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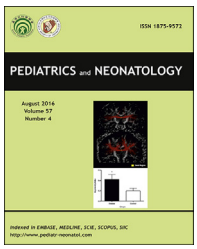

Original Article

Association of umbilical cord insulin-like growth factor 1 levels with severe retinopathy in extremely preterm infants

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Key Words
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Background: The association between umbilical cord blood insulin-like growth factor 1 (IGF-1) levels and retinopathy of prematurity (ROP) remains unclear. This study aimed to investigate whether umbilical cord blood IGF-1 levels can predict the development of severe ROP in extremely preterm infants.

Methods: This hospital-based retrospective cohort study included infants born at <37 weeks gestational age (GA) between 2019 and 2021 and then classified them into the two GA groups: extremely preterm, <28 weeks and preterm infants, 28–36 weeks. Extremely preterm infants were further subclassified into two groups according to the laser treatment as follows: the severe ROP (ROP-Tx) and ROP (No ROP-Tx) groups. Median umbilical cord blood IGF-1 values were compared between the groups. Perinatal risk factors were identified by univariate and multivariate analyses. Finally, umbilical cord IGF-1 cut-off values requiring ROP treatment with laser were determined by receiver operating characteristic (ROC) curve analyses.

Results: A total of 205 infants were enrolled, with 32 being extremely preterm (ROP-Tx: $n = 11$; No ROP-Tx: $n = 21$) and 173 being preterm. IGF-1 levels were significantly lower in extremely preterm (13.5 ng/mL) than preterm infants (36 ng/mL, $p < 0.001$). In extremely preterm infants, IGF-1 levels were significantly lower in the ROP-Tx group than the No ROP-Tx group (10 vs. 19 ng/mL, respectively, $p = 0.024$). Only GA, umbilical cord blood IGF-1 levels, birth head circumference, and birth chest circumference were identified as risk factors by univariate analysis ($p < 0.05$). Multivariate analysis showed that only umbilical cord blood IGF-1 was an independent risk factor (odds ratio: 1.26, $p = 0.021$). ROC curves revealed an IGF-1 cut-off value of 14 ng/mL.

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Conclusion: The need of laser treatment for ROP was found to be associated with low umbilical cord blood IGF-1 levels in extremely preterm infants. Umbilical cord blood IGF-1 can be used as a biomarker for the risk of developing severe ROP.

1. Introduction

Retinopathy of prematurity (ROP) is a leading cause of blindness in children worldwide.[1] Therefore, it is important to extract infants at high risk of ROP. Prematurity, high oxygen concentration, sepsis, blood transfusion, intraventricular hemorrhage, and the use of erythropoietin have been identified as risk factors for the development of ROP.[2–5] In recent years, vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1), which are involved in the development of retinal blood vessels, have played an important role as biomarkers.[6,7] Regarding the pathogenesis of ROP, Hallström et al. suggested that IGF-1 is involved in the delay of early retinal vascular development, while VEGF is involved in the pathogenesis of the vasoproliferative phase.[6] Thus, in recent years, anti-VEGF therapy, in which antibodies against VEGF are administered intraocularly to delay the development of ROP, has been used in clinical practice. Meanwhile, no therapeutic method using IGF-1 has been established to date. However, a method of selectively administering synthetic IGF-1 to patients with low serum IGF-1 levels to prevent the onset of ROP has been studied and is expected to be a future treatment method.[8]

IGF-1 plays an important role in fetal and neonatal growth and development of the cardiovascular system, central nervous system, and lungs.[9–11] Therefore, low IGF-1 levels at birth, especially in extremely preterm infants, may have a significant impact not only on growth retardation in the early postnatal period but also on delayed retinal vascular development. Long-term low serum IGF-1 levels from birth have been reported to be associated with postnatal growth retardation, impaired brain development, ROP, and chronic lung disease.[12–16] However, there have been no reports examining the relationship between umbilical cord blood IGF-1 levels and severe ROP requiring laser treatment. Therefore, this study aimed to clarify the relationship between umbilical cord IGF-1 and severe ROP in extremely preterm infants.

