Development of Growth Hormone and Adrenocorticotrophic Hormone Deficiencies in Patients with Prenatal or Perinatal-Onset Hypothalamic Hypopituitarism Having Invisible or Thin Pituitary Stalk on Magnetic Resonance Imaging

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Abstract. A gradual loss of anterior pituitary hormones is suspected in patients treated with irradiation due to brain tumors. Development of growth hormone deficiency (GHD) with age has been documented in patients with idiopathic GHD. A gradual loss of adrenocorticotrophic hormone (ACTH) secretion has been also shown in a patient with severe GHD and an invisible pituitary stalk on magnetic resonance imaging (MRI). The purpose of this longitudinal and cross-sectional study was to evaluate the gradual loss of growth hormone (GH) and ACTH in a homogeneous group of patients with hypopituitarism. Twenty-eight patients (23 males, 5 females) from four hospitals were diagnosed as having prenatal or perinatal-onset hypothalamic hypopituitarism. They had an abnormal pituitary stalk on MRI (invisible in 18 patients, thin in 10 patients) without any other organic disease of the brain. Each patient had GHD upon initial evaluation. Height (n=20) was analyzed as standard deviation score (SDS). Longitudinal (n=8) and cross-sectional (n=28) GH secretion capacity was evaluated by GH peaks, in response to insulin tolerance test (ITT) and growth hormone releasing factor test (GRF test). Longitudinal (n=10) and cross-sectional (n=28) ACTH secretion capacity was evaluated by cortisol peaks in response to ITT. Height SDS decreased each year in all the untreated patients after birth. GH peaks decreased gradually with age. Longitudinal data showed decreased GH peaks with age in seven out of eight patients using ITT and in all four patients using GRF tests. Cortisol peaks also decreased gradually together with signs and symptoms for adrenal deficiency such as general fatigue. Cortisol peaks of less than 414 nmol/L (15 µg/dl) in response to ITT were seen in 24% of the tests before age 10 and 56% before age 25. In conclusion, GHD and ACTH deficiency developed gradually in patients with prenatal or perinatal-onset hypothalamic hypopituitarism who had invisible or thin pituitary stalks examined by MRI.

Key words: GHD, ACTH deficiency, Hypopituitarism, Invisible pituitary stalk, MRI

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cretion has been also documented in patients with idiopathic GH deficiency (GHD) [2–4]. In a previous study, Hasegawa and coworkers demonstrated a gradual loss of adrenocorticotrophic hormone (ACTH) secretion in a patient with severe GHD and invisible pituitary stalk on magnetic resonance imaging (MRI) [5]. However, there has been only one study of the longitudinal function of the anterior pituitary hormones in which the subjects were patients treated with irradiation [1]. Past studies were either based on the findings from one or two patients [2–5] or based on relatively heterogeneous subjects with various accompanying diseases and therapies including irradiation [1, 3].

The purpose of this study was to evaluate the pattern of GH and ACTH secretion over 10–20 years using a homogeneous group of patients who suffered from prenatal or perinatal-onset hypothalamic hypopituitarism, having invisible or thin pituitary stalk on MRI without any other apparent brain abnormality or a history of irradiation.

Participants and methods

Participants

Twenty-eight patients (23 males, 5 females) were evaluated in the authors' hospitals, in Tokyo, Nagasaki, Hiroshima, and Kanagawa. Inclusion criteria for this study were (1) prenatal or perinatal-onset hypopituitarism including GHD, (2) invisible or thin pituitary stalk on MRI, and (3) no other brain abnormality (Table 1). A diagnosis of hypopituitarism was made when the patients were on average 3.4 years old (SD=1.5) due to growth retardation.

Prenatal or perinatal-onset of hypopituitarism was suspected for each patient because all 28 patients had a history of complicated delivery such as breech presentation or asphyxia and exhibited decreased growth velocity during infancy. In addition, four had prolonged neonatal jaundice, two microphallus, and one neonatal hypoglycemia. Microphallus is considered to be a sign of prenatal-onset. No other minor anomalies besides microphallus were noted in any subjects.

All the patients had GHD upon initial evaluation using the standard GH provocative tests such as insulin tolerance tests (ITT) or arginine tolerance tests.

