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Postnatal Serum Insulin-Like Growth Factor I and Retinopathy of Prematurity

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Abstract

INTRODUCTION—Low serum insulin-like growth factor 1 (IGF-1) has been associated with development of severe retinopathy of prematurity (ROP), but no U.S. studies have been reported. We sought to determine the relationship between postnatal serum IGF-1 levels and severe ROP in a racially diverse U.S. cohort.

METHODS—Prospective cohort study of 74 infants with birth weight (BW) <1251g and a known ROP outcome at 3 Philadelphia hospitals. Weekly postnatal filter-paper bloodspot IGF-1 assays were measured through 42 weeks postmenstrual age (PMA).

RESULTS—The cohort included 20 Caucasian, 45 black, 2 Asian, and 9 other infants; median gestational age (GA) 27.6 weeks (range 23–33); median BW 975g (range 490–1250). During PMA weeks 28 to 33, mean IGF-1 was 20.0 ng/mL (SE 0.52) for no ROP (n=46), 18.0(0.49) for stage 1 or 2 (n=23), and 17.0(0.70) for stage 3 (n=5, 2 lasered) (p=0.003). Adjustment for BW and GA showed similar results.

CONCLUSION—Presence and timing of an association between low postnatal serum IGF and ROP in a racially diverse U.S. sample were found to be consistent with European cohorts. This association provides the pathophysiological basis for growth-based predictive models, which could improve efficiency of ROP screening.

Keywords

Insulin-like growth factor 1; Prematurity; Retinopathy of prematurity

Retinopathy of prematurity (ROP) is a disease of the developing retinal vasculature and is a leading cause of blindness in children worldwide.^{1–3} ROP pathogenesis is thought to involve multiple factors, including stage of retinal development and metabolic demand, retinal

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oxygen levels, local vascular endothelial growth factor (VEGF) production, and systemic insulin-like growth factor 1 (IGF-1) levels. VEGF is a hypoxia-induced vasoproliferative factor produced locally by developing avascular retina to stimulate new vessel growth anterior to its avascular border, where a hypoxic environment predominates.⁴⁻⁵ Normal VEGF-stimulated vessel growth requires sufficient serum levels of IGF-1, which increase with gestational age.⁶⁻⁸ The primary source of IGF-1 in the intrauterine environment is maternal, so in premature infants postnatal IGF-1 is deficient compared to developmentally matched intrauterine levels, and VEGF activity is curtailed.⁸⁻¹¹ As metabolic demands increase with the developing and increasingly thick retina, VEGF accumulates. With increasing postmenstrual age and weight, systemic IGF-1 levels rise, permitting VEGF activity and the development of ROP.

There is both laboratory and clinical evidence to support this model.^{4-7, 9, 12-17} Low postnatal serum IGF-1 levels have been associated with the subsequent development of severe ROP in Swedish and Spanish infants.^{9, 16, 17} Hellstrom et al. found serum IGF-1 levels at postmenstrual age (PMA) weeks 30-33 to be most predictive.⁹ Perez-Munuzuri et al. found that low IGF-1 levels during the third postpartum week were predictive of subsequent development of ROP.¹⁶ Slow postnatal weight gain, an assumed surrogate measure for serum IGF-1, has also been found to be predictive of severe ROP in European, North American, South American, and Asian cohorts.¹⁸⁻²⁹ Interestingly, there is increasing evidence that ethnicity may be an independent risk factor for the development of severe ROP.³⁰⁻³³ However, no North American studies on IGF-1 and ROP have been reported to our knowledge.

We sought to determine the relationship between postnatal serum IGF-1 levels and the subsequent development of ROP in a racially diverse United States cohort of premature infants. We also aimed to identify a developmental time period during which the association appeared to be robust, prior to the age at which severe ROP might be expected to develop.

