Retinopathy of Prematurity and Ethnicity in Hawai'i: A Retrospective Study (1996 – 2006) of Medical Records from Kapi'olani Medical Center for Women and Children

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Abstract

The objective of this research was to identify risk factors for Retinopathy of Prematurity (ROP) in Hawai'i's ethnically unique population, with a focus on ethnicity. The study design focused on a 10-year retrospective chart review of neonates at Kapi'olani Medical Center in Honolulu, Hawai'i. Results showed that 23.3% of infants of Native Hawaiian and/or Pacific Islander ethnicity (NHPI) developed ROP. Necrotizing enterocolitis, intraventricular hemorrhage, and the severity of respiratory disease were significantly related (P < .001) to the incidence and severity of ROP. In a multiple logistic regression model, gestational age, birth weight, bronchopulmonary dysplasia, and postnatal steroids were significant predictors (P < .001) for presence of ROP. Significant predictors for severe ROP included gestational age (P < .001), birth weight (P = .001), postnatal steroids (P = .001), necrotizing enterocolitis (P = .025), and NHPI ethnicity (P = .004). Further research is recommended.

Keywords

retinopathy of prematurity, retrospective review, co-morbidities of prematurity, multiple logistic regression

Introduction

Retinopathy of prematurity (ROP) is a developmental vascular disorder of the retina. It is characterized by abnormal growth of retinal blood vessels and can result in disease that is mild and spontaneously resolves, or in progressive disease that can cause retinal detachment and blindness. Normal growth of retinal blood vessels begins at approximately 16 weeks gestation and is completed between 35 and 44 weeks postmenstrual age. If an infant is born prematurely before these blood vessels have reached the edges of the retina, normal vessel growth may be affected resulting in ROP.[1]

ROP was first recorded in 1942. ROP incidence decreased in the late 1950s and early 1960s following the publication of research results identifying oxygen exposure at more than 40% as a causal factor. With advances in neonatology and the increased survival of premature infants, ROP incidence increased in the 1970s. At the time, there were no agreed upon criteria for measuring the progression of ROP or when to begin intervention, leading to wide frustration among pediatric professionals. Consequently, an international group of ophthalmologists and the National Eye Institute published new and effective criteria in 1984.[1] As part of the same effort to reduce ROP, a large multi-center research project was conducted (CRYO-ROP Study Group).[2-6] The CRYO-ROP Study Group identified multiple contributing factors that were associated with ROP, the most important of which were early gestational age (GA), low birth weight (BW), oxygen exposure, and ethnicity.[2,3,6,7]

With regard to ethnicity, the CRYO-ROP Study Group found a decreased incidence of progression to severe ROP in black infants when compared to white infants.[2,3,6-8] No uniform results, however, have emerged from further research into ethnicity and ROP. In two studies of Alaska Native people, as well as in a small group of Asian neonates, there was an increased incidence of severe ROP.[9,10] In studies of Asian groups there was no statistical difference in the incidence or severity of ROP in infants of Asian ethnicity.[9,11,12] However, Aralikatti, et al, found that Asian and black infants had a higher risk of developing threshold ROP compared to white infants in the United Kingdom.[13] Hispanics showed no significant difference in the risk of ROP, although a greater incidence was attributed to their lower birth weight and gestational age at birth.[14]

The relationship between ethnicity and severe ROP is of interest given the findings by the CRYO-ROP Study Group which found that infants of certain ethnicities were less likely to progress to threshold ROP. With a condition like ROP that develops after birth and must be managed by a watch and wait methodology, factors that may result in the spontaneous resolution of a condition are worth exploring. Moreover, ethnicity is a risk factor of particular interest given Hawai'i's unique and varied ethnic population. The study of ROP in Hawai'i provides an opportunity for comparison with both Western and foreign studies that have more homogeneous populations.[15-18]

Materials/Subjects and Methods

Subjects

Kapi'olani Medical Center (KMC) for Women and Children (Honolulu, Hawai'i) is located in Honolulu, Hawai'i. It is Hawai'i's only children's hospital and the state's only 24-hour pediatric emergency room and pediatric intensive care unit.

Cases for this study were extracted from the "Neonatal Summary Note" captured in Karelink, an electronic database maintained by KMC for billing purposes. Each case drawn from the database was validated against their paper chart. A case was selected if the child fit the following criteria: (1) admitted or transferred between January 1, 1996 and December 30, 2006; (2) gestational age of ≤32 weeks or weighing <1500 grams; and (3) if the subject reached 35 days of life (DOL). Cases were excluded if: (1) the subject was transferred out of Hawai'i; (2) if either GA or BW were missing or undeterminable. Data collection was approved by the Western Institutional Review Board.

