Growth hormone (GH) deficiency (GHD) in adulthood leads to altered body composition, abnormal lipid, glucose, carbohydrate, and bone metabolism, decreased quality of life (QoL) and physical performance, and increased mortality due to cardiovascular disease [1-3]. Numerous studies have demonstrated that growth hormone replacement therapy, approved for use in adults in the United States and Europe in the mid-1990s [4], ameliorates many of the adverse consequences of GHD (reviewed in [5]). These studies have also increased our understanding of the baseline clinical characteristics of adults with GHD.

Although the general pattern of clinical characteristics in Caucasian adults with GHD is consistent, evidence suggests that the extent of alterations in clinical characteristics may vary among adults from different countries [6-9]. There is evidence suggesting that Japanese adults with GHD have similar clinical characteristics to their Caucasian counterparts [10-15]. However, the studies performed in Japan to date have been either small-scale clinical trials, single institution studies, or survey studies that may not reflect the characteristics of the population of Japanese adults with GHD seen in clinical practice. Given that the clinical characteristics of Caucasian adults with GHD from different countries can vary, larger clinical practice studies are needed to more accurately define the clinical characteristics of Japanese adults with GHD. Definition of these clinical characteristics will enhance the ability of clinicians to identify and treat Japanese adults with GHD.
ity of clinicians to identify and treat Japanese adults with GHD.

The aim of our study was to describe the clinical characteristics, including cause of GHD, body composition, metabolism, and QoL, of Japanese adults with GHD. The participants included in our study were enrolled in the Hypopituitary Control and Complications Study (HypoCCS) [16], a post-marketing observational study of patients receiving GH replacement therapy (approved in Japan in 2006) in the Japanese clinical practice setting.

Materials and Methods

Study design
All participants were enrolled in the HypoCCS [16] between April 2006 and March 2009 at 122 sites throughout Japan.

The HypoCCS was conducted in accordance with the Declaration of Helsinki and Good Post-Marketing Surveillance Practice and was approved by the Institutional Review Boards of each participating site. Each enrolled participant provided written informed consent. Participants were not obligated to receive GH replacement therapy after providing informed consent. Thus, not all participants in our study received subsequent GH replacement therapy.

Participants
Japanese adults (aged between 18 and 64 years) with a confirmed diagnosis of GHD who were naïve to GH treatment were eligible for inclusion in the study. Participants with either adult-onset (AO) or childhood-onset (CO) GHD were eligible for inclusion, as were participants taking antihypertensive or antidyslipidemic medications.

Growth hormone deficiency was diagnosed by GH stimulation tests (insulin tolerance, arginine, glucagon, L-DOPA, or GH releasing peptide-2) performed at the discretion of study site investigators. For insulin tolerance, arginine, glucagon, and L-DOPA GH stimulation tests, GHD was diagnosed if the peak serum GH concentration was < 1.8 ng/mL [17]. For the GH releasing peptide-2 GH stimulation test, GHD was diagnosed if the peak serum GH concentration was < 9.0 ng/mL [18]. Two positive GH stimulation tests were required for the diagnosis of GHD in participants with isolated GHD (i.e., no additional pituitary hormone deficiencies) or idiopathic CO GHD [19].

Participants who had any contraindication to GH replacement therapy according to the Japanese prescribing information [20] were excluded from the HypoCCS.

Baseline characteristics
Demographic (age and sex) and physical characteristics (body mass index, waist circumference, and systolic and diastolic blood pressure) were recorded at baseline. Baseline serum concentrations of total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, and insulin-like growth factor-I (IGF-I) were measured at each participating study site using standard methods.

Baseline GHD-related characteristics were also recorded, including the cause of GHD, tumor type that caused GHD (if applicable), time since diagnosis of GHD, and the number of other pituitary hormone deficiencies.

Pre-existing conditions, identified by examining medical records, were also recorded at baseline.

Baseline participant QoL was assessed using the validated Japanese version of the short form-36 (SF-36) survey [21, 22]. The SF-36 contains eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.

Statistical analysis
Continuous data are presented as mean ± standard deviation, whereas categorical data are presented as number (percent). Standard deviation scores (SDS) were calculated for IGF-I concentrations using reference data from age- and sex-matched healthy Japanese individuals [23]. For each SF-36 domain, Z-scores were calculated using reference data from age- and sex-matched healthy Japanese individuals [24].

Results
A total of 349 adults with GHD were included in this study. Complete data were not available for all participants.

Demographic and clinical characteristics
There were several differences in demographic and clinical characteristics between participants with AO GHD and participants with CO GHD (Table 1). The majority of participants (280 of 349; 80.2%) had AO
with CO GHD (Table 2). Despite the mean age of CO GHD (28.0 ± 8.6) is lower than one of AO GHD (53.6 ± 14.9), participants with CO GHD had a higher mean serum LDL concentration than their AO GHD counterparts.

