

Incidental Focal ^{18}F -FDG Uptake in the Pituitary Gland: Clinical Significance and Differential Diagnostic Criteria

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The purpose of this study was to identify the incidence and clinical significance of incidental pituitary uptake on whole-body ^{18}F -FDG PET/CT. **Methods:** We evaluated 13,145 consecutive subjects who underwent ^{18}F -FDG PET/CT. The final diagnosis of pathologic or physiologic uptake was based on brain MRI and follow-up PET scanning. Receiver-operating-characteristic curve analysis was performed to determine an optimal cutoff for detecting pathologic uptake. **Results:** We found that 107 (0.8%) subjects showed incidental pituitary uptake. In 29 of 71 subjects with the final diagnosis, the pituitary uptake was pathologic: macroadenomas ($n = 21$), microadenomas ($n = 5$), and malignancy ($n = 3$). When a maximum standardized uptake value of 4.1 was used as an optimal criterion for detecting pathologic uptake, the diagnostic sensitivity, specificity, and accuracy were 96.6%, 88.1%, and 91.5%, respectively. **Conclusion:** Although incidental pituitary uptake is an unusual finding, the degree of ^{18}F -FDG accumulation is helpful in identifying pathologic pituitary lesions that warrant further diagnostic evaluation.

Key Words: pituitary gland; focal uptake; incidentaloma; ^{18}F -FDG; PET/CT

J Nucl Med 2011; 52:547–550

DOI: 10.2967/jnumed.110.083733

With advances in diagnostic imaging modalities, incidentalomas of the pituitary gland have been described with increasing frequency (1–3). The widespread use of ^{18}F -FDG PET has also resulted in an increase of incidentally detected pituitary lesions (4–7). In practice, incidental pituitary uptake is a diagnostic dilemma, and its differential diagnosis is challenging yet important for clinical decision making. Patients with pituitary incidentalomas should be evaluated for tumor hypersecretion, and patients with macroadenomas should be evaluated for hypopituitarism and other mass effects (3). Several previous studies have reported the clinical significance of incidentally detected focal ^{18}F -FDG uptake on whole-body PET (8–11). Studies of

incidental pituitary lesions on PET scans are limited to case reports (4,6,7) and only 1 large cohort study that was recently published (5). However, there are limited published data regarding a criterion for discriminating between clinically significant pathologic pituitary uptake and nonspecific physiologic pituitary uptake.

The purpose of this study was to identify the incidence and clinical significance of incidentally detected focal pituitary uptake on whole-body ^{18}F -FDG PET/CT in a large cohort of patients. Additionally, we investigated differential findings between pathologic and physiologic pituitary uptake.

MATERIALS AND METHODS

Patient Population

We evaluated 13,145 consecutive subjects who underwent whole-body ^{18}F -FDG PET/CT from May 2004 to May 2008. PET scans were obtained for 11,986 patients (91.2%) for assessment of known or suspected malignancy and for 1,159 healthy subjects (8.8%) for cancer screening. Among this population, only patients with incidental pituitary uptake were identified through a database search of medical records.

Of the 13,145 subjects, 107 (57 men, 50 women; age range, 33–83 y; mean age, 57 y) showed incidental focal ^{18}F -FDG accumulation in the pituitary gland. Clinical records and imaging data were reviewed for these 107 patients. Incidental foci of ^{18}F -FDG uptake were correlated with brain MRI findings. Brain MRI was performed using a 1.5-T MRI system (Signa; GE Healthcare). Imaging protocols included at least nonenhanced axial and sagittal T1-weighted images, axial and coronal T2-weighted images, and contrast-enhanced T1-weighted images after administration of gadolinium. Axial and sagittal images were acquired with a section thickness of 5 mm. Coronal images were acquired with a section thickness of 3 mm. If brain MRI results were unavailable, a follow-up PET scan was used for validation of the initial PET scan. The final diagnosis of pathologic or physiologic uptake was available in 71 (66.4%) patients. We excluded 36 patients from further analysis because the final diagnosis was unavailable. The ethics committee of our institution reviewed and approved the study protocol.