All GH peaks for the provocative tests were less than 7 $\mu\text{g/L}$. At their last visit (ages ranging from 10 to 24 years), 24 patients had thyroid stimulating hormone (TSH) deficiency, 18 ACTH deficiency, 19 gonadotropin deficiency, and 3 diabetes insipidus. All of these were treated appropriately.

In all patients the pituitary stalk was either invisible ($n=18$) or thin ($n=10$) on MRI. An ectopic posterior pituitary lobe was present in 23 patients. The radiologists at each site judged that the anterior pituitary was either absent or small in 20 of the patients. In the remaining eight patients the size of the anterior pituitary was either not recorded ($n=4$) or considered normal ($n=4$). Because of the nature of the multicenter study, we could not do further analytical evaluation on the size of the pituitary stalk or the pituitary. No other brain abnormalities were observed on MRI. Obesity more than 20% for ideal weight was not seen in any of the participants.

Methods

Measurements of height and other medical examinations were performed three or four times every year. Height was measured in a conventional way and heights of untreated patients were evaluated using height standard deviation scores (Ht SDS) based on Japanese norms [6]. $\Delta\text{Ht SDS at age X years} = \text{Ht SDS at age X years} - \text{Ht SDS at birth}$. Eight patients with birth weight less than 2500 g were excluded from the height analyses because growth can be affected by low birth weight.

Longitudinal height SDS was evaluated auxologically in 20 patients before starting GH treatment. Longitudinal hormonal tests were done using both ITT and GRF test. Initial endocrine tests were done before the patients began to receive GH treatment. The second tests were done two to eight years after initial treatment, following a suspension of the GH treatment or discontinuation of GH therapy for at least three weeks. GH for ITT was analyzed at 0, 15, 30, 45, 60, 90, 120 min after 0.05–0.1 U/kg of intravenous insulin injection. GH for GRF test was measured at 0, 15, 30, 45, 60, 90, 120 minutes after 1 $\mu\text{g/kg}$ of intravenous GRF injection.

The presence of symptoms compatible with ACTH deficiency, such as fatigability, weakness, or hypoglycemia was recorded three or four times every year.

ACTH secretion capacity was evaluated longitudi-

Table 1. The clinical profile of the participants

Patient No.	sex	birth weight (g)	history of complicated delivery	asphyxia	other complications	abnormalities on MRI			deficient pituitary hormones	auxological data	age at diagnosis	age at latest visit
						stalk	posterior lobe	anterior lobe				
1	M	3450	B	×		I	I	S	GH, TSH, ACTH, Gn	○	8:02	16:00
2	M	2650	B	×		I	E	S	GH, TSH, ACTH	○	4:02	10:07
3	M	2400	B	○	protracted jaundice, hypoglycemia	I	E	U	GH, TSH, Gn		5:05	18:07
4	M	2815	F	○	birth paralysis	I	U	U	GH, TSH	○	9:02	15:04
5	M	2278	B	○		I	E	U	GH, TSH, ACTH		3:07	7:03
6	M	2950	B	○		I	E	N	GH, TSH, ACTH, Gn, ADH	○	4:00	19:03
7	M	3100	B	○		T	E	S	GH, TSH, ACTH, Gn, ADH	○	7:09	24:05
8	M	3420	B	○		T	N	S	GH, TSH, ACTH, Gn	○	8:10	23:07
9	M	4000	B	○		I	E	S	GH, TSH, ACTH, Gn	○	8:05	18:10
10	M	3770	B, V	×		I	E	S	GH, TSH	○	3:06	12:02
11	M	3330	B	○		I	E	S	GH, TSH, ACTH, Gn	○	8:07	15:05
12	M	3080	F	○		I	E	S	GH, TSH	○	5:03	11:11
13	M	2800	B	○		T	E	S	GH, TSH, ACTH, Gn	○	3:07	29:00
14	M	2950	B, Fd	○		I	E	A	GH, TSH, ACTH, Gn	○	9:09	27:06
15	M	3520	V	×		T	N	S	GH, TSH	○	8:05	21:04
16	M	4200	F	○		T	N	N	GH	○	3:07	17:11
17	M	3440	B	○		T	E	S	GH, TSH, ACTH, Gn	○	3:05	23:11
18	M	2430	F	○	protracted jaundice	T	E	N	GH		4:02	21:02
19	M	3000	B	○		I	E	A	GH, TSH, ACTH, Gn	○	7:11	26:05
20	M	2550	B	○		I	E	S	GH, TSH, ACTH, Gn, ADH	○	3:00	24:09
21	M	3475	B, V, Fd	○	microphallus	T	E	A	GH, TSH, ACTH, Gn	○	6:11	16:07
22	M	2680	B	×	microphallus	I	E	A	GH, TSH, ACTH, Gn	○	7:07	17:05
23	M	2000	B	○		T	E	A	GH, TSH, ACTH, Gn, ADH		5:06	16:07
24	F	1000	B	unknown		I	E	U	GH, TSH, ACTH, Gn		5:09	15:09
25	F	3050	B, Fd	○		I	E	S	GH, TSH, ACTH, Gn		11:02	24:06
26	F	2550	F	○	protracted jaundice	I	E	N	GH, TSH, Gn	○	4:03	18:02
27	F	2530	F	○		I	E	S	GH, TSH, ACTH, Gn		5:07	23:00
28	F	865	B	○	protracted jaundice	T	E	N	GH		10:03	14:05

