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Case Report

Diagnostic Usefulness of 3 Tesla MRI of the Brain for Cushing Disease in a Child

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Abstract. It is sometimes difficult to confirm the location of a microadenoma in Cushing disease. Recently, we experienced an 11-yr-old female case of Cushing disease with hyperprolactinemia. She was referred to our hospital because of decrease of height velocity with body weight gain. On admission, she had typical symptoms of Cushing syndrome. Although no pituitary microadenomas were detected on 1.5 Tesla MRI of the brain, endocrinological examinations including IPS and CS sampling were consistent with Cushing disease with hyperprolactinemia. Oral administration of methyrapone instead of neurosurgery was started after discharge, but subsequent 3 Tesla MRI of the brain clearly demonstrated a 3-mm less-enhanced lesion in the left side of the pituitary gland. Finally, transsphenoidal surgery was performed, and a 3.5-mm left-sided microadenoma was resected. Compared with 1.5 Tesla MRI, 3 Tesla MRI offers the advantage of a higher signal to noise ratio (SNR), which provides higher resolution and proper image quality. Therefore, 3 Tesla MRI is a very useful tool to localize microadenomas in Cushing disease in children as well as in adults. It will be the first choice of radiological examinations in suspected cases of Cushing disease.

Key words: cushing disease, microadenoma, IPS sampling, CS sampling, 3 Tesla MRI

Introduction

Cushing disease is one of the most demanding entities to diagnose and treat (1). However, radiographic visualization of a pituitary microadenoma associated with Cushing disease is sometimes difficult on standard 1.5 Tesla (1.5T) magnetic resonance imaging (MRI) (2). For patients with Cushing disease in whom standard MRI does not reveal a pituitary microadenoma with certainty, IPS (inferior petrosal sinus) or CS (cavernous sinus) sampling may be performed in order to distinguish the central source from ectopic ACTH secretion and to localize the suspected corticotroph microadenoma to one side of the pituitary (3). However, venous sampling of the pituitary is asymmetric, and its potential for inaccuracy is well documented (4). Currently, high-field MRI

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scanners operating at 3 Tesla (3T) are entering routine clinical use and are becoming available from most manufacturers. They can offer improved quality and spatial resolution in conditions with subtle differences between normal and abnormal tissue (5, 6).

We recently treated an 11-yr-old female who had Cushing disease with hyperprolactinemia. We were unable to locate the patient's pituitary microadenoma on 1.5T MRI, although venous sampling was positive for the presence of a tumor. However, 3T MRI of the brain, which was performed 3 mo later, clearly demonstrated a microadenoma in the left side of the pituitary gland. It wad also useful for follow-up after transsphenoidal surgery. Herein, we describe the diagnostic usefulness of 3T MRI of the brain for Cushing disease in a child.

Case Report

The patient, an 11-yr-old girl, was admitted to our university hospital because of low height velocity with body weight gain. She was born by normal delivery and had previously been healthy. Sudden body weight gain had been noted for 3 yr prior to admission, and a decrease in height velocity had been noticed beginning at 9 yr of age. Her most recent height growth rate was only 2.5 cm/yr. On admission, she had a body temperature of 36.8C, blood pressure of 120/66 mmHg and heart rate of 60/min. Her height and weight were 131.1 cm (–1.88 SD) and 37.3 kg (body mass index: 21.6 kg/m^2, 90th percentile), respectively. Moon face, acne on the cheek, buffalo hump and hirsutism were found. There were no abnormal findings on the chest or abdomen. Her breast and pubic hair development were both judged as Tanner stage III. Bone age was 10.1 yr by the Tanner-Whitehouse (TW2) method standardized for Japanese children. Her psychomotor development was normal.

Endocrinological examinations revealed hypercortisolism (serum cortisol level of 21.2–35.0 μg/dl, urinary free cortisol (UFC) level of 326.0–492.0 μg/d) with no diurnal variation of serum cortisol levels. A CRH test revealed a normal basal ACTH level and elevated basal cortisol level with positive responses to CRH stimulation. High-dose dexamethasone suppressed 24-h UFC collection from 492.0 μg/d to 115.0 μg/d (Table 1). In the radiological findings, abdominal CT revealed swelling of the bilateral adrenal glands, but 1.5T MRI of the brain by SPGR (spoiled gradient recalled echo) demonstrated no microadenomas in the pituitary gland (Fig. 1a). Subsequent IPS and CS sampling revealed a remarkable step-up of plasma ACTH in the left side and of serum PRL levels in both sides of the gland (Table 2). The peripheral serum PRL level was elevated to 33.4 ng/ml.