MATERIALS AND METHODS

We conducted a prospective observational cohort study of infants born at three Philadelphia hospitals. The study was approved by the Institutional Review Boards of The Children's Hospital of Philadelphia, the Hospital of the University of Pennsylvania, and Pennsylvania Hospital, and conformed to the requirements of the United States Health Insurance Portability and Accountability Act. The inclusion criteria for infants were birth weight (BW) less than 1251 grams and informed consent obtained from the parent or guardian. This BW criterion was chosen so as to obtain an enriched sample with regards to incidence of severe ROP. A BW criterion was chosen instead of a GA criterion, because BW is more reliably measured than GA, which is often imprecise and based upon clinical judgment of multiple factors in the best obstetrical estimate. Subjects were excluded if they did not have sufficient ophthalmological follow up to determine a ROP outcome for both eyes, defined as mature retinal vasculature, stage 3 or worse ROP, regressed stage 1 or 2 ROP, ROP treatment with laser photocoagulation, or immature retinal vasculature in zone 3 for two consecutive exams.

ROP was classified according to the International Classification for ROP (IC-ROP).³⁴ As part of routine ROP surveillance, examinations performed by a pediatric ophthalmologist with expertise in ROP began at 31 weeks PMA or 4 weeks after birth, whichever occurred later. For each eye, the presence or absence of ROP, ROP stage, ROP zone, and the presence of pre-plus or plus disease were recorded at every exam. Examinations continued every 1 or 2 weeks depending on disease severity as determined by the clinician's examination, and ended when retinal vascular maturity was reached or when ROP regressed either spontaneously or following laser surgery. Demographic and medical data were also extracted from the medical record on enrollment and throughout the infant's hospital admission until 42 weeks PMA.

Filter-paper bloodspot IGF-1 samples were collected on enrollment and at weekly intervals through 42 weeks PMA or hospital discharge, whichever occurred first. The samples were obtained at the time of routine clinical blood draws or heel sticks. Whole blood was dripped onto filter paper blood spot cards by the nurse or care provider obtaining the blood sample. The volume of blood applied was approximately 200 microliters in total, consisting of two drops of blood (approximately 50 microliters per drop) on each of two half-inch filter circles on Whatman 903 filter paper cards. This sample volume was not felt to be adversely clinically significant by the treating neonatologists. Card samples were allowed to dry at room temperature for 2 hours, and then transported to the Clinical and Translational Research Center biochemistry laboratory at The Children's Hospital of Philadelphia. Filter paper samples were frozen and later thawed in batches for sample extraction and IGF-1 assays using an enzyme-linked immunosorbent assay kit from R&D Systems (Minneapolis, MN) in a previously validated manner.³⁵

For statistical analysis, subjects were stratified into one of three ROP outcome groups by worst ROP stage in either eye: no ROP, mild to moderate (ROP stage 1 or 2), or severe (ROP stage 3 or worse). Weekly IGF-1 levels were compared among these groups by PMA week. A developmental time period based upon the postmenstrual age during which any association between IGF-1 and the subsequent development of ROP was most robust was identified. This period was determined by starting a priori with 30 to 33 weeks PMA, as previously reported by Hellstrom et al.⁹ We then extended the lower boundary of the period by examining the weekly IGF-1 levels of our cohort in a post hoc analysis to determine if a relationship appeared to be present during those weeks, but we limited the upper boundary in order to obtain a time period before which severe ROP would be expected to develop. The association during this period was assessed with both univariate analyses and multivariate analyses, controlling for BW and GA. Generalized linear modeling was used to account for the correlation of repeated measures at each PMA week. A statistical linear trend test was performed to evaluate whether increasing severity of ROP is associated with lower IGF-1 level. Pre-specified stratified analyses for children with GA less than 27 weeks PMA and GA greater than or equal to 27 weeks PMA were performed, because we hypothesized that there may be a shift in the relevant PMA periods for infants with higher GA; the onset of ROP is tied to developmental age (PMA), rather than chronological age, so infants with lower GA develop ROP at a later chronological age than infants with higher GA. Comparisons of baseline characteristics among ROP groups was performed using one way analysis of variance for means, the Kruskal-Wallis test for medians, and the Fisher's exact

test for proportions. Diversity of cohort was an important reason for conducting this study. Therefore, sub-analyses were performed to examine potential effects of race on the study results. Overall and weekly mean IGF-1 levels were compared between white and black infants. In addition, a stratified analysis was performed in which the association between IGF-1 during PMA weeks 28-33 and ROP was evaluated separately for black and white infants, and a statistical test of heterogeneity was done to determine if the associations observed differed between the racial strata. Data analysis was done using SAS statistical software v9.1 (SAS Institute Inc, Cary, NC).