2. Methods

2.1. Study design

A hospital-based retrospective cohort study was conducted at Nihon University Itabashi Hospital, Tokyo, Japan. Written informed consent was obtained from the parents of all infants. This study was approved by the Ethics Committee of Nihon University School of Medicine (no. RK-190910-3) and it was carried out in accordance with the relevant guidelines and regulations. Infants born at <37 weeks gestational age (GA) between 2019 and 2021 were enrolled and then classified into the two GA groups: extremely preterm, <28 weeks and preterm infants, 28–36 weeks. Extremely preterm infants were further subclassified into two groups according to the ROP with laser treatment as follows: the severe ROP (ROP-Tx) and the ROP (No ROP-Tx) groups. The same ophthalmologist performed fundus examinations periodically after birth to diagnose the presence or absence of ROP and determine the indication for laser treatment according to the U.S. ROP guidelines.[3]

2.2. Umbilical cord blood IGF-1 level

At birth, the umbilicus was double-clamped, and cord blood was sampled from the umbilical vein. Median umbilical cord blood IGF-1 levels were compared between all groups. Umbilical cord blood IGF-1 levels were measured using the radioimmunoassay solid phase method.[17,18]

2.3. Study methods

First, umbilical cord blood IGF-1 levels and other factors at birth were compared between extremely preterm and preterm infants and between ROP and non-ROP infants. Second, perinatal and neonatal risk factors were identified by univariate and multivariate analyses, including the following: GA, body weight (BW), BW standard deviation score (SDS), body length (BL), BL SDS, birth head circumference, birth head circumference SDS, birth chest circumference, gender, small-for-gestational age (BW < 10th percentile for GA), Apgar score (at 1 and 5 min), the use of mechanical artificial ventilation, use of oxygen therapy, duration of mechanical artificial ventilation, duration of oxygen therapy, blood transfusion, the use of erythropoietin therapy, respiratory distress syndrome, ligation of patent ductus arteriosus, necrotizing enterocolitis (required surgical intervention and confirmed pathological finding), intraventricular hemorrhage and periventricular leukomalacia (diagnosed by brain ultrasonography and magnetic resonance imaging), histological chorioamnionitis and funisitis (Blanc stage ≥1),[19] premature rupture of the membrane (diagnosed as rupture before the start of labor), hypertension disorders of pregnancy, and placenta abruption. Finally, umbilical cord IGF-1 cut-off values for ROP treatment were determined by constructing receiver operating characteristic (ROC) curves.

2.4. Statistical analyses

To compare umbilical cord blood IGF-1 levels and other factors at birth between extremely preterm and preterm

infants and between ROP and non-ROP infants, the Wilcoxon signed-rank test or Chi-squared test was used. The aforementioned perinatal and neonatal factors associated with ROP requiring laser treatment were analyzed by univariate analysis using the Wilcoxon signed-rank test or Fisher's exact test and multiple logistic regression analysis. The umbilical cord blood IGF-1 cut-off value associated with laser treatment was determined using the maximum Youden index of the ROC curve. The Youden index is the point farthest from the boundary delineating the area under the curve and represents the [sensitivity + specificity − 1] value.[20] Statistical analyses were performed using JMP version 14 (SAS Institute Inc., Tokyo, Japan). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Umbilical cord blood IGF-1 levels

A total of 205 infants were enrolled, of whom 32 were extremely preterm (ROP-Tx: n = 11; No ROP-Tx: n = 21) and 173 preterm. ROP was developed in 94% of 32 extremely preterm infants and 9% of 173 preterm infants (Table 1). No preterm infants required treatment for ROP. No infants received anti-VEGF therapy.

The median umbilical cord blood IGF-1 level was 30 ng/mL in the 205 infants. Umbilical cord blood IGF-1 levels of extremely preterm infants were significantly lower than those of preterm infants (median value: 13.5 vs. 36 ng/mL, respectively, p < 0.001, Table 1 and Supplementary Figure 1A). Umbilical cord blood IGF-1 levels of ROP infants were significantly lower than non-ROP infants (13 vs. 38 ng/mL, respectively, p < 0.001, Table 2). Furthermore, umbilical cord blood IGF-1 levels were lower in the ROP-Tx group than the No ROP-Tx group (median value: 10 vs. 19 ng/mL, respectively, p = 0.024, Table 3 and Supplementary Fig. 1B).

3.2. Associated factors for severe ROP with laser treatment

In extremely preterm infants, only GA, umbilical cord blood IGF-1 levels, birth head circumference and birth chest circumference were identified as risk factors by univariate analysis (p < 0.05, Table 3).

3.3. Multivariate analyses

Multiple logistic regression analyses using GA, BW SDS, and umbilical cord blood IGF-1 were performed. Only umbilical cord blood IGF-1 was an independent risk factor for severe ROP requiring laser treatment (odds ratio: 1.26, p = 0.021, Table 4).

3.4. Umbilical cord blood IGF-1 cut-off value for ROP with laser treatment

An umbilical cord blood IGF-1 cut-off value of 14 ng/mL was associated with laser treatment according to the Youden index based on the ROC curve analysis (Table 5).