**Pre-existing conditions**

There were several differences between participants with AO GHD and participants with CO GHD in the prevalence of pre-existing conditions (Table 3). The

### Table 1 Demographic and clinical characteristics of Japanese adults with growth hormone deficiency enrolled in the Hypopituitary Control and Complications Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adult-Onset GHD</th>
<th>Childhood-Onset GHD</th>
<th>All GHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53.6 ± 14.9</td>
<td>28.0 ± 8.6</td>
<td>48.6 ± 17.2</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>164 (58.6)</td>
<td>32 (46.4)</td>
<td>196 (56.2)</td>
</tr>
<tr>
<td>Women</td>
<td>116 (41.4)</td>
<td>37 (53.6)</td>
<td>153 (43.8)</td>
</tr>
<tr>
<td>Time since diagnosis, years</td>
<td>4.7 ± 7.1</td>
<td>19.0 ± 10.6</td>
<td>7.4 ± 9.6</td>
</tr>
<tr>
<td>IGF-I, ng/mL</td>
<td>81.3 ± 44.5</td>
<td>66.1 ± 49.2</td>
<td>78.1 ± 45.8</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>-2.37 ± 1.79</td>
<td>-5.11 ± 2.74</td>
<td>-2.94 ± 2.30</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation, except where indicated. 
Abbreviations: GHD = growth hormone deficiency, IGF-I = insulin-like growth factor-I, SDS = standard deviation score.

### Table 2 Metabolic characteristics of Japanese adults with growth hormone deficiency enrolled in the Hypopituitary Control and Complications Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adult-Onset GHD</th>
<th>Childhood-Onset GHD</th>
<th>All GHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>25.5 ± 4.9</td>
<td>23.8 ± 4.5</td>
<td>25.1 ± 4.9</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>90.5 ± 9.4</td>
<td>85.3 ± 9.5</td>
<td>89.6 ± 9.6</td>
</tr>
<tr>
<td>Women</td>
<td>82.0 ± 10.1</td>
<td>83.3 ± 14.0</td>
<td>82.4 ± 11.4</td>
</tr>
<tr>
<td>All</td>
<td>87.7 ± 10.4</td>
<td>84.2 ± 12.1</td>
<td>86.8 ± 10.9</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>122.4 ± 16.8</td>
<td>111.1 ± 16.4</td>
<td>120.7 ± 17.2</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>73.7 ± 11.8</td>
<td>71.0 ± 9.4</td>
<td>73.3 ± 11.5</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>210.0 ± 41.7</td>
<td>212.4 ± 54.5</td>
<td>210.4 ± 44.2</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>124.8 ± 34.5</td>
<td>135.4 ± 41.7</td>
<td>127.0 ± 36.1</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>54.5 ± 20.9</td>
<td>59.1 ± 20.6</td>
<td>55.4 ± 20.8</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>175.2 ± 106.7</td>
<td>142.0 ± 86.1</td>
<td>169.1 ± 103.8</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation. 
Abbreviations: BMI = body mass index, DBP = diastolic blood pressure, GHD = growth hormone deficiency, HDL = high-density lipoprotein, LDL, low-density lipoprotein, SBP = systolic blood pressure.
prevalence of dyslipidemia was greater in participants with AO GHD than in participants with CO GHD, as was the prevalence of visual field loss, hypertension, cerebrovascular disease, diabetes, anxiety, cardiovascular disease, and renal dysfunction. There were no instances of diabetes, cardiovascular disease, renal dysfunction, arthritis, or multiple endocrine adenomatosis among participants with CO GHD.

**Causes of GHD**

There were both similarities and differences between participants with AO GHD and participants with CO GHD in the underlying causes of GHD (Fig. 1). Hypothalamo-pituitary tumors were the most common cause of GHD in both participants with AO GHD and participants with CO GHD. Other organic causes, including pituitary bleed / rupture, empty sella syndrome, and sarcoidosis, were the second most common cause of GHD in both participants with AO GHD and CO GHD. However, GHD was caused by other organic means in a greater proportion of participants with CO GHD than participants with AO GHD. Similarly, GHD was idiopathic in a greater proportion of participants with CO GHD than participants with AO GHD.