B; breech presentation F; foot-presentation V; vacuume extraction Fd; forceps delivery I; invisible T; thin E; ectopic N; normal A; absent S; small U; unknown

nally and cross-sectionally using ITT. Initial test of ACTH secretion capacity was done for all the subjects at the time when diagnosis of GHD was first made. Longitudinal data was available for 10 of the 28 patients before they began to take a supplemental dose of hydrocortisone (2.5–5.0 mg/m²/day). ACTH secretion capacity was also evaluated following suspension of cortisol for one to two days.

GH levels were measured using radioimmunoassay (RIA, Eiken, Tokyo) and immunoradiometric assay [7] (IRMA, Eiken, Tokyo) in five hospitals. GH levels measured by RIA were converted into IRMA values [7]. Sensitivity of IRMA assay was 0.05 µg/L. Intra- and inter-assay variation was 2–6% at three different concentrations.

ACTH and cortisol levels were measured using commercially available assays. Sensitivity of ACTH measurements was 5 pg/ml (1.1 pmol/L) and sensitivity of cortisol was 0.64 µg/dl (17.7 nmol/L). Intra- and interassay covariation was 3–7% for both assays.

Statistical analysis and ethics

Wilcoxon signed-ranks tests were used to compare Ht SDS at different ages. Chi-square test was used to test significance of cross-sectional decrease of cortisol secretion. Statistical significance was set at $P < 0.05$. Appropriate informed consent was taken from the participants and/or their parents.

Results

All 28 patients showed gradual growth retardation on each growth curve before starting GH treatment. Twenty of the 28 subjects (excluding prematures, <2500 g at birth) studied had Ht SDS below the -2.0 SDS level by age three. Changes in Ht SDS after birth (Δ Ht SDS) are shown in Fig. 1. Δ Ht SDS was significantly different between the ages of 0 and 1 ($p < 0.01$), 3 and 1 ($p < 0.01$), 5 and 3 ($p < 0.01$), and 7 and 5 ($p < 0.01$), being consistent with gradual growth retardation with age.

GH peaks from the provocative tests showed a gradual decrease over time. GH peaks from ITT are shown in Fig. 2; GH peaks in seven out of eight patients who were studied longitudinally decreased with age. Similar patterns were observed from GRF test for all four patients for whom the test was done twice over a 4 to 8 year period; GH peak after GRF decreased from 23.9 (age 8) to 4.8 ng/ml (age 16), from 32.2 (age 4) to 11.2 ng/ml (age 11), from 7.3 (age 9) to 3.4 ng/ml (age 15) and from 9.6 (age 3) to 5.9 ng/ml (age 7) in patient 1, 2, 4 and 5, respectively. GH peaks from GRF tests were higher than those from ITT, suggesting hypopituitarism is functionally hypothalamic; for example, the GH peak after ITT was 3.4 ng/ml in patient 1 at age 8 and 2.4 ng/ml in

patient 2 at age 4 years (compare the GH peaks after GRF at the same age as described above).