4. Discussion

In this Japanese retrospective study, we found that a low umbilical cord blood IGF-1 was an independent risk factor for developing severe ROP requiring laser treatment in extremely preterm infants. Furthermore, an umbilical cord blood IGF-1 cut-off value of 14 ng/mL was associated with

Table 1 Comparisons of factors at birth and insulin-like growth factor 1 in umbilical cord blood between extremely preterm and preterm infants.

	Extremely preterm n = 32	Preterm n = 173	p-value
GA, weeks	25 (22–27)	34 (28–36)	<0.001
BW, g	678 (278–1224)	1809 (424–3126)	<0.001
BW SDS	−0.47 (−3.95-+1.76)	−0.56 (−5.0–+2.41)	0.815
BL, cm	30.5 (24.0–37.5)	42.5 (27.0–51.5)	<0.001
BL SDS	−0.865 (−3.12–+2.7)	−0.58 (−4.2–+2.3)	0.475
Birth head circumference, cm	22.5 (17.0–27.0)	30.2 (20.0–35.5)	<0.001
Birth head circumference SDS	−0.175 (−2.32–+2.37)	−0.1 (−2.72–+2.51)	0.670
Birth chest circumference, cm	18.55 (15.5–22.6)	27.0 (15.5–35.0)	<0.001
Male	13 (41)	77 (45)	0.684
SGA	8 (25)	49 (28)	0.700
ROP	30 (94)	16 (9)	<0.001
ROP with leaser treatment	11 (34)	0 (0)	<0.001
IGF-1, ng/mL (10%ile)	5	10.4	
IGF-1, ng/mL (25%ile)	9	19.5	
IGF-1, ng/mL (50%ile)	13.5 (4–48)	36 (4–121)	<0.001
IGF-1, ng/mL (75%ile)	20	52	
IGF-1, ng/mL (90%ile)	30.7	70.6	

Data are shown as median (range) or number (percentage).
BL, birth length; BW, birth weight; GA, gestational age; IGF-1, insulin-like growth factor 1; SDS, standard deviation score; SGA, small-for-gestational age.

Table 2 Comparisons of factors at birth and insulin-like growth factor 1 in umbilical cord blood between infants with and without retinopathy of prematurity.

	ROP n = 46	non-ROP n = 159	p-value
GA, weeks	26 (22–33)	34 (26–36)	<0.001
BW, g	778 (278–1446)	1895 (686–3126)	<0.001
BW SDS	−0.90 (−5.0–+1.76)	−0.39 (−4.23–+2.41)	0.005
BL, cm	33.0 (24.0–42.0)	43.0 (30.0–51.5)	<0.001
BL SDS	−1.04 (−4.2–+2.7)	−0.48 (−3.8–+2.3)	0.004
Birth head circumference, cm	24.0 (17.0–28.8)	30.5 (20.0–35.5)	<0.001
Birth head circumference SDS	−0.30 (−2.32–+2.37)	0.02 (−2.72–+2.51)	0.023
Birth chest circumference, cm	19.5 (15.5–25.7)	27.3 (18.5–35.0)	<0.001
Male	19 (41)	71 (45)	0.687
SGA	19 (41)	38 (24)	0.020
IGF-1, ng/mL (10%ile)	5	12	
IGF-1, ng/mL (25%ile)	8.8	23	
IGF-1, ng/mL (50%ile)	13 (4–77)	38 (4–121)	<0.001
IGF-1, ng/mL (75%ile)	23.3	52	
IGF-1, ng/mL (90%ile)	35.3	71	

Data are shown as median (range) or number (percentage).
BL, birth length; BW, birth weight; GA, gestational age; IGF-1, insulin-like growth factor 1; SDS, standard deviation score; SGA, small-for-gestational age.

laser treatment. These findings clearly indicated that low umbilical cord blood IGF-1 level might be associated with need of ROP treatment in extremely preterm infants.

4.1. IGF-1 levels

In fetus, IGF-1 level is influenced by nutrients delivered through placenta rather than by fetal pituitary growth hormone.[21] Thus, low IGF-1 levels in cord blood indicate a decrease in nutrients from the placenta, which may affect the development of fetal blood vessels and ROP after birth.

A study regarding cord blood IGF-1 level in only term infants has been reported; mean cord blood IGF-1 level were 58.4 ng/mL.[22] In a report of IGF-1 levels in preterm infants at 33 weeks' corrected GA, the mean IGF-1 level was 23.1 (range: 15.44–39.75) ng/mL, and there was no difference in IGF-1 levels between males (23.1 ng/mL) and females (23.1 ng/mL).[23] In our study, median cord blood IGF-1 level of 205 preterm infants was 30 ng/mL. There was no difference by sex between males [n = 90, median: 31.5 (range: 4.0–121.0) ng/mL] and females [n = 115, 30.0 (4.0–92.0) ng/mL] (p = 0.969, data not shown).

