HHS Public Access

Author manuscript

Ophthalmology. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:

Ophthalmology. 2021 August ; 128(8): 1242–1244. doi:10.1016/j.ophtha.2020.12.024.

Fundus Pigmentation in the Diagnosis and Treatment of Retinopathy of Prematurity

Kenneth C. Fan, MD MBA[a], **Sarah P. Read, MD PhD**[a,b], **Nimesh A. Patel, MD**[a], **Elizabeth A. Vanner, PhD**[a], **Hasenin Al-khersan, MD**[a], **Diana M. Laura, MD**[a], **Parastou Pakravan, MS**[a], **Catherin I. Negron, MBA**[a], **Audina M. Berrocal, MD**[a]

[a]Department of Ophthalmology, Bascom Palmer Eye Institute, Miller School of Medicine, University of Miami, 900 NW 17th Avenue, Miami, FL, 33136, USA

[b]Retinal Consultants of Hawaii, Honolulu, HI, 96732

Abstract

1,259 premature infants at risk for ROP were evaluated. 29% were diagnosed with ROP and 39.4% had light fundus pigmentation (FP). Light FP had a higher association with ROP diagnosis and higher risk ROP features.

Introduction

Retinopathy of prematurity (ROP) is a complex disease driven by vascular abnormalities of the premature retina.[1] Identifying diagnostic and prognostic variables for ROP is critical in preventing morbidity.[2,3] Limited studies have suggested that retinal pigmentation plays a role in the development of ROP through the protective nature of intraocular melanin.[4] We aim to explore the association between fundus pigmentation (FP) and ROP severity.

Materials and Methods

This study adhered to the Health Insurance Portability and Accountability Act of 1996, the tenets of the Declaration of Helsinki, was approved by the Institutional Review Board of the University of Miami, and obtained informed consent from all patients.

This consecutive retrospective case series included patients screened for ROP at Jackson Memorial Hospital Neonatal Intensive Care Unit (NICU). Eligible patients were those who met ROP screening criteria between October 2012 and June 2019. All included patients were evaluated by a single pediatric retinal physician. Exclusion criteria included >1500g BW and >32 weeks GA, and those transferred to our institution for higher level care.

Corresponding Author & Address for Reprints Audina M. Berrocal MD, 900 NW 17th St, Miami, FL 33136, Phone Number: 305-326-5100 Fax Number: 305-326-6417 aberrocal@med.miami.edu.

Conflict of Interest: No conflicting relationship exists for any author

Data Collection

Demographic data collected included gender, birthweight (BW), gestational age (GA), and multiparity birth status. Dilated examinations were performed with standard dilation protocols and indirect ophthalmoscopy. Screening data included presence of ROP, zone, stage, plus disease, and level of FP, and was graded at the time of initial examination. FP was graded as follows: light as defined by presence of visible choroidal vessels in the macula, medium as defined by visible choroidal vessels outside the arcades, but not in the macula, and dark as defined by no visible choroidal vessels in the posterior pole and macula (see Figure 1, available at https://www.ophthalmologyretina.org/). Treatment threshold was in accordance with the Early Treatment for Retinopathy of Prematurity (ETROP) protocol.

Statistical analysis

Explanatory variables were assessed with Pearson chi-square, Fisher exact, or exact chi-square tests (see Table 1). Univariate and multivariate, forward-stepwise logistic regressions were used to explore associations between explanatory variables and ROP and FP. All tests were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A p-value ≤ 0.05 was considered statistically significant.

Results

A total of 1,259 infants were included in the study (table 1, available at https://www.ophthalmologyretina.org/). Of those, 39.4% (496) had light FP, 58.4% (735) had medium FP, and 2.2% (28) had dark FP. Patients with medium and dark FP were combined for analysis. Mean overall BW and GA were 1185.1g and 28.9w, respectively. There was no statistically significant difference in BW or GA between the two groups (light vs. medium/dark, p = 0.79 and 0.82, respectively). A total of 29% (360) of patients had ROP and 4.8% (61) of patients had plus disease. 23% (284) of patients were born in multiple births.

