Hypopituitarism with Invisible Pituitary Stalk: Two Case Reports of Males with Micropenis Suggesting Fetal Onset of Hypopituitarism

YUKIHIRO HASEGAWA, TOMONOBU HASEGAWA, NORIKO TANAKA, HITOSHI ISHIZAKA, TAIJI ASO, MAKOTO YAMADA, SHINOBU KOTOH, YUTAKA TSUCHIYA, AND GEORGES BORDAGE*

Division of Endocrinology and Metabolism, Tokyo Metropolitan Kiyose Children’s Hospital, Tokyo 204, Japan, and Department of Medical Education, College of Medicine, University of Illinois of Chicago, Chicago 60680, USA

Abstract. The presence of hypopituitarism and invisible pituitary stalk on a magnetic resonance image (MRI) is commonly attributed to birth trauma. Two patients with severe hypopituitarism and invisible pituitary stalk are presented. One was born by breech delivery, the other by Cesarean section. The presence of a micropenis since early infancy in these two patients suggested that their hypopituitarism might have begun during early fetal life thus effecting penile growth during the second and third triministers of gestation. These findings raise the possibility that the association of hypopituitarism and invisible pituitary stalk may have multiple etiologies including hormonal abnormalities during early fetal life.

Key words: Hypopituitarism, Micropenis, Abnormal delivery, Invisible pituitary stalk.

IN PATIENTS with severe hypopituitarism particularly with a history of abnormal delivery such as breech delivery and asphyxia, invisible pituitary stalk (pituitary stalk transection) on magnetic resonance image (MRI) has been reported [1]. This MRI finding is generally supposed to be a cause of hypopituitarism [2]. Although it is theoretically possible that the MRI finding is a secondary radiological finding due to severe hypopituitarism, we do not think this is likely. Clinicians know that not all patients with severe hypopituitarism show this MRI finding.

Although the exact onset of the invisible pituitary stalk on MRI remains to be clarified, the MRI finding in patients with a history of abnormal delivery was considered to be caused at delivery [2]. First, because the pituitary stalk is vulnerable to mechanical extraction (based on the study of autopsies [2]), breech delivery may be a mechanical cause of the transection [2]. Similarly, asphyxia may result in damage to the blood supply to the pituitary stalk [2]. Second, some patients with invisible pituitary stalk after brain injury that occurred long after uneventful delivery have also been reported [2], suggesting that a similar mechanical injury during delivery may lead to the MRI finding of invisible pituitary stalk.

There has, however, been no direct evidence that invisible pituitary stalk and hypopituitarism occurred at the delivery. It was reported that some patients with hypopituitarism who showed invisible pituitary stalk on MRI had a micropenis [3]. We have reported one patient (case 1) with invisible pituitary stalk and a micropenis, suggesting
the possible onset of hypopituitarism before birth [4]. Here another case (case 2) of hypopituitarism with micropenis is reported to show prenatal onset of hypopituitarism with invisible pituitary stalk on MRI.

Case Report

Case 1

We previously reported this case [4]. He was the 2.9 kg product of a 39-week uncomplicated gestation. He had a history of breech delivery and asphyxia. His newborn period was uneventful except for prolonged jaundice and a micropenis with descended testes. His jaundice was treated with p.o. phenobarbital. His penile length at the newborn period was not recorded and his micropenis had never been treated. He was referred to our clinic because of short stature (mean \(-4.5\) SD) at the age of 4 years. Physical examination showed a characteristic face for growth hormone deficiency (GHD) and a micropenis (penile length, less than 2 cm). No other abnormalities on physical examination were noted. A two centimeter penile length would have been less than the normal lowest limit in the newborn period [5, 6]. We diagnosed him as having GH and TSH deficiencies at the age of 4 years (Table 1). He showed catch-up growth after treatment with GH and thyroxine supplements (mean \(-2.7\) SD, at the age of 11 years). At the age of 11 years, MRI revealed invisible pituitary stalk, small anterior pituitary and high signal intensity of an ectopic posterior lobe. At the age of 12 years, ACTH and gonadotropin deficiencies were also diagnosed, based on his clinical signs and laboratory data (Table 1). Testosterone treatment was started at the age of 15 years, when he showed no pubertal signs or symptoms and his penile length was still less than 2 cm.

