Demographic characteristics of children with growth hormone deficiency from 1996 to 2015 in Japan: 20 years of data from the foundation for growth science in Japan

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Abstract. Growth hormone (GH) deficiency (GHD) in children is a heterogeneous condition that includes several entities of various severities. GH treatment has been affected by various factors. Because comprehensive analyses for Japanese children with GHD over time are scarce, we investigated the baseline characteristics of patients with GHD at the start of GH treatment between 1996 and 2015 using data from the Foundation for Growth Science in Japan. During the registration period, 19,717 subjects were determined to be eligible for GH treatment as GHD. Overall analyses revealed that there were twice the number of male patients as female patients, and the etiology was idiopathic in 91.1%, central nervous system (CNS) tumor at the hypothalamus–pituitary area in 1.7%, CNS tumor distant from the hypothalamus–pituitary area in 0.68%, other tumors in 0.91%, congenital CNS malformations in 0.83%, and other diseases in 1.1% with their specific characteristics. The latest average age, height standard deviation score (SDS), insulin-like growth factor–1 SDS, and proportion of severe GHD at GH treatment initiation were 8.8 years, –2.76, –1.42, and 19.5%, respectively. The proportions of breech delivery and asphyxia gradually decreased, whereas that of caesarean section gradually increased during the registration period with the latest values of 2.2%, 4.9%, and 19.5%, respectively (all analyses: $p < 0.0001$). In contrast, the proportion of idiopathic GHD with breech delivery seemed to reach the lowest level among those with a birth year before 2000. This study identified the characteristics and changes of patients with GHD over 20 years.

Key words: Growth hormone, Growth hormone deficiency, Breech delivery, Asphyxia, Nationwide cohort

GROWTH HORMONE (GH) deficiency (GHD) in children is a very heterogeneous condition that includes several entities and various severities. GH replacement is a vital and standard treatment for those with GHD and is effective in improving adult height [1-4]. In Japan, a pituitary-extracted human GH (phGH) was approved and the medical fee was covered by health insurance and the Grant-in-aid Program for Chronic Diseases in Childhood, in 1975, but the supply was limited so that GH treatment was restricted to selected patients with severe GHD, i.e., those with a height standard deviation score (SDS) of ≤–3.0 and maximum peak GH levels of ≤5 μg/L in two GH stimulation tests. After the advent of an unlimited supply of methionyl recombinant human GH (mhGH) in 1986 and authentic recombinant human GH (rhGH) in 1988, the eligibility of patients with GHD for GH treatment was expanded to those with milder severities.

The universal health insurance system in Japan is compulsory for all residents who have lived for ≥3 months. The system covers 70%-90% of the medical cost, based on age and employment status of the resident or that of the household head in case of children [5].
Since hGH is very expensive, GH treatment in Japan has been supported by the Grant-in-aid Program for Chronic Diseases in Childhood, a medical aid program (currently, the Medical Aid for Chronic Pediatric Diseases of Specified Categories by the Intractable/Rare Diseases) sponsored by the Ministry of Health, Labor, and Welfare (MHLW), which was launched in 1974. Initially, all patients with GHD who had obtained authorization for GH treatment from the Foundation of Growth Science (FGS) in Japan were eligible for support under this program. However, in 1997 strict criteria for eligibility were introduced because the cost of GH treatment had significantly increased to 40% of the total medical costs covered by the program after the advent of rhGH [6]. Eligible patients were restricted to those with severe or moderate GHD, and the height SD score was revised from ≤−2 to ≤−2.5 as an eligibility criterion in patients without organic abnormalities. At the same time, the MHLW issued a notice that the decision on GH treatment could be reached by the committee of each prefecture without the need for the FGS authorization, which resulted in a reduction of the number of patients with GHD registered with the FGS. In addition, the second revision of the criteria adopted in 2005 established a serum insulin-like growth factor 1 (IGF-1) level of <200 ng/mL (<150 ng/mL for those younger than 5 years of age) as the cutoff value for treatment eligibility. Notably, these revisions were introduced solely based on socioeconomic concerns and are not included in the academic GHD criteria [7], and a height SD score of ≤−2 is a diagnostic criterion for GHD. Therefore, after 1997 patients with GHD and a height SD score between −2 and −2.5 in the absence of organic abnormalities were expected to pay a certain portion of the medical charges.

On the other hand, local governments have provided medical support programs for children since the 1960s and target ages have been gradually expanded by many local governments to currently include children ≥15 years in age. In fact, the proportion of local governments that established a target age of ≤15 years has increased from 1% in 2001 to 80% in 2016 [8]. In patients with GHD who are eligible for this program, GH treatment can be available without medical charges.

