Physical Growth and Retinopathy in Preterm Infants: Involvement of IGF-I and GH

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ABSTRACT

GH and IGF-I are important for physical growth. We measured serum levels of these factors in preterm infants. The study population ($n = 81$) was divided into three groups according to the gestational age. We evaluated differences in serum GH and IGF-I levels among groups with regard to physical growth and development of retinopathy of prematurity. Serum GH levels in extremely preterm infants born at <28 wk of gestational age were significantly higher than levels in those born between 28 and 34 wk at 1 and 2 mo of age. In contrast, serum IGF-I levels in extremely preterm infants remained low, whereas those in the other two groups gradually increased. Evaluation of the effects of GH and IGF-I on physical growth in very low birth weight infants (<1500 g) showed that IGF-I concentrations were positively related to physical growth for several months after birth,

whereas no relationship was observed between GH and physical growth. Multivariate analysis demonstrated that high GH concentration at 1 mo of age was significantly associated with development of severe retinopathy of prematurity. In conclusion, persistent low serum IGF-I levels may explain the slow physical growth during neonatal life, and exposure of high GH may cause, at least in part, severe retinopathy of prematurity in preterm infants. (*Pediatr Res* 50: 732–736, 2001)

Abbreviations

ROP, retinopathy of prematurity
SDS, SD score
VEGF, vascular endothelial growth factor

Intrauterine and postnatal growth is affected by genetic, nutritional, hormonal, and environmental factors (1, 2). Growth factors derived from placental and maternal tissues have profound effects on fetal growth. Especially, GH and IGFs play an important role in regulation of fetal growth. Disruption of IGF-I, IGF-II, or their receptor genes in mice results in intrauterine growth retardation (3, 4). In humans, homozygous defect of the IGF-I gene was associated with growth failure before and after birth (5), and there was a positive correlation between cord blood IGF-I concentration and fetal growth or newborn birth weight (6, 7). During postnatal period, hormonal factors such as insulin and IGF-I largely contribute to the regulation of physical growth in addition to exogenous factors (8). With regard to preterm or extremely preterm infants, physical growth may be additionally influenced by immaturity of organs, neonatal diseases, and a variety of medical treatments (1).

GH is essential for the balanced growth of organs and body compositions in children. GH levels are higher in fetuses and

newborns than in children and adults (9). Especially in preterm infants, remarkably high GH and low IGF-I values in serum continue until 1 y of age (10–12). However, the growth effect of GH does not become apparent until about 18 mo of age, and the clinical significance of GH for perinatal growth has not been well understood (1).

Besides the effect on physical growth, GH has various biologic functions. It has been postulated that GH plays a role in initiating and sustaining angiopathic processes. In previous reports, the association between GH exposure and ischemia-induced retinal neovascularization was determined in diabetic patients (13–16). Accordingly, it is likely that continuous exposure to high GH causes progression of ROP in preterm infants. To the best of our knowledge, however, there have been no reports on the association between serum GH levels and physical growth or development of ROP in preterm infants.

We performed serial determinations of serum GH and IGF-I levels in preterm infants for several months after birth. Then, we have investigated whether GH or IGF-I levels influence the physical growth during neonatal period, and evaluated the development and severity of ROP in preterm infants.

METHODS

Study population. Preterm infants born at <35 wk of gestational age in Kyushu University hospital between 1995 and

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1998 were enrolled in this study. Infants with chromosomal aberrations and major morphologic anomalies, such as congenital heart diseases and brain anomalies, were excluded from this study. This study was approved by the Kyushu University Hospital Ethics Committee, and informed consent was obtained from the infants' parents. Gestational ages ranged from 24 to 34 wk, and birth weights, from 505 to 2196 g. Infants were divided into three groups according to their gestational age: group A included infants born from 24 to 27 wk of gestational age (29 infants; median birth weight, 854 g); group B, born from 28 to 31 wk (33 infants; median birth weight, 1366 g); and group C, born from 32 to 34 wk (19 infants; median birth weight, 1620 g; Table 1).

