Studies of Very Severe Short Stature with Severe GH Deficiency: From the Data Registered with the Foundation for Growth Science

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Abstract. The ratio, clinical characteristics, and therapeutic efficacy of hGH treatment in patients with severe short stature (HtSDS below -4 SD) with severe GHD (all peak GH values to provocation tests: below $2 \mu\text{g/L}$) were studied. From March 1986 to January 1998, 23,110 patients with idiopathic GH deficiency (IGHD) were registered with the Foundation for Growth Science, Japan. These subjects were divided into 5 groups as follows: Group 1 (G1), all subjects; Group 2 (G2), at least one GH peak to provocative test $\geq 5 \mu\text{g/L}$; Group 3 (G3), $2 \mu\text{g/L} \leq \text{GH peak} < 5 \mu\text{g/L}$; Group 4 (G4), all GH peaks $< 2 \mu\text{g/L}$ and HtSDS > -4 ; Group 5 (G5), all GH peaks $< 2 \mu\text{g/L}$ and HtSDS ≤ -4 . The ratio of G5 was 139 patients (0.6%) out of 23,110 patients with IGHD. In G5, there were no significant differences in birth weight, birth length, gestational age and parental height between G2, G3 and G4. However, asphyxia at delivery was more frequent in G5 and G4 than G2 and G3. Chronological age (CA), bone age (BA) and BA/CA ratio at registration were significantly lower in G5 than G2, G3 and G4. Further, the IGF-I SD score in G5 was significantly lower than those in G2 and G3. After hGH treatment, the final height and final height SDS in G5 remained the lowest, while the ΔHtSDS value in G5 was the greatest among G2 to G5 groups. In conclusion, the ratio of severe short stature with severe GH deficiency (G5) is only 0.6% of all IGHD cases. Growth failure in G5 seems to occur after birth, and its etiology in G5 seems to be different from that of patients with other forms of IGHD. Early diagnosis and hGH treatment are needed to attain better final height.

Key words: Severe short stature, Severe GHD, Idiopathic GHD

(Endocrine Journal 52: 37–43, 2005)

RECENTLY, many growth disorders caused by genetic abnormalities, such as GH-1 gene, its transcrip-

tion factors (Pit-1, PROP-1, HESX-1), GHRH-receptor gene, GH receptor gene and IGF-I receptor gene have been reported [1–3]. These cases, except for patients with gene mutations of GH receptor or IGF-I receptor, usually show severe short stature (height SD score below -4 to -4.5) together with severe GH deficiency (peak GH value below $4 \mu\text{g/L}$ in conventional provo-

Received: February 4, 2004

Accepted: September 7, 2004

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cation tests) [4].

Short stature associated with GH deficiency is reported to be between 1 in 4,000 and 1 in 10,000 of the population in several studies [5–8]. However, the exact incidence of severe short stature with severe GH deficiency (GHD) among total short stature patients (HtSDS below -2), and the proportion of GH-related gene abnormalities in severe short stature with severe GHD have yet to be clarified. In the present study, we examined the ratio of patients with severe short stature and severe GHD in total idiopathic GHD (IGHD), and studied the clinical characteristics and therapeutic efficacy of hGH in these patients.

Subjects and Methods

Patients with IGHD who were approved by the Foundation for Growth Science (FGS), Japan from March, 1986 to January, 1998, to receive hGH treatment, were studied. These patients were non-organic and received no gonadal suppression therapy.

IGHD was diagnosed according to the following criteria: (1) age matched height SDS (HtSDS) was below -2 or growth rate/year was below -1.5 SD over 2 years, and (2) poor GH responses (peak GH value to provocation test was below $10 \mu\text{g/L}$) to two provocative stimuli; or the poor GH response to at least one stimulus and significantly low IGF-I value; or (3) low mean nocturnal GH value (below $3 \mu\text{g/L}$) for 3 hr samplings at 20 min intervals together with low IGF-I and low urinary GH values despite normal GH responses to exogenous stimuli (so-called GH neurosecretory dysfunction). After registration with the Foundation for Growth Science (FGS), these patients were treated with recombinant human GH with the doses of $0.5\text{IU} = 0.17 \text{ mg/kg/week}$ mainly 6 to 7 times a week.