The FGS was founded in 1977 to collect pituitary glands in Japan to send them to countries where phGH was produced for the compensation of its shortage and to select eligible patients for GH treatment by using diagnostic criteria for GHD [6, 9]. After mhGH became available in 1986, the FGS stopped collecting pituitary glands, but the registration system has continued for the proper use of GH. Since then, the FGS has been monitoring the use of GH through its registration system and determines candidate eligibility for GH treatment using the diagnostic criteria for GHD, Turner syndrome, and other pertinent disorders [9]. Physicians are encouraged to register each candidate for GH treatment at the FGS using an application form that includes patient baseline characteristics, such as pretreatment anthropometric measurements, height, GH stimulation test results, serum IGF-1 concentration, GHD etiology, thyroid function, bone age, complications, perinatal history, presence of puberty, presence of cranial irradiation, and evidence of informed consent from each subject regarding the use of data for scientific purposes. Notably, almost all the patients with GHD were registered with the FGS until 1997 because the FGS authorization was mandatory for the approval of the Grant-in-aid Program for Chronic Diseases in Childhood; however, the FGS registration rates have been decreasing since then, which were 98.3%, 61.8%, 52.6%, 34.9% and 24.2% of all patients with GHD in 1998, 2000, 2005, 2010 and 2015, respectively, as calculated from the data compiled by the grant-in-aid program [10]. Importantly, the FGS has the largest database of patients with GHD in Japan.

Early studies showed that the proportion of patients with breech delivery and/or asphyxia was significantly higher among those with idiopathic GHD or multiple pituitary hormone deficiency than in the healthy population [11-15]. It is suggested that perinatal insult caused hypothalamic dysfunction, leading to hypopituitarism, including GHD [11-15]. On the other hand, the number of cases with GHD associated with breech delivery seems to have declined recently in clinical practice, possibly due to the advancement of perinatal practices. Indeed, elective caesarean section has been more frequently applied for babies with breech presentation than in elective vaginal delivery, especially after a report in 2000 that indicated the former was better than the latter for term fetuses in the breech presentation (the term breech trial) [16]. In fact, caesarian section for breech presentation in Japan has significantly increased from 1981 to 2010, with rates of 41.9%, 70.4%, 86.7%, and 94.4% in 1981, 1990, 2000 and 2010, respectively, according to the data from the Tokyo Operation group [17]. Therefore, there is a possibility that the baseline characteristics of idiopathic GHD have changed over time in terms of neonatal histories, especially after 2000. However, no reports have investigated these changes using a substantial number of patients after the report summarizing the data in the FGS between 1986 and 1995 [18].

In this study, we first analyzed the overall baseline characteristics of patients with GHD at the start of GH treatment during the 20 years between 1996 and 2015 using the data compiled in the FGS. Next, we analyzed changes in these characteristics over specific time periods.
defined according to the changes introduced to the eligibility criteria for the Grant-in-aid Program for Chronic Diseases in Childhood. Finally, we investigated whether baseline neonatal history and characteristics changed or not in patients with idiopathic GHD who were born at full term after 2000.

Materials and Methods

Subjects

Subject data from 1996 to 2015 were retrieved from the FGS database. During this period, 22,594 subjects with informed consent were registered in this database as candidates for GHD, of which 19,717 were determined to be eligible for GH treatment. The subjects’ diagnoses were confirmed by reviewing application forms according to the criteria established by the Study Group of Hypothalamo-Pituitary Disorder of the MHLW [7]. In addition, subjects were classified into three categories based on GHD severity depending on the results of their GH provocation tests following the diagnostic criteria. Severe GHD was defined as patients with maximum peak GH levels ≤3 μg/L; moderate GHD, those with maximum peak GH levels ≤6 μg/L, except for those with severe GHD; and mild GHD, those with maximum peak GH levels >6 μg/L but with at least two peak GH levels ≤6 μg/L. It is of note that the cutoff peak GH levels for severe and moderate/mild GHD had formerly been 5 μg/L and 10 μg/L, respectively, but an attempt to standardize the GH assays was made in 2005, which changed the cutoff values to the ones described above [19]. Subjects were also classified into seven categories according to their GHD etiology via a detailed review of application forms: idiopathic GHD, central nervous system (CNS) tumor at the hypothalamus–pituitary area (e.g., craniopharyngioma, germinoma, pituitary adenoma, etc.), CNS tumor distant from the hypothalamus–pituitary area (e.g., teratoma, medulloblastoma, glioma, etc.), other tumors (e.g., leukemia, lymphoma, neuroblastoma, etc.), congenital CNS malformations (e.g., septo-optic dysplasia, pituitary hypoplasia, invisible stalk, Rathke’s cyst, empty sella syndrome, etc.), other diseases (e.g., congenital syndrome, chromosomal abnormality, kidney disease, etc.), and “not described.” Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Height/length and BMI SDSs were calculated using Japanese standards for normal children by sex and age [20-22]. Insulin-like growth factor 1 (IGF-1) SDS was also calculated using Japanese standards [23].