Except for patient 6, none of the subjects had severe signs or symptoms of adrenal insufficiency. Patient 6 had an overt crisis of adrenal insufficiency at age 12 year 7 months [5]. There were no severe signs or symptoms of adrenal insufficiency in the remaining patients who were finally treated with hydrocortisone. General fatigue and poor activity were documented at the start of hydrocortisone treatment in the remaining patients.

Cross-sectional and longitudinal analyses showed that peak cortisol levels decreased with age as described below. Peak cortisol levels from ITT are shown in Fig. 3; data obtained during cortisol replacement therapy with one to two day suspension of hydrocortisone treatment and all the longitudinal data were included and the total number of the data was 50. Twenty-four percent (12 out of 50) of the levels of cortisol peaks at age 10 or less were less than 15 μ g/dl (lower limit of normal for peak cortisol response to ITT in our laboratory [5]). Fifty-six percent (28 out of 50) of cortisol peaks at age 25 or less were less than 15 μ g/dl. The difference in percentages between the two groups was statistically significant by chi-square test.

Longitudinal data from six of the ten patients in Fig. 3 also showed a gradual loss of ACTH secretion capacity with age. The data of the remaining four patients fluctuated over time with peak cortisol levels being both above and below 15 μ g/dl; the fluctuation was definite in three subjects (patients 2, 3, 5) and was equivocal in one of the patients (patient 4). All four patients were treated with l-thyroxine at the time of the test for adrenal function.

There was no clear relationship between peak cortisol levels and thyroid functions in these patients. In patients 3 and 5, the basal cortisol levels and peak cortisol levels from ITT were higher when thyroid function was decreased compared to when it was normal, which is consistent with previous reports [8–11] (patient 3: cortisol peak levels were 10.8 μ g/dl when free triiodothyronine level was 5.6 pg/ml (8.6 pmol/L) and 21.8 μ g/dl when free triiodothyronine level was 1.6 pg/ml (2.5 pmol/L) at age 18 years; patient 5: cortisol peak levels were 29.1 μ g/dl when free triiodothyronine level was 1.82 pg/ml and 17.1 μ g/dl when free triiodothyronine level was 4.8 pg/ml at age 3). However, in patient 5, fluctuation at age 7

Fig. 1. Δ Ht SDS at the age of X years
 Δ Ht SDS was defined as follows:
 Δ Ht SDS at the age of X years = Ht SDS at the age of X years - Ht SDS at birth. The numbers of the participants who did not start GH treatment at each age were 20 at 0 to three years, 19 at four years, 16 at 5 years, 12 at six years, 11 at seven years, eight at eight years, and two at nine years. Bar at each age mean $\pm$ 1 SD.

Fig. 2. GH peaks of ITT

GH peak decreased generally with age. Eight subjects were studied longitudinally. Note that one ng/ml of GH is equal to one $\mu\text{g/L}$ of GH.

was not correlated with thyroid status (data not shown). There were also fluctuations in peak cortisol levels in patients 2 and 4 but without any overt change in thyroid status.

The variation of hypoglycemia after insulin infusion cannot fully explain the fluctuations. All levels of nadir blood sugar levels after ITT were below 40 mg/dl (2.2 mmol/L). In patient 2, the fluctuation at age 6 may be related with the variation of the nadir blood sugar levels; the lowest blood sugar level after ITT at age 6 in this subject was extremely low, 15 mg/dl, which may be the reason for the higher cortisol peak compared with cortisol peaks after ITT at age 5 or 7.

The timing of evolution of ACTH deficiency was roughly correlated with the severity of the MRI findings. Five of the six patients with peak cortisol levels lower than 15 $\mu\text{g/dl}$ by age 10 had invisible pituitary stalk and small anterior pituitary on MRI. The other patient had a thin pituitary stalk and small anterior pituitary on MRI.