In a study evaluating the relationship between IGF-1 levels and nutrition in 87 infants born at 24–32 weeks of gestation, an inverse relationship between parenteral nutrition and IGF-1 levels was reported in the second week of life, and total energy intake was positively associated with IGF-1 levels, especially at 30–33 weeks' corrected GA.[24] In another report, IGF-1 levels in cord blood strongly correlated with birth weight, leptin, fat mass, and body fat percentage measurements, indicating that IGF-1 may be an important factor in neonatal fat accumulation *in utero*,[22] but its relationship with ROP remains unclear. Our study showed that cord blood IGF-1 levels in extremely preterm infants were low, especially those with the ROP treatment with laser, and they were an independent risk factor regardless of GA. IGF-1 levels may be associated with nutritional status *in utero* in extremely preterm infants.

In another study of preterm infants with birth weight <1251 g in the U.S., the mean IGF-1 level at 28–33 weeks' corrected GA was 20.0 ng/mL (standard error: 0.52) without ROP, 18.0 (0.49) in stage 1 or 2, and 17.0 (0.70) in stage 3; and an association with ROP was reported.[25] This indicates that infants with persistently low serum IGF-1 levels after birth may frequently require treatment for ROP.

4.2. Factors related to exacerbation of ROP

Prematurity, high oxygen concentration, sepsis, blood transfusion, intraventricular hemorrhage, and the use of erythropoietin have been reported as risk factors for the development of ROP.[2–5] In our study, only extremely preterm infants required treatment for ROP. Because low GA at birth is the highest risk factor for the development of ROP,[4] only extremely preterm infants were used for further analyses. In a comparison between the two groups of extremely preterm infants with and without laser treatment, the group that required laser treatment had significantly shorter GA and smaller birth length, head circumference, and chest circumference (Table 3). In the analysis of perinatal factors, there were no significant differences in the duration of ventilator and oxygen use, blood transfusion, or use of erythropoietin.

4.3. Potential for treatment with IGF-1 products

Supplementation with recombinant human (rh) IGF-1 and its binding protein-3 (rhIGFBP-3) is being developed as a treatment to promote growth and maturation and reduces morbidity in extremely preterm infants.[8] Another study stated that a deletion of *IGF-1 gene* is associated with central nervous system disorders, such as learning

Table 3 Factors associated with treated retinopathy of prematurity in extremely preterm infants.

	Laser treatment		
	Yes, n = 11	No, n = 21	p-value
GA, weeks	25 (22–27)	25 (24–27)	0.035
BW, g	602 (278–1224)	740 (464–1087)	0.096
BW SDS	−0.11 (−3.95–+1.76)	−0.53 (−3.82–+0.8)	0.258
BL, cm	29.0 (24.0–34.2)	31.5 (26.5–37.5)	0.091
BL SDS	−0.37 (−3.12–+0.8)	−0.9 (−3.1–+2.7)	0.968
Birth head circumference, cm	20.7 (17.0–26.0)	23.5 (20.0–27.0)	0.009
Birth head circumference SDS	−0.4 (−2.32–+2.37)	−0.1 (−1.8–+1.61)	0.226
Birth chest circumference, cm	17.0 (15.5–22.0)	19.0 (16.4–22.6)	0.035
Male	3 (27)	10 (48)	0.450
SGA	3 (27)	5 (24)	1.000
Apgar score, 1 min	2 (0–5)	3 (1–7)	0.234
Apgar score, 5 min	4 (1–8)	7 (1–9)	0.190
Use of mechanical artificial ventilation	11 (100)	21 (100)	–
Use of oxygen therapy	11 (100)	21 (100)	–
Duration of mechanical artificial ventilation, days	37 (16–85)	36 (9–81)	0.361
Duration of oxygen therapy, days	90 (71–142)	94 (32–172)	0.579
Blood transfusion	7 (64)	15 (71)	0.703
Use of erythropoietin therapy	11 (100)	21 (100)	–
RDS	11 (100)	21 (100)	–
PDA with ligation	1 (9)	2 (10)	1.000
NEC	0 (0)	0 (0)	–
IVH	3 (27)	1 (5)	0.106
PVL	1 (9)	2 (10)	1.000
Chorioamnionitis	9 (82)	12 (57)	0.248
Funisitis	6 (55)	4 (19)	0.056
PROM	1 (9)	6 (29)	0.374
HDP	1 (9)	5 (24)	0.637
Placenta abruption	1 (9)	1 (5)	1.000
IGF-1, ng/mL (10%ile)	4.2	5.6	
IGF-1, ng/mL (25%ile)	7	10	
IGF-1, ng/mL (50%ile)	10 (4–19)	19 (4–48)	0.024
IGF-1, ng/mL (75%ile)	14	25.5	
IGF-1, ng/mL (90%ile)	18.4	31	