PET/CT and Analysis

All of the patients fasted for at least 6 h before the PET study. Whole-body PET and unenhanced CT images were acquired using a PET/CT scanner (Discovery LS; GE Healthcare). After the whole-body CT scan, an emission scan was obtained from the upper thigh to the skull vertex, for 5 min per frame at 45 min after intravenous injection of 370 MBq of ^{18}F -FDG. The attenuation-corrected transverse PET images (matrix, 128 × 128; voxel size,

Received Oct. 1, 2010; revision accepted Dec. 20, 2010.

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4.3 × 4.3 × 3.9 mm) using the CT data were reconstructed using an ordered-subsets expectation maximization algorithm (28 subsets, 2 iterations). The standardized uptake value (SUV) was corrected for the injected dose of ^{18}F -FDG and the patient's body weight.

Focal ^{18}F -FDG accumulation in the pituitary gland was defined as increased ^{18}F -FDG uptake localized in the sellar area that was greater than background activity in adjacent tissues. For semi-quantitative analysis, a 10-mm-diameter circular region of interest was placed over the single axial slice with maximum activity within the sellar area. The intensity of ^{18}F -FDG uptake was measured as the maximum SUV (SUV_{max}) and average SUV (SUV_{avg}). We also measured the SUV_{avg} of mediastinal blood-pool structures as a reference background tissue and calculated a tumor-to-background ratio (TBR). The maximum TBR (TBR_{max}) was determined by the ratio of lesion SUV_{max} to background SUV_{avg}. The average TBR (TBR_{avg}) was determined by the ratio of lesion SUV_{avg} to background SUV_{avg}.

Statistical Analysis

Receiver-operating-characteristic (ROC) curve analysis was performed to determine an optimal cutoff for differentiating pathologic from physiologic uptake. The area under the ROC curve (AUC) was calculated to compare the diagnostic performance of PET parameters. To analyze the distribution of PET parameters in subsets of patients, results were expressed as mean and SD. Differences between 2 independent groups were determined by a *t* test. All statistical tests were 2-tailed, and a *P* value

of less than 0.05 was considered significant. MedCalc 11.1 (MedCalc Software) and JROCFIT (John Eng, Johns Hopkins University, available at: www.jrocfit.org) were used for statistical analyses.

RESULTS

Incidentally detected focal ^{18}F -FDG accumulation in the pituitary gland was found in 107 of 13,145 subjects, accounting for an incidence of 0.8%. Correlative brain MRI was available in 55 (51.4%) of the 107 subjects (Fig. 1). In 29 (52.7%) of 55 subjects, brain MRI confirmed the existence of pituitary macroadenomas ($n = 21$), microadenomas ($n = 5$), lung cancer metastasis ($n = 1$), breast cancer metastasis ($n = 1$), and non-Hodgkin lymphoma involvement ($n = 1$). The size of the pituitary adenomas ranged from 4 to 35 mm. There were no significant pituitary abnormalities on brain MRI in the remaining 26 subjects. Although correlative brain MRI was unavailable in 52 patients, normalized pituitary uptake on the follow-up PET scan represented physiologic uptake in 16 subjects (Fig. 2). Therefore, final diagnosis was available in 71 subjects: uptake was pathologic in 29 subjects and physiologic in 42.

The degree of ^{18}F -FDG accumulation was a mean SUV_{max} of 5.3 (range, 2.6–25.6) for the initial study