Description of Variables

GA in completed weeks was collected from an inspection of medical records. This variable was derived from a comparison of chart values, which included gestational age in weeks plus days and gestational age by Ballard Maturational Assessment. If the value of any of these differed by more than two weeks, the chart was evaluated by one of our team doctors in order to determine the most accurate figure.

Ethnicity was derived from self-reported labels used in the KMC medical records. The wide variety of labels that appeared in the records was collapsed into the following categories for use in this research: Asian Mixed, Caucasian, Filipino, Native Hawaiian & Pacific Islander (NHPI), and Others/Unknown. NHPI included the self-reported categories found in the medical record of Hawaiian, Part Hawaiian, Pacific Islander, Other Pacific Islander, Marshallese, and Samoan. Others/Unknown was a category collected by KMC and was retained as a viable category.

ROP was coded as present for any noted classification of ROP. ROP classification was based on position (zone), severity (stage), and extent (clock hours); and also includes whether or not there is "plus disease" (tortuosity of vessels) present. Serial eye examinations are necessary to identify and monitor the progression of ROP and to determine which neonates will become candidates for further treatment. Treatment recommendations are made based on threshold disease, which is defined as stage 3 with plus disease in zone 1 or zone 2, or 5 contiguous, or 8 cumulative clock hours of plus disease.[1] Treatment is usually either cryotherapy or laser therapy, which stops the process of abnormal vascular growth in the retina. The KMC medical record used in this study did not record in a consistent way the diagnosis of threshold disease. Therefore, the treatment recorded—in this case the presence or absence of treatment (either cryotherapy or laser therapy)—was used as a surrogate for severity of ROP.

The study controlled for two other factors: (1) general illness of the infant and (2) the types of treatment administered. The illness variables used were four co-morbidity variables. These included respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH). Three measures of treatment that might change the course of ROP included antenatal steroids and postnatal steroids, and whether or not an infant was discharged on nasal cannula oxygen.

Data Analysis

All analyses were performed with PASW/SPSS statistical software, version 23 (IBM SPSS).

Univariate analysis of risk factors and co-morbidities in relation to the presence/absence of any stage ROP and also between severity of ROP were conducted using Chi-square ($\chi 2$) and Student's *t* test as appropriate with statistical significance at $P < .05$. All variables were binary except GA and BW, which were continuous. GA was used as completed weeks and BW as grams. A categorical GA was created for univariate analysis (See Table 1).

The variables identified as significant at $P < .05$ in univariate analyses were entered into a multivariate logistic regression model. Logistic regression analysis was employed to predict the probability that an infant would have ROP or be treated for severe ROP. A model was constructed using an iterative maximum likelihood procedure. A process of refitting was performed with individual predictors deleted and verified at each stage. The fit of the models was checked with the Hosmer-Lemeshow goodness-of-fit statistic. The predictor variables used were GA, BW, RDS, BPD, surfactant, postnatal steroids, NEC, IVH, and ethnicity. In the first model, RDS, surfactant, IVH, and ethnicity were not significant so they were not used in the final analysis. However, ethnicity was retained as a variable because it is of primary interest.

Results

Descriptive Analysis

There were 1525 cases that met the criteria for selection (Table 1). The mean birth weight was 1312 g and the mean GA was 29 weeks. The ratio of male to female was about the same at 1.14:1 (data not shown). Of the 1525 cases, 19.9% (303) were diagnosed with ROP. An independent-samples t-test was conducted to compare the mean birth weight or mean gestational age for infants diagnosed with ROP and those without. There was a significant difference in mean gestational age for ROP infants compared to non-ROP infants ($P = .012$). Similarly there was a significant difference in the birth weight of ROP infants compared to non-ROP infants ($P < .001$). The same appeared to be true for those treated for severe ROP although they make up only 3.74% (57) of the study population.

A large proportion of the subjects were NHPI (521 of 1525 = 34.2%) (Table 2). Also, 19.8% of NHPI infants were in the earliest GA category (23-26 weeks), and 28% of NHPI infants were in the smallest BW category (0-1000 g). However, no significant differences in GA ($P = .068$) or BW ($P = .179$) were observed by ethnicity.

ROP occurred in similar proportions across all ethnic groups ($P = .068$), whereas severe ROP varied significantly by ethnicity ($P = .002$), with NHPI infants accounting for most of the cases (59.6%) (Table 3).

