Usefulness of composite methionine–positron emission tomography/3.0-tesla magnetic resonance imaging to detect the localization and extent of early-stage Cushing adenoma

Clinical article

HIDETOSHI IKEDA, M.D., PH.D.,¹ TAKEHIKO ABE, M.D., PH.D.,² AND KAZUO WATANABE, M.D., PH.D.³

¹Research Institute for Pituitary Disease, ²Department of Radiology, and ³Research Institute for Neuroscience, Southern Tohoku General Hospital, Koriyama, Japan

Object. Fifty to eighty percent of Cushing disease is diagnosed by typical endocrine responses. Recently, the number of diagnoses of Cushing disease without typical Cushing syndrome has been increasing; therefore, improving ways to determine the localization of the adenoma and making an early diagnosis is important. This study was undertaken to determine the present diagnostic accuracy for Cushing microadenoma and to compare the differences in diagnostic accuracy between MR imaging and PET/MR imaging.

Methods. During the past 3 years the authors analyzed the diagnostic accuracy in a series of 35 patients with Cushing adenoma that was verified by surgical pituitary exploration. All 35 cases of Cushing disease, including 20 cases of “overt” and 15 cases of “preclinical” Cushing disease, were studied. Superconductive MR images (1.5 or 3.0 T) and composite images from FDG-PET or methionine (MET)–PET and 3.0-T MR imaging were compared with the localization of adenomas verified by surgery.

Results. The diagnostic accuracy of superconductive MR imaging for detecting the localization of Cushing microadenoma was only 40%. The causes of unsatisfactory results for superconductive MR imaging were false-negative results (10 cases), false-positive results (6 cases), and instances of double pituitary adenomas (3 cases). In contrast, the accuracy of microadenoma localization using MET-PET/3.0-T MR imaging was 100% and that of FDG-PET/3.0-T MR imaging was 73%. Moreover, the adenoma location was better delineated on MET-PET/MR images than on FDG-PET/MR images. There was no significant difference in maximum standard uptake value of adenomas evaluated by MET-PET between preclinical Cushing disease and overt Cushing disease.

Conclusions. Composite MET-PET/3.0-T MR imaging is useful for the improvement of the delineation of Cushing microadenoma and offers high-quality detectability for early-stage Cushing adenoma.

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KEY WORDS • positron emission tomography • methionine • Cushing disease • magnetic resonance imaging • fluorine-18–labeled fluorodeoxyglucose

Cushing disease is a serious endocrinopathy that, if untreated, greatly increases morbidity and carries a 4-fold increased risk of mortality, which is largely related to associated cardiovascular complications and abnormal glucose metabolism. The duration of Cushing disease is a significant predictor of cardiovascular risk. Cardiovascular disease is a major cause of morbidity and death in patients with Cushing syndrome, and further risk remains in effectively treated patients. Furthermore, the standard mortality ratio has been reported to be attributable to an increased mortality rate within the 1st year after diagnosis. Hence, early diagnosis and treatment for Cushing disease is highly desirable.

Cushing disease, which sometimes shows a false-negative or false-positive reaction to various hormone-loading tests, does not always meet the diagnostic crite-
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Typical Cushing disease that exhibits an endocrine reaction to various loading tests has been reported to be 50–80% of cases. Moreover, neuroradiological assessment, such as CT or MR imaging, has sometimes failed to detect Cushing adenoma. Despite the abnormal signal seen on MR images in cases of Cushing disease, this technique does not guarantee the localization of the lesion associated with this illness, as microadenomas have been found in 10–14% of autopsy cases. The development of superselective cavernous sinus sampling has far improved the accuracy of diagnosis for central Cushing disease; however, the stress experienced by patients during the examination is too high, demonstrating that this is still an inappropriate examination method for the localization of a Cushing adenoma.

Positron emission tomography was applied to clinical use in the 1990s, but image resolution has been poor and unsuitable for evaluating the accurate localization of pituitary microadenomas. Therefore, high-quality functional imaging to detect the localization of Cushing adenoma is greatly desirable. In this study, we compared data describing the adenoma location obtained through surgical exploration with composite PET (MET or FDG) and 3.0-T MR images. We found a high rate of correspondence between the MET-PET images and the operative findings where the area and localization of the adenoma were concerned. In this paper, we stress the usefulness of MET-PET/MR imaging, which advances the surgical treatment of Cushing disease.