Sample preparation. The sample collection was performed initially within 24 h after birth and before any medical treatment, and afterward, monthly during hospitalization. Samples of venous blood were collected at approximately 0800 at the time of routine hematologic or biochemical studies just before the intake of milk. Sera were immediately separated by centrifugation at 3000 rpm for 10 min at 4°C and stored at -30°C until assay.

Measurement of GH and IGF-I. Serum GH concentrations (in nanograms per milliliter) were measured by RIA using the assay kit from Daiichi Isotope Research Institute (Tokyo, Japan). The sensitivity of the assay was 0.1 ng/mL, and the intraassay and interassay coefficients of variation were less than 1.3% and 2.1%, respectively. Serum IGF-I levels (in nanograms per milliliter) were measured by RIA kit from Bayer Medical Corp (Tokyo, Japan). The sensitivity of the assay was 6.3 ng/mL, and the intraassay and interassay coefficients of variation were less than 3.3% and 7.0%, respectively.

Evaluation of the growth variables. We routinely checked the weight of each baby almost every day, whereas we measured the babies' length at birth, and thereafter, every month during hospitalization. SDS for body length and weight of very low birth weight infants (<1500 g; $n = 45$) were calculated because a standard growth chart for the population of low birth weight infants only is presently available (17). The growth rates of length and weight were shown as Δ SDS-length and Δ SDS-weight values, respectively, which indicate the changes

of SDS per month. IGF-I values of several points except those at birth were used to calculate the mean values of serum IGF-I levels in individual infants.

Ophthalmologic examinations. All the preterm infants in this study repeatedly underwent ophthalmologic examinations, and the condition of neovascular proliferation was evaluated according to the international criteria for ROP (Table 1) (18).

Statistical analyses. We evaluated differences of clinical factors among groups using χ^2 test or Kruskal-Wallis test. All results of serum GH and IGF-I values in respective groups were expressed as the median values with ranges, and statistical analysis was performed using the Mann-Whitney U test for comparison between two groups of GH or IGF-I values. The correlations between GH and IGF-I, or between Δ SDS-length or Δ SDS-weight and IGF-I, were evaluated using linear regression analysis. For the study of the association between GH and ROP, the likelihood ratio test was performed. We also executed tests for trends in proportions at every point by the Mantel-Haenszel procedure, by dividing all patients into two groups. Values of $p < 0.05$ were considered to be significant for all statistical tests.

RESULTS

Longitudinal evaluation of serum GH. Serum GH levels at birth were remarkably high in all groups in comparison with those at 1, 2, or 3 mo of age (Fig. 1A). GH values of infants of groups B and C gradually declined after birth, whereas those in group A were persistently high until 3 mo after birth. Comparison of each value among groups demonstrated that groups A and B showed significantly higher serum GH levels than group C at 1 mo of age (*A versus C*, $p = 0.010$; *B versus C*, $p = 0.028$, respectively), and that group A had higher values than groups B and C at 2 mo of age (*A versus B*, $p = 0.0009$; *A versus C*, $p = 0.0053$, respectively). In addition, when GH levels at 30, 34, and 38 wk of postconceptional age were evaluated, serum GH level in group A was also significantly higher than that in group B or C at 38 wk of postconceptional age (*A versus B*, $p = 0.0029$; *A versus C*, $p = 0.032$, respectively; Fig. 1B).

Table 1. Clinical profiles and ophthalmologic evaluation of study population

Characteristic	Group A ($n = 29$)	Group B ($n = 33$)	Group C ($n = 19$)	p value
Gestational age (wk)*	26 [24–27]	30 [28–31]	32 [32–34]	
Clinical profiles				
Birth weight (g)*	854 [505–1165]	1366 [590–2020]	1620 [955–2360]	<0.0001†
Male:Female	19:10	17:16	10:9	0.4946
CLD	27	4	0	<0.0001
Blood transfusion	25	3	0	<0.0001
Ophthalmologic evaluation				NE
ROP stage 0	1	19	15	
stage 1	11	9	3	
stage 2	5	0	1	
stage 3	10	5	0	
stage 4	2	0	0	

* Median [range].