Based on these findings, Cushing disease with hyperprolactinemia was suspected. However, we selected adrenal-directed therapy instead of neurosurgery for our patient because no microadenomas were detected in her pituitary gland. Oral administration of metyrapone (750 mg/d) was started after her discharge. Her plasma cortisol levels decreased to between 12 μg/dl and 16 μg/dl. Three months later, 3T MRI of the brain using the SPGR method was carried out to detect pituitary microadenoma. As shown in Fig. 1b, coronal T1-weighted images with gadolinium clearly demonstrated a 3-mm less-enhanced lesion in the left side of her pituitary gland. Ultimately, transsphenoidal surgery was performed, and a 3.5-mm microadenoma was totally resected from the left side (Fig. 2a). In hematoxylin and eosin (H & E) staining of the microadenoma, diffuse proliferation of slightly large and basophilic cells was found (Fig. 2b). Immunohistochemical examinations demonstrated that the microadenoma stained positively for only ACTH (Fig. 2c). PRL-immunohistochemical staining was negative. Consequently, the diagnosis of an ACTH-secreting microadenoma was confirmed, and a mixed tumor with ACTH- and PRL-positive cells was excluded. Her hypercortisolism and hyperprolactinemia were resolved after the

Table 1 Endocrinological studies

Circadian rhythm of the pituitary-adrenal axis

Time (h)	8:00	16:00	24:00
ACTH (pg/ml)	45.2	55.0	38.4
Cortisol (μg/dl)	26.5	21.2	22.1

CRH test

Time (min)	Pre	15	30	60	90	120
ACTH (pg/ml)	32.1	118.0	98.1	42.0	28.2	27.2
Cortisol (μg/dl)	35.0	53.5	50.9	44.4	35.2	29.3

Dexamethasone suppression test

Dose of dexamethasone	30 μg/kg/d			120 μg/kg/d		
	Pre	Day1	Day2	Day3	Day4	Day5
U-cortisol (μg/d)	492.0	460.0	328.0	195.0	115.0	
U-17-OHCS (mg/d)	10.1	17.2	11.5	17.1	10.1	
U-17-KS (mg/d)	8.1	13.1	12.3	24.0	13.5	
ACTH (pg/ml)	24.1			32.8		23.6
Cortisol (μg/dl)	24.4			18.1		17.5

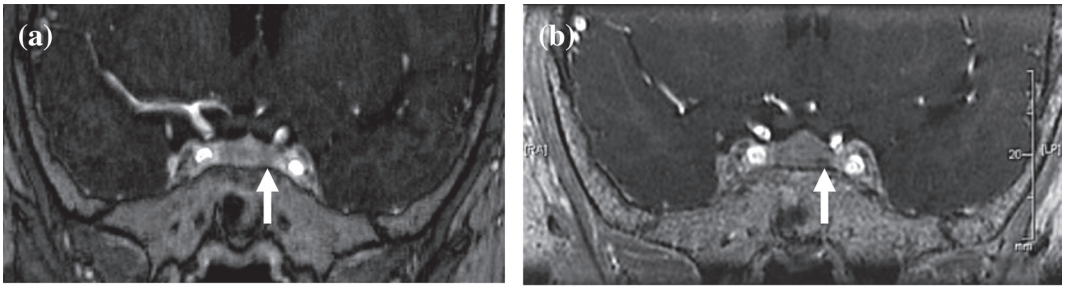

Fig. 1 3 Tesla and 1.5 Tesla Brain MRI images by the SPGR method. The superiority of 3 Tesla MRI in comparison with 1.5 Tesla MRI in the detection of microadenoma is demonstrated.

Table 2 IPS and CS sampling data

	Rt. CS	Lt. CS	Rt. IPS	Lt. IPS	Peripheral
ACTH (pg/ml)	31.4	–	26.1	3,270.0	21.8
C/P ratio	1.44	–	1.20	150	
PRL (ng/ml)	347.0	–	676.8	1,089.0	33.4
GH (ng/ml)	7.27	–	13.0	17.10	0.23

CS: cavernous sinus, –: not done. IPS: inferior petrosal sinus.