Methods

Definition of Preclinical Cushing Disease

The diagnostic criteria of preclinical Cushing disease are as follows: 1) an uncertain existence of pituitary tumor following diagnostic imaging (PET or MR imaging); 2) normal or high morning serum ACTH values and normal serum cortisol values; and 3) the lack of specific cushingoid features. If all 3 criteria are met and it remains unclear whether Cushing disease is present, additional screening is performed in which abnormality of cortisol secretion, which originates from autonomous ACTH secretion, is examined. Diagnostic factors from the screening inspection include the following: 1) a serum cortisol value ≥ 2.5 µg/dl when sleeping (measured at midnight); 2) a morning serum cortisol value ≥ 3 µg/dl after 0.5 mg dexamethasone suppression at night; and 3) paradoxical reaction of ACTH (≥ 1.5 times the former value) on a 1-deamino-8-d-arginine vasopressin (DDAVP) test. If ≥ 2 of these 3 items meet the criteria, there is evidence of cortisol secretion abnormalities due to autonomous ACTH secretion. To discriminate between ectopic ACTH syndrome, it was assumed that no abnormal findings following PET scanning were observed in the entire body.

Patient Population

We identified 39 patients with Cushing disease who underwent surgery in the past 3 years. An ACTH-secreting adenoma was histologically confirmed in 35 of these patients. One of the remaining 4 patients had gonadotroph cell adenoma, and the adenoma could not be histologically confirmed in the other 3 patients. Therefore, the diagnostic accuracy rate for Cushing disease was examined using the aforementioned 35 patients. Of these patients, 10 were male and 25 female. The patients’ mean age was 46.5 years (range 11–76 years). Of the 35 patients with Cushing disease, 20 cases consisted of “overt” Cushing disease and 15 cases of “preclinical” Cushing disease. These patients were admitted to our hospital with a high suspicion of Cushing disease after precise endocrinological investigations. Nineteen of 35 patients were examined using 3.0-T MR imaging, and of these, 12 were examined using PET scanning. The 16 remaining patients were examined using 1.5-T MR imaging. All patients underwent transphenoidal exploration of the pituitary gland by a skilled pituitary neurosurgeon (H.I.). Our prerequisites for surgery were that the preclinical diagnostic criteria for Cushing disease or overt Cushing disease were fulfilled. Concurrently, significantly high ACTH concentrations needed to be found in cavernous sinus blood using cavernous sinus sampling in those cases in which a visible pituitary mass was not demonstrated on MR imaging. Among 20 patients with overt Cushing disease, 18 harbored a microadenoma and 2 displayed macroadenoma. Moreover, among the 15 patients with preclinical Cushing disease, 12 had microadenoma and 3 had macroadenoma. To evaluate the background activity of a normally functioning pituitary gland on MET- and FDG-PET, 10 patients without pituitary disease were examined using MET- and FDG-PET/3.0-T MR imaging. We obtained institutional review board approval and patient written informed consent for this study.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed using a 3.0-T MR imaging unit (Signa HD, General Electric; or Achieva Quasar Dual 3.0T, Philips) and a 1.5-T MR imaging unit (Magnetom H15, Siemens). A standard circularly polarized head coil was used. The MR imaging studies of the brain were obtained in sagittal, coronal, and axial planes and consisted of T1-weighted spin echo images (TR/TE/number of excitations of 500 msec/10 msec/3 or 454 msec/11 msec/1) and T2-weighted spin echo images (TR/TE/number of excitations of 4000 msec/102 msec/3, or 4606 msec/90 msec/2; field of view 160 × 160 or 200 × 200 mm; matrix size 256 × 192 or 320 × 175). The slice thickness was 2, 2.5, or 3 mm, with a 0.2-mm slice gap. For contrast-enhanced studies, 0.1 mmol/kg body weight of Gd–diethylenetriamine pentaacetic acid was injected intravenously.

Positron Emission Tomography Imaging

The PET-CT studies were undertaken using the Discovery LS (General Electric). The PET machine used bismuth germanium oxide crystals. All patients fasted before the procedure and received intravenous injections of MET (4.6 × body weight [dose range 280–450 MBq, that is, 8–12 mCi]), which was prepared according to a method adapted from Comar et al. Five-minute emission scans were obtained starting 20 minutes after injection. Attenuation correction was performed by a transmission
scan. The MET-PET procedure was performed in 3D mode, which provided a set of 35 planes with a section thickness of 4.1 mm. One hour after the MET injection, 185 MGq (5 mCi) FDG was injected intravenously. Ten-minute PET scans were obtained starting 60 minutes after injection. Attenuation correction was performed by a transmission scan. The FDG-PET provided a set of 35 planes with a 4.1-mm section thickness in 3D mode.