Associations with ROP

The following explanatory variables were significantly associated with ROP by univariate logistic regression: lighter FP (OR=1.38, p=0.010), presence of tunica vasculosa lentis (TVL) (OR =12.24, p<0.001), lower gestational age (OR=23.09, p<0.001), lower birthweight (OR=24.94, p <0.001), and singleton birth status (OR=0.72, p=0.035, see Table 2, available at https://www.ophthalmologyretina.org). By multivariate logistic regression, lower BW (p < 0.01), lower GA (p < 0.01), and light FP (p < 0.01) remained significantly associated with diagnosis of ROP, though multiparity did not (p = 0.30).

Associations with Fundus Pigmentation

Regarding light FP, the following explanatory variables were significantly associated (see table 3): ROP (OR=1.38, p=0.01), plus disease (OR=4.01, p<0.01), multiparity birth status (OR=2.17, p<0.01), more posterior zone (OR=2.50, p<0.01), higher stage (OR=1.92, p<0.01), and treatment with intravitreal bevacizumab (IVB, OR=2.67, p<0.01). 68 patients (18.9%) in the study received IVB. Patients receiving IVB had greater odds of light FP (OR=2.67, p<0.01). No other significant associations were noted for treatment.

Discussion

The current study was prompted by observations that light FP in ROP patients was consistently associated with more severe disease. Although few have directly studied fundus pigmentation, some investigators have found that darker skin pigmentation confers a lower risk of severe ROP.[1,4,5] Our results confirm an association between light FP and the presence of ROP, plus disease, multiparous births, more posterior zone, higher stage, and treatment with IVB (table 3), independent of birthweight and gestational age.

The association between ROP and light FP may be explained by the regulation of reactive oxygen species (ROS) of the retina and choroid.[6] Melanin pigments are a protective antioxidant for the retinal milieu through the mechanism of removing ROS during stress and phototoxicity.[4,6] Therefore, the antioxidative effects of melanin may reduce the progression of ROP in stressful environments (such as the premature retina). Studies of diseases of the retina, RPE, and choroid, such as AMD, have found similar associations.[7]

This pathophysiology may also explain the stronger association of light FP with more severe disease and therefore treatment with IVB as well (table 3). As such, the presence of light FP can be used as a risk stratification indicator in premature infants and may raise clinical suspicion or prompt closer observation during the ROP screening process.

Our study also found that ROP was strongly associated with lower birth GA, lower BW, as well as presence of TVL, which have been established by previous authors.[1,2] Surprisingly, in our regression model, the presence of singleton births had a higher association with ROP, although previous authors have found mixed associations with singleton vs. multiparous births.[3] While lower BW and GA are known risk factors for ROP,[1] regression analysis did not find these significantly associated with fundus pigmentation in our study.

Many prediction models have been developed to ease the burden of ROP screening and improve detection of high-risk patients.[2] Our study has shown that FP is objective and generalizable, since all screenings require fundus evaluations and can be interpreted separately from race or skin pigmentation. As ophthalmologists increase their adoption of telemedicine and remote screening, we may wish to consider FP as a variable for prediction models and risk stratification.[2]

Limitations of our study include its retrospective nature. Changes in screening guidelines may have allowed some variability in the BW and GA of ROP infants across time. Some subjectivity of fundus pigmentation grading was likely present in the study.

Conclusion

In summary, the present study confirms the hypothesis that ROP and more aggressive features of ROP are associated with patients with light FP. In the future, validation of fundus pigmentation as a clinical and algorithmic predictor for ROP may help advance ophthalmological care in premature infants.

