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Growth hormone deficiency associated with short stature in a very low birth weight infant after treatment for suspected intracranial cavernous hemangioma

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Abstract

A female infant born at 30 weeks of gestation and weighing 1,276 g developed a suspected intracranial cavernous hemangioma invading the sella turcica at the age of one month. She received high-dose steroid treatment with 5 mg/kg/d of prednisolone, resulting in a reduction in the size of the hemangioma, and follow-up care began after discharge. At the age of six, it was noted that the girl's growth in height was insufficient. Head magnetic resonance imaging (MRI) showed pituitary atrophy, and the results of a loading test led to a diagnosis of growth hormone deficiency resulting in a short stature. However, the administration of growth hormone brought her height up to the average by the age of 11. The patient's intracranial lesion during the newborn period, which was suspected to be a cavernous hemangioma, may have contributed to her pituitary atrophy. The findings of this case suggest that infants who develop a space-occupying lesion in the sella turcica must be kept under long-term observation in view of the possible occurrence of a defective pituitary function.

Key words : growth hormone deficiency, short stature, very low birth weight infant, intracranial cavernous hemangioma

Introduction

Cavernous hemangiomas are benign vascular malformations of relatively low frequency, and congenital intracranial cavernous hemangiomas are particularly rare.[1] Clinical manifestations most often associated with intracranial cavernous hemangiomas include : seizures, hemorrhagic syndrome, and a mass lesion effect with hydrocephalus or focal neurological deficits.[2] We report a case of growth hormone deficiency resulting in a short stature after treatment for suspected intracranial cavernous hemangioma. To our knowledge, no reports have been published on intracranial cavernous hemangioma in relation to a growth hormone deficiency-associated short stature.

Case Report

The patient was a female appropriate-for-gestational-age infant born via emergency C-section at 30 weeks and 1 day, with a weight of 1,276 g and a height of 37 cm. The emergency C-section was performed because of the difficulty in managing the mother's hypertension induced by pregnancy, which had led to a loss of variability as indicated by cardiotocographic findings. Apgar scores were 6 at 1 and 7 at 5 minutes. An artificial pulmonary surfactant was administered for the respiratory distress syndrome, mechanical ventilation was continued for 3 days, and oxygen was administered for 7 days. By day 7 of life, a hemangioma-like erythema had appeared in the posterior cervical region, which gradually extended to the right and became raised. A

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dermatologist at our institution diagnosed this as possible cavernous hemangioma. On day 27 of life, right optic disk enlargement was found during the first ophthalmologic examination, suggesting optic nerve compression. However, no abnormal findings were seen on the ocular fundus. Head computed tomography (CT) performed on day 38 of life revealed a right orbital tumor compressing the optic nerve. This tumor was found to have invaded the intracranial space on the contrast enhanced CT images taken on day 47 of life. These images also showed that the contrast effect presented by the intracranial tumor was similar to that of the subcutaneous mass in the right posterior cervical region, which provided a reasonable ground to suspect that this tumor was a hemangioma (Fig. 1). Also, head MRI on day 46 of life detected a high-intensity signal in the cervical mass, which was radiologically determined to be consistent with the diagnosis of cavernous hemangioma. Based on these images, cutaneous findings, and follow-up observation, the patient's condition was clinically diagnosed as a possible intracranial cavernous hemangioma. In view of the site of the tumor as well as the patient's general physical condition including her constitution, treatment with high-dose prednisolone was initiated on day 49 of life. We administered 5 mg/kg/d of prednisolone for the first 6 weeks, after which the dose was tapered off over a period of 6 weeks before the administration was discontinued on day 134 of life.

On day 93 of life, the therapeutic efficacy was evaluated by means of contrast enhanced CT (Fig. 2), which showed a tumor with contrast effect extending from the right orbit to cavernous sinus that had invaded the suprasellar region. However, although the growth of the infant did not allow us to make an exact comparison with the same slices obtained on day 93 of life, our

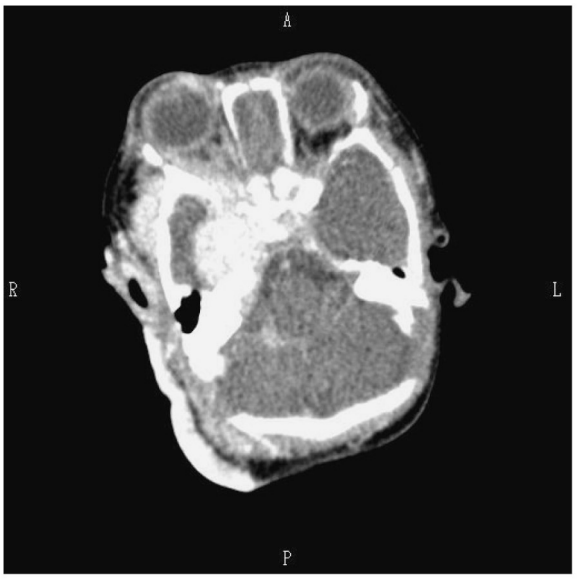

Fig. 1 Contrast-enhanced CT performed on day 47 of life, showing the invasion of a right orbital tumor into the intracranial space. The contrast effect presented by the intracranial tumor was similar to that of the subcutaneous mass in the right posterior cervical region.