RESULTS

74 infants met the inclusion and exclusion criteria. An additional 9 infants were excluded due to death (n=9), withdrawal (n=3), or transfer (n=1) before known ROP outcome. Race of the 74 infants in the study, as reported by the parents, was black in 45 infants, white in 20 infants, Asian in 2 infants, and other or unidentified in 7 infants. The median GA was 27.6 weeks (range 23 to 33 weeks), and the median BW was 975 grams (range 490 to 1250 grams). The baseline characteristics, including BW and GA, of the infants categorized by highest ROP stage in either eye appear in table 1. Forty-six infants did not develop ROP, 23 infants developed stage 1 or 2 ROP, and 5 infants developed stage 3 ROP. Two of the infants who developed stage 3 ROP received laser retinal photocoagulation.

A total of 817 IGF-1 assays or on average 11 assays per infant were completed over the course of the study. Serum IGF-1 levels were calculated for each PMA week among the three ROP severity groups and appear in Table 2. Based upon these weekly IGF-1 levels and the time periods reported in prior studies, the association between serum IGF-1 and ROP was assessed during the developmental time period falling between and including PMA weeks 28 and 33. The mean IGF-1 during PMA weeks 28 to 33 was 20.0 nanograms per milliliter (ng/mL) (SE 0.52) for infants with no ROP, 18.0 ng/mL (SE 0.49) for infants with mild to moderate ROP, and 17.0 ng/mL (SE 0.70) for infants with severe ROP (linear trend $p=0.003$ in univariate analysis and $p=0.06$ in multivariate analysis controlling for BW and GA)(Table 3). In univariate and multivariate subgroup analysis, the association between serum IGF-1 during this time period and ROP severity also appeared to exist for infants born at gestational age greater than or equal to 27 weeks PMA and infants born at less than 27 weeks gestational age (Tables 3), although the statistical significance was marginal for these subgroups due to the smaller numbers of infants in each subgroup.

We found that there was no significant difference in overall or weekly mean IGF-1 levels between white and black infants. In stratified analysis, the association between IGF during PMA weeks 28-33 and ROP was present for both black and white infants, and a test of heterogeneity between the strata showed that the association did not differ among the racial strata.

DISCUSSION

In this prospective observational cohort study, we found an association between lower postnatal serum IGF-1 levels and the subsequent development of increasingly severe ROP in

a racially diverse cohort of U.S. infants. The association was independent of gestational age and birth weight, and was significant despite the relatively small number of infants who developed severe ROP in the cohort. These findings are consistent with the association between IGF-1 and ROP reported by investigators in Europe^{9,16} and with studies of postnatal weight gain as a predictor of the development of severe ROP.¹⁸⁻²⁹ The generalizability to a diverse U.S. cohort lends support to clinical applications, including exogenous postnatal IGF-1 supplementation, which may prevent or reduce the severity of ROP, and risk prediction, particularly through the use of a more easily obtained surrogate measure such as postnatal weight gain.

While the relative correlation of serum IGF-1 with ROP group matches that of prior studies, the measured absolute levels in our cohort were somewhat lower. For example, Hellstrom et al. reported mean IGF-1 levels during PMA 30-33 weeks of 25 micro g/L (ng/mL) for infants with severe ROP, 29 with moderate ROP, and 33 with no ROP⁹; while we observed mean levels of 17, 18, and 20 for the same groups during PMA 28-33 weeks. Such differences may have implications for exogenous IGF-1 supplementation, with regards to therapeutic target levels, and for risk prediction, with regards to cut-off points for determining risk of ROP, because measured levels may vary predictably or unpredictably across laboratories. Variations may arise from the commercial IGF-1 assay kits being used, laboratory or sample processing techniques, or sample collection methods (e.g., filter paper cards versus venous blood draws). The small magnitudes of the differences in IGF-1 levels among groups further limit the practical use of serum IGF-1 levels for predicting ROP risk, as there is overlap among the groups. Postnatal weight gain measurements are a more practical and non-invasive alternative, and our findings support the pathophysiological rationale underlying BW, GA, and weight gain models, namely that prolonged low IGF-1 levels, identified as slow postnatal weight gain, inhibit VEGF activity and retinal vessel growth early in the course of ROP.