Case 2

He was born at 40-weeks gestation after Cesarean section due to cephalopelvic disproportion. Birth weight was 3.2 kg. Physical examination did not show any abnormal findings except for a micropenis with descended testes (penile length; 1.0 cm at the age of 1 month). His penile length was definitely short for his age [6]. The karyotypic analysis result was 46, XY. Hypopituitarism was suspected in his newborn period because of the micropenis, hypoglycemia, and low thyroxine levels. Multiple pituitary hormone deficiencies (GH, LH, FSH, ACTH, TSH; Table 1) were diagnosed by the age of 3 months. Thyroxine had been given since the age of 3 weeks. Hydrocortisone and GH were started at the age of 3 months. MRI showed invisible pituitary stalk, small anterior pituitary lobe and ectopic posterior lobe (pseudoposterior lobe) as shown in Fig. 1. Probably due to frequent episodes of hypoglycemia, he had developmental delay at the age of 6 months, after which he was followed up at another hospital. We could not get information after the age of 6 months except for the fact that he had been treated with GH, hydrocortisone, l-thyroxine and anticonvulsants.

Discussion

The micropenis in our cases, probably since birth, should be dated back to the critical period for penile growth during early fetal life. It is reported that the majority of the prenatal growth of

<table>
<thead>
<tr>
<th>Table 1. Anterior pituitary function of the two cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>peak GH (ng/ml)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Case 1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Case 2</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Peak GH and cortisol (F) levels during insulin tolerance test (0.1 U/kg), peak LH and FSH levels during LHRH test (100 U/m²), and basal thyroxine (T4) levels are shown. *; peak GH levels during arginine loading test (0.5 g/kg). The provocation test were done at the age of 12 years in case 1 and 3 months in case 2.
the penis occurs after 14 weeks of gestational age at an almost linear rate [5]. The penile length of our patients (about 1–2 cm) would have been the average length at 20–27 weeks of gestational age.

Since a micropenis is supposed to be related with hypopituitarism (either GH-related as GH receptor dysfunction [7] or GH and gonadotropin-related), the hypopituitarism in our cases should have had its onset not at delivery but at or before 20–27 weeks of gestational age. It is not surprising that hypopituitarism is caused during early fetal life, because some patients with GHD have anomalies such as cleft lip and cleft palate, central incisor syndrome [7].

Invisible pituitary stalk on MRI is generally thought to be a cause of hypopituitarism as we mentioned earlier. The invisible pituitary stalk in our two patients may therefore have originated at 20–27 weeks of gestational age or earlier. Invisible pituitary stalk may be due to some developing anomalies resulting in severe hypoplasia of the pituitary stalk during early fetal life. In case 1, however, the apparent transection (invisible pituitary stalk on MRI) might have occurred at the time of his breech delivery due to mechanical factors, independently of the onset of hypopituitarism and micropenis during the early fetal life.

Descended testes in both two cases can be explained by one of the following two possibilities. One possibility is that descent of the testes is not so closely associated with hypopituitarism as micropenis [8]. If descent of the testes is related with hypopituitarism, the other possibility can be drawn: hypopituitarism might have occurred after descent of the testes. Since descent of the testes is believed to occur during the latter two thirds of gestation with some individual variation [8] (namely, beginning possibly from about 13 weeks of gestational age), it is theoretically possible that in our patients the testes had descended before the speculated onset of hypopituitarism and micropenis (at 20–27 weeks of gestational age or earlier).

In summary, at least some patients with hypopituitarism who have a micropenis and invisible pituitary stalk on MRI have the onset of the hormonal abnormalities early in pregnancy (critical period of penile growth). The existence of these cases provides evidence that invisible pituitary stalk and hypopituitarism do not necessarily occur due to abnormal delivery. The onset of hypopituitarism with invisible pituitary stalk on MRI may vary. Further clinical studies are necessary.

References


