Clinical Characteristics, Etiologies and Pathophysiology of Patients with Severe Short Stature with Severe GH Deficiency: Questionnaire Study on the Data Registered with the Foundation for Growth Science, Japan

KUNIHKO HANEW, KATSUHIKO TACHIBANA, SUSUMU YOKOYA, KENJI FUJIEDA, TOSHIKI TANAKA, YUTAKA IGARASHI, AKIRA SHIMATSU, HIROYUKI TANAKA, TAKAKUNI TANIZAWA, AKIRA TERAMOTO, YOSHIKAZU NISHI, YUKIHIRO HASEGAWA, NAOMI HIZUKA, TAKEKI HIRANO AND KEINOSUKE FUJITA; GH Treatment Study Committee, The Foundation for Growth Science, Japan

Abstract. In this study, we sent questionnaires to doctors treating severe short stature with severe GH deficiency (GHD) (height SDS (HtSDS) below –4 and all peak GH to provocative stimuli below 2 µg/L) (abbreviated as Severe Case), and obtained effective replies of 51 cases. The clinical characteristics, etiologies, and pathophysiology of these patients were examined. Among the 51 Severe Cases no consanguinity was observed, 44 were IGHD (24 males and 20 females), 3 were GH-1 gene deletion, 2 were Pit-1 gene mutation, and 2 were achondroplasia. HtSDS in these Severe Cases was already remarkably low at 12 (–3.0) and 24 months old (–3.9), while their birth weight and birth length were within normal ranges. Among 44 patients with IGHD, 12 were isolated GHD, and the remaining 32 were combined pituitary hormone deficiency (CPHD). Pituitary MRI was undergone in 25 idiopathic GHD, and abnormal findings (pituitary atrophy, interruption of stalk, and ectopic posterior lobe) were observed in 21 patients with CPHD. More than half of these patients had the history of breech delivery. Three patients with GH-1 gene deletion showed normal pituitary MRI, whereas one of two patients with Pit-1 mutation showed pituitary atrophy and narrowing of pituitary stalk. In conclusion, Severe Cases tended to have CPHD, and the incidence of Severe Case was only 0.6% of total IGHD. Although GHD due to genetic disorders is considered to be extremely rare (0.06% of total IGHD), the incidence reaches high levels (9.8%) among Severe Cases. Growth disorders in these Severe Cases seem to occur soon after delivery. Much earlier diagnosis and hGH treatment are desirable to attain better final height in the Severe Cases. GH-1 and Pit-1 gene analyses are crucial, when genetic abnormalities other than achondroplasia are suspected.

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

Received: July 11, 2005 Accepted: December 19, 2005

Correspondence to: Dr. Kunihiko HANEW, Hanew Endocrine Clinic, 2-2-14 Kashiwagi, Aobaku, Sendai 981-0933, Japan
ABNORMALITIES of genes related to GH secretion can cause severe GH deficiency (GHD) and severe short stature [1–3]. In these patients, height SDS (HtSDS) are reported to be below –4 to –4.5, and peak GH values after conventional provocative stimuli are below 4 µg/L [4].

We have previously reported that the frequency of severe short stature with severe GHD (abbreviated as Severe Case) among cases of idiopathic GHD (IGHD), which were registered with the Foundation for Growth Science Japan, and had not received any gonadal suppression therapy, is only 0.6% (139 out of 23,110 patients), and that such growth failure occurred after delivery [5].

In addition, we speculated that the etiologies of the Severe Cases are different from the majority of other short children. The final height and final HtSDS in these Severe Cases remained the lowest even after hGH treatment, while the increase of HtSDS (ΔHtSDS) was the greatest among IGHD patients.

In this study, we sent questionnaires to doctors treating such Severe Cases, and examined the clinical characteristics, etiologies, and pathophysiology of these patients.