The developmental time period identified in our study (28 to 33 weeks PMA) overlaps that of prior studies.^{9,16} Hellstrom et al. focused upon the period of 30-33 weeks PMA⁹, and Perez-etc. highlighted 3 weeks chronological age regardless of GA at birth¹⁶. The weekly IGF-1 levels in our study (Table 2) reveal a relationship that may persist as far out as 36 weeks PMA; however, we restricted our time period to 33 weeks PMA, because we wanted to determine if an association was present prior to the potential development of severe ROP, the time period of interest with regards to the clinical utility of the results. We also performed a subgroup analysis based upon GA, because while the onset of ROP is tied to PMA, it will generally not develop in the first few weeks of life regardless of GA, so for infants born around this period (28-33 weeks PMA), the period of interest could be shifted towards later PMA weeks. We found that the relationship between IGF-1 and subsequent ROP during this period was still present in both subgroups. The borderline statistical significance of the subgroup analyses could be due to the smaller numbers of infants in the subgroups. Interestingly, there was one time period (41 weeks PMA) during which the severe ROP group had a markedly higher mean IGF-1 level. This also could be due to a small subgroup size of only three children. However, another hypothesis relates to the current model of ROP pathogenesis. Although low IGF-1 early causes poor VEGF activity and poor retinal vessel development, presumably it is only when IGF-1 rises later that VEGF

is activated and neovascular ROP develops. Therefore, it is possible that robust increases in IGF-1 levels, which are preceded by prolonged deficits in IGF, could be associated with more robust neovascularization.

Strengths of our study included a racially diverse cohort of infants, confirmed ROP outcomes to the point of disease regression or vascular maturity, and the use of filter paper samples, which require less blood than whole blood samples, have greater sample stability, transportability, and storage, and therefore which may help facilitate further exploration of this association in other cohorts.

Several limitations of our study should be noted as well. As discussed above, the absolute differences in IGF-1 levels among ROP severity groups were small, limiting the applicability of using IGF-1 levels to stratify ROP risk. However, these differences were still statistically significant and provide further evidence of our current understanding of the pathophysiology of ROP. Similarly, although a relatively small number of infants developed severe disease (n=5), the association still reached statistical significance. Therefore, the study sample size was not a limitation with regards to statistical power. We selected the time period 28 to 33 weeks PMA empirically based on our data, but the nature of this aspect of our study was intentionally investigative and this was our plan a priori. Finally, our results can not be generalized to countries with developing neonatal care systems where older GA infants develop severe ROP. Infants born at GA of 32 to 36 weeks may already be producing IGF-1 levels comparable to normal intrauterine levels, so IGF-1 plays less of a role in the pathogenesis of ROP and oxygen supplementation becomes the dominant etiologic factor. This hypothesis is supported by the poor performance of weight gain based ROP predictive models in older GA infants in these countries.²⁴ Therefore, it is important to study the association between IGF-1 and ROP separately in these infants.

We found that low postnatal serum IGF-1 was associated with the subsequent development of ROP. The presence and timing of this association in our racially diverse U.S. sample were found to be consistent with European cohorts. These findings provide further evidence of the scientific rationale underlying growth-based predictive models, which could improve efficiency of ROP screening, and IGF-1 supplementation to reduce ROP risk in the U.S. Similar studies might help clarify ROP pathogenesis in world regions where growth-based models perform less well, oxygen supplementation plays more dominant a role, and more mature babies are at risk.

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Brief Summary Statement

Low serum insulin-like growth factor 1 (IGF-1) was associated with the subsequent development of severe ROP, confirming this relationship for the first time in a racially diverse U.S. cohort. The association provides the pathophysiological basis for growth-based predictive models, which could improve efficiency of ROP screening.

Figure 1. Mean serum insulin-like growth factor 1 (IGF-1) levels by postmenstrual age week for 74 infants at risk for retinopathy of prematurity.

Table 1

Characteristics of 74 premature infants, categorized by worst stage of ROP diagnosed in either eye.