These subjects were arbitrarily divided into 5 groups as follows: Group 1 (G1), all subjects; Group 2 (G2), at least one GH peak to provocative test $\geq 5 \mu\text{g/L}$; Group 3 (G3), $2 \mu\text{g/L} \leq \text{GH peak} < 5 \mu\text{g/L}$; Group 4 (G4); all GH peaks $< 2 \mu\text{g/L}$ and $\text{HtSDS} > -4$ and; Group 5 (G5), all GH peaks $< 2 \mu\text{g/L}$ and $\text{HtSDS} \leq -4$. In this category, G1 is not simply the sum of G2, G3, G4 and G5, since one case which performed only one provocative test and whose peak GH value was below $5 \mu\text{g/L}$, or one case whose one peak GH value was below $2 \mu\text{g/L}$ while the other value was more than 2 and below 5, were included in G1 but excluded from the other groups.

These five groups were analyzed based on the following parameters: (1) the number of each group at registration to FGS, (2) birth weight, (3) birth length, (4) gestational age, (5) incidence of asphyxia at delivery, (6) chronological age (CA) and (7) bone age (BA) at registration, (8) BA/CA ratio, (9) height at start of hGH treatment, (10) Height SDS (HtSDS) at start of hGH treatment, (11) SD score of serum IGF-I value (measured by RIA using extraction method) calculated from values of age-matched controls [9] at start of hGH treatment, (12) father's height, (13) mother's height, (14) final height (when growth rate fell below 2 cm/yr), (15) final height SDS, (16) ΔHtSDS (final HtSDS–pretreatment HtSDS).

Data are expressed as mean $\pm$ S.E.M. and statistical analysis was conducted using Student's non-paired t-test or chi-square test for the comparison of the two parameters.

Results

1) Number of each group of idiopathic GH deficiency

As shown in Table 1, total number of patients (G1) in this study was 23,110. Among them, the majority of patients (89.1%) were G2. So-called classical severe GHD (all GH peaks to provocation tests less than $5 \mu\text{g/L}$) was 10.5% (2428 cases) of the total, and severe short stature with severe GHD (G5) was only 0.6% (139 cases).

2) Birth weight, birth length, gestational age and asphyxia at delivery in the 5 groups

In all groups, birth weight (G1: boy, $2913.3 \pm 4.0 \text{ g}$, $n = 15,487$; girl $2840.1 \pm 5.7 \text{ g}$, $n = 7,128$; G5: boy, $2978.4 \pm 61.6 \text{ g}$, $n = 81$; girl, $2939.3 \pm 94.9 \text{ g}$, $n = 54$) (Table 2a), birth length (G1: boy, $48.1 \pm 0.04 \text{ cm}$, $n = 4,431$; girl, $47.6 \pm 0.07 \text{ cm}$, $n = 2,163$; G5: boy,

Table 1. Numbers of each group of idiopathic GH deficiency

	boy	girl	total	rate (%)
G1	15,824	7,286	23,110	100
G2	14,033	6,568	20,601	89.1
G3	1,341	550	1,891	8.2
G4	306	92	398	1.7
G5	83	56	139	0.6

46.5 ± 2.56 cm, n = 5; girl, 47.3 ± 0.87 cm, n=6) (Table 2b) and gestational age [G1 (total), 39.1 ± 0.01 weeks, n = 22,110; G5 (total), 38.9 ± 0.24 weeks, n = 129] (Table 2c) were within normal ranges. The birth weight of patients in G5 was slightly greater than G2, G3 and G4 (P = NS). There were no significant differences in these parameters between G5 and G2, G3, G4; and no differences between each group.

Asphyxia at delivery was seen in 12.3% of total cases, and the rate was significantly higher in G5 (21.8% vs G2, G3, P<0.01; vs G4, P = NS) and G4 (19.5% vs G2 and G3, P<0.01) (Table 3).

