Neonatal Identification of Congenital Hypopituitarism with an Invisible Pituitary Stalk and Pituitary Aplasia: Usefulness of Early Growth Hormone Replacement

Keisuke Nagasaki¹, Tsukasa Ohashi², Makoto Hiura¹, Toru Kikuchi¹, Masashi Suda² and Makoto Uchiyama¹,
¹Division of Pediatrics, Department of Homeostatic Regulation and Development, Niigata University Graduate School of Medicine and Dental Sciences, Niigata,
²Department of Pediatrics, Niigata Prefectural Central Hospital, Niigata, Japan

Abstract. We report a case of male neonatal onset congenital hypopituitarism with an invisible pituitary stalk and pituitary aplasia. He had a micropenis at birth and experienced multiple episodes of apnea, cyanosis, hypotonia and hypothermia, associated with severe hypoglycemia during the first few days of life. He was diagnosed as having congenital hypopituitarism due to the findings of low serum GH and cortisol levels during hypoglycemia, low free T4 and pituitary magnetic resonance imaging findings. He was started on hydrocortisone and levothyroxine at 12 d of life and GH replacement at 1 mo of life. Early GH replacement is effective not only for stabilizing blood glucose but also for improving the quality of life.

Key words: congenital hypopituitarism, pituitary aplasia, micropenis, hypoglycemia, GH

Introduction

Neonatal onset hypopituitarism is a very rare condition. Major clinical features are respiratory distress, hypotonia, severe hypoglycemia, hypogenitalism, and cholestatic jaundice. In particular, males with congenital absence of the anterior pituitary gland show respiratory distress and hypoglycemia during the first few days of life, as well as micropenis (1, 2). Early diagnosis is important for suitable replacement therapy. The association of micropenis with hypoglycemia is suggestive of congenital hypopituitarism and should prompt endocrine assessment and a magnetic resonance imaging (MRI) scan of the brain as soon as possible.

GH is a potent regulator of somatic growth that can cause different metabolic features such as nitrogen retention and increased fat mobilization and oxidation (3). After GH treatment in children and adults with GH deficiency, patients have shown changes in resting energy expenditure, the thermic effect of food and vigor (3, 4). We report a case of male neonatal onset congenital hypopituitarism with an invisible pituitary stalk and pituitary aplasia in whom early GH replacement was effective not only for stabilizing blood glucose but also for improving the quality of life.
Clinical course before admission

The male patient was born at term after an uneventful pregnancy by vaginal delivery at a local hospital. His parents were not consanguineous, and he had no signs of perinatal distress. Apgar score was 9 at 1 min. Birth weight was 3.2 kg and length was 50.5 cm. On examination, a micropenis was noted, but no pigmentation was found. During the first few days of life, he had multiple episodes of apnea, cyanosis, hypotonia and hypothermia, associated with severe hypoglycemia.

On day 10 of life, his pituitary hormone levels were assessed during hypoglycemia and a severe combined pituitary hormone deficiency was found: GH <0.1 ng/ml, cortisol 1.0 µg/dl, TSH 2.8 µIU/ml, free T4 0.43 ng/dl, ACTH 7.3 pg/ml. Invisible pituitary stalk, aplasia of the anterior pituitary gland and an ectopic posterior pituitary gland were revealed by MRI scan of the pituitary gland (Fig. 1). The patient was diagnosed as having congenital hypopituitarism. Replacement therapy with l-T4, 20 µg daily, and hydrocortisone, 10 mg daily, was started at day 12 of life, and within a few days hypoglycemia had improved. However, the patient was not active and he did not cry for milk. He was referred to our hospital for further examinations at the age of 1 mo.

Clinical course after admission

The patient’s length was 50.5 cm and weight was 3.5 kg on admission. A micropenis (length 1.4 cm, width 0.6 cm) and hypertrichosis were noted. Ophthalmological findings were normal. At the ages of 1 mo and 6 mo, his anterior pituitary function was studied and multiple pituitary hormone deficiencies were diagnosed (Table 1).

We judged that the dosage of hydrocortisone was excessive and decreased it gradually to 5 mg while measuring 24-h urinary cortisol and fasting blood glucose levels. When he was fed every 2–3 h, obvious hypoglycemia was not found (blood glucose levels before feeding were 60–100 mg/dl),
but after 5–6 h of fasting he sometimes had hypoglycemia of less than 50 mg/dl and he did not cry for milk. At the age of 40 d, we started GH replacement due to unstable blood glucose levels after 5–6 h of fasting. After GH replacement, the levels of blood glucose before feeding increased by about 15 mg/dl (Fig. 2), and no hypoglycemia was shown even after 5–6 h of fasting. The IGF-1 levels increased from 9 to 29 ng/dl due to GH replacement, and he became sufficiently active and cried for milk. His body temperature did not change (about 37 degrees C), but he began to sweat. The micropenis was successfully treated with Tenantate 25 mg im, monthly for 3 mo (at the moment penile length is about 2.5 cm). He was treated with GH, hydrocortisone, l-T4 and his mental development is normal for the age of 7 mo.