Methods

We investigated the baseline demographic characteristics in children with GHD in Japan from several perspectives by reviewing their application forms at the FGS. First, all data were analyzed according to sex and etiologies to show the overall baseline characteristics of patients with GHD in Japan during the 20 years of the study period. Next, to explore the changes in baseline characteristics of patients with GHD over the study period, analyses were conducted by dividing the subjects into groups based on three defined time periods according to the changes in the criteria for the Grant-in-aid Program for Chronic Diseases in Childhood. In fact, when the annual time course of the registered number at the FGS was constructed, apparent declines were detected in response to the abovementioned changes in criteria (Supplemental Fig. 1). We also noticed that the number of registered patients has been decreasing gradually since around 2010, which might be due to the gradual increase in the availability of medical support programs for children provided by local governments. Therefore, the following three time periods were used to categorize the subjects in the current study: 1996–1997, 1998–2004, and 2005–2015. Finally, we sought to explore whether the baseline characteristics of patients with idiopathic GHD changed in response to the recent trends in the mode of delivery, in which elective caesarean section has been applied more often for babies with breech presentation than in elective vaginal delivery after the term breech trial in 2000 [16]. In the final analysis, we focused on subjects with idiopathic GHD who were born at full term (gestational age: 37–41 weeks), as perinatal complications are more often observed in premature or postmature deliveries. Then, we compared demographic characteristics between those born in 2000 or before 2000 and those born after 2000. However, one bias of this analysis is that the registration period for each group is the same (i.e. 1996–2015) although subjects born earlier have more chance to be registered, so the nature of the population is different between two groups. Recently born subjects are supposed to be registered in younger ages than those born earlier; therefore, there are more subjects born in 2000 or before 2000 than those after 2000. To overcome this bias, an additional analysis was performed by extracting subjects in equal condition for each group. To create the equal condition between two groups, we took into consideration both birth year and registration period. Therefore, we extracted two groups as follows: those born between 1996 and 2000 and then registered until 2010, and those born between 2001 and 2005 and then registered until 2015.

This study was performed with approval from the Ethics Committee of Teikyo University School of Medicine (approval No. 17-072).
Statistical analyses

The results are expressed as means ± SD or frequencies and percentages. Comparisons of groups were performed using one-way analysis of variance (ANOVA) or unpaired t test for continuous variables, and chi-square test or Fisher’s exact test for discrete variables. When the result was significant in continuous variables, the differences between groups were subjected to two-by-two comparisons with post hoc Bonferroni correction for multiple comparisons. Trend tests for discrete variables were analyzed with Cochran–Armitage test over time. All analyses were conducted using JMP 12 (SAS Institute Inc., Cary, NC, USA), and p values <0.05 were considered statistically significant.

Results

Table 1 summarizes the baseline characteristics of patients with GHD in this cohort by sex. In the overall cohort, the average age, height/length SDS, BMI SDS, IGF-1 SDS, and proportion of severe GHD were 9.1 years, –2.76, –0.44, –1.23, and 16.4%, respectively. Although GHD is associated with truncal obesity, average BMI SDS was not high in this study, which was consistent with previous reports, considering that more than 90% of patients were idiopathic in this cohort [24-26]. Average birth length and weight were a little smaller than those of normal population as reported [27]. The number of patients and baseline characteristics were significantly different between male and female patients. There were approximately twice the number of male patients than female patients, which was identical to a previous report using the FGS data between 1986 and 1995 [18]. Age, height/length SDS, IGF-1 SDS, birth length, birth weight, and proportion of severe or idiopathic GHD were significantly lower in female patients than in male patients (all analyses: p < 0.0001), whereas parent height, ratio of bone age to chronological age, and proportions of organic GHDs or other diseases with concomitant GHD and that of cranial irradiation were significantly higher in female patients than in male patients (p = 0.026, p = 0.013, p < 0.0001, p < 0.0001, p < 0.0001, and p < 0.0001, respectively). Female subjects were younger and smaller than male subjects at the start of GH treatment, which is consistent with a universal tendency [28]. On the other hand, the proportions of breech delivery, caesarean section, or asphyxia were not different between the sexes, and age distributions were bimodal in both male and female subjects (Fig. 1).

Table 2 presents the comparisons of baseline characteristics among the defined GHD etiologies, and Fig. 2 shows the age distributions in each GHD etiology. The etiology was idiopathic in 91.1%, CNS tumor distant from the hypothalamus–pituitary area in 1.7%, CNS tumor distant from the hypothalamus–pituitary area in 0.68%, other tumors in 0.91%, congenital CNS malformations in 0.83%, and other diseases in 1.1%. Distinctive characteristics were detected in each etiology, especially in patients with organic GHD. In patients with CNS tumor at the hypothalamus–pituitary area, approximately half of the patients (44.2%) were female, although the overall female proportion (34.6%) was comprised of about half males (65.4%). In addition, BMI SDS (mean [SD]: 0.52 [1.33]) and the proportion of severe GHD (82.9%) were the highest values, whereas IGF-1 SDS (–3.60 [1.93]) was the lowest among all etiologies. In those with other tumors, approximately half of the patients (43.9%) were female. In those with congenital CNS malformations, age (6.6 [4.4]) and the ratio of bone age to chronological age (61.5% [22.8%]) were the lowest values, whereas the proportions of breech delivery (8.0%) and cesarean section (17.8%) were the highest values. In those with other diseases, about half of the patients (45.9%) were female, and height/length SDS (–3.30 [1.20]), birth length (47.0 [4.4]), and birth weight (2.73 [0.75]) were the lowest values. In terms of age distributions, an obvious difference was also detected according to the etiologies. We observed bimodal distributions in those with idiopathic GHD and other tumors, whereas they were not detected in other etiologies. In addition, patients with CNS tumors were more registered during the period of pubertal ages, whereas those with congenital CNS malformation were registered at earlier ages.