### Table 3 Pre-existing conditions in Japanese adults with growth hormone deficiency enrolled in the Hypopituitary Control and Complications Study

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adult-Onset GHD (n = 280)</th>
<th>Childhood-Onset GHD (n = 69)</th>
<th>All GHD (N = 349)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>162 (57.9)</td>
<td>33 (47.8)</td>
<td>195 (55.9)</td>
</tr>
<tr>
<td>Visual field loss</td>
<td>59 (21.1)</td>
<td>8 (11.6)</td>
<td>67 (19.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>58 (20.7)</td>
<td>1 (1.4)</td>
<td>59 (16.9)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>43 (15.4)</td>
<td>11 (15.9)</td>
<td>54 (15.5)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>32 (11.4)</td>
<td>9 (13.0)</td>
<td>41 (11.7)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>18 (6.4)</td>
<td>2 (2.9)</td>
<td>20 (5.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (6.1)</td>
<td>0</td>
<td>17 (4.9)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12 (4.3)</td>
<td>2 (2.9)</td>
<td>11 (3.2)</td>
</tr>
<tr>
<td>Depression</td>
<td>9 (3.2)</td>
<td>2 (2.9)</td>
<td>11 (3.2)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>9 (3.2)</td>
<td>0</td>
<td>9 (2.6)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>7 (2.5)</td>
<td>0</td>
<td>7 (2.0)</td>
</tr>
<tr>
<td>Pathologic fracture</td>
<td>4 (1.4)</td>
<td>1 (1.4)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>2 (0.7)</td>
<td>0</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Multiple endocrine adenomatosis</td>
<td>1 (0.4)</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

Values are number (%). Abbreviation: GHD = growth hormone deficiency.

* In Adult-Onset GHD, 77 out of 162 patients with dyslipidemia received medication and in Child-Onset GHD, 11 out of 33 patients with dyslipidemia received medication.

* Caused by hypothalamic or pituitary disorder.

* Deforming or inflammatory.

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**Fig. 1** Causes of growth hormone deficiency (GHD) in Japanese adults enrolled in the Hypopituitary Control and Complications Study. Findings are stratified by adult-onset GHD and childhood-onset GHD. Data are presented as the proportion of participants (the numbers of participants in each group are shown).
Rathke’s cyst did not cause GHD in any participants with CO GHD.

**Tumor types**

The types of tumors that caused GHD varied considerably between participants with AO GHD and participants with CO GHD (Fig. 2). Pituitary adenomas were the most common cause of GHD in participants with AO GHD, followed by craniopharyngiomas, germ cell tumors, and meningiomas. In contrast, germ cell tumors and craniopharyngiomas were the most common causes of GHD in participants with CO GHD, whereas pituitary adenomas were a far less common cause of GHD. Meningiomas did not cause GHD in any participants with CO GHD.

**Other pituitary hormone deficiencies**

The majority of participants had multiple pituitary hormone deficiencies. Specifically, in AO GHD, 32 of 280 (11.4%) participants had isolated GH deficiency, while 62 (22.1%), 57 (20.3%), 82 (29.3%), and 47 (16.8%) participants were deficient in two, three, four, and five pituitary hormones (including GH), respectively. In CO GHD, 7 of 69 (10.1%) participants had isolated GH deficiency, while 2 (2.9%), 14 (20.3%), 22 (31.9%), and 24 (34.8%) participants were deficient in two, three, four, and five pituitary hormones (including GH), respectively.

**Quality of life**

Participants with GHD had reduced QoL compared with age- and sex-matched healthy Japanese individuals (Fig. 3). Regardless of the timing of GHD onset, participants had lower than normal median QoL Z-scores in seven (physical functioning, role physical, general
health, vitality, social functioning, role emotional, and mental health) of the eight domains. Quality of life Z-scores were similar between participants with AO GHD and CO GHD.

**Discussion**

This is the first large-scale, multicenter, clinical practice study to examine the clinical characteristics of Japanese adults with GHD. Our findings confirm those of previous Japanese studies indicating that the clinical characteristics of Japanese adults with GHD are similar to those of Caucasian adults with GHD. Confirmation of these clinical characteristics will increase the awareness of adult GHD as a clinical entity in Japan and enhance the ability of clinicians to identify Japanese adults with GHD. The timely identification of Japanese adults with GHD is important given the growing body of evidence demonstrating that GH replacement can be an effective treatment for this condition [11, 13, 18, 25].

In this study, we found that a greater proportion (80%) of Japanese adults had AO GHD than CO GHD, a finding similar to those of previous studies in Caucasian adults [4, 6, 7]. In contrast, in a previous study of Japanese adults with GHD [14], only 45% of participants were reported to have AO GHD. That study, however, included a smaller number of participants than were included in our study and was conducted at a single institution. Our findings suggest that the majority of Japanese adults with GHD become deficient in adulthood.