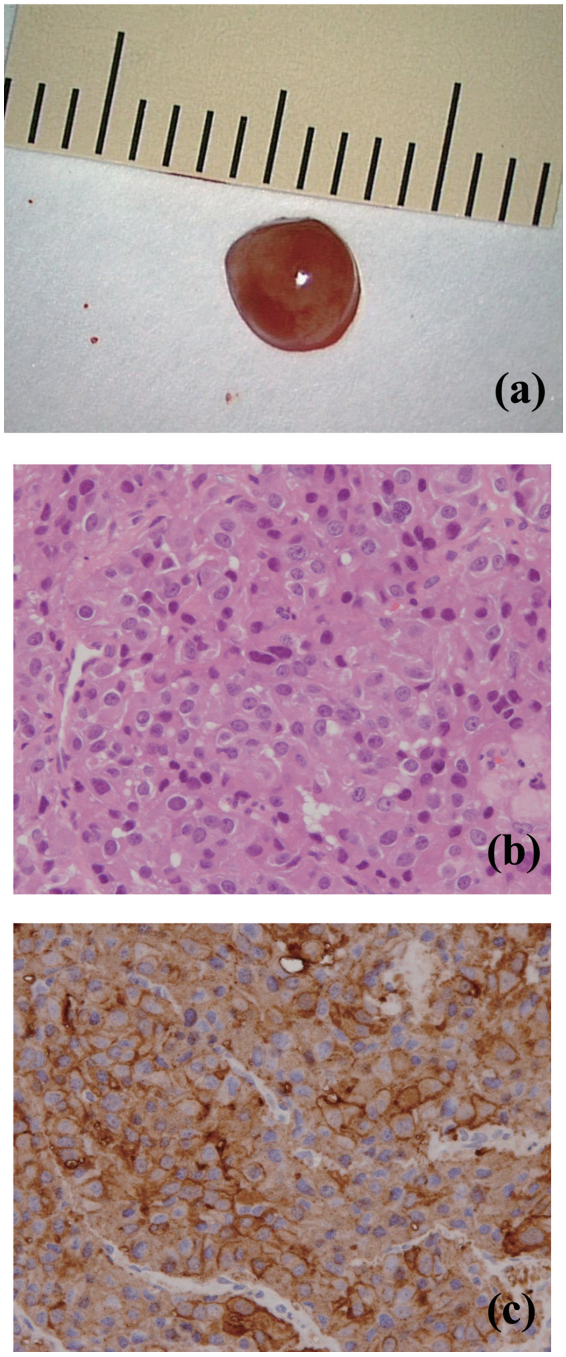

Fig. 2 Pathological findings. (a) A 3.5-mm microadenoma was totally resected. (b) H & E staining. Diffuse proliferation of slightly large and basophilic cells was found. (c) ACTH immunohistochemistry by using anti-human ACTH (X50, DAKO) and a BenchMark system (VENTANA). The microadenoma stained positively for only ACTH.

operation. Follow-up 3T MRI revealed no relapse of microadenoma in her pituitary gland.

Discussion

ACTH-secreting microadenomas are visible on 1.5T MR images in 36–63% of cases in patients with Cushing disease (7). Therefore, proving that the source of ACTH secretion is from the pituitary gland is not a simple process. Recently, 3T MRI has entered clinical use in some university hospitals in Japan. Compared with 1.5T MRI, 3T MRI offers the advantage of a higher signal-to-noise ratio (SNR), which provides higher resolution and proper image quality within an acceptable scanning time (8, 9). Pinker *et al.* reported that 3T MRI was superior to 1 or 1.5T MRI for predicting the invasion of adjacent structures in patients with pituitary adenomas and that it improves surgical planning of sellar lesions (3). Some studies have shown that 3T MRI might ameliorate the imaging difficulties associated with ACTH-secreting pituitary adenomas (2, 9). In particular, high-field MR imaging by the SPGR method can detect very small but hormonally active sellar lesions such as microadenomas.

In our patient, a 3-mm less-enhanced lesion was clearly identified in the left side of the anterior pituitary by 3T MRI of the brain using the SPGR method. This finding supported the result of CS and IPS sampling. Figures 1a and 1b demonstrate the superiority of 3T MRI in comparison with 1.5T MRI in the detection of microadenoma in our case, although these pictures were not taken simultaneously. On the other hand, it has been reported in another study that 3T MRI failed to determine the site of the microadenoma in some patients with Cushing disease (2). Therefore, to identify a pituitary microadenoma in Cushing disease more correctly, both 3T MRI of the brain and venous sampling will be necessary in addition to endocrinological examinations.

It is also interesting that our case featured

markedly elevated PRL levels in venous sampling of the pituitary gland, but did not have a separate prolactinoma. Her hyperprolactinemia improved after operation. In the series of 11 adult patients reported by Caufriez *et al*., 10 of whom had preoperative elevation of morning PRL levels, serum PRL normalized after transsphenoidal surgery as in our case (10). On assessing menstrual abnormalities in Cushing disease, Lado-Abeal *et al*. found mildly elevated serum PRL levels in 20% of female patients, although the serum PRL and menstrual abnormalities were not correlated (11). Yamaji *et al*. also indicated preoperative PRL elevation in 23% of Japanese patients with Cushing disease (12). Elevated preoperative PRL levels in Cushing disease are still of unproven diagnostic significance (13). However, we need to consider the complications of hyperprolactinemia even for Cushing disease in children.

In summary, 3T MRI is a very useful tool for localizing microadenomas and is necessary to evaluate the prognosis for Cushing disease in children as well as in adults. It will be the first choice of radiological examinations in suspected cases of Cushing disease.

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