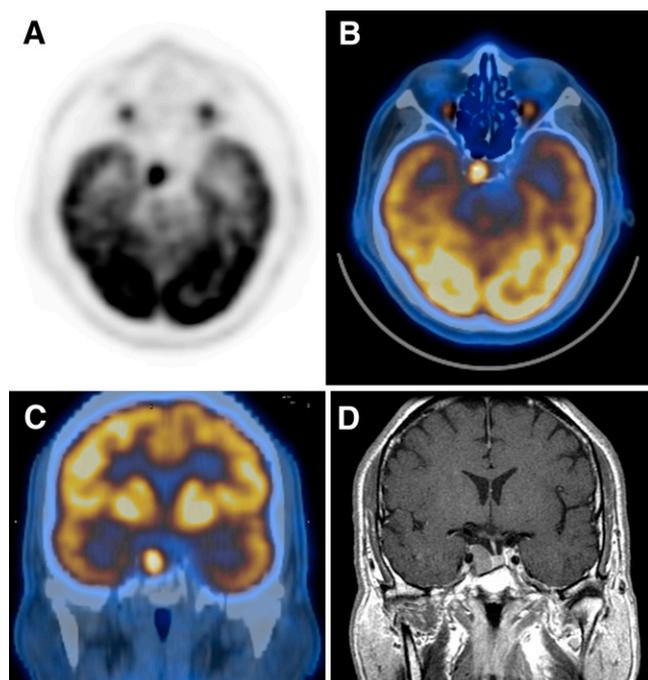


FIGURE 1. Incidental focal ^{18}F -FDG uptake in 60-y-old man who underwent PET/CT examination for initial staging of tonsillar cancer. Transaxial PET (A), transaxial PET/CT (B), and coronal PET/CT (C) images show focus of increased ^{18}F -FDG uptake in sellar region, with SUV_{max} of 12.4 and SUV_{avg} of 6.8. (D) T1-weighted coronal MR image after administration of gadolinium shows focal area of low signal intensity on right side of pituitary gland. Correlative brain MRI confirmed existence of 14-mm pituitary macroadenoma corresponding to incidental focal ^{18}F -FDG uptake.

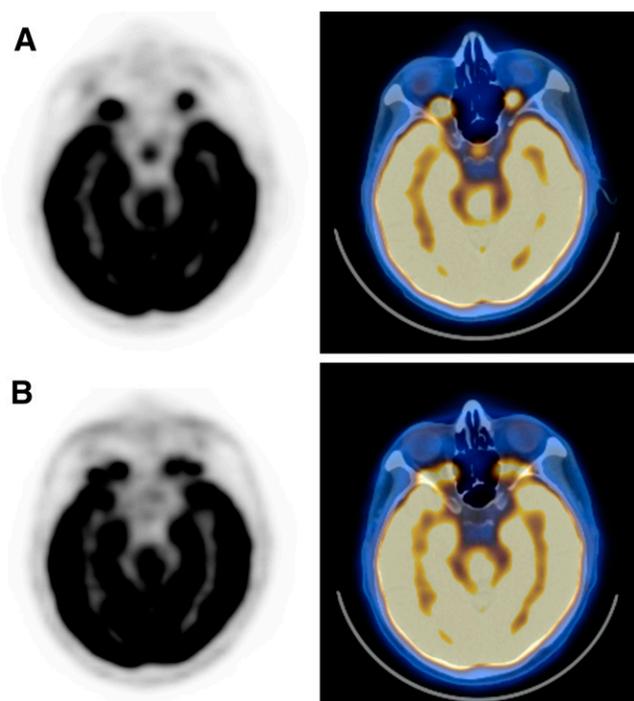


FIGURE 2. Incidental focal ^{18}F -FDG uptake in 66-y-old man with stomach cancer who was undergoing routine follow-up examination. (A) Transaxial PET and PET/CT images show focus of increased ^{18}F -FDG uptake in pituitary gland, with SUV_{max} of 3.8 and SUV_{avg} of 2.6. (B) At 3-mo follow-up, transaxial PET and PET/CT images show normalized ^{18}F -FDG uptake in pituitary gland, with SUV_{max} of 2.2 and SUV_{avg} of 2.0. Focal ^{18}F -FDG uptake on first PET scan represents physiologic pituitary uptake.

