)
If No Severe ROP:	N=15295
Cerebral Injury	47/2687 (1.7%)
No Cerebral Injury	27/12608 (0.2%)
If Cerebral Injury:	N=4074
Severe ROP	86/1387 (6.2%)
No Severe ROP	47/2687 (1.7%)
If No Cerebral Injury:	N=15789
Severe ROP	53/3181 (1.7%)
No Severe ROP	27/12608 (0.2%)

Abbreviation: ROP, Retinopathy of Prematurity.