The correlation between the increase in insulin-like growth factor I and the growth improvement induced by growth hormone treatment in short children born small for gestational age

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Background: Insulin-like growth factor I (IGF-I) is an important marker of growth hormone (GH) treatment and its increase is known to have a positive correlation with growth improvement [1-3]. However, the correlation between the growth improvement and the increase of IGF-I by the first injection of GH, which can be evaluated right after the initiation of therapy, remains elucidated.

Objective: We report the correlation between the GH treatment induced increase in IGF-I and growth improvement in short children born small for gestational age (SGA).

Method: We retrospectively reviewed 14 pre-pubertal short children born SGA (ten boys, four girls) who received GH treatment for more than 1 year. Nine of them continued treatment for more than 2 years. The characteristics of the subjects are shown in Table 1. Birth weight and length for gestational age were both less than 10 percentile, and either birth weight or length for gestational age was below -2.0SD in all subjects. The standards of birth weight and length used was those of Itabashi et al [4]. The etiology of SGA is shown in Table 2. Pre-pubertal stage was defined as both testes volumes ≦3 ml in boys and Tanner stage B I in girls. We had performed at least two GH stimulation tests for all subjects to confirm that they are not GH deficient before the initiation of GH treatment. All patients started the GH treatment with the dose of 0.23 mg/kg/week, which is divided by six or seven injections. We confirmed that patients perform injection regularly at each visit.
We retrospectively analyzed the correlation between the following parameters: 1) IGF-I SD score increase (ΔIGF-I SDS) at 24 hours, 1 year, or 2 years after GH treatment initiation; 2) height SD score increase (ΔHSDS) at 1 year or 2 years. The IGF-I SDS was calculated using the IGF-I standards of Isojima et al [5]. The HSDS was calculated by the calculator published by The Japanese Association for Human Auxology and The Japanese Society for Pediatric Endocrinology [6].
We used paired t test to analyze the difference of IGF-I and IGF-I SDS between those before the initiation of treatment and those 24 hours after the initiation. P <0.05 was thought to be significant. The correlations between ΔIGF-I SDS and ΔHSDS were analyzed by Peason's correlation coefficient test. We judged that there was a positive correlation when r was 0.4 or greater and P <0.05 was thought to be significant.

Table 1 Characteristics of the subjects

	1st year			2nd year		
	n	Mean	SD	n	Mean	SD
At birth						
Sex male %	14	71		9	67	
Gestational age	14	35w3d	2w2d	9	35w2d	2w5d
Weight SDS	14	-2.7	0.7	9	-2.6	0.8
Length SDS	14	-2.4	0.7	9	-2.4	0.7
Target height SDS	14	-0.7	1.1	9	-0.7	1.2
At GH treatment initiation						
Age	14	5y9m	2y0m	9	5y10m	1y3m
Height SDS	14	-3.1	0.4	9	-3.0	0.4
Weight SDS	14	-1.9	0.6	9	-1.8	0.7
Height Velocity (cm/year)	14	5.4	1.0	9	5.2	0.7
Bone age-chronological age	11	-1y7m	7m	6	-1y6m	6m
GH dose (mg/kg/week)	14	0.23	0.01	9	0.23	0.02

Table 2 Etiology classification of SGA

	ESPE code [7]	KIGS code [8]	n
SGA without stigmata	1A.2	3.4.ff	8
Cause known	-	3.4.1	2
Multiplets	-	-	0
Eclampsia	-	-	1
Smoking	1A.2y	3.5.9	1
Causes unknown	1A.2z	3.4.2	6
SGA with minor dysmorphic stigmata	-	3.5.ff	2
Prenatal infections	-	3.5.1	0
Drugs (alcohol, etc.)	1A.2y	3.5.2	0
Others	-	3.5.9	2
SGA with major dysmorphic stigmata	-	-	2
Diaphragmatic hernia, anal atresia	-	-	1
Cleft hand	-	-	1
Silver-Russell syndrome	14B.31	3.3.1	2

Results: The results are shown in Figure 1 and Figure 2.