Materials and Methods

From March 1986 to January 1998, 23,110 patients with IGHD, who were non-organic and receiving no gonadal suppression therapy, were registered with the Foundation for Growth Science (FGS), Japan. Among them, 139 patients were severe short stature (height SDS below –4) with severe GH deficiency (all peak GH values to provocation tests: below 2 µg/L) (Severe Case) [5]. The total number of provocation tests was 58,740, and the test most employed was arginine tolerance test (25.6%), followed by insulin tolerance (25.2%), L-dopa (17.5%), clonidine (9.8%), GHRH (8.3%), glucagon (6.8%), glucagon-propranolol (5.8%), clonidine-propranolol (0.8%), and others (L-dopa-propranolol, insulin-propranolol, arginine-propranolol) (0.2%). GH value was determined using Daiichi RI IRMA (% of total kits used: 50.4%), Pharmacia IRMA (16.5%), Dainabot RIA (13.9%), Eiken RI (6.1%), Eiken IRMA (6.0%), Tosoh IEMA (1.8%), others (5.3%); the standard GH employed was pituitary derived (WHO No. 66/217 & No. 80/505) and the value was corrected referring to the GH value determined by Dainabot RIA. The corrected GH value was regarded as 60% of GH value assayed using recombinant GH as standard.

The following questionnaire was sent to physicians in charge of these patients: 1) etiologies and clinical characteristics of Severe Cases; i.e. presence of GH related gene abnormalities, achondroplasia, hypochondroplasia, Turner syndrome, chronic renal failure, and the complication of other diseases causing growth failure, 2) body height at 12 and 24 months after delivery, 3) presence of consanguinity, 4) defective pituitary hormones other than GH, 5) MRI findings of pituitary atrophy, interruption of pituitary stalk, and ectopic posterior lobe, 6) hormone replacement therapy other than hGH, 7) endocrinological data at diagnosis and at present, 8) requirement of GH-related gene analysis.

Results

Fifty-six replies were obtained from doctors of the 139 Severe Cases. Among them, 51 cases were able to be analyzed, and the remaining cases were not possible due to dropping out or missing data.

1) Etiologies and clinical characteristics of 51 Severe Cases

Among 51 Severe Cases, 44 were IGHD (24 male and 20 female) and 3 were GH-1 gene mutations (one case: type IA (6.7 kb deletion); two cases: type II (point mutation of intron 3; IVS3 + 5G → A, IVS3 + 5G → C)) [6, 7], 2 were Pit-1 gene mutation [8], and 2 were achondroplasia (Table 1). Hypochondroplasia, Turner syndrome, and chronic renal failure were not included, and complications of other diseases causing growth failure were not observed.

2) Body height of 12 and 24 months after delivery

As was reported previously [5], there were no significant differences in birth length or birth weight between Severe Cases and the majority of other patients with IGHD. The birth weight in 3 patients with GH-1 gene mutation and one patient with Pit-1 gene mutation (2,900 to 3,622 g) exceeded the mean value of the majority of IGHD (group 2, 2886.8 g) (see Ref. 5), although it was slightly low in one patient with Pit-1 gene mutation (2,580 g). However, HtSDS in these
Severe Cases decreased remarkably within the short term: i.e. it was –3.01 ± 0.40 (mean ± SEM, n = 32) at 12 months and –3.92 ± 0.41 (n = 21) at 24 months (Table 2).

3) Presence of consanguinity

Among 51 Severe Cases, 50 were sporadic and one patient with Type II GH-1 gene mutation (IVS3 + 5G → A) [6] was familial, i.e. her brother and father had the same type of gene mutation. However, there was no consanguinity in any of 51 severe cases including IGHD as well as patients with genetic disorders.

4) Defective pituitary hormones other than GH

Defective pituitary hormones were based on the judgment by each doctor, based on basal and stimulated hormone levels as well as clinical manifestations. Among 44 patients with IGHD, 12 were isolated GHD, and the remaining 32 patients were combined pituitary hormone deficiency (CPHD). In these patients with CPHD, pituitary hormone deficiency other than GH was as follow: LH, FSH, and TSH deficiencies were most frequent (9 patients); LH and FSH in 6; LH, FSH, TSH and ACTH in 4; LH, FSH, TSH, ACTH, ADH in 3; TSH in 2; LH, FSH, TSH, ACTH, PRL, ADH in 2; LH, FSH, TSH, ACTH, PRL and ADH in 1; and ADH in 1 patient (Table 3). Namely, the combined deficiency most frequently observed was gonadotropin (28/32 = 88%), followed by TSH (23/32 = 72%), and ACTH (11/32 = 34%).

5) MRI findings of the pituitary gland

Pituitary MRI was undergone in 25 idiopathic GHD, and abnormal findings (pituitary atrophy, interruption or narrowing of stalk, and ectopic posterior lobe) were observed in 21 patients. In these 21 patients, every patient had CPHD and 13 had history of breech delivery and 6 asphyxia at delivery (Table 4).