3) Chronological age (CA), bone age (BA) and ratio of BA/CA in 5 groups at registration

Although, the mean chronological age of G1 at registration was 9.5 ± 0.02 yr (n = 23,109), G5 was significantly younger (8.7 ± 0.4 yr, n = 139) than G2, G3 and G4 (P<0.005) (Table 4a). Mean bone age in G5 (4.8 ± 0.33 yr, n = 120) was also significantly younger than G2, G3 and G4 [the totals of G2, G3 and G4 were 6.9 ± 0.02 yr, n = 19,955; 7.4 ± 0.09 yr, n = 1,711 and 7.4 ± 0.20 yr, n = 339, respectively] (P<0.001) (Table 4b).

Further, the ratio of BA/CA in G5 (0.52 ± 0.02,

Table 2. Birth weight (a), birth length (b) and gestational age (c) in the five groups

a) Birth weight

	total			boy			girl		
	Mean (g)	SEM	No.	Mean (g)	SEM	No.	Mean (g)	SEM	No.
G1	2,890.2	3.3	22,615	2,913.3	4.0	15,487	2,840.1	5.7	7,128
G2	2,886.8	3.4	20,188	2,910.2	4.2	13,758	2,836.5	5.9	6,430
G3	2,915.0	12.0	1,828	2,937.2	14.8	1,295	2,860.9	20.2	533
G4	2,935.9	25.4	385	2,944.2	28.1	294	2,909.1	57.1	91
G5	2,962.7	53.0	135	2,978.4	61.6	81	2,939.3	94.9	54

b) Birth length

	total			boy			girl		
	Mean (cm)	SEM	No.	Mean (cm)	SEM	No.	Mean (cm)	SEM	No.
G1	47.9	0.04	6,594	48.1	0.04	4,431	47.6	0.07	2,163
G2	47.9	0.04	6,214	48.1	0.05	4,158	47.6	0.07	2,056
G3	48.0	0.15	324	48.3	0.18	237	47.4	0.26	87
G4	48.4	0.59	32	49.0	0.55	22	47.0	1.35	10
G5	46.9	1.26	11	46.5	2.56	5	47.3	0.87	6

c) Gestational age

	total			boy			girl		
	week	SEM	No.	week	SEM	No.	week	SEM	No.
G1	39.1	0.01	22,110	39.1	0.02	15,117	39.2	0.02	6,993
G2	39.1	0.01	19,791	39.1	0.02	13,472	39.2	0.02	6,319
G3	39.1	0.06	1,756	39.1	0.07	1,241	39.2	0.10	515
G4	39.2	0.11	357	39.1	0.12	271	39.3	0.28	86
G5	38.9	0.24	129	38.9	0.30	76	38.9	0.40	53

Table 3. Asphyxia at delivery in the five groups

	total					boy					girl				
	Asphyxia		unknown	sum	rate of Asphyxia	Asphyxia		unknown	sum	rate of Asphyxia	Asphyxia		unknown	sum	rate of Asphyxia
	(+)	(-)				(+)	(-)				(+)	(-)			
G1	2,654	18,405	592	21,651	12.3%	1,844	12,521	423	14,788	12.5%	810	5,884	169	6,863	11.8%
G2	2,343	16,732	507	19,582	12.0%	1,613	11,361	357	13,331	12.1%	730	5,371	150	6,251	11.7%
G3	227	1,321	65	1,613	14.1%	166	922	53	1,141	14.5%	61	399	12	472	12.9%
G4	57	222	14	293	19.5%	45	156	10	211	21.3%	12	66	4	82	14.6%
G5	22	74	5	101	21.8%	15	40	2	57	26.3%	7	34	3	44	15.9%

n = 120) was significantly lower than G2, G3 and G4 ($P < 0.001$). The value of G4 (0.69 ± 0.01 , n = 339) was also significantly lower than G2 (0.72 ± 0.001 , n = 19,954) ($P < 0.01$) and G3 (0.71 ± 0.005 , n = 1,711) ($P < 0.05$) (Table 4c).