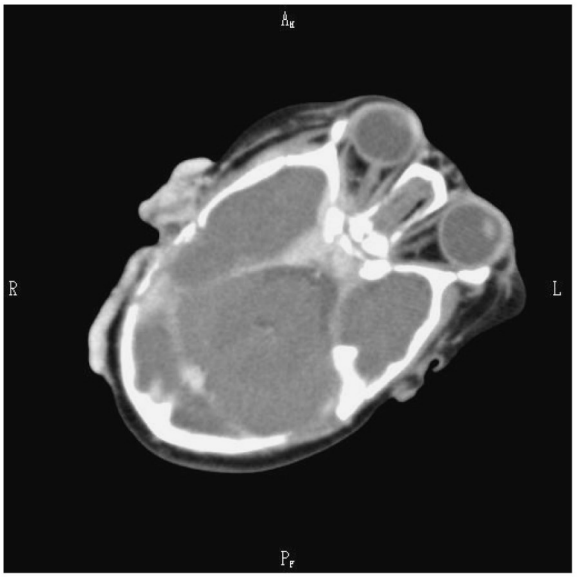

Fig. 2 Contrast-enhanced CT performed on day 93 of life, showing invasion of the tumor into the sella turcica.

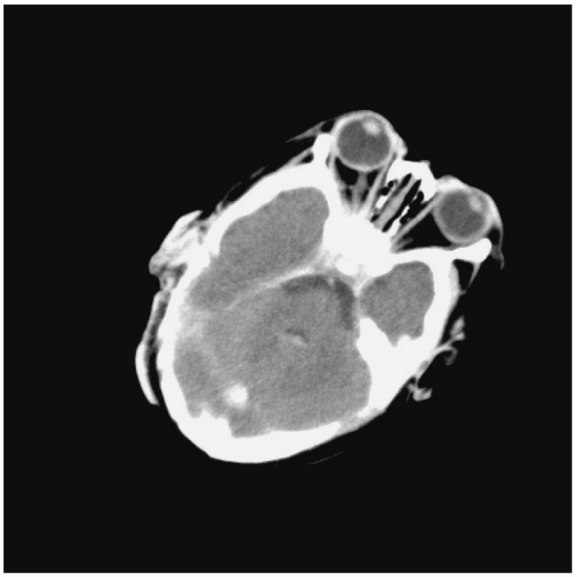

Fig. 3 Contrast-enhanced CT obtained on day 124 of life, showing tumor shrinkage.

Table Results of hormone stimulation tests

Before	30 min.	60 min.	90 min.	120 min.	
Arginine (0.5 g/kg)					
GH (ng/mL)	0.31	0.11	0.40	0.28	0.29
L-DOPA (10 mg/kg)					
GH (ng/mL)	0.24	0.35	0.44	0.32	0.27
Insulin (0.1 U/kg)					
GH (ng/mL)	0.8	0.23	0.37	0.42	0.80
LH-RH (2.6 μg/kg)					
LH (mIU/mL)	0.5>	0.5>	0.5>	0.5>	0.5>
FSH (mIU/mL)	1.2	4.3	7.1	9.6	10.1
TRH (10 μg/kg)					
TSH (μU/mL)	1.6	8.1	6.6	7.2	5.3

GH : growth hormone, L-DOPA : levodopa, LH-RH : luteinizing hormone releasing hormone, LH : luteinizing hormone, FSH : follicle-stimulating hormone, TRH : thyrotropin releasing hormone, TSH : thyroid stimulating hormone

radiologist diagnosed tumor shrinkage based on contrast enhanced CT on day 124 of life, which was 10 days before treatment discontinuation (Fig. 3). The images obtained on day 146 showed no sign of relapse. For the cervical hemangioma, we performed cryocoagulation using liquid nitrogen initially on day 95 of life followed by two more times. As a result, it macroscopically reduced in size.