Discussion

Hypopituitarism in the 28 participants in this study is due to hypothalamic rather than pituitary dysfunction. This hypothesis of a hypothalamic origin of the hypopituitarism is supported by the following three facts. First, a discrepancy between the initial results of GRF tests and ITT was seen in nine of the patients (part of data shown), that is, relatively high GH peaks with GRF tests despite low GH peaks with ITT. Second, the results of thyrotropin-releasing hormone (TRH) tests done for 14 patients showed typical hypothalamic hypothyroidism, that is, delayed and exaggerated response of TSH for all 14 patients (data not shown). Finally, in these patients the more severe the findings with MR, the earlier the decrease of ACTH secretion capacity appeared. Although the MRI findings on the pituitary stalk reflect either a primary abnormality of the stalk or a secondary abnormality from insufficient stimulus of the hypothalamic hormones, hypopituitarism is functionally hypothalamic in either case.

Fig. 3. Cortisol peaks of ITT in the total subjects

Cortisol peak decreased generally with age. Ten patients were studied longitudinally. Note that one $\mu\text{g/dl}$ of cortisol is equal to 27.6 pmol/L of cortisol.

A gradual loss of GH was demonstrated by laboratory data, together with a decrease in height with age, in the present study. Although we cannot completely deny the possibility of the decline due to two different assays (even after the conversion as stated before) or that of the decline associated with hypogonadism, the gradual loss of GH with age is well correlated with the gradual loss of ACTH with age. It has been reported that physiological GH secretion in normal subjects does not decrease with age during childhood [12, 13], but does increase during puberty. The gradual loss of GH may be due to the progressive atrophy of the GH-producing cells in the anterior pituitary because the second GH peak with GRF tests was lower than the initial one in four patients who were analyzed longitudinally. The gradual atrophy of GH-producing cells may reflect a long-standing absence of adequate GRF stimulation through the pituitary stalk.

A gradual loss of ACTH was documented by cross-sectional and longitudinal laboratory data in

more than half of the patients as described in detail, together with clinical signs and symptoms such as fatigue and poor activity. Peak cortisol levels in response to ITT were not decreased with age in the reference group [5]. Development of ACTH deficiency may be due similarly to an inadequate stimulus of CRF for 10 to 20 years.

The reason for the fluctuations in peak cortisol levels is not known. First, an interaction between cortisol levels and thyroid hormone levels cannot fully explain the fluctuation. Second, the fluctuations in peak cortisol levels may be a limitation of the provocative test, such as a variation in the severity of hypoglycemia induced by insulin and that in the reaction of CRH-ACTH-cortisol axis after hypoglycemia. Finally, the fluctuations seen in this study may reflect insufficient ACTH secretion capacity.

The present results showed that GH secretion may be less sustained than ACTH secretion after the prenatal or perinatal-onset in the subjects. This order of susceptibility is consistent with the order of

the previous report in patients with brain tumor and irradiation [1].

ACTH deficiency should be analyzed in patients with hypopituitarism due to hypothalamic causes, five to ten years after the onset of hypopituitarism. Furthermore this analysis should be repeated even after normal ACTH secretion capacity is documented. The following two points should be kept in mind. First, ACTH deficiency in some of the patients can occur abruptly without any prior overt clinical signs or symptoms before. Patient 6 presented in a state of shock. Second, the fluctuation of peak cortisol levels with ITT in this study indicates the necessity of repeating ITT at regular intervals to verify the diagnosis of ACTH deficiency since this fluctuation may reflect ACTH deficiency as speculated above.

In order to confirm ACTH deficiency in these patients, follow-up by morning serum cortisol levels or 24 hour urinary free cortisol assay is probably useful, although we do not have data supporting this method of follow-up. Repetition of ITT or other tests for adrenal function such as CRH test may require them to be done in order to finally reach the diagnosis of ACTH deficiency.

The timing of cortisol supplement therapy is not entirely clear in patients with suspected laboratory findings for ACTH deficiency but no overt clinical signs or symptoms. Hydrocortisone therapy during stressful periods (30–60 mg/m²) or daily therapy of low dose hydrocortisone (2.5–5.0 mg/m²) was started in our unit in these patients (Tokyo Metropolitan Kiyose Children's Hospital).

In conclusion, GHD and ACTH deficiency gradually developed in patients who had abnormalities of the pituitary stalk on MRI following perinatal complications, comprising the most common group of patients with hypopituitarism during childhood. The initial sign of ACTH deficiency in some of the patients was shock. Any patients with hypothalamic hypopituitarism can show these kinds of gradual patterns of GH and ACTH deficiencies and also a similar pattern of LH, FSH and/or TSH deficiency.

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