Table 3 shows the changes in baseline characteristics over the defined periods. Age, gestational week, birth length, and birth weight decreased gradually during the periods (all analyses: p < 0.0001). Similar decreasing trends were detected in the proportion of breech delivery, asphyxia, and mild GHD (all analyses: p < 0.0001). Since we divided the subjects into three groups according to the changes in the criteria for the Grant-in-aid Program for Chronic Diseases in Childhood, apparent changes were detected in the proportions of patients with GHD who were not eligible due to the criteria change by the time periods. On the other hand, parent height and the proportion of cesarean section, severe GHD, moderate GHD, idiopathic GHD, or congenital CNS malformations increased gradually during the periods (all analyses: p < 0.0001). There was no upward trend in the proportion of female patients (p = 0.17) despite the differences among the three defined periods (p < 0.0001). We also noticed that there was no change of BMI SDS.

Supplemental Table 1 shows the results of the comparisons of the baseline characteristics of full-term patients with idiopathic GHD between those born in or before
There were significant differences in all categories, which is difficult to interpret, because the nature of the population is different from each other as mentioned above. When we created the equal condition between two groups by dividing subjects based on the birth year of 2000 and conducted the same analyses (Table 4), we found that the proportion of asphyxia was significantly different between the two groups ($p = 0.0008$), whereas that of breech subjects was not significantly different ($p = 0.63$). In this additional analysis, we noted significant differences in age, IGF-1 SDS, and mother’s height ($p < 0.0001$, $p = 0.0042$, and $p = 0.026$, respectively).

### Discussion

We conducted comprehensive analyses of the baseline characteristics of patients with GHD in Japan during the 20 years between 1995 and 2015. This is the largest analysis of baseline characteristics at the start of GH treatment during this period in Japan.

Over the registration period, the proportions of patients with GHD with breech delivery and asphyxia have been decreasing, whereas that of caesarean section has been increasing. However, this trend was present only in the proportion of asphyxia in the analysis of full-term patients with idiopathic GHD exhibiting the same condition who were divided into two groups based on the birth year of 2000. Similar results were also detected in

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**Table 1** Baseline characteristics of Growth hormone deficiency (GHD) patients by sex

|                        | Number of patients | Male ($n = 19,717$) | Male ($n = 12,890$, 65.4%) | Female ($n = 6,827$, 34.6%) | $p$ value |
|------------------------|--------------------|---------------------|-----------------------------|-----------------------------|-----------|
| **Age (year)**         | 19,717             | 9.1 (3.4)           | 9.4 (3.5)                   | 8.6 (3.2)                   | <0.0001   |
| BH/BL SDS              | 19,717             | -2.76 (0.67)        | -2.72 (0.65)                | -2.83 (0.70)                | <0.0001   |
| BMI SDS                | 19,717             | -0.44 (1.15)        | -0.45 (1.15)                | -0.43 (1.06)                | 0.35      |
| Bone age/Chronological age (%) | 19,712          | 76.8 (16.3)         | 76.0 (16.7)                 | 78.1 (15.3)                 | <0.0001   |
| IGF-1 SDS              | 17,971             | -1.23 (1.28)        | -1.10 (1.06)                | -1.60 (1.38)                | <0.0001   |
| Gestational age (week) | 17,759             | 38.7 (2.3)          | 38.6 (2.3)                  | 38.8 (2.2)                  | <0.0001   |
| Birth length (cm)      | 15,535             | 47.6 (3.1)          | 47.8 (3.2)                  | 47.3 (3.1)                  | <0.0001   |
| Birth weight (kg)      | 18,451             | 2.81 (0.54)         | 2.84 (0.55)                 | 2.77 (0.53)                 | <0.0001   |
| Father’s height (cm)   | 18,159             | 166.8 (5.6)         | 166.8 (5.6)                 | 166.9 (5.7)                 | 0.026     |
| Mother’s height (cm)   | 18,265             | 153.5 (5.2)         | 153.4 (5.2)                 | 153.6 (5.2)                 | 0.013     |
| Breech delivery (n (%))| 19,717             | 596 (3.0%)          | 391 (3.0%)                  | 205 (3.0%)                  | 0.91      |
| Caesarian section (n (%)) | 19,717         | 2,404 (12.2%)       | 1,538 (11.9%)               | 866 (12.7%)                 | 0.13      |
| Asphyxia (n (%))       | 19,717             | 3,240 (16.4%)       | 2,201 (17.1%)               | 1,039 (15.2%)               | <0.0001   |
| **Severity (n (%))**   |                    |                     |                             |                             |           |
| Severe GHD             | 19,717             | 344 (1.7%)          | 192 (1.5%)                  | 152 (2.2%)                  |           |
| Moderate GHD           |                    | 134 (0.68%)         | 83 (0.64%)                  | 51 (0.75%)                  | <0.0001   |
| Mild GHD               |                    | 179 (0.91%)         | 100 (0.78%)                 | 79 (1.2%)                   |           |
| **Diagnosis (n (%))**  |                    |                     |                             |                             |           |
| Idiopathic GHD         | 19,717             | 17,968 (91.1%)      | 11,812 (91.6%)              | 6,156 (90.2%)               |           |
| Central nervous system (CNS) tumor at the hypothalamus-pituitary area |         | 344 (1.7%)          | 192 (1.5%)                  | 152 (2.2%)                  |           |
| CNS tumor distant from the hypothalamus-pituitary area |         | 134 (0.68%)         | 83 (0.64%)                  | 51 (0.75%)                  | <0.0001   |
| Other tumors           | 19,717             | 179 (0.91%)         | 100 (0.78%)                 | 79 (1.2%)                   |           |
| Congenital CNS malformations |         | 163 (0.83%)         | 107 (0.83%)                 | 56 (0.82%)                  |           |
| Other diseases         |                    | 220 (1.1%)          | 119 (0.92%)                 | 101 (1.5%)                  |           |
| Not described          |                    | 709 (3.6%)          | 477 (3.7%)                  | 232 (3.4%)                  |           |
| Cranial irradiation (n (%)) | 18,234        | 354 (1.9%)          | 191 (1.6%)                  | 163 (2.6%)                  | <0.0001   |