An explanation of the relationship between severe ROP and ethnicity benefited from an exploration of the general illness of an infant. NEC was used as one measure of infant illness. Overall, 26.5% of NHPI infants with ROP were treated for NEC compared with 17.4% of all other infants ($P < .001$) (Table 4). Finally, because of the recognized association between ROP and oxygen, we examined the proportion of NHPI infants with BPD. Ninety seven percent of NHPI infants with severe ROP were treated for BPD compared to 87% of other infants ($P < .01$).

Table 1. Independent-samples t-test comparing GA & BW for ROP and severe ROP infants.							
		N 1525[a]	Mean	Standard Deviation	t –value	Degrees of Freedom	Significance (*P*)
Gestational Age Mean = 29 weeks	No-ROP	1219	30.23	2.01	32.25	1520	.012
	Yes-ROP	303	26.17	1.74	35.17	531.42	
	No-Severe ROP	1441	29.59	2.4	14.42	1496	< .001
	Yes-Severe ROP	57	24.96	1.2	26.58	74.44	
Birth weight Mean = 1312 g	No- ROP	1219	1422.89	341.98	27.29	1520	< .001
	Yes- ROP	303	860.07	218.83	35.32	714.64	
	No-Severe ROP	1441	1334.35	380.85	11.97	1496	< .001
	Yes Severe ROP	57	728.3	164.56	25.26	82	

[a]ROP missing values = 3, Severe ROP missing values = 27.
BW, birth weight; g, grams; GA, gestational age; ROP, retinopathy of prematurity.

Table 2. Crosstabulation of gestational age[a] and birth weight[b] by ethnicity.							
		Native Hawaiian & Pacific Islander	Asian Mixed	Filipino	Caucasian	Other/ Unknown[c]	Total
GA (weeks) [% (N)] Mean: 29	23-26	19.8 (103)	13.9 (44)	13.8 (41)	16.9 (29)	15.6 (34)	16.5 (251)
	27-31	57.2 (298)	59.8 (189)	60.7 (181)	64 (110)	66.5 (145)	60.5 (923)
	>31	23 (120)	26.3 (83)	25.5 (76)	19.2 (33)	17.9 (39)	23 (351)
	Total	100 (521)	100 (316)	100 (298)	100 (172)	100 (218)	100 (1525)
Birth Weight (g) [% (N)] Mean: 1312	0-1000	28 (146)	20.6 (65)	22.5 (67)	25.6 (44)	22.9 (50)	24.4 (372)
	1001-1250	17.7 (92)	17.7 (56)	22.1 (66)	21.5 (37)	20.6 (45)	19.4 (296)
	1251-1500	24.6 (128)	28.5 (90)	25.8 (77)	25 (43)	19.7 (43)	25 (381)
	>1500	29.8 (155)	33.2 (105)	29.5 (88)	27.9 (48)	36.7 (80)	31.2 (476)
	Total N	100 (521)	100 (316)	100 (298)	100 (172)	100 (218)	100 (1525)

[a]X2 (8, 1525) = 14.58, *P* = .068. [b]X2 (12, 1525) = 16.27, *P* = .179.
[c]Other/Unknown = category collected by KMC hospital not a missing value.
BW, birth weight; g, grams; GA, gestational age.

Table 3. Crosstabulation of ROP[a] and severe ROP[b] by ethnicity.							
		Hawaiian & Pacific Islander	Asian Mixed	Filipino	Caucasian	Other/ Unknown[c]	Total
ROP	[% (N)]	23.3 (121)	14.9 (47)	19.8 (59)	19.8 (34)	19.4 (42)	303
	Total N	520	316	298	172	216	1522[d]
Severe ROP	[% (N)]	6.6 (34)	1.9 (6)	2.7 (8)	1.8 (3)	2.9 (6)	57
	Total N	516	310	292	170	210	1498[e]

[a]X2(4, 1522) = 8.74, *P* = .068. [b]X2(4, 1498) = 17.24, *P* = .002. [c]Other/Unknown = category collected by KMC hospital not a missing value. [d]Missing values, N = 3. [e]Missing values, N = 27.

Table 4. Crosstabulation of severe ROP by NEC[a] by BPD[b].							
		NEC [% (N)]	No NEC	Total	BPD	No BPD	Total
Hawaiian & Pacific Islander	Severe ROP	26.5 (9)	73.5 (25)	100 (34)	97.1 (33)	2.9 (1)	100 (34)
	No Severe ROP	7.3 (35)	92.7 (446)	100 (481)	29.3 (141)	70.7 (340)	100 (481)
	Total	8.5 (44)	91.5 (471)	100 (515)	33.8 (174)	66.2 (341)	100 (515)
All Others	Severe ROP	17.4 (4)	82.6 (19)	100 (23)	87 (20)	13 (3)	100 (23)
	No Severe ROP	4.6 (44)	95.4 (914)	100 (958)	25.1 (240)	74.9 (718)	100 (958)
	Total	4.9 (48)	95.1 (933)	100 (981)	26.5 (260)	73.5 (721)	100 (981)

[a]FET(1, 1496) = 10.5, *P* = <.001. [b]FET(1, 1496) = 67.8, *P* = <.001.
NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia.