In the majority of patients (20 patients), pituitary atrophy (hypoplastic pituitary and empty sella) was observed, and pituitary stalk interruption in 13, ectopic posterior lobe in 9, and narrowing of pituitary stalk in one patient. Among 13 patients who had pituitary stalk interruption, 8 showed ectopic posterior lobe, and 4 showed lack of posterior high signal intensity. Con-
versely, pituitary stalk interruption (8 patients) and stalk narrowing (one patient) were observed in all patients with ectopic posterior lobe. In 8 patients, pituitary atrophy and ectopic posterior lobe, as well as pituitary stalk interruption or stalk narrowing, were simultaneously observed.

Four patients who showed normal pituitary and stalk morphology, two were isolated GHD; one was GH and TSH deficient; and the remaining one was GH, LH, FSH, and TSH deficient. Interestingly, the latter two cases had a history of breech delivery together with asphyxia at delivery. Patients with history of breech delivery and asphyxia did not necessarily have pituitary and stalk abnormalities.

Among 7 patients with gene mutations, 5 underwent pituitary MRI. In two patients with Pit-1 mutation, one showed normal pituitary and the other showed pituitary atrophy and narrowing of pituitary stalk on MRI. The remaining 3 patients with GH-I gene mutations showed normal pituitary morphologies (Table 4).

6) Hormone replacement therapy other than hGH

Glucocorticoid, tetraiodothyronine, and desmopressin have been replaced in every patient with ACTH, TSH and ADH deficiencies. In patients with gonadotropin deficiencies, hCG, hMG were replaced in 10 patients, estrogen and progesterone (Kaufmann therapy) in 5, and testosterone depot injection in 2 when these patients reached late pubertal ages. The remaining 8 patients were untreated because of prepubertal age or other unknown reasons, and 3 were unable to be followed (drop out).

7) Endocrinological data at diagnosis and at present

Regarding the endocrinological data at diagnosis and at present, pituitary function was not always examined precisely. However, in the reported cases no additional hormone defect according to aging was observed.

8) Requirement of GH-related gene analysis

Two out of 51 GHD patients were considered to be desirable for GH-related gene analysis. Each patient was IGHD with CPHD (#1, LH, FSH, TSH, ACTH, PRL; #2, LH, FSH, PRL). Fetal position was vertex for both, but one patient (#1) was also asphyxic at delivery. Pituitary atrophy was observed in both, and transection of stalk in one patient (#1). GH-I gene proved to be intact in patient #2.

### Discussion

After sending questionnaires to each doctor treating 139 patients of severe short stature with severe GHD, 51 effective answers were obtained. Among 51 Severe Cases, 44 were IGHD and 7 were due to genetic disorders, namely, 3 were GH-I gene mutations, 2 were Pit-1 gene mutations, and 2 were achondroplasia. In these cases, HtSDS at 12 and 24 months after delivery were already remarkably low (both below –3), indicating
that growth disorders in Severe Cases occur not in utero but after delivery since body height and body weight at delivery were not different between these patients and the majority of other IGHD [5]. The birth weights in three patients with GHI-1 gene mutation and two patients with Pit-1 gene mutation were not different with that of the majority of IGHD, as was previously reported [9].

Among 44 cases of IGHD, 12 were isolated GHD and the remaining 32 were CPHD. In CPHD, the most frequently defective hormones except GH were gonadotropins (88%), followed by TSH (72%), and ACTH (34%). Therefore, the frequency of pituitary hormone deficiencies is similar to the order of pituitary hormone deficiency due to compression by non-functioning macro-pituitary adenomas [10].

Pituitary MRI was undergone in 25 IGHD, and 23 were CPHD and only two were isolated GHD. Among 23 patients with CPHD, the majority (21 patients) showed abnormal MRI findings (pituitary atrophy, pituitary stalk interruption, and ectopic posterior lobe). The remaining two patients and two isolated GHD showed normal findings. More than half of these patients had history of breech delivery.

It is reported that patients with CPHD of idiopathic origin are apt to have pituitary hypoplasia and stalk interruption as well as history of breech delivery and hypoxemia [11]. In this survey, therefore, CPHD and abnormality of pituitary (and stalk) might arise from some perinatal insult [11]. However, we must take into consideration the possibility of PROP-1 and Pit-1 gene mutations, which show CPHD, since such patients infrequently show hypoplastic pituitary [11–14].