	Severe ROP (Stage 3) (n=5)	Mild to Moderate ROP (Stage 1-2) (n=23)	No ROP (n=46)	P Value
Gestational age (weeks)				
Mean (SE)	24.9 (0.54)	27.1 (0.47)	28.5 (0.28)	0.0002 *
Median (min, max)	25.0 (23.0, 26.1)	26.7 (24.0, 33.1)	28.4 (23.3, 32.3)	0.0002 **
Birth weight (grams)				
Mean (SE)	614 (82.3)	851 (45.9)	1014 (25.9)	<0.0001 *
Median (min, max)	530 (490, 930)	800 (506, 1250)	1028 (500, 1250)	0.0002 **
Male, n (%)	3 (60.0%)	11 (47.8%)	21 (45.7%)	0.87 **
Race				0.88 ***
Caucasian	1 (20.0%)	6 (26.1%)	13 (28.3%)	
Black	4 (80.0%)	13 (56.5%)	28 (60.9%)	
Other	0 (0.0%)	4 (17.4%)	5 (10.9%)	

* ANOVA for comparison of means

** Kruskal-wallis test for comparison of means

*** Fisher Exact test.

Table 2

Mean postnatal serum IGF-1 levels by postmenstrual age week among 74 infants at risk for ROP.

PMA	Severe ROP (n=5)		Moderate ROP (n=23)		No ROP (n=46)	
	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
23	1	11.4 (---)			1	18.3 (---)
24	1	9.8 (---)	3	17.0 (2.78)	2	17.9 (3.10)
25	3	15.20 (3.09)	5	18.8 (2.12)	3	16.5 (1.14)
26	5	16.4 (2.90)	9	19.1 (1.48)	6	16.1 (1.58)
27	5	18.8 (1.01)	17	18.0 (0.78)	12	19.4 (1.40)
28	5	16.0 (1.87)	19	17.5 (0.92)	24	18.3 (0.68)
29	5	16.9 (2.40)	20	16.5 (1.06)	32	19.6 (0.75)
30	5	16.3 (1.79)	20	17.9 (0.96)	38	18.0 (0.63)
31	5	15.8 (0.95)	21	19.7 (0.99)	42	20.3 (0.66)
32	5	18.1 (2.28)	21	18.2 (0.78)	43	20.1 (0.87)
33	4	19.6 (1.02)	21	18.2 (0.86)	42	22.5 (1.03)
34	3	19.4 (1.01)	23	20.1 (0.97)	39	22.8 (1.14)
35	5	19.9 (1.14)	22	21.9 (1.03)	36	22.2 (0.81)
36	4	21.7 (2.30)	18	22.2 (1.24)	31	24.0 (0.99)
37	5	25.3 (3.13)	14	24.3 (1.17)	23	25.2 (1.13)
38	4	22.9 (1.56)	11	23.7 (2.68)	12	25.6 (2.28)
39	4	26.0 (0.61)	9	23.2 (2.60)	9	31.8 (1.83)
40	3	23.2 (5.20)	10	25.9 (2.00)	6	25.7 (2.55)
41	3	32.2 (3.31)	8	25.3 (3.07)	4	22.5 (2.82)
42	1	23.8 (---)	1	25.0 (---)	1	36.1 (---)

Table 3

Longitudinal modeling of mean postnatal serum IGF-1 levels during postmenstrual age weeks 28 to 33 among 74 infants at risk for ROP. GA, gestational age; ROP, retinopathy of prematurity.

Cohort	ROP group	Mean (SE) of IGF-1	
		Univariate Analysis	Adjusted Analysis [*]
All infants (n=74)	No (n=46)	20.0 (0.52)	19.7 (0.49)
	Mild/Moderate (n=23)	18.0 (0.49)	18.3 (0.54)
	Severe (n=5)	17.0 (0.70)	17.9 (0.97)
	P Value [†]	0.011	0.17
	Linear Trend P Value	0.003	0.06
GA ≥ 27 weeks (n=48)	No (n=37)	20.1 (0.62)	19.9 (0.56)
	Mild/moderate (n=11)	17.3 (0.98)	17.9 (0.75)
	P Value [†]	0.043	0.048
GA <27 weeks (n=26)	No (n=9)	19.6 (0.81)	19.6 (0.86)
	Mild/Moderate (n=12)	18.6 (0.33)	18.6 (0.36)
	Severe (n=5)	17.0 (0.70)	16.9 (0.74)
	P Value [†]	0.15	0.17
	Linear Trend P Value	0.059	0.07

^{*} Adjusted by birth weight and gestational age.

[†] P value is from the Generalized Linear Model to account for correlation of repeated measures at each PMA week.