† Evaluated by Kruskal-Wallis test; others by χ^2 test.

Abbreviations used: CLD, chronic lung disease; NE, not examined.

Longitudinal evaluation of serum IGF-I. Serum IGF-I levels in all groups of infants did not significantly differ at birth (Fig. 2). Thereafter, serum IGF-I level in group C gradually increased, whereas that in group A remained low for at least 3 mo after birth. When we compared serum IGF-I levels among groups, the IGF-I level in group A was significantly lower than that in group B or C at 1 and 2 mo after birth (at 1 mo: A versus B, $p < 0.0001$; A versus C, $p < 0.0001$; at 2 mo: A versus B, $p = 0.0036$; A versus C, $p < 0.0001$). At 3 mo of age, serum IGF-I level in group A was also lower than that in group B ($p = 0.041$; Fig. 2A).

Evaluation of the IGF-I level with respect to postconceptional age demonstrated that IGF-I level in group A was also remarkably low from birth at least until 38 wk of postconceptional age. When IGF-I levels among groups were compared at 30, 34, and 38 wk of postconceptional age, the IGF-I level in group A was significantly lower than that in group B or C at 30, 34, and 38 wk of postconceptional age (30 wk: group A versus B, $p = 0.0023$; 34 wk: A versus B, $p < 0.0001$; A versus C, $p = 0.015$; 38 wk: A versus B, $p = 0.0029$; A versus C, $p = 0.032$; Fig. 2B).

Figure 1. Serum GH concentrations in preterm infants. A, GH levels at birth, 1, 2, and 3 mo of age. B, GH levels at 30, 34, and 38 wk of postconceptional age. Boxes represent the interquartile range (25th to 75th percentiles), and lines within the boxes are the median; bars represent the upper (90th percentile) and the lower (10th percentile) adjacent values. Dotted, hatched, and open boxes demonstrate serum GH values of groups A, B, and C, respectively. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure 2. Serum IGF-I concentrations in preterm infants. A, IGF-I levels at birth, 1, 2, and 3 mo of age. B, IGF-I levels at 30, 34, and 38 wk of postconceptional age. Boxes represent the interquartile range (25th to 75th percentiles), and lines within the boxes are the median; bars represent the upper (90th percentile) and the lower (10th percentile) adjacent values. Dotted, hatched, and open boxes demonstrate the serum IGF-I values of groups A, B, and C, respectively. Symbols are the same as shown in Figure 1.

Correlation between GH and IGF-I. GH levels were negatively correlated with IGF-I levels at 1 ($r^2 = 0.28$, $p < 0.0001$; Fig. 3A) and 2 mo ($r^2 = 0.34$, $p = 0.0001$; Fig. 3B) of age, but not at 3 mo of age because of the small sample number. On the other hand, GH and IGF-I levels showed a similar correlation at 38 wk of postconceptional age ($r^2 = 0.25$, $p = 0.0012$), but not at birth or at 30 and 34 wk (data not shown).

Relationship between IGF-I and growth rate during early infancy. Very low birth weight infants showed that mean values of serum IGF-I levels were positively related to the Δ SDS-length ($p = 0.013$, $r^2 = 0.144$), but not to the Δ SDS-weight ($p = 0.14$, $r^2 = 0.052$), irrespective of their gestational ages (Fig. 4). There was no relationship between serum GH levels at any age and Δ SDS-length ($p = 0.51$, $r^2 = 0.012$) or Δ SDS-weight ($p = 0.23$, $r^2 = 0.014$).

