Intracranial pathology in children with growth hormone deficiency: Experience from a single-center in Japan over a 12-year period

Yuji Koike, Yukako Yokouchi

TO THE EDITORS

Short stature is defined as a height more than 2.0 standard deviations (SD) below the population standard for chronological age and sex, and can have various causes, including genetic, nutritional, psychological, or hormonal problems, or chronic systemic disease [1]. However, it is well known that most children with short stature who are referred to an outpatient pediatric clinic are idiopathic [2] and otherwise healthy [3].

Of the potential etiologies of short stature, growth hormone (GH) deficiency (GHD) is one of the most common conditions in children with short stature. GHD is characterized by reduced secretion of GH relative to the standard value, which is attributed to problems related to the GH-insulin-like growth factor (IGF) axis. The diagnosis of GHD in children requires various comprehensive clinical and auxological assessments, combined with biochemical tests of GH secretion and radiological evaluation. The GH-IGF axis is more susceptible to disruption by acquired conditions than other hypothalamic-pituitary axes [4]. Therefore, GHD could be caused by intracranial mass lesions (regardless of whether they are benign or malignant), traumatic head injury, or the use of radiotherapy [5], in addition to the problems described above. Central nervous system imaging using computed tomography (CT) or magnetic resonance imaging (MRI) in radiological evaluation for GHD is recommended [5]. Because MRI can clearly provide a much more detailed anatomical view of the hypothalamus, pituitary gland, pituitary stalk, and adjacent structures in the saddle area. It is considered the best diagnostic method for identifying GHD in children. In contrast, with the increasing use of MRI, it is recognized that an incidental abnormality within the hypothalamic-pituitary region may be detected on MRI.

In this study, we conducted a retrospective analysis of intracranial pathology in children with short stature who were diagnosed with GHD. From January 2007 to December 2018, children with short stature (more than 2.0 SD below the standard for Japanese boys and girls) who were diagnosed with GHD at the Department of Pediatrics, Disaster Medical Center, Tokyo, Japan, were included. All patients underwent physical and neurological examinations; primary screening laboratory tests, including complete blood count, routine chemistry, thyroid function, and IGF-1; urinalysis; and bone age (BA) analysis. They also underwent GH provocation tests with insulin tolerance and arginine or clonidine loading. When the diagnosis was confirmed by the two GH provocation tests (both the peak GH levels were below 6.0 ng/mL measured by using recombinant GH for the standard), all the patients underwent brain MRI examinations. Images obtained were analyzed and interpreted by two experienced clinicians (one radiologist and one pediatrician). Thirty Japanese children (20 boys and 10 girls) with an average age of 8.2 (range, 3.4–13.8) years were diagnosed with GHD within the study period (Table 1). At the initial visits, they were healthy, preadolescent, and had no history of any other chronic disease. Their neurological milestones and learning were normal, and the proportions of their extremities were considered as within normal limits for Japanese children. The average height was −2.6 SD relative to the age- and sex-matched standard, and their BA was delayed by more than one year relative to their chronological ages. Their laboratory findings were almost normal, apart from low levels of IGF-1 (average, 106 ng/mL). The average peak GH concentration with insulin tolerance was 4.04 ng/mL.

Of the patients, two (6.7%) had intracranial pathology; one patient (Case 1) had a middle cranial fossa arachnoid

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cyst (MFAC) [5] and one patient (Case 2) had pituitary stalk interruption syndrome (PSIS). The remaining patients (93.3%) had no specific brain lesions revealed by brain MRI (Table 1).

Case 1 (Figure 1) [6]: A 10-year-old boy was referred to our outpatient clinic for evaluation of his short stature. He was born at 38 weeks gestation by normal vaginal delivery (NVD) weighing 2482 g (a low-birth-weight infant, which was appropriate for the gestational age). His growth had followed the −2.5 SD line of normal Japanese boys. At that time, his height was 120.8 cm (−2.6 SD) and his BA was 7 years and 6 months. IGF-1 was 87 ng/mL, and peak GH levels were 5.46 ng/mL with insulin tolerance and 1.10 ng/mL with arginine loading. Brain MRI revealed an extra-axial unilocular cyst in the left middle cranial fossa, which was consistent with MFAC (Figure 1A). The pituitary gland was considered to be normal; however, its stalk was slightly deviated to the right side. As he was considered to have no other endocrinological complications, we decided to treat the patient with recombinant human GH (rhGH). Consequently, his growth accelerated soon without any symptoms. At the age of 15 years, his height was 157.0 cm (−1.6 SD), we ceased therapy and considered that 5-years of therapy did not affect the lesion because no changes in the features of MFAC were observed on serial brain MRI (Figure 1B). Four weeks after cessation of rhGH therapy, IGF-1 was 589 ng/mL, and peak GH levels were 46.1 ng/mL with insulin tolerance. These findings suggested that his GH-IGF-1 axis resumed.

Case 2 (Figure 2): A boy, born at 39 weeks gestation by NVD weighing 3115 g, was referred to our outpatient clinic for evaluation of his marked short stature. At the first visit, he was 3 years and 5 months old, his height was 81.8 cm (−1.6 SD), and his BA was 7 years and 6 months. IGF-1 was 87 ng/mL, and peak GH levels were 5.46 ng/mL with insulin tolerance and 1.10 ng/mL with arginine loading. Brain MRI revealed an absent pituitary stalk, hypoplasia of the anterior pituitary gland, and ectopic posterior pituitary gland (bright on T1-weighted imaging, located at the level of the median eminence), which was consistent with PSIS (Figure 2A). As he was considered to have no other complications, we decided to treat the patient with only rhGH. He is now 7 years and 10 months old, his height is 112.8 cm (−2.2 SD), his IGF-1 level is 219 ng/mL. The therapy seems to have been successful, with no apparent sequelae (Figure 2B).