Uptake of glucose and MET during PET scanning was evaluated using an SUV, allowing semiquantitative analysis of this variable. The SUV was obtained using the following equation: SUV = tissue radioactivity (MBq/g) in area concerned/(MET dosage [MBq/g]). Background activity of normal pituitary tissue in patients with Cushing disease and the 10 patients without pituitary disease were measured using PET/3.0-T MR imaging.

**Image Postprocessing**

The MR and PET images were coregistered to Gd-enhanced T1-weighted images and T2-weighted images using the software workstation (Zio, Amin). For coregistration between MR images and PET images, MR imaging data sets were fused 3-dimensionally based on the CT skull shape ascertained by PET-CT. Anatomical landmarks used by the program must be defined to transform target images so that they match the reference image (Advantage Registration, General Electric). This registration procedure is recommended when the target image has enough anatomical information to define 3 landmarks, such as optic nerves, the internal occipital protuberance, the vestibular cochlear nerve, and so on. A minimum of 3 landmarks is required to perform full-volume registration. The PET images were first registered to the CT series, and then the MR images were registered to the CT series. Thereafter, the PET scans overlaid onto the MR images were automatically viewed. The PET-MR image was analyzed for preoperative estimation in this study.

**Pathological Examination**

Surgical specimens were fixed in 10% neutral buffered formalin and embedded in paraffin. Three-micrometer-thick slices were prepared and stained with H & E. Immunohistochemical staining was performed using the avidin-biotin complex method using the following antibodies: polyclonal adrenocorticotropic hormone (DAKO), polyclonal growth hormone (DAKO), polyclonal prolactin (DAKO), monoclonal thyroid-stimulating hormone–β (Neo markers), monoclonal luteinizing hormone–β (Neo markers), monoclonal follicle-stimulating hormone–β (Neo markers), polyclonal α-subunit (DAKO), and monoclonal Ki 67 (DAKO).

**Results**

**Diagnostic Quality of Superconductive MR imaging**

Although superconductive MR imaging (1.5 or 3.0 T), which improves the signal-to-noise ratio, resulted in better resolution, accuracy of the localization of the Cushing adenoma was shown to be unsatisfactory. The accuracy of microadenoma diagnosis using 1.5-T MR imaging in patients with preclinical Cushing disease and overt Cushing disease was 40 and 67%, respectively. By contrast, the accuracy of microadenoma diagnosis using 3.0-T MR imaging in patients with preclinical Cushing disease and overt Cushing disease was 14 and 33%, respectively (Table 1). Thus, the frequency with which adenomas in preclinical Cushing disease could be visualized with MR imaging was low. Moreover, contrary to our expectation, adenoma detectability decreased, despite the use of 3.0-T MR imaging with a raised signal-to-noise ratio. Consequently, of the 30 microadenomas assessed by MR imaging only 12 (40%) demonstrated good correlation to surgical findings. Ten cases had false-negative results, 6 had false-positive results, and 3 cases had double pituitary adenomas.

**Diagnostic Quality of Superconductive PET/MR Imaging**

Accumulation of FDG was observed in 8 (67%) of 12 cases of Cushing disease, while MET accumulation was observed in all 11 examined cases (Fig. 1). Background activity in normal pituitary tissue in this study showed a mean (± SD) MET SUV<sub>max</sub> of 1.3 ± 0.23, and a mean FDG SUV<sub>max</sub> of 3.19 ± 0.74. The background activity of normal pituitary tissue from PET examination in the 10 individuals who did not have pituitary disease was 0.74 ± 0.18 (range 0.50–1.0) for MET SUV<sub>max</sub> and 2.72 ± 0.96 (range 1.3–4.5) for FDG SUV<sub>max</sub>. Thus, background noise in proposed adenoma cases was higher than that in cases with normally functioning pituitary glands, probably due to tumor uptake artifact. Moreover, in cases with a MET SUV<sub>max</sub> < 3.0, FDG had no significant uptake (Table 2). The FDG uptake was probably not detected in adenomas with low activity because the background activity of FDG was greater than that of MET. Thus, the sensitivity of MET-PET/MR imaging for the visualization of Cushing adenoma was superior to FDG-PET/MR imaging. In addition, the specificity of MET-PET/MR imaging to delineate the area of the Cushing adenoma was superior to FDG-PET/MR imaging. All 5 patients with preclinical Cushing disease showed accumulation of MET (Table 2). There was no significant difference in SUV<sub>max</sub> of MET-PET between overt Cushing disease and preclinical Cushing disease (Mann-Whitney U-test). At the same time, there were also no significant differences in SUV<sub>max</sub> of adenoma in FDG-PET between overt Cushing disease and preclinical Cushing disease (Mann-Whitney U-test).