Relationship between GH and ROP. The ophthalmologic evaluation showed that the more immature the infants were, the more frequently they developed more severe ROP (Table 1). The multivariate analysis demonstrated that high GH level at 1 mo of age was an independent risk factor for the development of severe ROP (Table 2). To exclude a possible influence of immaturity itself on the severity of ROP, we reevaluated the effect of high GH on the severity of ROP by dividing the whole

Figure 3. Correlations between serum GH and IGF-I levels. A, at 1 mo of age. B, at 2 mo of age. Negative correlations between serum GH and IGF-I levels are seen at both ages (1 mo, $r^2 = 0.28$, $p < 0.0001$; 2 mo, $r^2 = 0.34$, $p = 0.0001$). Open circles, triangles, and squares demonstrate individuals belonging to groups A, B, and C, respectively.

Figure 4. Correlations between serum IGF-I level and growth variables. Comparison between Δ SDS-length (A) or Δ SDS-weight (B) and mean value of serum IGF-I levels is shown. Positive correlation between serum IGF-I level and Δ SDS-length is presented but not Δ SDS-weight (A: $p = 0.013$, $r^2 = 0.14$; B: $p = 0.14$, $r^2 = 0.052$). Symbols are the same as shown in Figure 3.

patient population into two groups according to gestational age (<28 wk and $\geq$ 28 wk of gestational age). The correlation between high serum GH and severity of ROP did not depend on gestational age in preterm infants (Table 3). Blood transfusion was marginally correlated with the development of ROP ($p = 0.05$) (Table 2).

DISCUSSION

Newborns show a state of GH resistance, characterized by GH hypersecretion and a low serum IGF-I level (11, 12). We observed that this unique profile was more prominent in extremely preterm infants and continued for 3 mo after birth. One of the factors to influence IGF-I production in the liver is the content and total calories of nutrition (19). Although preterm infants showed lower IGF-I levels (Fig. 2), there were no differences in the nutritional states among the three groups because of strict nutritional management in the neonatal intensive care unit (data not shown). Another explanation may include the functional immaturity of hepatocytes for IGF-I synthesis in preterm infants, resulting in acceleration of GH production in the pituitary gland by negative feedback process. A normalization of excess GH secretion in preterm infants might be caused either by an increased IGF-I level secondary to a maturation of GH receptor function or by an independent maturation of a somatostatinergic inhibitory mechanism.

GH and IGF-I are important growth factors for physical growth during childhood (20). However, the precise contributions of GH and IGF-I to the physical growth of newborn infants have not been defined. The present study clearly showed that IGF-I in the serum influenced physical growth during infancy of preterm infants, whereas GH did not. As the growth rate of preterm infants is slower than that of full-term

infants (1, 17), we speculate that persistence of low IGF-I levels causes the slow growth rate of preterm infants. Additionally, regulatory factors for IGF-I function, such as circulating IGF-binding proteins (10), or other synergistic growth factors, including IGF-II, may also be involved in the growth of preterm infants. Thus, it is plausible that the measurement of serum IGF-I levels with other related factors predicts the physical growth rate of preterm infants within several months after birth. It was reported that supplement of milk-borne IGF-I apparently enhanced growth in newborn rats (21). Supplement of IGF-I by injection or oral administration may have a therapeutic potential for growth retardation in preterm infants. However, because IGF-I is likely to be important for VEGF-induced retinal neovascularization, as evidenced by inhibition of this process by an IGF-I receptor antagonist (22), further evaluation of the role of IGF-I in the pathogenesis of ROP is essential before use of this factor can be considered in this population.