**DISCUSSION**

During the examination and investigation of short stature and GHD, it is necessary to rule out intracranial lesions and evaluate the pituitary gland [7]. Computed tomography is appropriate for recognizing intracranial tumors or suprasellar calcification associated with craniopharyngioma. Recently, as MRI provides more information than CT, brain MRI is recommended in the

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**Table 1: Characteristics of patients diagnosed with growth hormone deficiency**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Height SD score</th>
<th>IGF-1 (ng/mL)</th>
<th>Peak GH (ng/mL) (insulin tolerance)</th>
<th>Brain MRI findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Male: 20</td>
<td>Mean: 8.2</td>
<td>Mean: −2.6</td>
<td>Mean: 106</td>
<td>Mean: 4.04</td>
</tr>
<tr>
<td>(n = 30)</td>
<td>Female: 10</td>
<td>Range: 3.4 to 13.8</td>
<td>Range: −4.0 to −2.0</td>
<td>Range: 18 to 191</td>
<td>Range: 0.44 to 5.97</td>
</tr>
<tr>
<td>Case 1</td>
<td>Male</td>
<td>10.0</td>
<td>−2.6</td>
<td>87</td>
<td>5.46</td>
</tr>
<tr>
<td>After therapy</td>
<td>15.0</td>
<td>−1.6</td>
<td>589</td>
<td>46.1</td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td>Male</td>
<td>3.4</td>
<td>−4.0</td>
<td>18</td>
<td>4.65</td>
</tr>
<tr>
<td>After therapy</td>
<td>7.8</td>
<td>−2.2</td>
<td>219</td>
<td>Not done</td>
<td></td>
</tr>
</tbody>
</table>

*PSIS: pituitary stalk interruption syndrome.

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Figure 1: Brain MRI (coronal view, T1-weighted imaging) and growth chart from Case 1. Brain MRI (A) revealed an arachnoid cyst in the left middle cranial fossa. The pituitary stalk was slightly deviated to the right side (white arrow). The patient received recombinant human growth hormone replacement therapy (rhGH). (B) His growth accelerated soon after with no sequelae.
evaluation of pediatric patients with GHD. In contrast, MRI can be particularly frightening because it is noisy and involves lying still in an enclosed space, owing to which some children need to be deeply sedated or anesthetized [8]. Although brain MRI should be carried out in children diagnosed with GHD, there are few studies concerning intracranial lesions in patients with idiopathic GHD. Maghnie et al. [9] reported brain MRI findings in 15,043 children with GHD (including 10,378 idiopathic GHD patients) retrieved from KIGS database until January 2011. Consequently, the prevalence of the diagnoses, in descending order, was as follows: 1178 patients (7.8%) with pituitary hypoplasia, 1019 patients (6.8%) with PSIS, 449 patients (3.0%) with empty sella (ES), 82 patients (0.5%) with arachnoid cyst (AC), 76 patients (0.5%) with microadenoma, and 31 patients (0.2%) with Rathke cyst. They pointed out that there are particular difficulties in measuring and establishing the size of the anterior pituitary gland, which varies with age, sex, pubertal status, and shape [9]. More recently, Xu et al. [10] conducted a retrospective analysis on clinical data obtained from 577 pediatric patients with short stature caused by GHD. In their study, apart from pituitary dysplasia, they diagnosed 68 patients (11.8%) with ES, 45 patients (7.8%) with PSIS, 38 patients (6.6%) with Rathke cyst, and two patients (0.3%) with AC, based on the MRI findings. Therefore, we speculate that definite intracranial lesions, i.e., PSIS, Rathke cyst, or AC, could be present at a relatively constant rate in children with idiopathic GHD.

Arachnoid cyst accounts for approximately 1% of all intracranial mass lesions [11] and is frequently asymptomatic, but may cause headache. AC, especially suprasellar AC, causes various endocrine disorders such as central precocious puberty, amenorrhea, GHD, obesity, tall stature, and panhypopituitarism [12]. Although the long-term effect of rhGH for patients with GHD associated with AC is unclear, the therapy is suggested to be safe and effective to treat patients like those in our report [6].

Pituitary stalk interruption syndrome is characterized by the triad of an absent or interrupted pituitary stalk, hypoplasia of the anterior pituitary gland, and an ectopic posterior pituitary gland, which is often detected as a bright spot at the base of the hypothalamus on MRI T1-weighted imaging [13]. The prevalence of PSIS is estimated to be approximately 0.5/1,000,000 births [14]. Pituitary stalk interruption syndrome can either cause isolated GHD or deficiency of multiple anterior pituitary hormones, and patients present with severe short stature, but normal posterior pituitary function. Pituitary stalk interruption syndrome is considered a good prognostic factor for the response to rhGH replacement therapy [13], and a diagnosis of PSIS following MRI is beneficial for patients with GHD. In our case, the patient’s growth accelerated soon after initiation of rhGH and the therapy seems to have been successful, with no sequelae to date.

In conclusion, intracranial pathology could be associated with GHD, even if the patient is otherwise healthy. Clinicians should perform brain MRI when they diagnose a child with short stature as having GHD.

**Keywords:** Brain, Magnetic resonance imaging, Provocation test, Short stature

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**REFERENCES**


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Author Contributions
Yuji Koike – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Yukako Yokouchi – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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