Seven Severe Cases were due to genetic disorders, i.e. 3 GH-1 gene mutation, 2 Pit-1 mutation, and 2 achondroplasia cases. The distributions of gene abnormality were different with the previous report [11], where the number of patients with GH-1 gene mutation was 4, Pit-1 mutation 1, PROP-1 mutation 5, and GHRH-R (receptor) gene mutation 5 among 76 patients with isolated GHD and CPHD. Although, the exact reason is not clear, gene mutations of PROP-1 and GHRH-R seem to be very rare in Japan [15, 16].

Three patients with GH-1 gene mutation showed normal pituitary MRI. Related to this, Osorio et al. [11] reported that 3 patients with 6.7 kb GH-1 deletion showed normal MRI of pituitary and stalk, whereas one patient with 7.6 kb GH-1 deletion showed hypoplastic pituitary and normal stalk, but ectopic posterior lobe.

In this study, one of two patients with Pit-1 mutation showed pituitary atrophy together with narrowing of pituitary stalk. This is compatible with previous reports as has already been mentioned.

In every patient with CPHD, glucocorticoids, tetraiodothyronine, and desmopressin were replaced. It is noteworthy that two patients with CPHD who showed ectopic posterior lobes on MRI, which indicates functional integrity of hypothalamic ADH neurons, are receiving DDAVP. Related to this, similar cases have been reported previously [17, 18]. It is possible that the releasing or secretory mechanism of ADH by exocytosis into the blood stream may be impaired at the ectopic posterior lobe, since postoperative transient diabetes insipidus occurs even in the presence of ectopic posterior lobe [19].

Patients with gonadotropin deficiencies received gonadal stimulation therapy, e.g. Kaufmann therapy or testosterone depot injection, when these patients reached late pubertal ages. These treatments are apt to be started late to keep bone ages younger for attaining better final height. Therefore, some patients were not treated by these methods due to prepubertal age or for unknown reason.

In 51 Severe Cases, no consanguinity of parents was observed. However, only one patient with Type II GH-1 gene mutation was familial. This is a quite different observation with previous reports that patients with gene mutations are frequently familial or consanguineous [4, 11].

Two out of 44 IGHD patients were considered to be desirable for GH-related gene analysis and in one of the two the GH-1 gene was proved to be intact. GH related genes in the remaining 42 IGHD was regarded by their doctors to be intact (from lack of small face, frontal bossing, saddle nose, and anti-GH antibody during hGH treatment), although the possibility of genetic abnormality in a gene not studied cannot be excluded.

Accordingly, if we assume that these 42 patients as IGHD, and the two cases that required further gene analysis had no gene abnormality, the incidence of GH-related gene abnormalities among total IGHD is quite low (5/51 × 139/23,110 = 0.06%), while the incidence among the Severe Cases is considerably high (5/51 = 9.8%). The prevalence of GH-1 gene abnormality actually determined is 6% (3/51), and is not substantially different from previous reports [4, 20].

It is noteworthy that the majority of the Severe Cases was not due to genetic abnormality even though
their growth failure occurred soon after delivery. However, the following possibilities cannot be excluded: that patients without severe GHD have some GH-related gene abnormalities, and that the other severe cases, who were considered non-genetic, may have a genetic abnormality that was not detected.

As morphological abnormalities of pituitary were observed in many of the Severe Cases, perinatal insult or abnormality of some other factors participating hypothalamo-pituitary development has been taken into consideration [11]. Further examination, including genetic analysis, is required in these cases to clarify the etiology of such morphological abnormalities.

In conclusion, the ratio of Severe Cases, who were non-organic and receiving no gonadal suppression therapy and were registered with the Foundation for Growth Science (FGS), Japan, is only 0.6% of IGHD. In addition, GHD with genetic disorders were considered to be extremely rare (0.06%) among total IGHD, although the ratio increases to 9.8% among Severe Cases. Growth disorders in these Severe Cases seem to occur soon after delivery. Much earlier diagnosis and hGH treatment is desirable to attain better final height in the Severe Cases. GH-1 and Pit-1 gene analyses are important when genetic abnormalities other than achondroplasia are suspected.

Acknowledgment
We thank Steve Sugino for assistance in manuscript preparation.

References