Patients with severe GH deficiency (G4 + G5; all GH peaks to provocative stimuli were below $2 \mu\text{g/L}$) showed a significantly lower BA/CA ratio compared to G2 and G3, while the ratios of the latter two groups were not significantly different.

4) Height, height SDS and serum IGF-I SD score in the 5 groups just before hGH treatment

As it was arbitrarily classified, pretreatment height (103.0 ± 2.0 cm, n = 139) and HtSDS (-4.98 ± 0.08 , n = 139) in G5 were significantly lower than G2, G3 and G4 ($P < 0.001$) (Table 5a, 5b).

HtSDS in G3 was significantly lower than that in G2 ($P < 0.01$), and HtSDS in patients with severe GH deficiency (G4 + G5) were significantly lower than that in G2 and G3 ($P < 0.001$).

Mean pretreatment serum IGF-I values (SDS) in G5

(-2.38 ± 0.48 , n = 18) was significantly lower than in G2 and G3 (G2, -1.38 ± 0.01 , n = 9,982; G3, -1.64 ± 0.06 , n = 564) ($P < 0.001$ and 0.05) (Table 6). There were no significant differences between the values in G4 and G5. The IGF-I SD score in G3 and patients with severe GH deficiency (G4 + G5) were significantly lower than that in G2 (both $P < 0.01$), but there was no difference in the values between the former two groups.

5) Parental height in the 5 groups

Parental height of each group was within the normal ranges and there were no differences among G2 to G5 groups (Table 7).

6) Improvement of HtSDS, final height and final HtSDS in the 5 groups after hGH treatment

Improvement of HtSDS (ΔHtSDS) by hGH treatment was the greatest in G5 ($+2.02 \pm 0.51$, n = 16) [vs G2 ($+0.99 \pm 0.02$, n = 1,482), G3 ($+0.97 \pm 0.08$, n = 250) and G4 ($+0.93 \pm 0.09$, n = 80), $P < 0.025$].

Table 4. Chronological age (yr) (a), bone age (yr) (b) and ratio of bone age/chronological age (c) in the five groups at registration

a) CA									
	total			boy			girl		
	Mean	SEM	No.	Mean	SEM	No.	Mean	SEM	No.
G1	9.5	0.02	23,109	9.6	0.03	15,824	9.1	0.04	7,285
G2	9.4	0.02	20,600	9.5	0.03	14,033	9.1	0.04	6,567
G3	10.1	0.08	1,891	10.3	0.10	1,341	9.7	0.14	550
G4	10.6	0.17	398	10.8	0.20	306	9.8	0.35	92
G5	8.7	0.40	139	8.7	0.52	83	8.9	0.65	56
b) BA									
	total			boy			girl		
	Mean	SEM	No.	Mean	SEM	No.	Mean	SEM	No.
G1	7.0	0.02	22,186	7.0	0.03	15,182	7.0	0.04	7,004
G2	6.9	0.02	19,955	6.9	0.03	13,603	6.9	0.04	6,352
G3	7.4	0.09	1,711	7.4	0.11	1,207	7.3	0.16	504
G4	7.4	0.20	339	7.3	0.24	257	7.6	0.37	82
G5	4.8	0.33	120	4.5	0.43	69	5.1	0.51	51
c) BA/CA									
	total			boy			girl		
	Mean	SEM	No.	Mean	SEM	No.	Mean	SEM	No.
G1	0.72	0.001	22,185	0.70	0.001	15,182	0.75	0.002	7,003
G2	0.72	0.001	19,954	0.70	0.001	13,603	0.75	0.002	6,351
G3	0.71	0.005	1,711	0.70	0.006	1,207	0.74	0.008	504
G4	0.69	0.011	339	0.67	0.013	257	0.75	0.020	82
G5	0.52	0.018	120	0.50	0.022	69	0.55	0.029	51