Hypothalamo-pituitary tumors, in particular pituitary adenomas, were the most common cause of GHD in Japanese adults enrolled in our study, and most participants had multiple pituitary hormone deficiencies. Findings from previous studies have also revealed that hypothalamo-pituitary tumors are the most common cause of GHD in both Japanese [11, 12, 22, 25] and Caucasian [4, 6-9] adults. Interestingly, idiopathic GHD was a less common cause of GHD in our study than previously reported [4, 6, 7, 11, 14, 22, 25], particularly in participants with CO GHD [7, 11, 14]. In contrast, other organic causes of GHD were more common in our study than in previous studies [4, 6, 7, 11, 14, 22, 25]. The differences between our study and previous studies may reflect the different subspecialties of the recruiting clinicians. Consistent with previous studies conducted in Japan [14] and Europe [16], we found that 89% of participants had multiple pituitary hormone deficiencies. Taken together, our findings confirm that hypothalamo-pituitary tumors are the predominant cause of GHD in Japanese adults and that multiple pituitary hormone deficiencies are very common in these patients. Thus, rigorous follow-up of patients treated for hypothalamo-pituitary tumors, for example by neurosurgeons, should include specific tests for deficiencies in GH and other pituitary hormones.

We also found that dyslipidemia, hypertension, and liver disease were common pre-existing conditions in Japanese adults with GHD. Previous studies have also consistently reported that lipid metabolism is altered in Japanese [10-12, 14] and Caucasian [7, 26] adults with GHD (reviewed in [1]). Liver dysfunction [14] and hypertension [14, 27] are also common in adults with GHD. Our findings and those from previous studies [10-12, 14] emphasize that Japanese clinicians, in particular neurosurgeons who treat patients with hypothalamo-pituitary tumors, should be aware that dyslipidemia, hypertension, and liver disease may reflect underlying GHD. The importance of recognizing the potential link between these conditions and GHD is reinforced by the findings of several studies demonstrating that GH replacement therapy can ameliorate hypertension and improve lipid profiles in adults with GHD (reviewed in [28]).

In keeping with previous studies, we found that QoL was decreased in participants with GHD compared with age- and sex-matched healthy Japanese individuals. Previous studies have consistently shown that QoL is reduced in both Japanese [15, 22] and Caucasian [29, 30] adults with GHD. Interestingly, we did not find any marked difference in QoL between participants with AO GHD and those with CO GHD. This contrasts with the findings from a study of Japanese adults [15] and several studies of Caucasian adults [7, 31] in which participants with AO GHD had lower QoL scores than participants with CO GHD. The disparity in findings may reflect different study populations, which includes different ethnicities, [7, 15, 31] and/or the use of different QoL assessment tools [7, 31]. Nevertheless, our findings and those from the two previous studies performed in Japan [15, 22] confirm that QoL is decreased in Japanese adults with GHD. Confirmation that Japanese adults with GHD have reduced QoL is important because the findings from several studies, including two performed in Japan [13, 14], suggest that GH
replacement therapy may improve QoL in adults with GHD (reviewed in [32]).

The results of our study are strengthened by the multicenter, clinical practice design and the assessment of a broad range of clinical characteristics. Previous studies conducted in Japan have been limited to small-scale clinical trials, single institution studies, or survey studies and have been less comprehensive in assessing the clinical characteristics of adults with GHD [10-12, 14, 15, 22, 25]. Further, as we included both participants who subsequently received GH replacement and those who did not, any possible inclusion bias was minimal.

Our study does have several limitations that must be acknowledged. One limitation is that we did not include a group of participants without GHD for comparison. A second limitation is that data were not available for all clinical characteristics for all participants. However, we must emphasize that missing data are very common in clinical practice studies [33]. Despite these limitations, our study included a larger number of participants than were included in most other studies performed in Japan [10, 11, 14, 15, 22, 25] and may more accurately reflect the clinical characteristics of Japanese adults with GHD.

In conclusion, our clinical practice findings confirm that the clinical characteristics, notably the causes of GHD, pre-existing conditions, and QoL, of Japanese adults with GHD are similar to those of Caucasian adults with GHD. Our findings also emphasize that GH deficiency has adverse effects on the health of Japanese adults, in particular metabolism and QoL. Japanese clinicians, in particular neurosurgeons, should be aware of the clinical characteristics of GHD in adults to facilitate timely diagnosis and, if appropriate, initiation of GH replacement therapy.

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Role of the sponsor

In collaboration with the authors, Eli Lilly Japan K.K. was involved in the study design, data collection, data analysis, and preparation of the manuscript. All authors had full access to the data upon request. The authors had final responsibility for the decision to submit for publication.

Conflict of interest

Both AS and KC have served on advisory boards for Eli Lilly and Company. ST is employed by Eli Lilly Japan K.K. TT and AT have nothing to declare.

References