All the data are expressed as means (SD) or frequencies (%). $P$ values refer to differences between groups as determined by unpaired $t$ test and chi-square test for numeric variables and categorical variables, respectively.
the analysis of only patients with severe or moderate GHD (data not shown). These results suggest that the baseline characteristics, in terms of neonatal history, of patients with idiopathic GHD have not changed much after 2000 despite the decline in breech delivery in Japan during the same period [17]. To put these unexpected results in context, the proportion of breech delivery was already low (4.1%) in the earliest group registered between 1996 and 1997. The early nationwide survey in Japan reported that 56.2% of patients with idiopathic GHD had a history of breech delivery, and 47.5% of them had asphyxia during the 10 years between 1965 and 1974 [13]. A study using Swedish registry data between 1973 and 1986 reported that the proportions of breech delivery and asphyxia were 7.1% and 5.2%, respectively [12]. In one of the latest studies using KIGS (Pfizer International Growth database) data between 1987 and 2004, the proportion of breech delivery in patients with idiopathic GHD younger than 3 years of age and between 7 and 8 years of age was reported to be 9.4% and 4.7%, respectively [29]. In addition, the FGS data between 1986 and 1995 showed that the proportion of breech delivery declined from 11.5% to 6.0% and that of asphyxia had fluctuated between 9.8% and 13.9% [18]. Collectively, we can recognize that the proportions have been decreasing over time, and it is likely that the proportion of breach delivery reached almost a bottom level before 2000 in Japan. However, it should be noted that the proportion of asphyxia significantly decreased in our further analysis, which suggests that improvements in perinatal clinical practices have affected the characteristics of patients with idiopathic GHD in Japan during the 20 years between 1996 and 2015.

We also found that the baseline characteristics of
patients with GHD, including age and the proportion of patients with specific GHD severities, have changed constantly over time, in contrast to height/length SDS and IGF-1 SDS, which have fluctuated during the same time. Since the eligible criterion for height SDS in patients without organic abnormalities was changed in 1997, it is reasonable to assume that height/length SDS worsened from 1996–1997 to 1998–2004 After the second revision of the criterion, we speculate that patients with severe GHD tended to be diagnosed earlier with less growth deficit between 2005 and 2015 compared to those diagnosed between 1998 and 2004, so that an average height/length SDS in the most recent time period is higher than that in the prior time period. It is difficult to uncover the cause of the increase in IGF-1 SDS between the 1996–1997 and 1998–2004 time periods based on the available data, whereas the decrease between the 1998–2004 and 2005–2015 time periods should be impacted by the second revision of the criteria. It is also difficult to reveal the reason for constant changes of the proportion of patients with specific GHD severities using the available data. One possibility is that milder cases tended to be treated without the registration, considering the recent decreasing trend of the registered patients to the FGS.

An apparent male predominance was observed in patients with overall GHD (65.4%), idiopathic GHD (65.7%), CNS tumor distant from the hypothalamus–pituitary area (61.8%), and congenital CNS malformations (65.4%), whereas the male proportion was lower in those with CNS tumor at the hypothalamus–pituitary area (55.8%), other tumors (56.9%), and other diseases (54.1%; Tables 1 and 2). A similar gender bias was reported in GH treatment for patients with several etiologies from different countries and health systems [28,
Fig. 2  Age distributions at the start of growth hormone (GH) treatment in patients with GH deficiency (GHD) according to each etiology. (a) Idiopathic GHD. (b) GHD with central nervous system (CNS) tumor at the hypothalamus–pituitary area. (c) GHD with CNS tumor distant from the hypothalamus–pituitary area. (d) GHD with other tumors. (e) GHD with congenital CNS malformations. (f) GHD with other diseases. It is of note that the vertical scale in patients with idiopathic GHD was different from that of others.
Differences, and health care systems have been proposed. In this study, we aimed to evaluate the incidence rates of childhood-onset growth hormone deficiency (GHD) in patients with central nervous system (CNS) tumors at the hypothalamus–pituitary area, about half were female. It is a reasonable proportion for the underlying diagnoses, because the main tumors at the area were craniopharyngioma and pituitary germinoma, which occur equally in both sexes [36, 37], but other factors such as underlying diagnosis, socioeconomical differences, and health care systems have been proposed as well [28, 31]. In fact, a population-based study from Denmark identified a significantly higher incidence rate in males in childhood-onset GHD [33]. Our data showed that in patients with CNS tumor at the hypothalamus–pituitary area, about half were female. It is a reasonable proportion for the underlying diagnoses, because the main tumors at the area were craniopharyngioma and pituitary germi