TABLE 1
Comparison of Intensity of ^{18}F -FDG Uptake Between Pathologic and Physiologic Uptake

| Parameter | Pathologic uptake ($n = 29$) | Physiologic uptake ($n = 42$) | P |
|---------------|--------------------------------|---------------------------------|--------|
| SUVmax | | | |
| Mean \pm SD | 9.4 \pm 6.4 | 3.6 \pm 0.7 | <0.001 |
| Range | 3.6–25.6 | 2.6–6.6 | |
| SUVavg | | | |
| Mean \pm SD | 5.5 \pm 3.5 | 2.5 \pm 0.3 | <0.001 |
| Range | 2.4–17.0 | 1.7–3.6 | |
| TBRmax | | | |
| Mean \pm SD | 5.6 \pm 3.9 | 2.3 \pm 0.6 | <0.001 |
| Range | 1.7–17.1 | 1.4–4.2 | |
| TBRavg | | | |
| Mean \pm SD | 3.2 \pm 2.2 | 1.6 \pm 0.3 | <0.001 |
| Range | 1.1–11.3 | 1.1–2.7 | |

group of 107 patients and a mean SUVmax of 5.9 (range, 2.6–25.6) for the final study group of 71 patients. A statistically significant difference was found in the intensity of ^{18}F -FDG uptake between pathologic and physiologic uptake (Table 1). Nine of 29 patients with pathologic uptake had a pituitary macroadenoma that required surgery. These patients were treated successfully with endonasal transsphenoidal removal of the pituitary tumor. In pathologic uptake, there were no significant differences in SUVs between surgical and nonsurgical lesions or between malignant and benign lesions. The overall ^{18}F -FDG uptake of macroadenomas was significantly higher than that of microadenomas, according to SUVmax (10.9 \pm 7.0 vs. 4.7 \pm 0.9, $P = 0.01$), SUVavg (6.3 \pm 3.8 vs. 3.0 \pm 0.6, $P = 0.01$), TBRmax (6.3 \pm 4.2 vs. 2.8 \pm 0.6, $P = 0.01$), and TBRavg (3.6 \pm 2.4 vs. 1.8 \pm 0.3, $P = 0.03$).

ROC curve analysis showed the AUC for each PET parameter (Fig. 3). The diagnostic performance was the best with SUVmax, followed by SUVavg, TBRmax, and TBRavg. The AUC of the absolute SUV was greater than that of TBR: SUVmax vs. TBRmax ($P = 0.01$) and SUVavg vs. TBRavg ($P = 0.03$). There was no significant difference in AUC between the maximum value and average value: SUVmax vs. SUVavg ($P = 0.40$) and TBRmax vs. TBRavg ($P = 0.69$). Optimal diagnostic cutoff values according to ROC analysis were an SUVmax of 4.1 and an SUVavg of 2.8. When an SUVmax of 4.1 was used as a criterion to discriminate between pathologic and physiologic uptake, the resulting sensitivity, specificity, and accuracy for detecting pathologic uptake were 96.6%, 88.1%, and 91.5%, respectively. When an SUVavg of 2.8 was used as a cutoff, the resulting sensitivity, specificity, and accuracy were 89.7%, 85.7%, and 87.3%, respectively.

DISCUSSION

Incidental pituitary uptake was found in 0.8% of the present study population. This study showed that 40.8% of pituitary ^{18}F -FDG uptake with the final diagnosis was pathologic lesions; pituitary adenomas (89.7%) were the most common cause of these pathologic lesions. When cut-

off values are used for interpretation of ^{18}F -FDG uptake, the SUVmax or SUVavg of the sellar region could be an optimal criterion for discriminating between pathologic and physiologic uptake.

A recent meta-analysis reported that the overall prevalence of pituitary adenoma was 16.7% (12). These figures indicate that pituitary adenomas are fairly common in the general population. However, contrary to our study, most of the lesions were small microadenomas. This difference is due to the lower spatial resolution and partial-volume effect of PET, which is limited in the detection of pituitary microadenomas smaller than 10 mm. Two previous studies found the prevalence of macroadenoma to be 0.16%–0.20% (13,14). In the present study population, the estimated prevalence of macroadenoma was 0.24%, which is comparable to previous reports.

