Letters

RESEARCH LETTER

Association Between Severe Retinopathy of Prematurity and Nonvisual Disabilities at Age 5 Years

Severe retinopathy of prematurity is a serious complication of neonatal intensive care for preterm infants.[1,2] Before effective screening and treatment became available, approximately 5% of infants with birth weights of 1250 g or less had visual acuity of 20/200 or worse at 5.5 years.[3] In such children, the severity of retinopathy was a predictor of functional disability in multiple domains.[1] Although the incidence of severe retinopathy has increased since the late 1980s,[4] blindness caused by retinopathy has become rare in developed countries.[5] Consequently, clinicians and parents may conclude that severe retinopathy is no longer associated with childhood impairments. We investigated whether infants with severe retinopathy who were diagnosed and treated under modern protocols retain an increased risk of nonvisual disabilities compared with those without severe retinopathy.

Methods | This exploratory analysis used data from the inception cohort assembled for the Caffeine for Apnea of Prematurity trial. Study participants were infants with birth weights between 500 g and 1250 g who were born at 31 centers between 1999 and 2004 and followed-up at age 5 years (2005-2011).[6]

Severe retinopathy of prematurity was defined as unilateral or bilateral stage 4 or 5 disease or as receipt of retinal therapy in at least 1 eye. The incidence in this cohort was 6.5% but only 0.9% of participants were bilaterally blind at 5 years. Five-year outcomes included motor impairment, cognitive impairment, behavioral problems, poor general health, severe hearing loss, and bilateral blindness.[6] Infants from intervention and placebo groups were analyzed together in this observational study. We expressed the association between severe retinopathy of prematurity and 5-year outcomes as an odds ratio (OR) estimated via a logistic model with adjustment for prespecified baseline covariates (gestational age, sex, antenatal steroid exposure, multiple birth, and maternal educational level). SAS version 9.2 was used (SAS Institute Inc). All *P* values were 2-sided and considered significant if <.05. Research ethics boards at all centers approved the protocol and written informed consent was obtained from parents or guardians.

Results | Of 2006 infants enrolled, 191 died or were born in centers that did not participate in the 5-year follow-up. Of 1815 eligible survivors, 1582 children (87%) had complete (n = 1523) or partial (n = 59) 5-year assessments; 95 had severe retinopathy. Children with severe retinopathy had lower gestational age and less exposure to antenatal corticosteroids than those without or with less severe retinopathy (**Table 1**). Of the children with severe retinopathy, 39.5% had at least 1 nonvisual disability at 5 years compared with 15.8% of children without it (adjusted OR, 2.89; 95% CI, 1.77-4.72; *P* < .001; **Table 2**). Fourteen of 94 children (14.9%) with and 36 of 1487 children (2.4%) without severe retinopathy had more than 1 nonvisual disability at 5 years (adjusted OR, 6.98; 95% CI, 3.27-14.89; *P* < .001).

Motor impairment, cognitive impairment, and severe hearing loss were 3 to 4 times more common in children with severe retinopathy than those without severe retinopathy.

Discussion | In this cohort of very low-birth-weight infants, we observed a strong association between the development of severe retinopathy of prematurity and the presence of 1 or more nonvisual disabilities at age 5 years. This observation may help improve the ability to counsel parents and to select high-risk infants for long-term follow-up.

Table 1. Characteristics of the Children and Their Families[a]

Characteristics	No. (%) of Participants		*P* Value
	Severe ROP (n = 95)	No Severe ROP (n = 1487)[b]	
Children			
Gestational age, mean (SD), wk	25.6 (1.2)	27.5 (1.7)	<.001
Girl	40 (42.1)	732 (49.2)	.18
Exposure to antenatal corticosteroids	75 (78.9)	1324 (89.0)	.003
Singleton birth	65 (68.4)	1041 (70.0)	.74
Educational level of maternal caregivers at 5-y follow-up			
≤High school or equivalent	20 (21.1)	300 (20.2)	.58
Completed high school or equivalent	19 (20.0)	374 (25.2)	
Some college or university	15 (15.8)	259 (17.4)	
University graduate	41 (43.2)	554 (37.3)	

Abbreviation: ROP, retinopathy of prematurity.

[a] These data are for the 1582 children with known neonatal ROP status who had partial or complete assessments at the age of 5 years.

[b] Defined as no ROP or ROP without receipt of retinal therapy and less than stage 4 disease.

Table 2. Rates of Disabilities at Age 5 Years in Children With and Without Severe Retinopathy of Prematurity (ROP)

Impairment[a]	No./Total (%) of Infants		Odds Ratio (95% CI)		*P* Value
	Severe ROP (n = 95)	No Severe ROP (n = 1487)[b]	Unadjusted	Adjusted for Patient Characteristics[c]	
≥1 Impairment[d]	41/92 (44.6)	226/1433 (15.8)	4.29 (2.78-6.62)	3.57 (2.23-5.71)	<.001
Motor[e]	12/93 (12.9)	36/1483 (2.4)	5.96 (2.99-11.88)	4.16 (1.95-8.93)	<.001
Cognitive[f]	12/81 (14.8)	64/1437 (4.5)	3.73 (1.92-7.24)	4.24 (2.02-8.93)	<.001
Behavioral problem[g]	10/86 (11.6)	85/1435 (5.9)	2.09 (1.04-4.18)	1.86 (0.88-3.94)	.11
Poor general health[h]	6/94 (6.4)	59/1486 (4.0)	1.65 (0.69-3.92)	1.47 (0.58-3.68)	.41
Severe hearing loss[i]	12/91 (13.2)	35/1480 (2.4)	6.27 (3.13-12.55)	4.20 (1.96-9.01)	<.001
Bilateral blindness[j]	12/89 (13.5)	2/1466 (0.1)	114 (25-519)	143 (23.0-895)	<.001
≥1 Nonvisual impairment[k]	34/86 (39.5)	226/1433 (15.8)	3.49 (2.22-5.49)	2.89 (1.77-4.72)	<.001

[a] Data for all outcomes exclude children who were alive but were not tested.