### Table 3 Changes in baseline characteristics of growth hormone deficiency (GHD) patients over times

|                        | Number of patients | 1996–1997 (n = 4,376) | 1998–2004 (n = 8,557) | 2005–2015 (n = 6,804) | p value |
|------------------------|--------------------|------------------------|-----------------------|------------------------|---------|
| Sex (Female (%))       | 19,717             | 1,501 (34.3%)          | 3,053 (35.8%)         | 2,273 (33.4%)          | 0.0085  |
| Age (year)             | 19,717             | 9.6 (3.3)              | 9.1 (3.4)             | 8.8 (3.5)              | <0.0001 |
| BH/BL SDS              | 19,717             | –2.62 (0.72)           | –2.84 (0.67)          | –2.76 (0.62)           | <0.0001 |
| BMI SDS                | 19,717             | –0.41 (1.15)           | –0.45 (1.18)          | –0.46 (1.12)           | 0.036   |
| Bone age/Chronological age (%) | 19,712 | 76.4 (16.4) | 76.3 (16.6) | 77.5 (15.8) | <0.0001 |
| IGF-1 SDS              | 19,717             | –1.28 (1.34)           | –1.14 (1.32)          | –1.42 (1.19)           | <0.0001 |
| IGF-1 ≥200 (age ≥5) or ≥150 (age <5) (Number (%)) | 17,941 | 934 (24.3%) | 1,742 (23.7%) | 559 (8.4%) | <0.0001 |
| Gestational age (week) | 17,759             | 39.0 (2.1)             | 38.7 (2.3)            | 38.5 (2.4)             | <0.0001 |
| Birth length (cm)      | 15,535             | 48.1 (2.7)             | 47.6 (3.1)            | 47.3 (3.4)             | <0.0001 |
| Birth weight (kg)      | 18,451             | 2.88 (0.52)            | 2.81 (0.55)           | 2.77 (0.55)            | <0.0001 |
| Father’s height (cm)   | 18,159             | 166.2 (5.6)            | 166.7 (5.7)           | 167.4 (5.5)            | <0.0001 |
| Mother’s height (cm)   | 18,265             | 152.9 (5.1)            | 153.4 (5.2)           | 154.0 (5.2)            | <0.0001 |
| Caesarian section      | 19,717             | 416 (9.5%)             | 1,039 (12.2%)         | 949 (14.0%)            | <0.0001 |
| Asphyxia               | 19,717             | 395 (9.0%)             | 631 (7.4%)            | 331 (4.9%)             | <0.0001 |
| Severity (n (%))       |                      |                        |                       |                        |         |
| Severe GHD             | 19,717             | 479 (11.0%)            | 1,433 (16.8%)         | 1,328 (19.5%)          | <0.0001 |
| Moderate GHD           | 1,727 (39.5%)      | 2,170 (49.6%)          | 4,437 (52.0%)         | 4,554 (66.9%)          | <0.0001 |
| Mild GHD               | 1,727 (39.5%)      | 2,170 (49.6%)          | 4,437 (52.0%)         | 4,554 (66.9%)          | <0.0001 |
| Idiopathic GHD         |                      | 3,858 (88.2%)          | 7,755 (90.8%)         | 6,355 (93.4%)          |         |
| Central nervous system (CNS) tumor at the hypothalamus-pituitary area | 93 (2.1%) | 138 (1.6%) | 113 (1.7%) | |
| CNS tumor distant from the hypothalamus-pituitary area | | | | |
| Other tumors           | 19,717             | 29 (0.66%)             | 60 (0.70%)            | 45 (0.66%)             | <0.0001 |
| Congenital CNS malformations | 21 (0.48%) | 66 (0.77%) | 75 (1.10%) | |
| Other diseases         |                      | 55 (1.3%)              | 108 (1.3%)            | 57 (0.84%)             |         |
| Not described          | 282 (6.4%)          | 309 (3.6%)             | 118 (1.7%)            | | 
| Cranial irradiation    | 18,234             | 94 (2.2%)              | 159 (2.0%)            | 101 (1.6%)             | 0.079   |

All the data are expressed as means (SD) or frequencies (%). P values refer to differences between groups as determined by ANOVA and chi-square test for numeric variables and categorical variables, respectively.

a: p < 0.0001 for 1996–1997 vs. 1998–2004; b: p < 0.0001 for 1996–1997 vs. 2005–2015; c: p = 0.0003 for 1996–1997 vs. 2005–2015; d: p < 0.0001 for 1996–1997 vs. 2005–2015; e: p < 0.0001 for 1998–2004 vs. 2005–2015; f: Cochran-Armitage test p < 0.0001; g: Cochran-Armitage test p = 0.0003; h: Cochran-Armitage test p = 0.0007; i: Cochran-Armitage test p = 0.011, j: Cochran-Armitage test p = 0.022. 