At the corrected age of 4 months, the patient's head circumference was of average size, and head MRI confirmed that myelination was sufficient for the age. No obvious abnormalities were identified in the pituitary gland or hypothalamus, and, although we did not run any endocrinological tests while she was hospitalized, neonatal screening tests performed during the early neonatal period and prior to discharge showed no thyroid-stimulating hormone (TSH) abnormality. After discharge on day 189 of life (corrected age : 4 months and 15 days) with a weight of 4,840 g, she was followed up as an outpatient. Although she could only sense light with her right eye due to optic nerve compression caused by the tumor, her neurological development was normal. However, her height development gradually slowed down and had become well below average by the age of 6. She was hospitalized for further examination, and the bone age of her left hand joint bones was evaluated at 2 years and 6 months. The insulin-like growth factor-1 (IGF-1) value was markedly low, at 35 ng/mL (median value for Japanese 6-year-old females : 147 ng/mL). A growth hormone (GH) secretion loading test indicated a marked secretion deficit (Table). While a thyrotropin-releasing hormone loading test showed a slightly insufficient response of thyroid-stimulating hormone, it did not indicate pituitary dysfunction. Furthermore, responses of the luteinizing and follicle-stimulating hormones on a luteinizing hormone release hormone loading test showed no obvious anomalies for a prepubertal child. However, head MRI showed pituitary atrophy (Fig. 4). We started the administration of GH (0.16 mg/kg/week) when she was 6 years and 3 months old and 100.8 cm tall (-2.9 SD), which led to improvement in height development during the following years. When her height was 144.2 cm (-0.2 SD) at the age of 11 years and 3 months, the treatment was completed (Fig. 5). Her first menstruation started at the age of 11 years and 9 months, and the development of secondary sexual characteristics and psychomotor development were normal. She attended regular classes at an elementary school.

Discussion

Although we were unable to establish a definite pathological diagnosis for the intracranial lesion in this case, findings based on head images were consistent with cavernous hemangioma. The differential diagnosis of vascular lesions

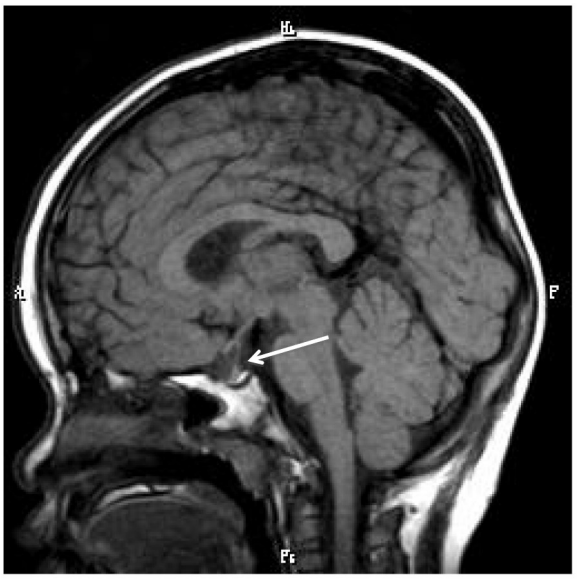

Fig. 4 Sagittal T1-weighted head MRI, showing pituitary atrophy (arrow).

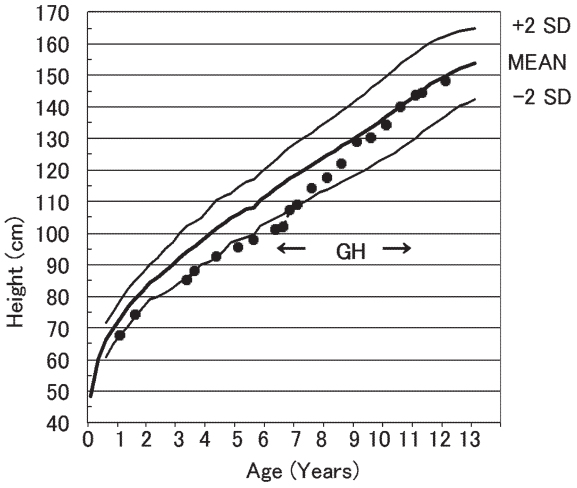

Fig. 5 Comparison of a standard growth chart for girls' stature with the patient's growth chart (●). Period of growth hormone administration is indicated by (←GH→).