The values represent those for children with or without short stature. Values are shown as median (range) or number (percentage).
BL, birth length; BW, birth weight; GA, gestational age; HDP, hypertension disorders of pregnancy; IGF-1, insulin-like growth factor 1; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PROM, premature rupture of the membrane; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; SDS, standard deviation score; SGA, small-for-gestational age.

Table 4 Results of multivariate analysis.

Factors	OR (95% CI)	p-value
GA, weeks	2.06 (0.95–4.49)	0.068
BW SDS	0.66 (0.30–1.48)	0.318
IGF-1 in umbilical cord blood, ng/mL	1.26 (1.04–1.54)	0.021

BW, birth weight; CI, confidence interval; GA, gestational age; IGF-1, insulin-like growth factor 1; OR, odds ratio; SDS, standard deviation score.

disabilities and brain growth restriction. Treatment of preterm infants with recombinant IGF-1 has been reported to potentially prevent ROP and central nervous system disorders.[26] A basic study using a rat model of periventricular leukomalacia reported that IGF-1 was effective in reducing the number of early neurons in the subventricular zone and in increasing the survival of mature neurons in the cerebral cortex.[27] In a rat model of cerebral hypoxia-ischemia, rhIGF-1 inhibited apoptotic cell death by activating the Akt signaling pathway and also promoted proliferation of neurons and oligodendroglial progenitor cells, suggesting that rhIGF-1 may be useful for clinical therapy.[28] In primary IGF-1 deficient mice without tissue *IGF-1 gene* expression, recombinant IGF-1 can be used to maintain a long-term elevation of serum IGF-1 to establish normal body size, body composition, and maintenance of skeletal structure and function.[29] Clinical trials conducted to determine whether intravenous supplementation of human recombinant IGF-1 to normal serum concentrations can improve growth and development and reduce morbidity

Table 5 Cut-off values of umbilical cord blood insulin-like growth factor 1 levels for severe retinopathy of prematurity with laser treatment.

IGF-1, ng/mL	Sensitivity	Specificity	Accuracy	Youden index
4	0.091	0.952	0.656	0.043
5	0.182	0.905	0.656	0.087
7	0.273	0.905	0.688	0.178
8	0.364	0.857	0.688	0.221
9	0.455	0.762	0.656	0.217
10	0.546	0.762	0.688	0.307
11	0.546	0.714	0.656	0.260
12	0.636	0.619	0.625	0.255
13	0.727	0.619	0.656	0.346
14	**0.818**	**0.619**	**0.686**	**0.437**
16	0.909	0.524	0.656	0.433
19	1.000	0.429	0.625	0.429
20	1.000	0.333	0.563	0.333
23	1.000	0.286	0.531	0.286
24	1.000	0.238	0.500	0.238
27	1.000	0.191	0.469	0.191
30	1.000	0.143	0.438	0.143
31	1.000	0.048	0.375	0.048
48	1.000	0	0.344	0

The Youden index is the point farthest from the boundary delineating the area under the curve and represents the [sensitivity + specificity − 1] value.
IGF-1, Insulin-like growth factor-1.

associated with extremely preterm infants are currently in progress.[30] The reports of extremely preterm infants receiving continuous infusions of rhIGF-1/rhIGFBP-3 have shown that high interleukin-6 and IGFBP-1 levels preceded low IGF-1 levels, and it is necessary to evaluate whether inflammation or infection suppresses serum IGF-1 levels.[31]

4.4. Limitations

Limitations of this study are as follows: 1) This study was conducted with a small cohort in a single Japanese center. 2) We were not able to assess whether the low IGF-1 levels persisted after birth in extremely preterm infants who required treatment for ROP. Further prospective clinical studies with a large global cohort are needed. Nevertheless, our result indicates that cord blood IGF-1 level is clearly associated with the development of ROP requiring laser treatment in extremely preterm infants.

5. Conclusion

In conclusion, the need of laser treatment for ROP was found to be associated with low umbilical cord blood IGF-1 levels in extremely preterm infants. Umbilical cord blood IGF-1 can be used as a biomarker for risk of developing severe ROP requiring laser treatment.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijhydene.2022.09.020.