Multivariate Analysis

A multiple regression analysis was conducted to assess whether ethnicity predicted presence of ROP (Table 5) and severe ROP (Table 6) while controlling for measures of prematurity (GA, BW), measures of illness (IVH, NEC, BPD), and medical treatments (steroids, discharged on nasal cannula oxygen). For the ROP model, GA (P <.001), BW (P < .001), BPD (P = .006), and postnatal steroids (P < .001) had significant partial effects (Table 5). NHPI ethnicity as compared to all other ethnicities combined did not have a significant effect (P = .612). In the severe ROP model (Table 6), infants of NHPI ethnicity did appear as a significant variable (P = .004). Also in the severe model, NEC (P = .025) and postnatal steroids (P = .005) were significant.

Table 5. Multiple logistic regression, Presence of ROP.

Predictor Variables	B	Wald X2	*P*	OR (95% CI)
GA	-.475	50.37	< .001	.622 (.546-.709)
BW	-.309	38.13	<.001	.734 (.665-.810)
BPD (Y/N)	-.601	7.51	.006	.548 (.357-843)
Postnatal Steroids (Y/N)	-1.037	18.35	<.001	.354 (.220-570)
Native Hawaiian & Pacific Islander Ethnicity[a]	-.103	.258	.612	.902 (.605-1.344)

[a]Reference group = All other ethnicities.
BPD, bronchopulmonary dysplasia; BW, birth weight; CI, confidence intervals; GA, gestational age; OR, odds ratio; ROP, retinopathy of prematurity.

Table 6. Multiple logistic regression, Severe ROP.

Predictor Variables	B	Wald X2	*P*	OR (95% CI)
GA	-.498	12.33	<.001	.608 (.460-.803)
BW	-.420	11.93	.001	.657 (.518-.834)
Postnatal Steroids (Y/N)	-1.007	8.07	.005	.365 (.182-.732)
NEC (Y/N)	-.955	5.02	.025	.385 (.167-.887)
Hawaiian & Pacific Islander Ethnicity[a]	-.977	8.843	.004	.376 (.195-.728)

[a]Reference group = All other ethnicities.
BW, birth weight; CI, confidence intervals; GA, gestational age; NEC, necrotizing enterocolitis; OR, odds ratio; ROP, retinopathy of prematurity.

Discussion

In this study, ROP infants and those who progressed to severe illness were born earlier and smaller than the study population as a whole. Similarly, the NHPI infants with ROP and severe ROP were also born earlier and smaller. Our statistics also suggested that NHPI infants with severe ROP were more ill and exposed to oxygen; thus, partially explaining the high representation of this ethnicity in the severe ROP group. These are expectable results given the pathophysiology of ROP and based on previous research (See Introduction).

The results of the multiple regression analysis found that NHPI ethnicity was a significant variable for severe ROP. Ethnicity remained significantly associated with severe ROP after adjusting for BW and GA. This implies that there is some other factor currently unaccounted for that explains the association. Future studies should examine other variables, including socio-economic status (SES) variables. This study did not collect reliable variables for measures of SES.

One limitation of this study involves the effects of recording bias on important variables like ethnicity. The largest group in this study was Native Hawaiian & Pacific Islanders (n = 521, 34%). This category of ethnicity was a combination of several labels; the most frequent of which was the label "Part Hawaiian." The category accounted for 28% (n = 425) of the study population. Because the study did not directly collect information on ethnicity but instead relied on the self-reported ethnicity in the medical record, there was no control or uniform criteria for determining the ethnicity "Part Hawaiian." The investigators chose to believe that there was validity to the choice and therefore Part Hawaiian became the largest part of the Native Hawaiian & Pacific Islander variable.

Our focus in this research was on retinopathy of prematurity and ethnicity in Hawai'i's unique ethnically diverse populations. Understanding ethnicity as a factor in the progression or lack thereof in the pathophysiology of retinopathy of prematurity gives the pediatric professional one more factor that will help them as they work toward keeping premature infants alive.

Conflict of Interest

None of the authors identify any conflict of interest.

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