involving the neuraxis in infancy includes hemangioma, hemangioblastoma, vascular malformation, and other neonatal tumors, such as soft-tissue sarcoma. The presence of radiologically indistinguishable extracranial tumor and concordant changes in size of the extracranial and intracranial lesions should suggest neuraxial hemangioma.[3] That the contrast effect presented by the intracranial tumor was similar to that of the subcutaneous mass in the right posterior cervical region suggests that the intracranial tumor in this case was a cavernous hemangioma as was the case with the cutaneous lesion. On the other hand, just because the intracranial tumor and the cervical mass reduced in size concordantly with each other does not necessarily mean that not only the cervical mass but the intracranial lesion also was cavernous in nature, considering that cryocoagulation had been performed on the cervical mass. However, since intracranial hemangiomas are often accompanied by cutaneous lesions as in this case, and cases without cutaneous lesions have rarely been reported,[4] the intracranial lesion in this case was considered most likely to be a cavernous hemangioma. Cavernous hemangiomas are histologically identical to what is categorized as infantile hemangiomas.[3] Spontaneous regression of extracranial cavernous hemangiomas during childhood is common, while congenital intracranial cavernous hemangiomas can exhibit a progressive reduction in size after birth.[5] In the case presented here, however, immediate treatment was considered necessary because the tumor was pressing on the optic nerve, indicating a marked likelihood of the manifestation of other symptoms. The use of steroids and interferon is reportedly effective for the treatment of cavernous hemangiomas.[6,7] Moreover, transcatheter coil embolization has been used in some cases of neonatal hepatic cavernous hemangiomas with favorable results.[8] While surgical excision is considered to be the most reliable therapy for intracranial cavernous hemangiomas in particular,[2] stereotactic radiosurgery for the management of cerebral cavernous malformations remains controversial.[9] Taking into account the general physical condition of our patient, including her constitution, it was determined that any surgical or invasive therapies would be too risky, and so we opted for high-dose steroid treatment, as described in the report by Sadan et al.[10] This treatment resulted, as expected, in the shrinkage of the tumor without any major complications. Although we did not foresee any pituitary disorders after the hemangioma treatment, we nevertheless periodically tracked and monitored our patient's growth and development because her weight at birth was very low. As a result of these follow-ups, she was found to have growth hormone deficiency accompanied by a short stature at the age of six.

While this type of deficiency is almost always of idiopathic origin, there have also been cases with other causes, including organic, hereditary, and congenital. One of the organic causes of GH

deficiency accompanied by a short stature is pituitary stalk transection associated with perinatal abnormalities such as breech delivery and neonatal asphyxia,[11] and, in recent years, cases of GH deficiency after traumatic brain injuries have also been receiving marked attention.[12]

GH deficiency in our case was thought to have been caused by pituitary atrophy. Although morphological variation of the pituitary gland is not necessarily accompanied by functional disorders, when a circulatory disorder due to some external factor causes degeneration or necrosis of the anterior pituitary, its function can be impaired depending on the severity of the degeneration or necrosis.[13] As mentioned above, some cases of pituitary atrophy are known to occur in association with pituitary stalk transection due to perinatal disorders, such as abnormal delivery or neonatal asphyxia,[12] ischemia,[14] and cranial radiation.[15] Our patient was not born by breech delivery, but given that she was a very low birth weight infant with mild neonatal asphyxia, the possibility remains that the pituitary atrophy was indeed a result of perinatal abnormality. On the other hand, the incidence rate of GH deficiency is not particularly high in preterm infants, and our patient's perinatal period followed a course typical for a very low birth weight infant except for the onset of the hemangioma and the subsequent high-dose steroid therapy. The fact that the hemangioma was found to have invaded the sella turcica suggests that this was the cause of the pituitary atrophy. While it is difficult to establish at what degree of tumor invasion destruction of the pituitary gland occurs based on images, the pituitary gland can become flattened even by spinal fluid infiltrating the sella turcica, which, in turn, causes endocrine disruption.[16] Moreover, a suprasellar tumor can cause irreversible pituitary dysfunction.[17] A diagnosis of GH deficiency accompanied by a short stature is typically established after the patient has reached the age of three to four, when GH is thought to exert its greatest effect on height growth, and yet it becomes evident that the increase in height has slowed down. It can thus be assumed that our patient's growth had been sustained until she turned 3 or 4 by factors other than GH, such as nutrition and thyroid hormones. This is consistent with our supposition that the tumorous compression impaired her pituitary gland in an irreversible fashion during early infancy. Although a high dose of steroids was administered, no reports, as far as we can determine, have associated steroid administration with pituitary atrophy or a manifestation of GH deficiency after a long period of time. Also, while the incidence of a short stature in small for gestational age infants has been drawing much attention in recent years,[18] it is not likely the case here since our patient was an infant with an appropriate stature for her gestational age. Moreover, a short stature in small for gestational age infants is usually not accompanied by GH deficiency.

Hypopituitarism after traumatic brain injuries, which has also attracted attention in recent years, is considered to be caused by various factors including mechanical damage to the hypothalamic-pituitary system,[19] and this kind of hypopituitarism can progress with age.[20] If a similar type of mechanical damage had been involved in the GH deficiency in our case, various symptoms may therefore occur in the future, necessitating life-long follow-up not only of her GH secretory state but of her overall pituitary function as well.

The authors declare no financial conflict of interest.

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