Acknowledgments

Financial Support: The research was supported in part by the National Eye Institute Center Core Grant (P30EY014801), an unrestricted grant from the Research to Prevent Blindness, Inc., New York, NY to the Department of Ophthalmology, University of Miami Miller School of Medicine, and the Heed Ophthalmic Foundation.

Meeting presentations: Accepted for poster presentation at the American Academy of Ophthalmology Annual Meeting 2020

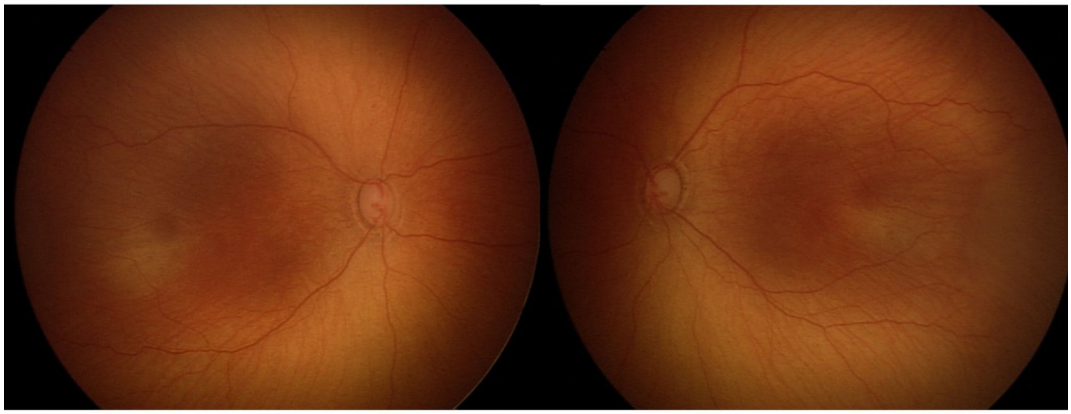
Abbreviations:

ROP	retinopathy of prematurity
FP	fundus pigmentation
BW	birthweight
GA	gestational age
NICU	neonatal intensive care unit
IVB	intravitreal bevacizumab

