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CORRESPONDENCE

Retinopathy of prematurity and neurodevelopmental outcomes in premature infants

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To the Editor:

Retinopathy of prematurity (ROP) is a leading cause of preventable childhood blindness among premature infants worldwide [1]. The development of neonatal intensive care units increased the survival rate of preterm infants, and consequently the incidence of ROP and its long-term sequelae [1].

Infants with ROP can develop early and late visual disabilities that may lead to poor neurodevelopmental (ND) outcomes [1]. Independent of visual deficits, premature infants are at increased risk for ND disabilities due to its associated brain damage [1–3]. Whether the severity of ROP, its treatment, its visual sequelae, or the prematurity-associated comorbidities is the reason for the resultant poorer ND outcomes in these children is unknown. While some studies demonstrated that ROP severity is a marker for subsequent functional disability, particularly in the presence of unfavourable visual acuity [4], others concluded that neither ROP severity nor its treatment was related to ND outcomes [1, 5].

To further examine ND outcomes in infants with ROP, we performed a retrospective analysis of premature infants between 2007 and 2016 using the IBM MarketScan database. Conditions and outcomes were identified using International Classification of Disease 9th and 10th editions diagnosis codes. Five major ND outcomes were compared between infants with ROP (±treatment) and premature infants without ROP using univariate and multivariate logistic regression analyses. The Stanford University Institutional Review Board ruled this analysis of de-identified administrative data exempt from approval.

The study population included 79,382 premature infants (Table 1). More infants with treated ROP had extremely low birth weight (<1000 g) and a gestational age of <30 weeks compared with infants with untreated ROP and premature infants without ROP. In addition, a larger proportion of these infants had multiple comorbidities, intellectual disabilities (75.2%), psychiatric and behavioural disorders (43.2%), speech and language impairment (32.4%), motor deficits (18%), and hearing loss (23.4%) at 1 and 2 years of age compared with the other groups. Multivariate logistic regression analysis revealed that both infants with treated and untreated ROP had increased odds of intellectual disabilities (OR 2.83, 95% CI 1.94–4.12; OR 1.70, 95% CI 1.57–1.83), psychiatric and behavioural disorders (OR 1.62, 95% CI 1.17–2.23; OR 1.36, 95% CI 1.23–1.49), speech and language impairment (OR 1.91, 95% CI 1.40–2.66; OR 1.34, 95% CI 1.22–1.48), motor deficits (OR 1.38, 95% CI 0.93–2.03; OR 1.73, 95% CI 1.53–1.96), and hearing loss (OR 1.51, 95% CI 1.07–2.14; OR 1.41, 95% CI 1.26–1.57) (Table 2).

Our large cohort study confirms that infants with ROP have worse ND outcomes compared with premature infants without ROP. We demonstrate that severity of ROP, as reflected by treatment-requiring disease, is likely associated with worse outcomes. The limitations of this study include lack of visual acuity data and reliance on diagnostic and procedural codes. An inability to account for coding or billing errors may have resulted in a falsely low number of treated ROP patients. Finally, infants who are covered by Medicaid (which may be up to 40% of insured infants) are not represented in this study. In conclusion, our findings emphasize the importance of ND assessment and monitoring along with ophthalmic monitoring.

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Table 1 Baseline demographic and clinical characteristics of premature infants with treatment-requiring retinopathy of prematurity (treated ROP), no treatment-requiring ROP (untreated ROP), and no ROP in the IBM MarketScan database 2007–2016.

Characteristic	Treated ROP $n = 222$	Untreated ROP $n = 4945$	No ROP $n = 74206$	p value
Sex [n, (%)]				0.023
Male	112 (50.5)	2583 (52.2)	40,139 (54.1)	
Female	110 (49.5)	2362 (47.8)	34,067 (45.9)	
Gestational age				<0.001
≤30 weeks	193 (86.9)	2988 (60.4)	6314 (8.5)	
>30 weeks	14 (6.3)	1267 (25.6)	38,459 (51.8)	
Missing	15 (6.8)	690 (14.0)	29,433 (39.7)	
Birth weight[a]				<0.001
Extremely low	146 (65.8)	1309 (26.5)	2309 (3.1)	
Low	52 (23.4)	2724 (55.1)	28,643 (38.6)	
Normal	24 (10.8)	912 (18.4)	43,254 (58.3)	
Comorbidities [n, (%)].				
Intraventricular haemorrhage	103 (46.4)	1138 (23.0)	2090 (2.8)	<0.001
Hypoxic encephalopathy	24 (10.8)	283 (5.7)	1060 (1.4)	<0.001
Foetal haemorrhage	60 (27.0)	1000 (20.2)	11,060 (14.9)	<0.001
Perinatal infection	109 (49.1)	1077 (21.8)	6340 (8.5)	<0.001
Birth trauma	104 (46.8)	1162 (23.5)	2772 (3.7)	<0.001
Cardiac malformations	192 (86.5)	2445 (49.4)	11,694 (15.8)	<0.001
Lung malformations	71 (32.0)	596 (12.1)	2952 (4.0)	<0.001
Ocular malformations	86 (38.7)	1268 (25.6)	8476 (11.4)	<0.001
Other congenital malformations	68 (30.6)	925 (18.7)	6871 (9.3)	<0.001
Outcomes within 1 year [n, (%)].				
Intellectual disabilities	126 (56.8)	1751 (35.4)	8218 (11.1)	<0.001
Psychiatric and behavioural disorders	58 (26.1)	688 (13.9)	3136 (4.2)	<0.001
Speech and language impairment	11 (5.0)	217 (4.4)	1533 (2.1)	<0.001
Motor deficits	21 (9.5)	331 (6.7)	1409 (1.9)	<0.001
Hearing loss	34 (15.3)	409 (8.3)	2360 (3.2)	<0.001
Outcomes within 2 years [n, (%)].				
Intellectual disabilities	167 (75.2)	2274 (46.0)	11,090 (14.9)	<0.001
Psychiatric and behavioural disorders	96 (43.2)	1051 (21.3)	4834 (6.5)	<0.001
Speech and language impairment	72 (32.4)	840 (17.0)	5344 (7.2)	<0.001
Motor deficits	40 (18.0)	553 (11.2)	2231 (3.0)	<0.001
Hearing loss	52 (23.4)	673 (13.6)	3872 (5.2)	<0.001

[a]Normal birth weight presumed as not low or extremely low.