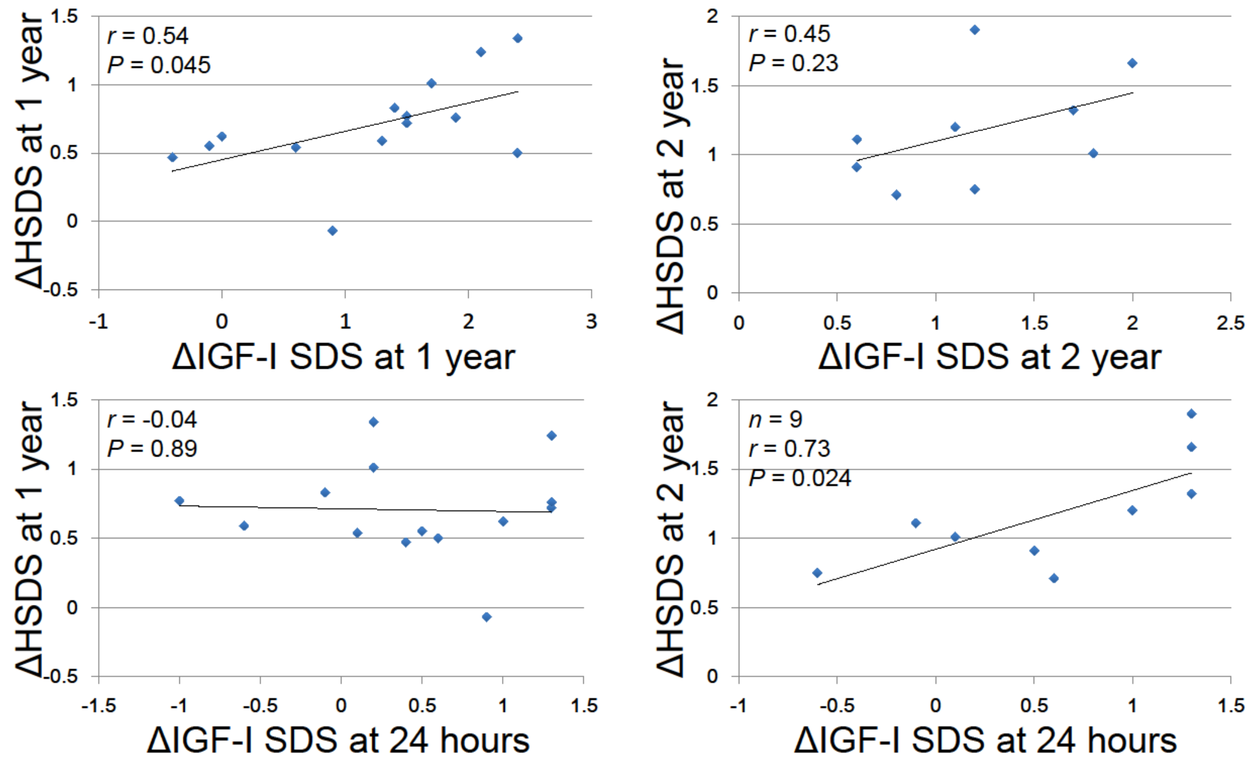

Figure 1 Correlation between ΔIGF-1 SDS and ΔHSDS

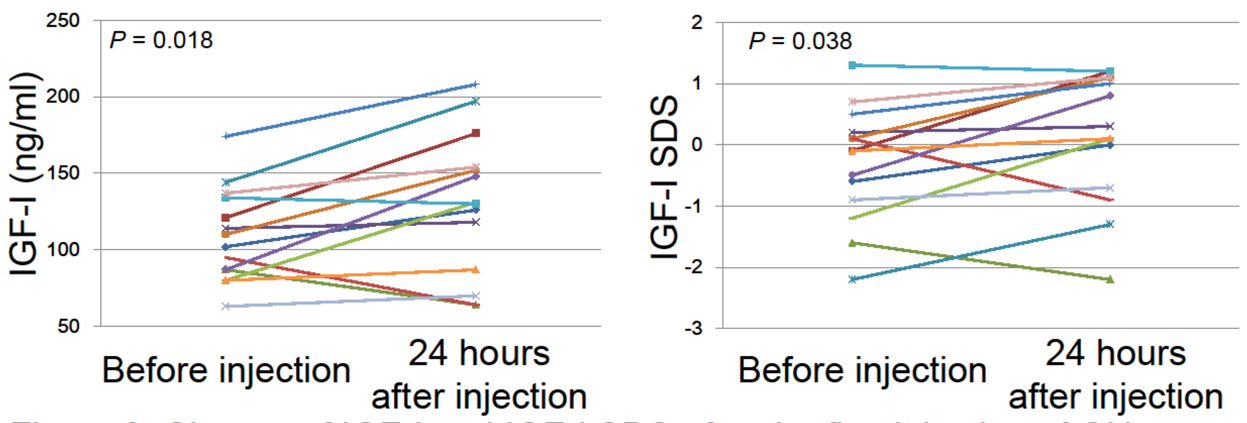

Figure 2 Change of IGF-I and IGF-I SDS after the first injection of GH

Discussion: Positive correlations between IGF-I increase and growth improvement at 1 year and 2 years after the initiation of GH treatment were compatible with previous reports [1-3]. Furthermore, there was also a correlations between the IGF-1 increase 24 hours after the initiation of treatment and growth improvement at 2 years after the treatment. We hypothesized that IGF-I increase by the first GH injection may reflect the GH sensitivity. IGF-I generation test is a test to assess GH sensitivity. Although there are several protocols for the test, those previously proposed takes a few days or need higher dose than the dose used for the initiation of GH treatment in short children born SGA [9]. It is more convenient if it is possible to predict the GH responsiveness by IGF-I increase by the first GH infection in the initiation dose for short children born SGA.
Although the result of our study is intriguing, there are several limitations. First, there was no correlation between ΔIGF-I SDS after 24 hours after the first GH injection and ΔHSDS at 1 year. There is a report that the height velocity during the first year of treatment is the most important predictor of the growth improvement during the second year [10]. The discrepancy of the results between 1 year and 2 years after the initiation of treatment in our study is inconsistent with the previous reports. Because it may be due to our small sample size, which is the second limitation, we need to analyze more patients in the future. The third limitation is that we didn't take into account the factors which affect GH responsiveness such as GH dose, age and weight SDS at the initiation of treatment, midparental height SDS, or etiology of SGA [10,11]. The fourth limitation is that the reproducibility of IGF-I generation test is uncertain [9,12]. Although the serum IGF-I levels were significantly elevated 24 hours after a single dose of GH injection which is used for the treatment in short children born SGA and the amount of increase was correlated with the growth improvement during 2 years after the initiation of treatment in our study, its reproducibility remains uncertain.
We need to confirm that the correlation between the increase of IGF-I 24 hours after the first GH injection and growth improvement remains significant in bigger sample size.

Conclusion: The increase of IGF-1 at 24 hours could be an important predictive factor for GH treatment-induced growth improvement, although there are several limitations which should be overcome.

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