One study recently reported that the incidence of incidental pituitary uptake on whole-body PET/CT scans

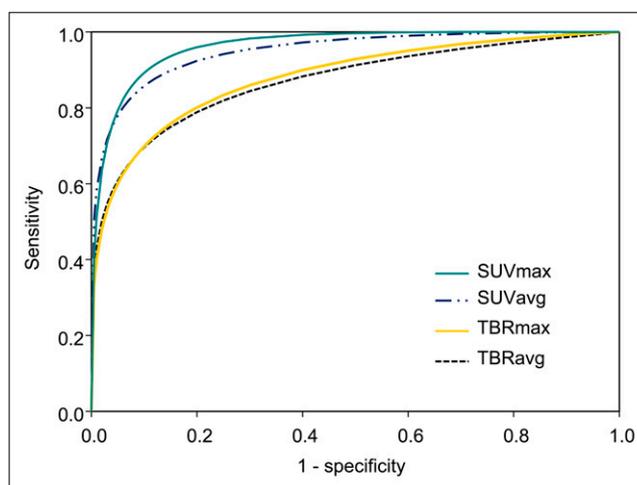


FIGURE 3. ROC curves for SUVmax, SUVavg, TBRmax, and TBRavg. AUC and SE were 0.96 \pm 0.02 for SUVmax, 0.95 \pm 0.02 for SUVavg, 0.88 \pm 0.04 for TBRmax, and 0.87 \pm 0.04 for TBRavg. Diagnostic performance was better with absolute SUV than with TBR.

was 0.073% (5). There is a large discrepancy between the present study incidence of 0.8% and this previously reported incidence of 0.073%. This discrepancy is probably due to the different detection rates derived from various consensus regarding pituitary uptake. For several years, incidentally detected focal ^{18}F -FDG uptake on whole-body PET/CT has been of interest to our group (8,15,16). As such, we have made an effort to carefully review pituitary uptake encountered in routine clinical practice. Consequently, we found relatively many examples of incidental pituitary uptake, and the overall intensity of focal pituitary uptake was lower than that of the previous report. Additionally, this variable result may be due in part to the multicenter study design, various acquisition and reconstruction protocols, and various models of PET/CT scanners used in the previous report.

In the present study, semiquantitative analysis using SUV showed a statistically significant difference between pathologic and physiologic uptake. Therefore, SUV could efficiently differentiate a pathologic lesion from physiologic uptake. We found optimal diagnostic cutoff values of 4.1 for SUV_{max} and 2.8 for SUV_{avg}. We agree that these cutoff values are not universally applicable to all PET centers because SUV is affected by many factors (17–19). However, there is no defined consensus or published data for the interpretation of focal ^{18}F -FDG uptake in the pituitary gland. Thus, we believe our data could serve as a reference for routine clinical practice.

Our study has several limitations. Because of the retrospective study design, final diagnosis was unavailable in about one third of the subjects with incidental pituitary uptake. We assumed that 16 instances of pituitary uptake that resolved on a subsequent PET scan might be physiologic. However, it is possible for a tumor to decrease as a natural course of the disease (3). Additionally, we have limited data concerning hormonal dysfunction and histopathologic findings because endocrinologic evaluation and tissue confirmation were performed only for a small number of the subjects. Furthermore, some focal pituitary uptake could have been missed, especially in pituitary microadenomas and tumors that were not ^{18}F -FDG-avid, possibly resulting in an underestimation of the actual incidence.

CONCLUSION

Although incidental focal pituitary uptake on whole-body ^{18}F -FDG PET/CT scans is an unusual finding, the prevalence of pathologic lesions is not low among subjects with focal pituitary uptake. The degree of ^{18}F -FDG accu-

mulation is helpful in identifying pathologic pituitary lesions that warrant further diagnostic evaluation.

ACKNOWLEDGMENT

This study was supported by a grant from the Samsung Biomedical Research Institute, Republic of Korea (C-B0-320-1).

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J Nucl Med. 2011;52:547-550.

Published online: March 18, 2011.

Doi: 10.2967/jnumed.110.083733

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The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

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