30–35]. One of the main reasons for the observation is reported to be an ascertainment bias [36, 37], but other factors such as underlying diagnosis, socioeconomical differences, and health care systems have been proposed as well [28, 31]. In fact, a population-based study from Denmark identified a significantly higher incidence rate in males in childhood-onset GHD [33]. Our data showed that in patients with CNS tumor at the hypothalamus–pituitary area, about half were female. It is a reasonable proportion for the underlying diagnoses, because the main tumors at the area were craniopharyngioma and pituitary germinoma, which occur equally in both sexes [38] and in 54.7% in male patients [39], respectively. On the other hand, our data in patients with idiopathic GHD are identical to a universal pattern with different reported proportions, which is thought to be affected by socioeconomical and cultural situations [28]. Since the cause of the male predominance remains unexplained thoroughly, further investigation is necessary to determine the role of sex differences in patients with GHD.
We also detected etiology-specific baseline characteristics. The proportion of patients with severe GHD was different in each etiology, with most patients (83.0%) having CNS tumor at the hypothalamus–pituitary area, and the least number of patients having idiopathic GHD (14.3%). The lowest age and height/length SDS at the start of GH treatment was observed in patients with congenital CNS malformations. These results could be understandable and reasonable for its etiology, although each etiology included several varieties of diseases, and it was sometimes difficult to classify patients into the proper etiology with only our data (e.g., invisible stalk).

In terms of an age distribution in idiopathic GHD, our result is similar to previous reports that showed a bimodal distribution with peaks detected first at 5 to 6 years and second at 11 to 13 years [34, 40]. These two groups are thought to be a separate etiology with different pathophysiological etiologies [29, 34, 40]. When we analyzed these data by sex, the first peak was almost the same in both sexes, but the second peak in females was 2 years earlier (Fig. 1, and data not shown), suggesting that the second one should be related to puberty. An age distribution in the group of CNS tumors at the hypothalamus–pituitary area showed a peak at 11–14 years of age. The incidence of craniopharyngioma in children is reported to be at the peak of 5–9 years [38], whereas pituitary germinoma in children is reported to occur at an average (SD) of 11.2 (3.5) years [39]. Considering that GH treatment should be started after tumor treatment, the detected peak in our cohort could be understandable.

This study has several limitations. First, this study has a certain selection bias. Given that registration of patients to the FGS is not compulsory and the registered number has been decreasing over time (2,192 in 1996, 1,273 in 2000, 953 in 2005, 750 in 2010, and 340 in 2015), subjects analyzed in this study might not be exactly representative of Japanese patients with GHD. Second, an etiology of GHD in this cohort was dependent on reports by physicians, so there is some possibility that diagnosable patients might be classified as “idiopathic GHD” or “not described” because of inadequate investigations. It is of note that approximately 90% of patients were classified with idiopathic GHD, and about 3.5% of patients had no described etiology. However, the characteristics of idiopathic GHD in this study

Table 4 Baseline characteristics of idiopathic growth hormone deficiency (GHD) patients with full-term birth by two generations

|                          | Number of patients | Birth year 1996–2000 (n = 2,341) | Birth year 2001–2005 (n = 1,461) | p value |
|--------------------------|--------------------|----------------------------------|----------------------------------|---------|
| Sex (Female (%))         | 3,802              | 859 (36.7%)                      | 532 (36.4%)                      | 0.8600  |
| Age (year)               | 3,802              | 7.6 (2.9)                        | 7.2 (2.9)                        | <0.0001 |
| BH/BL SDS                | 3,802              | –2.76 (0.55)                     | –2.73 (0.48)                     | 0.12    |
| BMI SDS                  | 3,802              | –0.33 (1.02)                     | –0.32 (1.03)                     | 0.87    |
| Bone age/Chronological age (%) | 3,800              | 73.6 (17.2)                      | 74.6 (18.0)                      | 0.071   |
| IGF-1 SDS                | 3,595              | –1.14 (1.10)                     | –1.25 (1.07)                     | 0.0042  |
| Gestational age (week)   | 3,802              | 39.3 (1.0)                       | 39.3 (1.0)                       | 0.37    |
| Birth length (cm)        | 3,459              | 47.8 (2.2)                       | 47.8 (2.1)                       | 0.75    |
| Birth weight (kg)        | 3,792              | 2.86 (0.39)                      | 2.86 (0.38)                      | 0.78    |
| Father’s height (cm)     | 3,715              | 166.9 (5.5)                      | 167.0 (5.6)                      | 0.43    |
| Mother’s height (cm)     | 3,738              | 153.4 (5.1)                      | 153.8 (4.9)                      | 0.026   |
| Breech delivery (n (%))  | 3,802              | 40 (1.7%)                        | 22 (1.5%)                        | 0.63    |
| Caesarian section (n (%))| 3,802              | 262 (11.2%)                      | 151 (10.3%)                      | 0.41    |
| Asphyxia (n (%))         | 3,802              | 108 (4.6%)                       | 37 (2.5%)                        | 0.0008  |
| Both breech delivery and asphyxia (n (%)) | 3,802 | 8 (0.34%)                        | 2 (0.14%)                        | 0.21    |
| Severity (n (%))         |                    |                                  |                                  |         |
| Severe GHD               | 3,802              | 347 (14.8%)                      | 210 (14.4%)                      | <0.0001 |
| Moderate GHD             |                    |                                  |                                  |         |
| Mild GHD                 |                    |                                  |                                  |         |