[b] Defined as no ROP or ROP without receipt of retinal therapy and less than stage 4 disease.

[c] The odds ratio has been adjusted for the gestational age and sex of the infant, maternal educational status at the assessment, antenatal administration of corticosteroids, and multiple births.

[d] Data for this outcome include children who were known to have at least 1 impairment, including blindness, and children without impairment who had undergone complete testing.

[e] Motor impairment was defined as a Gross Motor Function Classification System level of 2 through 5. Levels between 1 and 5 indicate increasing limitations of gross motor function.

[f] Cognitive impairment was defined as a Full Scale IQ of less than 70 on the Wechsler Preschool and Primary Scale of Intelligence III (2 SDs below the mean of 100).

[g] Behavioral problem was defined as a total problem t score (range, 28-100) of greater than 69 (2 SDs above the mean of 50) for the Parent Form of the Child Behavior Checklist.

[h] Poor general health was defined as 1 or more of the following: need for supplemental oxygen, positive airway pressure, feeding through a tube or intravenously, seizures occurring more frequently than once per month, or a recent admission to an intensive care unit for complications resulting from a neonatal morbidity.

[i] Severe hearing loss was defined as the prescription of hearing aids or cochlear implants.

[j] Bilateral blindness was defined as a corrected visual acuity less than 20/200 in the better eye.

[k] Data for this outcome include children who were known to have at least 1 nonvisual impairment, excluding blindness, and children without impairment who had undergone complete testing.

Although the risk of vision loss was increased after severe retinopathy, most children with severe retinal disease did not become bilaterally blind. Unfavorable exposures that promote the development of retinopathy may simultaneously damage the immature brain. We did not adjust our analysis for acquired neonatal comorbidities such as bronchopulmonary dysplasia because we wanted to investigate the prognostic importance of severe retinopathy, not the possible independent causal relationship between it and childhood disability. Limitations of our study include an attrition rate of 13% at 5 years. Compared with those analyzed, children not seen at 5 years were less likely to have been part of a multiple birth and had mothers who had less education. We likely underestimated the prevalence of multiple nonvisual disabilities because some impaired children had incomplete outcome assessments.

Severe retinopathy of prematurity remains an adverse outcome of neonatal intensive care with poor prognosis for child development, although blindness can mostly be prevented by timely retinal therapy.

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Study concept and design: Schmidt, Davis, Solimano, Roberts.
Acquisition of data: All authors.
Analysis and interpretation of data: Schmidt, Roberts.
Drafting of the manuscript: Schmidt.
Critical revision of the manuscript for important intellectual content: Davis, Asztalos, Solimano, Roberts.
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COMMENT & RESPONSE

Cardiovascular Event Risk After Noncardiac Surgery

To the Editor Dr Hawn and colleagues[1] evaluated the risk of undergoing noncardiac surgery following coronary stent placement. The analysis, which examines the outcomes of 28 029 veterans undergoing noncardiac surgery within 24 months of coronary stent implantation, found that emergency surgery and severity of cardiac disease were the principal factors associated with postoperative major adverse cardiovascular events (MACE).

Stent type (drug-eluting vs bare metal) and antiplatelet therapy cessation were not associated with MACE. As physicians involved in the care of patients who have presented with stent thrombosis shortly after discontinuing antiplatelet therapy in anticipation of surgery, we note that such adverse events would not have been included in this analysis because the study population included only those who ultimately underwent surgery. Exclusion of patients whose surgery was delayed or cancelled due to MACE could lead to selection bias, potentially influencing the study results, particularly those related to antiplatelet therapy cessation and stent type.

One of the most feared complications of surgery following coronary stent placement is stent thrombosis. The mechanism of stent thrombosis is related to multiple factors, of which early cessation of dual antiplatelet therapy and proinflammatory postsurgical state are major contributors.[2] Current guidelines recommend delaying elective surgery for 1 year following implantation of drug-eluting stents or at least 4 to 6 weeks for bare metal stents and reflect concern for stent thrombosis occurring not only in the postoperative period (as assessed in this study), but also in the preoperative period.[3]

In one of the original descriptions of late thrombosis associated with drug-eluting stents, McFadden et al[4] presented 4 cases, of which 3 were related to premature cessation of dual antiplatelet therapy leading up to surgery. Notably, 2 patients had events prior to surgery and would have been excluded from the current analysis.

Hawn et al[1] have conducted a comprehensive investigation of postoperative outcomes in patients with previous coronary stents; however, inferences on preoperative management and events are less clear. Whether current guidelines emphasizing stent type and surgical timing require reevaluation based on this evidence hinges, in part, on the magnitude of potential bias introduced by their cohort selection.

Selection of a cohort of patients scheduled to undergo surgery (analogous to an intention-to-treat analysis for a randomized trial) could overcome such a limitation and may be necessary to fully characterize the true risk of undergoing surgery in this population.

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In Reply Drs Rassi and Yeh raise an important limitation of our study addressing the risk of noncardiac surgery in patients with recent coronary stent placement. They correctly point out that our study only included patients who successfully underwent surgery. As such, patients scheduled for surgery who had an intervening acute coronary event (potentially due to antiplatelet therapy cessation) would not be included in our cohort.

Therefore, we could be underreporting the actual rate of MACE due to antiplatelet therapy cessation in relation to planned surgery. During our chart review for the study, we identified a single case in which a patient was admitted with an acute coronary event following antiplatelet therapy cessa-