Table 5. Pretreatment height (a) and height SDS (b) in the five groups just before hGH treatment

a) Ht

	total			boy			girl		
	Mean (cm)	SEM	No.	Mean (cm)	SEM	No.	Mean (cm)	SEM	No.
G1	118.3	0.1	23,110	119.4	0.1	15,824	115.9	0.2	7,286
G2	118.1	0.1	20,601	119.2	0.1	14,033	115.9	0.2	6,568
G3	120.3	0.4	1,891	121.6	0.5	1,341	117.0	0.8	550
G4	123.2	0.9	398	124.3	1.0	306	119.2	1.8	92
G5	103.0	2.0	139	103.1	2.6	83	102.8	3.3	56

b) HtSDS

	total			boy			girl		
	Mean	SEM	No.	Mean	SEM	No.	Mean	SEM	No.
G1	-2.74	0.01	23,110	-2.68	0.01	15,824	-2.87	0.01	7,286
G2	-2.70	0.01	20,601	-2.64	0.01	14,033	-2.83	0.01	6,568
G3	-2.93	0.02	1,891	-2.85	0.03	1,341	-3.11	0.04	550
G4	-2.74	0.03	398	-2.73	0.04	306	-2.80	0.07	92
G5	-4.98	0.08	139	-4.87	0.10	83	-5.14	0.13	56

Table 6. Pretreatment IGF-I SD score in the five groups

	total			boy			girl		
	Mean	SEM	No.	Mean	SEM	No.	Mean	SEM	No.
G1	-1.39	0.01	10,642	-1.38	0.01	7,253	-1.43	0.02	3,389
G2	-1.38	0.01	9,982	-1.36	0.02	6,776	-1.41	0.02	3,206
G3	-1.64	0.06	564	-1.60	0.08	415	-1.73	0.12	149
G4	-1.83	0.29	60	-1.73	0.39	41	-2.06	0.34	19
G5	-2.38	0.48	18	-2.58	0.78	8	-2.22	0.58	10

Table 7. Parental height in the five groups

Father

	total			boy			girl		
	Mean (cm)	SEM	No.	Mean (cm)	SEM	No.	Mean (cm)	SEM	No.
G1	165.4	0.05	22,464	165.4	0.06	15,382	165.5	0.07	7,082
G2	165.4	0.05	20,098	165.3	0.06	13,701	165.5	0.07	6,397
G3	165.5	0.18	1,785	165.6	0.20	1,261	165.4	0.38	524
G4	167.2	0.30	374	166.9	0.33	287	168.0	0.67	87
G5	166.0	0.56	131	165.8	0.73	77	166.5	0.87	54

Mother

	total			boy			girl		
	Mean (cm)	SEM	No.	Mean (cm)	SEM	No.	Mean (cm)	SEM	No.
G1	152.3	0.05	22,512	152.2	0.06	15,413	152.4	0.08	7,099
G2	152.2	0.05	20,141	152.2	0.06	13,729	152.4	0.08	6,412
G3	152.6	0.15	1,788	152.6	0.15	1,262	152.4	0.35	526
G4	153.8	0.25	376	153.8	0.30	289	154.0	0.46	87
G5	154.3	0.46	132	154.4	0.62	78	154.1	0.70	54

Table 8. Improvement of HtSDS (Δ HtSDS) (a), final height (b) and final HtSDS (c) after hGH treatment in the five groupsa) Δ HtSDS

	total			boy			girl		
	Mean	SEM	No.	Mean	SEM	No.	Mean	SEM	No.
G1	0.99	0.02	1,839	1.03	0.03	1,146	0.93	0.04	693
G2	0.99	0.02	1,482	1.02	0.03	894	0.93	0.04	588
G3	0.97	0.08	250	1.00	0.10	168	0.91	0.10	82
G4	0.93	0.09	80	0.97	0.09	68	0.73	0.27	12
G5	2.02	0.51	16	2.35	0.78	9	1.60	0.55	7

b) Final Ht

	total			boy			girl		
	Mean (cm)	SEM	No.	Mean (cm)	SEM	No.	Mean (cm)	SEM	No.
G1	155.7	0.2	1,841	160.6	0.2	1,148	147.5	0.2	693
G2	155.5	0.2	1,483	160.6	0.2	895	147.8	0.2	588
G3	155.8	0.6	250	160.4	0.6	168	146.3	0.6	82
G4	159.7	0.7	80	161.7	0.5	68	148.1	1.0	12
G5	149.4	3.2	17	154.8	4.5	10	141.6	2.3	7