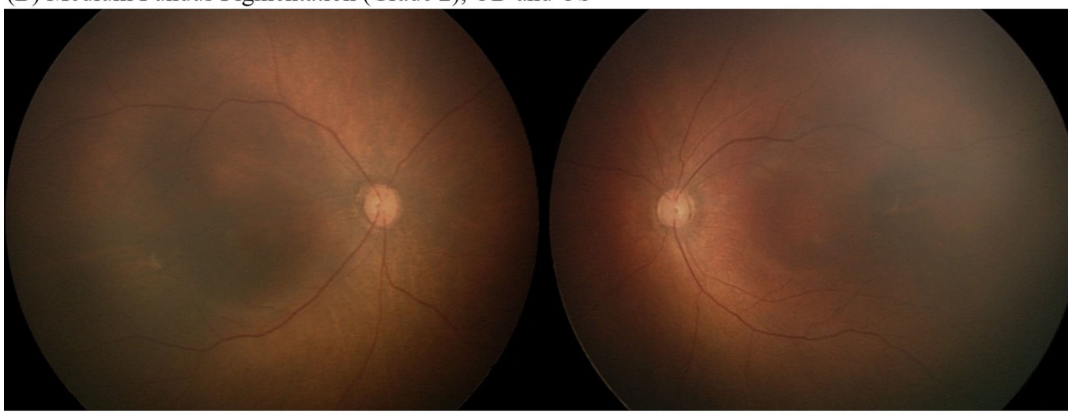
References

1. Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Ophthalmology. 1991;98(11):1628–1640. [PubMed: 1800923]
2. Hutchinson AK, Melia M, Yang MB, VanderVeen DK, Wilson LB, Lambert SR. Clinical Models and Algorithms for the Prediction of Retinopathy of Prematurity: A Report by the American Academy of Ophthalmology. Ophthalmology. 2016;123(4):804–816. [PubMed: 26832657]
3. Ludwig CA, Greven MA, Moshfeghi DM. Predictors of treatment-warranted retinopathy of prematurity in the SUNDROP cohort: influence of photographic features. Graefes Arch Clin Exp Ophthalmol. 2017;255(10):1935–1946. [PubMed: 28782073]
4. Monos T, Rosen SD, Karplus M, Yassur Y. Fundus pigmentation in retinopathy of prematurity. Pediatrics. 1996;97(3):343–348. [PubMed: 8604267]
5. Saunders RA, Donahue ML, Christmann LM, et al. Racial variation in retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Arch Ophthalmol. 1997;115(5):604–608. [PubMed: 9152127]
6. Katz ML, Robison WG Jr., Autoxidative damage to the retina: potential role in retinopathy of prematurity. Birth Defects Orig Artic Ser. 1988;24(1):237–248.
7. Dieguez HH, Gonzalez Fleitas MF, Aranda ML, et al. Melatonin protects the retina from experimental nonexudative age-related macular degeneration in mice. J Pineal Res. 2020;68(4):e12643.

(A) Light Fundus Pigmentation (Grade 1), OD and OS



(B) Medium Fundus Pigmentation (Grade 2), OD and OS



(C) Dark Fundus Pigmentation (Grade 3), OD and OS

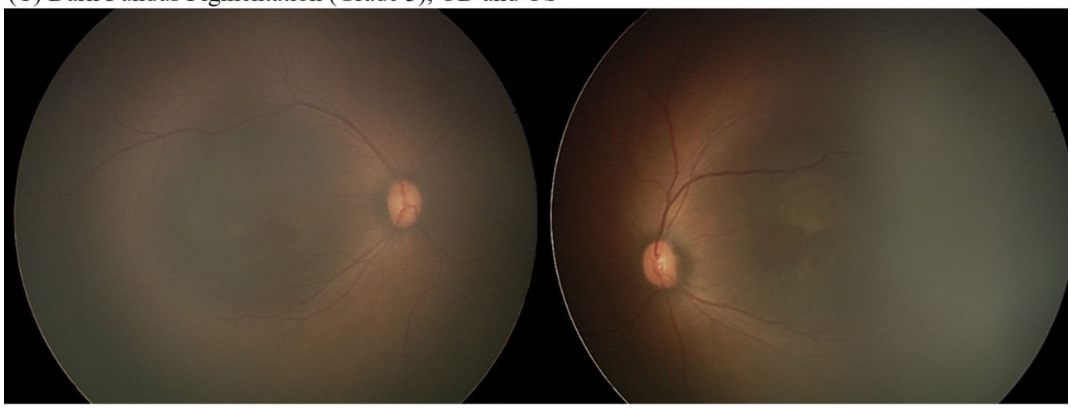


Figure 1 –.

Fundus pigmentation grading. Examples of fundus pigmentation grading to assess all screened patients with (A) representing examples of light (grade 1) fundus pigmentation, (B) medium (grade 2) fundus pigmentation, and (C) dark (grade 3) fundus pigmentation.

Table 1 –

Patient Demographics

	Fundus pigmentation						
	Light n = 496 (39.4%)		**Medium/Dark n = 763 (60.6%)**		**Total n = 1259**		**p-values (Light vs. Medium/Dark)**
Gender (female, %)	236	48%	342	45%	578	46%	0.25[a]
Patients with ROP (n, %)	162	33%	198	26%	360	29%	0.01[a]
Patients with Plus Disease (n, %)	38	7.7%	23	3.0%	61	4.8%	0.0002[a]
Multiparity Status (n, %)	153	31%	131	17%	284	23%	<0.0001[a]
Birth Weight							
Mean, std (grams)	1195.4	451.7	1178.5	408.6	1185.1	426.0	0.7881[b]
Gestational Age							
Mean, std (weeks)	28.9	2.9	28.9	2.8	28.9	2.8	0.8214[b]