GH functions as a pleiotropic factor and exerts its angiogenic ability in some pathologic conditions (23, 24). Several clinical studies showed that the pathogenesis of proliferative diabetic retinopathy was mediated by GH through its positive effect on the proliferation of endothelial cells (13–16). A previous case report demonstrated that patients with GH deficiency showed a reduced retinal vascularization during childhood (25), and GH replacement therapy for patients with GH deficiency induced diabetic-like retinopathy (26), which was remitted after discontinuation of GH treatment (27). In addition, GH and GH antagonist transgenic mice were shown to be susceptible to and protective against, respectively, hypoxia-induced neovascularization (28). Consistent with these previous findings, a high level of serum GH was associated with the development of severe ROP independent of the degree of immaturity in the present study. Taken together, GH

Table 2. Evaluation of risk factors for severe (stage $\geq$ 3) ROP by multivariate analysis

Risk factor	Group 1/2	Group 1		Group 2		<i>p</i> value
		total <i>n</i>	stage $\geq$ 3 <i>n</i> (%)	total <i>n</i>	stage $\geq$ 3 <i>n</i> (%)	
1 mo of age						
Gestational age (wk)	<28/ $\geq$ 28	18	7 (38.9)	35	3 (8.6)	0.32
GH (ng/mL)*	$\geq$ 61.6/<61.6	22	9 (40.9)	31	1 (3.2)	0.026
IGF-I (ng/mL)*	<15/ $\geq$ 15	21	8 (38.1)	32	2 (6.3)	0.38
CLD	+/-	19	7 (36.8)	34	3 (8.8)	0.30
Blood transfusion	+/-	18	8 (44.4)	35	2 (5.7)	0.05

* Divided into two groups by medians of respective values.

Table 3. Relationship between GH and development of severe (stage $\geq$ 3) ROP in two gestational age groups by Mantel-Haenszel analysis

Age	Groups*	Gestational age				<i>p</i> value†
		<28 wk		≥28 wk		
		total <i>n</i>	stage ≥3 <i>n</i> (%)	total <i>n</i>	stage ≥3 <i>n</i> (%)	
At birth	H	6	2 (33.3)	13	0 (0.0)	0.66
	L	11	3 (27.3)	8	2 (25.0)	
1 mo	H	11	6 (54.5)	10	3 (30.0)	0.024
	L	7	1 (14.3)	14	0 (0.0)	
2 mo	H	15	7 (46.7)	3	2 (66.7)	0.060
	L	5	1 (20.0)	12	0 (0.0)	
3 mo	H	7	5 (71.4)	1	1 (100)	0.040
	L	5	0 (0.0)	3	1 (33.3)	

* Divided into two groups H and L by each median value of GH at each point (at birth, 73.1 ng/mL; 1 mo, 61.6 ng/mL; 2 mo, 48.1 ng/mL; 3 mo, 42.6 ng/mL).

† *p* value for comparison within same age group.

H, $\geq$ median GH values; L, < median GH values.

may play an important role as an angiogenic growth factor in the development and progression of ROP in preterm infants. In addition, the development of ROP is affected by various environmental factors or medical treatments (29–34), including blood transfusion (33–35). As shown in Table 2, blood transfusion was marginally correlated with the development of ROP ($p = 0.05$). We speculate that anemia exacerbates retinal hypoxia, which stimulates retinal neovascularization, whereas frequent blood transfusion increases the delivery of oxygen to the retina as well as that of free iron, which induces retinal tissue damage, although the correlation between anemia or blood transfusion and ROP remains to be established (36). As another angiogenic factor, VEGF is intensively studied (37). In an animal study, production of VEGF induced by local retinal hypoxia has been reported to make a major contribution to the pathogenesis of neovascularization (38). Our preliminary study in preterm infants revealed no definite relationship between serum VEGF levels and development of ROP (data not shown). Therefore, it might be possible that GH functions as a systemic angioproliferative factor, whereas VEGF acts as a local angiogenic one (38, 39).

In conclusion, we showed that high GH and low IGF-I levels in the serum were observed in preterm infants, especially in extremely preterm infants. In addition, low IGF-I levels may explain the slow physical growth during the neonatal period of preterm infants. Furthermore, exposure to high GH may be involved, at least in part, in severity of ROP in preterm infants. If a role for GH in the development of ROP in preterm infants is confirmed, anti-GH treatment may have a therapeutic potential. Further evaluation will be needed to understand the pathogenesis of ROP in preterm infants, leading to the establishment of new treatment.

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