c) Final HtSDS

	total			boy			girl		
	Mean	SEM	No.	Mean	SEM	No.	Mean	SEM	No.
G1	-1.87	0.03	1,841	-1.75	0.03	1,148	-2.06	0.04	693
G2	-1.85	0.03	1,483	-1.74	0.03	895	-2.02	0.04	588
G3	-1.95	0.08	250	-1.79	0.11	168	-2.30	0.11	82
G4	-1.61	0.09	80	-1.55	0.10	68	-1.96	0.21	12
G5	-2.97	0.51	17	-2.80	0.81	10	-3.22	0.44	7

However, there were no significant differences among the other groups (G2 to G4) (Table 8a).

Although G5 had the best Δ HtSDS, the final height (boy, 154.8 ± 4.5 cm; girl, 141.6 ± 2.3 cm) and the final height SDS (total, -2.97 ± 0.51 ; boy, -2.80 ± 0.81 , $n = 10$; girl, -3.22 ± 0.44 , $n = 7$) of G5 were the lowest among the four (G2 to G5) groups ($P < 0.025$) (Table 8b, 8c).

Discussion

The ratio of very severe short stature with severe GH deficiency (G5) was 139 (0.6%) out of 23,110 patients with IGHD. In G5, there were no significant differences in birth length and gestational age between G2, G3, and G4. However, birth weight in G5 was slightly greater than those of the other groups and asphyxia at delivery was more frequent in G5 and G4, than in G2 and G3.

These results indicate that patients with very severe

GHD (G4 + G5) have greater risk of asphyxia at delivery compared to other groups despite normal intrauterine growth.

Parental height in G5 was similar to G2 to G4, but their chronological age (CA), bone age (BA) and BA/CA ratio at registration were significantly lower than these groups. As it was arbitrarily defined, pretreatment height and HtSDS in G5 were significantly lower than G2 to G4. IGF-I SD score in G5 was lower than G2 and G3, although there were no statistical differences between G5 and G4.

These results indicate that growth failure in G5 is not based mainly on familial origin, but is dependent upon their own GH deficiency. Such severe short stature might tend to make their parents to consult specialists earlier for growth disorders. It is reported that patients with severe GHD tend to have been diagnosed at a younger age [10, 11].

Although it did not reach statistical significance, mean IGF-I SD score in G5 was lower than that of G4. In addition, mean BA/CA ratio in G5 was significantly

lower than that of G4. Therefore, it seems that GH secretory capacity in G5 is more severely decreased than in G4. In patients with severe GHD (G4 + G5), pretreatment HtSDS and BA/CA ratio were both lower than those in G3. Accordingly, severe GHD is highly probable when all peak GH values to provocative stimuli are below 2 µg/L. Related to this, peak GH value is defined as below 3 µg/L after ITT (insulin tolerance test) for the diagnosis of profound adult GHD [12]. It is assumed that the etiology of G5 might be different from that of G2, G3 and G4.

Clinical and endocrine data might reveal a spectrum of difference according to the severity of GH deficiency, since HtSDS and IGF-I SD scores in G3 were both lower than those in G2.

After the hGH treatment, the final height and final height SDS in G5 remained the lowest. Nevertheless, the ΔHtSDS value in G5 was the greatest among the four (G2 to G5) groups. From these data, early treat-

ment starting before significant height deficit develops is desirable in G5 to achieve better final height [13], although hGH treatment in this group was started earlier than the other groups (G2 to G4).

In conclusion, the percentage of severe short stature with severe GH deficiency (G5) is only 0.6% of IGHD. Growth failure in G5 seems to occur after birth, and the etiology of growth failure might be different from that of other patients with IGHD. Further study is necessary to elucidate the precise incidence of the abnormalities of GH gene or GH related genes in G5. Early diagnosis and hGH treatment are needed to achieve better final height.

Acknowledgments

We thank Steve Sugino for his assistance of preparation with this manuscript.

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