**Discussion**

Inaccuracy exists in the endocrinological testing for Cushing disease. The frequency with which adenomas in preclinical Cushing disease could be visualized with MR imaging was low. Moreover, contrary to our expectation, adenoma detectability decreased, despite the use of 3.0-T MR imaging with a raised signal-to-noise ratio. Consequently, of the 30 microadenomas assessed by MR imaging only 12 (40%) demonstrated good correlation to surgical findings. Ten cases had false-negative results, 6 had false-positive results, and 3 cases had double pituitary adenomas.

**Table 1: Diagnostic accuracy of 1.5- and 3.0-T MR imaging**

<table>
<thead>
<tr>
<th>Stage of Disease</th>
<th>1.5 T</th>
<th>3.0 T</th>
</tr>
</thead>
<tbody>
<tr>
<td>preclinical CD</td>
<td>2/5 (40)</td>
<td>1/7 (14)</td>
</tr>
<tr>
<td>overt CD</td>
<td>6/9 (67)</td>
<td>3/9 (33)</td>
</tr>
<tr>
<td>total accuracy</td>
<td>8/14 (57)</td>
<td>4/16 (25)</td>
</tr>
</tbody>
</table>

* CD = Cushing disease.
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Cushing disease, consequently presenting a problem for diagnosis. For example, the dexamethasone suppression test results agree with diagnostic criteria in 50% of Cushing disease cases, whereas the corticotropin-releasing hormone stimulation test findings agree with diagnostic criteria in 70% of Cushing disease cases. Thus, in an important examination in the differential diagnosis of Cushing disease, it is difficult to clearly discriminate a pituitary lesion and an ectopic lesion. Additionally, the accuracy of neuroradiological imaging to aid in the diagnosis of Cushing disease is less than optimal; the diagnostic accuracy of Cushing disease on CT scans and 1.5-T MR imaging has been reported to be 42 and 52%, respectively. Similarly, the diagnostic accuracy of the Cushing microadenoma on MR imaging (1.5 or 3.0 T) proved to be 45% in this study. In general, dynamic MR imaging is considered to improve diagnostic accuracy. However, Tabarin et al. examined the diagnosis rate of MR imaging and dynamic MR imaging using 1.0-T MR imaging and showed that true positivity with MR imaging was 53%, while true positivity of dynamic MR imaging was 67%, illustrating that there were no significant differences between diagnostic accuracy using these 2 imaging techniques. Postcontrast spoiled-gradient recalled-acquisition has been reported to have a 64% diagnostic success rate; therefore, an adenoma is only confirmed, at most, in ~60% of cases using the imaging technique that gives the best image and diagnostic accuracy.

When Cushing disease is typical in nature, based on results of endocrinological tests and neuroradiological imaging, the diagnosis is easy and the surgical cure rate is favorable. However, when its nature is atypical, the operative procedure to improve the cure rate is still to explore the entire pituitary. Selective venous sampling from the cavernous sinus has appeared to improve the accuracy of the diagnosis for Cushing syndrome of CNS origin. The diagnostic accuracy of this method is 100%, but it is insufficient in gathering information detailing the localization of the microadenoma.

The existence of multiple pituitary adenomas is enumerated as a bias that influences the image diagnosis. Because of multiple adenomas, neurological images have resulted in false-positive findings. In our study, 3 (9%) of 35 patients appeared to harbor multiple adenomas. In autopsy cases, 17 (5.4%) of 316 cases were reported to have multiple pituitary adenomas. Other causes of false-positive results within the pituitary gland include small hemorrhages, infarcted areas, and age-related interstitial fibrosis.