All the data are expressed as means (SD) or frequencies (%). P values refer to differences between groups as determined by unpaired t test and chi-square test for numeric variables and categorical variables, respectively.

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are consistent with those of previous reports, as discussed above. Finally, this cohort includes only age at the start of GH treatment, not at diagnosis. GH treatment for patients with tumors is typically started after an underlying disease is determined, and the interval between the diagnosis and start of GH treatment differs with each etiology. Therefore, these limitations should be kept in mind when interpreting our demographic data.

In conclusion, in the present study we have uncovered three baseline characteristics of patients with GHD starting GH treatment. First, the recent baseline characteristics were updated in terms of anthropometric data, severity, and etiology. Second, the baseline characteristics have changed over time, which might be partly affected by medical support programs. Finally, our analyses identified that the proportions of breech delivery and asphyxia gradually declined during the 20-year registration period, whereas the proportion of idiopathic GHD with breech delivery seemed to reach the lowest level among those born before 2000.

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Disclosure

The authors declare that there are no conflicts of interest.

Supplemental Table 1  Baseline characteristics of patients with idiopathic growth hormone deficiency (GHD) with full-term birth by the birth year 2000

|                          | Number of patients | born in or before 2000 (n = 11,361) | born after 2000 (n = 2,064) | p value |
|--------------------------|--------------------|-------------------------------------|-----------------------------|---------|
| Sex (Female (%))         | 13,425             | 3,864 (34.0%)                       | 780 (37.8%)                 | 0.0010  |
| Age (year)               | 13,425             | 9.7 (3.2)                           | 6.5 (2.8)                   | <0.0001 |
| BH/BL SDS                | 13,425             | –2.72 (0.58)                        | –2.77 (0.54)                | 0.0007  |
| BMI SDS                  | 13,425             | –0.48 (1.11)                        | –0.21 (1.02)                | <0.0001 |
| Bone age/Chronological age (%) | 13,422            | 77.2 (15.2)                         | 74.5 (18.9)                 | <0.0001 |
| IGF-1 SDS                | 12,310             | –1.19 (1.19)                        | –1.25 (1.07)                | 0.047   |
| Gestational age (week)   | 13,425             | 39.5 (1.0)                          | 39.3 (1.0)                  | <0.0001 |
| Birth length (cm)        | 11,610             | 48.3 (2.2)                          | 47.8 (2.2)                  | <0.0001 |
| Birth weight (kg)        | 13,386             | 2.94 (0.40)                         | 2.86 (0.38)                 | <0.0001 |
| Father’s height (cm)     | 13,155             | 166.5 (5.5)                         | 167.1 (5.6)                 | <0.0001 |
| Mother’s height (cm)     | 13,216             | 153.2 (5.1)                         | 153.8 (5.0)                 | <0.0001 |
| Breech delivery (n (%))  | 13,425             | 298 (2.6%)                          | 34 (1.7%)                   | 0.0057  |
| Caesarian section (n (%))| 13,425             | 1,061 (9.3%)                        | 225 (10.9%)                 | 0.029   |
| Asphyxia (n (%))         | 13,425             | 607 (5.3%)                          | 53 (2.6%)                   | <0.0001 |
| Both breech delivery and asphyxia (n (%)) | 13,425 | 63 (0.55%)                          | 4 (0.19%)                   | 0.017   |
| Severity (n (%))         |                    |                                     |                             |         |
| Severe GHD               | 13,425             | 1,513 (13.3%)                       | 285 (13.8%)                 |         |
| Moderate GHD             | 13,425             | 6,227 (54.8%)                       | 1,491 (72.2%)               | <0.0001 |
| Mild GHD                 | 13,425             | 3,621 (31.9%)                       | 288 (14.0%)                 |         |

All data are expressed as means (SD) or frequencies (%). The p values refer to differences between groups as determined by unpaired t test and chi-square test for numeric variables and categorical variables, respectively.
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**Supplemental Fig. 1**  Annual time course of numbers of patients registered in the FGS with growth hormone deficiency.

Apparent declines were detected in response to the criteria of the medical aid changes (a and b). The number of registered patients has been gradually decreasing since about 2010 (c), which we think might be due to the gradual prevalence of a medical support program for children by local governments.
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