Abbreviations: ROP = retinopathy of prematurity, std = standard deviation;

[a] chi-square test,

[b] independent-samples t-test

Table 2 –

Association of Risk Factors with Retinopathy of Prematurity

Retinopathy of Prematurity	Fundus Pigmentation N (%)[#]		Lower Gestational Age[c] N (%)		Lower Birth Weight[d] N (%)		Tunica Vasculosa Lentis N (%)		Birth Status N (%)	
	Light	Medium/Dark	> 27 weeks	≤ 27 weeks	>750 grams	≤750 grams	Yes	No	Multiparous	Singleton
Yes	162	198	86	274	162	198	18	288	67	293
360	(45%)	(55%)	(24%)	(76%)	(45%)	(55%)	(5%)	(80%)	(19%)	(81%)
No	334	565	790	109	857	42	72	881	217	682
899	(37%)	(63%)	(88%)	(12%)	(95%)	(5%)	(8%)	(98%)	(24%)	(76%)
Total	496	763	876	383	1019	240	90	1169	284	975
1259	(39%)	(61%)	(70%)	(30%)	(81%)	(19%)	(7%)	(93%)	(23%)	(77%)
Odds of ROP (OR [95% CI] p-value)	1.38 [1.08–1.77] p = 0.01		23.1 [16.9–31.6] p <0.001		24.9 [17.2–36.2] p < 0.001		12.2 [7.2–20.9] p < 0.001		0.72 [0.53–0.98] p = 0.035	

All analyses performed with univariable logistic regression,

[c] comparison of greater than to less than 27 weeks,

[d] comparison of greater than to less than 750 grams,

[#] percentages expressed respective to ROP groups;

Abbreviations: ROP = retinopathy of prematurity, OR = odds ratio, CI = confidence interval

Table 3 –

Association of ROP Severity & Treatment with Light Fundus Pigmentation

Fundus pigmentation	ROP Status N (%)[#]		Plus Disease N (%)		Zone Severity N (%)		Stage Severity N (%)			Treatment Type N (%)	
	Yes	No	Yes	No	Zone 1	Zone 2 &3	Stage 1	Stage 2	Stage 3	IVB	Laser
Light	162	334	38	458	37	125	70	87	5	38	7
496	(33%)	(67%)	(7.7%)	(92%)	(7.5%)	(25%)	(14%)	(18%)	(1.0%)	(7.7%)	(1.4%)
Medium/Dark	198	565	23	740	25	169	99	86	13	23	8
763	(26%)	(74%)	(3.0%)	(97%)	(3.3%)	(22%)	(13%)	(11%)	(1.7%)	(3.0%)	(1.0%)
Total	360	899	61	1198	62	294	169	173	18	68	15
1259	(29%)	(71%)	(4.8%)	(95%)	(4.9%)	(23%)	(13%)	(14%)	(1.4%)	(5.4%)	(1.2%)
Odds of ROP (OR [95% CI] p-value)	1.38 [1.08–1.77] p = 0.01[b]		4.01 [2.00–8.04] p > 0.01[a]		2.50 [1.48–4.23] p > 0.01[b]	1.22 [0.94–1.60] p = 0.14[≠, b]	1.57 [1.08–2.3] p = 0.02[a]	1.92 [1.27–2.9] p > 0.01[a]	*	2.67 [1.57–4.54] p > 0.01[b]	*

[≠] Zone 2 & 3 had reduced odds of light fundus pigmentation as compared to Zone 1 (OR 0.49, p = 0.01);

[*] Associations for stage 3 severity and treatment with laser were not statistically significant; all analyses performed with logistic regression;

[a] forward stepwise multivariable logistic regression

[b] univariable logistic regression

[#] percentages expressed respective to fundus pigmentation groups; Abbreviations: ROP = retinopathy of prematurity, OR = odds ratio, CI = confidence interval, IVB = intravitreal bevacizumab