If a neuroimaging method were to exist by which viable cells within the pituitary gland could be confirmed, tumorous areas in the pituitary could be observed. Within cells, a system exists for the production of composition and secretion proteins. Vigorous synthesis of secretion proteins is a feature in pituitary cells. The effect of secretion protein synthesis was examined by treating primary cultures of pituitary tumor cells with Brefeldin A (BFA), which blocks part of the synthesis route (from rough endoplasmic reticulum to Golgi apparatus) of the secretion protein. The ultrastructural change of the pituitary tumor cells treated with BFA was sequentially observed using electron microscopy. As a result, we found that the precursor to the secretion protein could be recognized as electron-dense material in the rough endoplasmic reticulum.

Fig. 1. Cases 2 (A), 4 (B), 6 (C), 8 (D), and 10 (E). Axial FDG-PET/MR images (left panels), MET-PET/3.0-T MR images (center panels), and T2-weighted or Gd-enhanced (Gd(+)) MR images (right panels). The hypermetabolic area is defined within the pituitary gland.
The MET-PET/MR imaging method facilitates the judgment of surgical procedures, and it can clarify not only the abnormal changes within the pituitary gland, but also the area and the extent of the lesion. Thus, it can be expected that MET-PET/MR imaging can greatly contribute to the improvement of the operative results of Cushing disease.

Conclusions

The MET-PET/3.0-T MR imaging method provides a higher sensitivity for determining the location and delineating Cushing adenoma than other neuroradiological imaging techniques such as MR imaging, dynamic MR imaging, and CT scanning. The SUV$_{\text{max}}$ of MET- and FDG-PET images revealed no significant difference between overt Cushing disease and preclinical Cushing disease in terms of glucose and amino acid metabolism within the adenoma; therefore, MET-PET/MR imaging is useful in detecting early-stage Cushing adenoma.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References

11. Findling JW, Raff H: Cushing’s syndrome: important issues

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**TABLE 2: Summary of clinical data and MET and FDG SUV in patients with Cushing disease**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Pathology</th>
<th>MET (SUV$_{\text{max}}$)</th>
<th>FDG (SUV$_{\text{max}}$)</th>
<th>Adenoma Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73, F</td>
<td>CD</td>
<td>1.8</td>
<td>0</td>
<td>micro</td>
</tr>
<tr>
<td>2</td>
<td>32, M</td>
<td>preclinical CD</td>
<td>2.5</td>
<td>0</td>
<td>micro</td>
</tr>
<tr>
<td>3</td>
<td>51, F</td>
<td>CD</td>
<td>—</td>
<td>3.7</td>
<td>micro</td>
</tr>
<tr>
<td>4</td>
<td>11, F</td>
<td>CD</td>
<td>3.3</td>
<td>5.7</td>
<td>micro</td>
</tr>
<tr>
<td>5</td>
<td>52, M</td>
<td>preclinical CD</td>
<td>4.5</td>
<td>5.6</td>
<td>macro</td>
</tr>
<tr>
<td>6</td>
<td>39, F</td>
<td>CD</td>
<td>3.5</td>
<td>5.4</td>
<td>micro</td>
</tr>
<tr>
<td>7</td>
<td>60, F</td>
<td>CD</td>
<td>2.5</td>
<td>4.4</td>
<td>micro</td>
</tr>
<tr>
<td>8</td>
<td>38, F</td>
<td>CD</td>
<td>3.4</td>
<td>3.0</td>
<td>micro</td>
</tr>
<tr>
<td>9</td>
<td>53, F</td>
<td>CD</td>
<td>6.9</td>
<td>14.6</td>
<td>macro</td>
</tr>
<tr>
<td>10</td>
<td>26, M</td>
<td>preclinical CD</td>
<td>1.9</td>
<td>0</td>
<td>micro</td>
</tr>
<tr>
<td>11</td>
<td>55, F</td>
<td>preclinical CD</td>
<td>1.9</td>
<td>0</td>
<td>macro</td>
</tr>
<tr>
<td>12</td>
<td>21, F</td>
<td>preclinical CD</td>
<td>4.1</td>
<td>2.6</td>
<td>micro</td>
</tr>
</tbody>
</table>

*macro = macroadenoma; micro = microadenoma; — = not performed.

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Address correspondence to: Hidetoshi Ikeda, M.D., Ph.D., Research Institute for Pituitary Disease, Southern Tohoku General Hospital, 7-115 Yatsuyamada, Koriyama, Fukushima, 963-8563, Japan. email: ikeda@ssg.med.tohoku.ac.jp.