### Discussion

Males with congenital hypopituitarism often have micropenis, as was present in our case. The association of micropenis with hypoglycemia is suggestive of congenital hypopituitarism and should prompt endocrine assessment and MRI scan of the brain as soon as possible. Early diagnosis is important for suitable replacement therapy. Hasegawa et al. (5) reported that the presence of a micropenis from early infancy suggests that hypopituitarism might have begun during early fetal life. Also our case with an invisible pituitary stalk, a micropenis and no abnormal delivery, suggests the onset of hypopituitarism before birth.

Some multiple pituitary hormone deficiencies are associated with defects in transcription factors that are expressed during development of the anterior pituitary gland (6). Congenital pituitary hormone deficiencies and Hesx1, Pitx2, Lhx3, Lhx4, Prop-1, Pit-1 gene mutations have been reported in humans (6), however, there has been no report of a case with neonatal onset panhypopituitarism and pituitary aplasia to our knowledge. It is likely that pituitary aplasia may originate from mutations of a still unidentified gene involved in the early phases of pituitary development. Further studies are needed.

Many hypopituitary patients do not require

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Anterior pituitary function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon stimulation test (glucagon 0.03 mg/kg iv)</td>
<td>0</td>
</tr>
<tr>
<td>GH (ng/ml)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>41</td>
</tr>
</tbody>
</table>

This test was done at the age of 1 mo.

<table>
<thead>
<tr>
<th>CRH, TRH, GnRH stimulation test (CRH 1.5 µg/kg, TRH 0.5 mg/m², GnRH 0.1 mg/m² Iv)</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120 (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (µg/dl)</td>
<td>0.3</td>
<td>0.5</td>
<td>0.5</td>
<td>0.4</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>&lt;0.02</td>
<td>0.08</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>&lt;0.9</td>
<td>&lt;0.9</td>
<td>&lt;0.9</td>
<td>&lt;0.9</td>
<td>&lt;0.9</td>
<td>&lt;0.9</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>&lt;0.6</td>
<td>&lt;0.6</td>
<td>&lt;0.6</td>
<td>&lt;0.6</td>
<td>&lt;0.6</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>PSH (mIU/ml)</td>
<td>&lt;0.4</td>
<td>&lt;0.4</td>
<td>&lt;0.4</td>
<td>&lt;0.4</td>
<td>&lt;0.4</td>
<td>&lt;0.4</td>
</tr>
</tbody>
</table>

These provocation tests were done at the age of 6 mo on l-T4 replacement.
GH in addition to hydrocortisone to maintain euglycemia. In many cases, GH replacement is started at the time of the growth disturbance. Our case showed disappearance of obvious hypoglycemia after hydrocortisone replacement therapy, but his did not thrive. He did not cry for milk, and if the feeding interval was long, his fasting blood glucose levels became unstable. The patient was started on GH replacement due to unstable blood glucose levels and a lack of vigor at the age of 1 mo. After GH replacement, stabilized blood glucose levels, vigorous activity, and sweat were observed. Consistent with this, previously reported cases became euglycemia only after GH was added to hydrocortisone treatment (1). GH replacement might be more practical for keeping the glycemic condition after using replacement hydrocortisone alone.

GH is a potent regulator of somatic growth that can cause different metabolic features. In vitro and in vivo studies have shown that GH has anabolic, lipolytic and antinatriuretic actions (3). GH replacement therapy in adult growth hormone deficiency showed normalization of body composition, improvement in the quality of life and psychological well-being, reduction of risk factors for cardiovascular disease, increased muscle strength and exercise capacity and the normalization of metabolic processes (3). In our case, the patient became sufficiently active, cried for milk and started sweating after commencing GH replacement. GH replacement for adult growth hormone deficiency results in an increase in circulating tri-iodothyronine levels, in both patients on T4 replacement and those with normal thyroid function, indicating that GH is a physiological regulator of thyroid function in general and peripheral conversion of T4 in particular (3). In addition, GH replacement has been shown to increase fat oxidation and protein synthesis (3). The increase in energy expenditure is suspected to lead to a rise of body temperature and sweating. GH replacement therapy for complete neonatal GH deficiency may be effective for increasing vigor and improving the quality of life.

In conclusion, early GH replacement for neonatal onset congenital hypopituitarism with an invisible pituitary stalk and pituitary aplasia was effective not only for stabilizing blood glucose but also for improving the quality of life.

References