Table 2 Multinomial logistic regression model for odd of adverse neurodevelopmental outcomes within 1 and 2 years of age in premature infants with treatment-requiring retinopathy of prematurity (treated ROP) and no treatment-requiring ROP (untreated ROP) in the IBM MarketScan database 2007–2016.

Outcome	Within 1 year				Within 2 years			
	Treated ROP		Untreated ROP		Treated ROP		Untreated ROP	
	[a]Adjusted OR (95% CI)	p value	[a]Adjusted OR (95% CI)	p value	[a]Adjusted OR (95% CI)	p value	[a]Adjusted OR (95% CI)	p value
Intellectual disabilities	2.92 (1.98–4.33)	<0.001	1.71 (1.58–1.86)	<0.001	2.83 (1.94–4.12)	<0.001	1.70 (1.57–1.83)	<0.001
Psychiatric and behavioural disorders	1.42 (0.98–2.05)	0.062	1.36 (1.21–1.52)	<0.001	1.62 (1.17–2.23)	0.003	1.36 (1.23–1.49)	<0.001
Speech and language impairment	0.94 (0.48–1.84)	0.021	1.23 (1.03–1.48)	<0.001	1.91 (1.40–2.66)	<0.001	1.34 (1.22–1.48)	<0.001
Motor deficits	1.14 (0.69–1.90)	0.608	1.72 (1.48–2.01)	<0.001	1.38 (0.93–2.03)	0.109	1.73 (1.53–1.96)	<0.001
Hearing loss	1.55 (1.03–2.34)	<0.001	1.36 (1.19–1.56)	<0.001	1.51 (1.07–2.14)	0.019	1.41 (1.26–1.57)	<0.001

CI confidence interval, *OR* odds ratio.

[a]Reference group is premature infants without ROP. Adjusted analysis adjusts for: sex, gestational age, birth weight, and comorbidities reaching $p > 0.2$ in univariate analysis.

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Compliance with ethical standards

Conflict of interest DMM has the following conflicts of interest: 1–800 Contacts (board of directors, equity), Akceso Advisors AG (evaluation of DME market), Akebia (scientific advisory board for ROP), Alcon (data safety monitoring board for HAWK/HARRIER), Aldeyra Therapeutics (Site PI: ADX-2191-PVR-001 GUARD), Allegro (scientific advisory board), Apellis (Site PI: APL2-303 DERBY), Bayer Pharma AG (ROP imaging committee), CMEOutfitters.com (CME consultant), Cole Eye Institute (CME consultant), Congruence medical solutions (consultant), dSentz, Inc. (founder, board of directors, equity), Genentech (PROPER grant 2019), Grand Legend Technology, LTD (equity), Iconic Therapeutics (steering committee, unpaid), Irenix (scientific advisory board, unpaid), Linc (founder, equity, board of directors), Northwell Health (grand rounds), Novartis Pharmaceuticals (data safety monitoring board for HAWK/HARRIER, KITE/KESTREL, China nAMD/DME, pediatric advisory board), Ocular Surgery News (consultant), Pr3vent (founder, board of directors, equity), Praxis UNS, Inc. (consultant), Prime Medical Education (CME consultant), Promisight, Inc. (founder, board of directors, equity), Pykus (scientific advisory board, equity), Regeneron (CME consultant, ROP steering committee, PI for ROP trial), Retina Technologies LLC (advisor, consultant), Retina Today/Pentavision (consultant), Shapiro Law Group (ROP expert witness), SLACK, Inc. (CME consultant), University of Miami (CME consultant), VersI, Inc. (founder, equity), Vindico (CME consultant), Visunex (scientific advisory board, equity). The remaining authors declare that they have no conflict of interest.

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References

1. Beligere N, Perumalswamy V, Tandon M, Mittal A, Floora J, Vijayakumar B, et al. Retinopathy of prematurity and neurodevelopmental disabilities in premature infants. Semin Fetal Neonatal Med. 2015;20:346–53.
2. Goyen T-A, Todd DA, Veddovi M, Wright AL, Flaherty M, Kennedy J. Eye-hand co-ordination skills in very preterm infants <29 weeks gestation at 3 years: effects of preterm birth and retinopathy of prematurity. Early Hum Dev. 2006;82:739–45.
3. Allred EN, Capone A, Fraioli A, Dammann O, Droste P, Duker J, et al. Retinopathy of prematurity and brain damage in the very preterm newborn. J Aapos. 2014;18:241–7.
4. Msall ME, Phelps DL, DiGaudio KM, Dobson V, Tung B, McClead RE, et al. Severity of neonatal retinopathy of prematurity is predictive of neurodevelopmental functional outcome at age 5.5 years. Behalf of the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Pediatrics. 2000;106:998–1005.
5. Todd DA, Goyen T-A, Smith J, Rochefort M. Developmental outcome in preterm infants <29 weeks gestation with ≤Stage 3 retinopathy of prematurity (ROP): relationship to severity of ROP. J Dev Orig Health Dis. 2012;3:116–22.